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Clinical Development and Regulatory Affairs
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REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

A Phase 2, Randomized, Placebo-controlled Study of Safety and Efficacy Following Repeat-dose Administration of Evinacumab (Anti-Angptl3) in Patients with Severe Hypertriglyceridemia (sHTG) at Risk for Acute Pancreatitis

Compound:	Evinacumab
Protocol Number:	R1500-HTG-1522 Version 4GB
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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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
ADC	Apparent diffusion coefficient
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
APO	Apolipoprotein
AP	Acute pancreatitis
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Grafting
CI	Confidence interval
CM	Chylomicrons
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CV	Cardiovascular
CVD	Cardiovascular disease
DBTP	Double-blind treatment period
DW-MRI	Diffusion Weighted-Magnetic Resonance Imaging
ECG	Electrocardiogram
EOT	End of treatment
FAS	Full analysis set
FCS	Familial Chylomicronemia Syndrome
FFA	Free fatty acids
^{18}F-FDG PET	^{18}F-2-Fluoro-2-Deoxy-D glucose positron emission tomography
FSH	Follicle stimulating hormone
GI	Gastrointestinal
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HL	Hepatic lipase
HTG	Hypertriglyceridemia
ICH	International Council for Harmonization
ICF	Informed consent form

IDMC	Independent Data Monitoring Committee
IV	Intravenously
IVRS	Interactive voice response system
Ki	Incorporation rate
Kpatlak	Patlak clearance rate
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LOF	Loss of function
Lp(a)	Lipoprotein a
LPL	Lipoprotein lipase
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model with repeated measures
MRI	Magnetic resonance imaging
NMR	Nuclear Magnetic Resonance
PCI	Percutaneous Coronary Interventions
PCSV	Potentially clinically significant value
PET	Positron emission tomography
PK	Pharmacokinetic
PRO	Patient-Reported Outcomes
PT	Preferred term
Q4W	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBTP	Single-blind treatment period
SD	Standard deviation
SE	Standard error
sHTG	Severe hypertriglyceridemia
SOC	System organ class
TBR	Target to background ratio
TC	Total cholesterol
TEAE	Treatment-emergent adverse event

TG	Triglycerides
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL	Very-low-density lipoproteins
WBC	White blood cell

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-1522 study. The content of this SAP is inclusive of the interim, first, and second step analyses as described in the protocol.

This plan may be revised during the study to accommodate protocol amendments and adapt to unexpected issues in study execution that may affect planned analyses. These revisions will be based on blinded data review, and a final plan will be issued prior to the first interim database lock (i.e. before any treatment assignments become known). For the purposes of this document, REGN1500 will be referred to as "evinacumab".

1.1. Background/Rationale

Elevated levels of serum triglycerides (TG) are associated with the development of cardiovascular disease (CVD) and acute pancreatitis (AP). Studies suggest that mild to moderate elevations in TG levels are an independent risk factor for the development of CVD, and recent studies have demonstrated that genetic loss of function (LOF) variants which result in lower TG levels (eg, apolipoprotein C3 (APOC3), ANGPTL3, and ANGPTL4 LOF genetic variants) are associated with a decreased risk of myocardial infarction. Patients with severe elevations in TG levels (>1000 mg/dL) are at increased risk of pancreatitis and current lipid guidelines recommend lifestyle interventions and medications to lower TG levels to prevent AP.

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

Evinacumab (REGN1500) is a human IgG4 monoclonal antibody specific for ANGPTL3 and is being developed for treatment of dyslipidemia including hypertriglyceridemia (HTG) and hypercholesterolemia. 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 change in TG levels following 12 weeks of repeated IV doses of evinacumab in the subset of patients with a documented history of sHTG (TG ≥1000 mg/dL [11.3 mmol/L]), a TG level of at least 500 mg/dL (5.6 mmol/L) at screening, a history of acute pancreatitis and without LOF mutations in genes in the LPL pathway; and to assess whether a reduction in TG of at least 40% from the baseline placebo period has been achieved.

Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will be blinded to blood lipid measurements during the double-blind and single-blind treatment periods

1.2.2. Secondary Objectives

The secondary objectives of the study are:

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

1.2.3. Exploratory Objectives

- To assess the degree of pancreatic injury/inflammation in the placebo run-in period and following treatment with evinacumab, as assessed by biochemical markers (amylase and pancreatic lipase activity [measured without lipemia interference], hs-CRP, IL-6, and other inflammation markers)

- To evaluate the effect of evinacumab compared to placebo on the incidence of recurrent acute pancreatitis overall and in subgroups with homozygous or compound heterozygous LOF mutations, heterozygous LOF mutations, and without LOF mutations in genes in the LPL pathway
- To assess hospitalizations for abdominal pain, hospitalizations for pancreatitis, and hospitalizations for cardiovascular disease
- To assess the degree of pancreatic injury/inflammation through T2-weighted magnetic resonance imaging (T2-MRI) at baseline and the change from baseline following 12 and 24 weeks of treatment with evinacumab as assessed by T2 intensity and T2 relaxation time
- To assess the degree of pancreatic injury/inflammation through 18F-2-Fluoro-2-Deoxy-D glucose positron emission tomography (18F-FDG-PET) imaging at baseline (placebo run-in) and change from baseline following 12 weeks of treatment with evinacumab as assessed by 18F-FDG Ki or Kpatlak
- To evaluate the percent change from baseline of other lipid parameters (eg, total cholesterol [TC], TG, non-HDL-C, LDL-C, HDL-C, APOB, FFA, APOA-I) and lipoprotein subfraction composition (eg, chylomicrons [CM], VLDL, IDL, LDL [low-density lipoprotein], HDL [high-density lipoprotein], particle cholesterol, TG content, and apolipoprotein composition) after ultracentrifugation
- To evaluate change from baseline in metabolic parameters (fasting blood glucose, insulin, C-peptide, HbA1c) after 12 and 24 weeks of evinacumab treatment
- To evaluate change from baseline in post heparin LPL activity after evinacumab treatment.
- To evaluate changes in 18F-FDG-PET in atherosclerotic plaque (target to background ratio [TBR]) in carotids and/or aorta
- To evaluate change from baseline in MRI liver fat signal
- To evaluate changes in the number and percentage of stomach pain, pain and abdominal symptom-free days, defined as the number and percentage of stomach pain free days, number of pain free days, and the number of abdominal symptom free days, as assessed by the HAP-SS.
- To evaluate changes in the number and percentage of days where meals are avoided as assessed by the HAP-DB.

1.2.4. Modifications from the Statistical Section in the Final Protocol

The summary of modifications is listed in the following table.

Item	Protocol Section	Description
1	2.3 Exploratory Objective To assess medical visits/hospitalizations for abdominal pain or pancreatitis, medical visits/hospitalizations for pancreatitis, and medical visits/hospitalizations for cardiovascular disease	SAP Section 1.2.3: Modified exploratory objective for medical visits/hospitalizations to remove medical visits because it is not captured in e-CRF (consistent across all evinacumab studies).
2	2.3 Exploratory Objective	SAP Section 1.2.3, added two objectives: • To evaluate changes in the number and percentage of stomach pain, pain and abdominal symptom-free days, defined as the number and percentage of stomach pain free days, number of pain free days, and the number of abdominal symptom free days, as assessed by the HAP-SS. • To evaluate changes in the number and percentage of days where meals are avoided as assessed by the HAP-DB.
3	10.3.2 Safety Analysis Set The safety analysis set (SAF) includes all randomized patients who received any randomized study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.	SAP Section 3.2 and 3.3: Safety Analysis Set was divided to double-blind and single-blind period to be consistent with other evinacumab studies.
4	10.4.3.1 Primary Efficacy Analysis • "For the assessment of probability (computed from the likelihood function based on the observed data, which is equivalent to Bayesian posterior probability with uninformative prior) that mean TG percent change ≥40% ..." • "A natural log transformation will be applied to the TG levels prior to	SAP Section 5.7.1: • For this proof-of-concept trial, estimates in TG change will be reviewed for 40% reduction supporting future drug development planning i.e., body of evidence review. Due to a lack of historical data in this indication, the application of posterior probability is not informative. • To provide further clarification, TG baseline definition was changed to the

	analysis." "To reduce variability of TG baseline measurements, baseline at week 0 for patients randomized to active treatment is the geometric mean of the last 2 measurements during the placebo run-in (day -28, day -14) and week 0."	mean (arithmetic), since the log-transformed geometric mean of measurements is equivalent to the arithmetic mean of log-transformed measurements.
5	10.4.3.2 Secondary and Exploratory Efficacy Analysis	SAP Section 5.7.2, 5.9 to 5.12: • Analyses for each secondary and exploratory endpoint are specified in the corresponding sections for each endpoint. • The statement that "Continuous secondary and exploratory endpoints will be analyzed similarly to the primary endpoint" was deleted since for some continuous variables MMRM model may not converge due to the small number of visits/observations
6	10.4.5.3 Treatment Exposure The duration of exposure during the study will be presented and calculated as: (Date of last evinacumab injection - date of first evinacumab injection) + 24 weeks (length of follow-up period)	SAP Section 4.6: Duration of exposure was divided to double-blind and single-blind period and the duration definition was changed to "…+28 days/7" to be consistent with other evinacumab studies.

1.2.5. Revision History for Statistical Analysis Plan Amendments

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

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 2, randomized, placebo-controlled, study designed to evaluate the efficacy and safety of repeated doses of evinacumab in adult patients with severe HTG. Up to approximately 50 patients will be enrolled, randomized 2:1 (evinacumab:placebo) to receive evinacumab 15 mg/kg IV every 4 weeks (Q4W) or matching placebo IV Q4W for the 12-week double-blind treatment period (DBTP). After completion of the DBTP, all patients will enter a 12-week single-blind treatment period (SBTP) and receive open-label evinacumab 15 mg/kg IV Q4W. Investigators, Regeneron Study Director, Medical Monitor, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will be blinded to treatment assignment during the double-blind treatment period of

the study and blinded to blood lipid measurements during the double-blind and single-blind treatment periods. After SBTP, all patients will undergo a 24-week follow-up after the last dose of study treatment.

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

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

2.2. Sample Size and Power Considerations

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

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

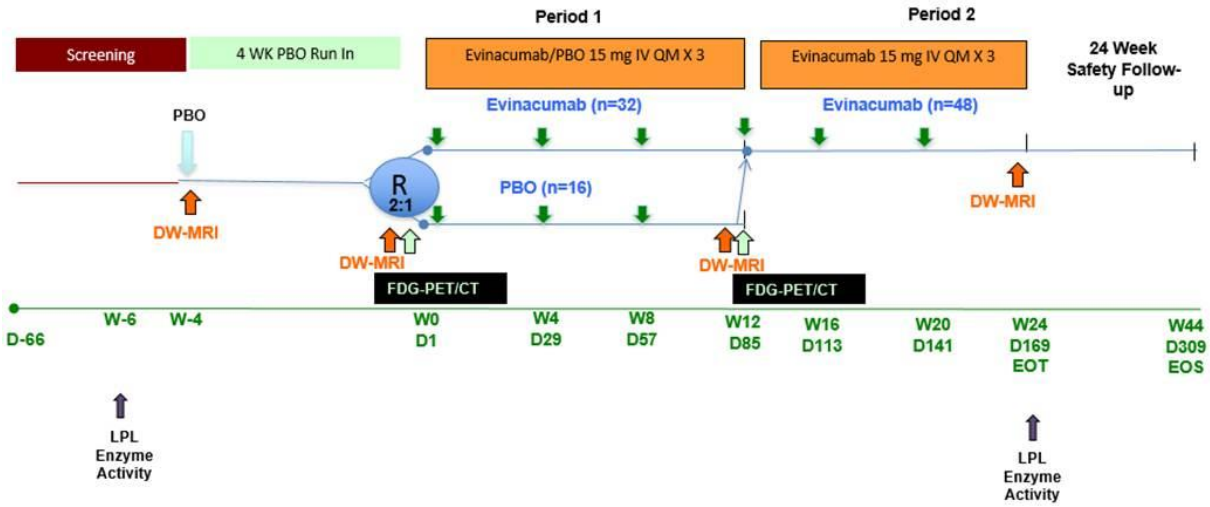
For the key MRI endpoint "mean f", which is the weighting coefficient between contrasting MRI regions (Klauss 2015), reported summary statistics yielded an SD estimate at most 5.96 for change from baseline. With this assumed SD, the N=24 patients with evinacumab post- and pre-values have 80% power to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

2.3. Study Plan

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

A study flow diagram is in Figure 1.

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 primary efficacy analysis population is the full analysis set (FAS) population. Additional patient populations are defined for safety, anti-drug (evinacumab) anti-body (ADA), pharmacokinetic (PK), total target (ANGPTL3), patient-reported outcomes (PRO), PET, MRI, biomarkers, and single-blind analyses. For the purposes of the definitions below, a patient is considered randomized to study treatment when they have been screened and received a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not.

As with all trials, odd cases (usually rare) occur for patient eligibility in the analysis populations. The following are three cases with the planned resolution of each type of case should they occur.

- Patients administered double-blind study treatment without randomization or before randomization will not be considered as "randomized" and therefore will not be included in any analysis population. The safety experience from these patients will be reported separately.
- For patients found to be randomized more than once in this trial, safety data from the first randomization will be included in the safety population, with safety data associated with the later randomization reported separately. Inclusion of efficacy data from the patient randomized more than once will be decided on a case-by-case basis prior to the unblinding of treatment assignments and documented in the study report.
- Patients successfully randomized and administered double-blind study treatment, but later found to violate inclusion/exclusion criteria, will be included in all analyses with appropriate documentation for the protocol deviation.

3.1. Full Analysis Set

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

3.2. Double-Blind Safety Analysis Set

The double-blind safety analysis set (SAF) considered for safety analyses 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 double-blind period, the treatment group allocation for as-treated analysis will be evinacumab.

3.3. Single-Blind Safety Analysis Set

The single-blind SAF considered for safety analyses will be the randomized population who received at least 1 dose or part of a dose of single-blind study drug.

3.4. Pharmacokinetic (PK) Analysis Set

The PK analysis set is defined as all randomized patients who received any study drug and have at least 1 non-missing measurement of evinacumab concentration following the first dose of the study drug. Treatment assignments for the DBTP are based on the treatment received (placebo or evinacumab).

The total target analysis set is defined as all randomized patients who received any study drug and have at least 1 non-missing measurement of total ANGPTL3 concentration following the first dose of study drug. Treatment assignments for the DBTP are based on the treatment received (placebo or evinacumab).

3.5. The Anti-evinacumab Antibody Analysis Set

The anti-evinacumab antibody (ADA) analysis set is defined as all randomized patients who received any study drug and have at least 1 non-missing ADA result following the first dose of study treatment. Treatment assignments for the DBTP are based on the treatment received (placebo or evinacumab).

3.6. Patient-Reported Outcomes (PRO) Analysis Set

The analyses of the PRO data in the respective treatment period (DBTP and SBTP) will be performed on all randomized patients who received any double-blind study treatment with a baseline and at least 1 non-missing post-baseline PRO evaluation. Treatment assignments for the DBTP are based on the treatment received (placebo or evinacumab).

3.7. PET Analysis Set

The analyses for PET will be performed on all randomized patients who received any double-blind study treatment with a baseline and a post-baseline PET evaluation. Treatment assignments are based on the treatment received (placebo or evinacumab).

3.8. MRI Analysis Set

The analyses for MRI in the respective treatment period (DBTP and SBTP) will be performed on all randomized patients who received any double-blind study treatment with a baseline and at least 1 post-baseline MRI evaluation. Treatment assignments for the DBTP are based on the treatment received (placebo or evinacumab).

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

For each patient, demographic and baseline characteristics, except TG, will be obtained from the last available value up to the date of the first double-blind study treatment administration (i.e. baseline definition). Baseline TG is defined as the mean of the last 2 measurements during the placebo run-in (day -28, day -14) and week 0. For patients randomized and not treated in R1500-HTG-1522, the baseline value is defined as the last available measurement prior to the date of randomization.

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, Other)
- Age in years (quantitative and qualitative variable: ≥18 to <45, ≥45 to <65, and ≥65)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)

Baseline Characteristics

- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) in kg/m² (quantitative and qualitative variable defined as <30, ≥30)
- Smoking Status (never, former, and current smoker)
- Current alcohol consumption (yes/no)

Baseline Disease Characteristics

- Lipid parameters - quantitative variables for all efficacy parameters
- HbA1c both quantitative variable and qualitative variable defined as: <5.7%, ≥5.7% to <6.5%, ≥6.5%
- Hs-CRP
- Lp(a): <30, ≥30 to <50, ≥50 mg/dL, and category ≥30 mg/dL (<75, ≥75 to <125, and ≥125 nmol/L, and category ≥ 75 nmol/L)
- Cohort assignment
- Patient genotype

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, high level term, 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: cardiovascular history and risk factors, and pancreatitis history. Primary and secondary CVD prevention, CV risk factors categorized by high and very high risk are also defined below from pre-defined risk factors collected on e-CRF.

Medical history of interest is defined as the occurrence of these diseases:

1. Coronary heart disease (CHD)
2. CHD risk equivalents
3. Cardiovascular (CV) risk factors other than hypercholesterolemia (hypertension, type 2 diabetes, type 1 diabetes, family history of premature CHD).
4. Family history of type 2 diabetes

CHD and CHD risk equivalents will be derived from the respective e-CRF as follows:

1. Coronary heart disease (CHD) (regardless if it is ongoing or not) is defined as the occurrence of at least one of the following events:
    - Acute myocardial infarction
    - Silent myocardial infarction
    - Angina (chronic stable or unstable)
    - Coronary revascularization procedure (e.g. PCI, CABG)
2. CHD risk equivalent (regardless if it is ongoing or not) is defined as the occurrence of at least one of the following events:
    - Peripheral arterial disease (PAD)
    - Ischemic stroke
    - Chronic kidney disease (CKD)
    - Known history of diabetes mellitus (type 1 or 2) AND 2 or more additional risk factors among:
        - History of ankle-brachial index ≤ 0.90
        - History of hypertension
        - History of microalbuminuria or macroalbuminuria
        - History of proliferative diabetic retinopathy
        - Known family history of premature CHD

Secondary CVD prevention is defined as patients with any of the following history of CVD (other patients will be classified as primary CVD prevention):

- History of CHD (as defined above)
- History of ischemic stroke
- History of PAD with severity criteria defined as one of the following events:
  - PAD and ankle brachial index ≤ 0.90
  - Peripheral revascularization procedure (angioplasty, stenting) for PAD
  - Thrombolysis for PAD
  - Peripheral revascularization surgery (arterial bypass) for PAD

CV Risk Factors are defined for this study as high risk and very high risk below.

- Very high CV risk patients are defined as patients with CHD or CHD risk equivalents.
- High CV risk patients are defined as all other patients.

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 and will be applied in the respective treatment periods (DBTP and SBTP).

- Prior medications are defined as medications for which the stop date is before the date of the first DBTP study treatment administration.
- Concomitant medications are defined as medications that are administered to the patients during the respective study treatment periods. Specifically:
  - Start date of the concomitant medication is on or after the first study treatment administration in respective study treatment periods (≥ DBTP Day 1 or ≥ SBTP Week 12); **or**
  - Start date of the concomitant medication is before the first study treatment administration in respective study treatment periods and is "Ongoing" during the treatment emergent period; **or**
  - Start date of the concomitant medication is before the first study treatment administration in respective study treatment periods, and the end date is on or after the first study treatment administration in respective study treatment periods (≥ DBTP Day 1 or ≥ SBTP Week 12).

The concomitant medication treatment emergent periods are defined as:

- For concomitant medications in the DBTP, the treatment emergent period is defined from the first day of double-blind study treatment administration to the last day of double-blind study treatment +168 days (for patients who do not continue into the SBTP) or to the day before the first single-blind study treatment administration (for patients who enter the SBTP).
- For concomitant medications in the SBTP, the treatment emergent period is defined from the first day of single-blind study treatment administration to the last day of single-blind study treatment +168 days.

  Note: In the case the start date is before first DBTP 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 7.8.1 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 double-blind treatment period milestone categories are defined below. As applicable, percentages will be calculated using the number of randomized patients in the denominator, with two exceptions. Specifically, the two exceptions will be for the screened and non-randomized 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 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.
- 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 as collected on the End of Treatment e-CRF.
- The total number of patients who completed the DBTP, defined as at least 12 weeks of study treatment exposure and visit week 12 performed.

- The total number of patients who prematurely discontinued study treatment during the double-blind period, and the reasons for discontinuation collected on the End of Treatment e-CRF.
- The total number of patients who do not proceed into SBTP and complete the last study follow-up visit (i.e. End of Study/Visit 18).

Patient SBTP milestone categories are defined below. As applicable, percentages will be calculated using a denominator of the number of patients administer single-blind study treatment.

- The total number of patients receiving single-blind study treatment.
- The total number of patients ongoing in SBTP (applicable for the interim and first step analyses)
- The total number of patients who completed the SBTP as collected on the End of Treatment e-CRF.
- The total number of patients who completed the SBTP, defined as at least 24 weeks of study treatment exposure and week 24 visit performed.
- The total number of patients who prematurely discontinued study treatment during the SBTP, and the reasons for discontinuation collected on the End of Treatment e-CRF.
- The total number of patients from SBTP who complete the last study follow-up visit (i.e. End of Study/Visit 18).

The following patient populations for analyses are defined below:

- Randomized population
- Full analysis set population
- Double-blind safety analysis set
- Single-blind safety analysis set
- Anti-evinacumab antibody (ADA) analysis set
- Pharmacokinetic (PK) analysis set and total target analysis set
- PRO analysis set
- PET analysis set
- MRI analysis set

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

4.6. Study Treatment Exposure and Compliance Variables

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

- Patient duration of double-blind study treatment exposure in weeks defined as: (last double-blind study treatment administration date +28 – first double-blind study treatment administration date)/7, regardless of unplanned intermittent discontinuations. Values will be rounded to one decimal place.
- The total number of double-blind study treatment infusions by patient.
- 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

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

- Patient duration of single-blind study treatment exposure in weeks defined as: (last single-blind evinacumab treatment administration date +28 – first single-blind evinacumab treatment administration date)/7, regardless of unplanned intermittent discontinuations. Values will be rounded to one decimal place.
- The total number of single-blind evinacumab treatment infusions by patient.
- 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

Study treatment exposure variables combining DBTP and SBTP are listed below for all patients who received evinacumab in the DBTP:

- Cumulative patient duration of evinacumab exposure in weeks defined as: double-blind treatment exposure plus single-blind treatment exposure, regardless of unplanned intermittent discontinuations.
- Cumulative total number of evinacumab treatment infusions by patient defined as: total number of double-blind infusions plus total number of single-blind infusions.
- The following categories will be used for cumulative patient 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

With respect to patient treatment administration compliance, the study treatment is administered during the investigative site visits and therefore study compliance will be accessed by infusion frequency for respective treatment periods, specifically:

- DBTP: 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 DBTP -1), for patients receiving at least 2 infusions.

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

All important and minor protocol deviations potentially impacting efficacy analyses, randomization 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. Efficacy Variables

Efficacy will be assessed through the following measurements:

- **Lipids**: LDL-C (Ultracentrifugation), HDL-C, total-C, fasting TG, non-HDL-C (calculated by subtracting HDL-C from Total-C), Apo B, Apo A1, Apo CIII, Apo B/Apo A1 ratio, and Lp(a)
- **Other variables**: Hemoglobin A1c, hs-CRP, post heparin LPL activity, APOC2, APOA5, and metabolic parameters
- **Imaging**: F-FDG-PET, DW-MRI, and T2-MRI

The baseline value, unless noted otherwise, is defined as the last available measurement prior to the date of the first double-blind study treatment administration (applicable to measurement derivations during both DBTP and SBTP). For patients randomized and not treated, the baseline value is defined as the last available value prior to the date of randomization.

4.7.1. Primary Efficacy Variable

The primary endpoint is the percent lowering of TG levels from baseline following 12 weeks of repeated IV doses of evinacumab in the subset of patients with a documented history of sHTG (TG >1000 mg/dL [11.3 mmol/L]), a TG level of at least 500 mg/dL (5.6 mmol/L) at screening, a history of acute pancreatitis, and without LOF mutations in genes in the LPL pathway.

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. Lipids Variables

Potential clinical benefits of study treatment will be explored through the following lipids parameters: LDL-C (Ultracentrifugation), HDL-C, total-C, fasting TG, non-HDL-C, Apo B, Apo A1, Apo CIII, Apo B/Apo A1 ratio, and Lp(a).

Baseline TG is defined as the mean of the last 2 measurements during the placebo run-in (day -28, day -14) and week 0.

Lipids parameters will be collected in a fasted state over the course of the study at time points listed in Appendix 10.4, and sent to the central laboratory for evaluation, including scheduled and unscheduled blood draws. Both the absolute change from baseline and the percent change from baseline will be calculated for each lipids parameter, and derivations will be presented in

both international and conventional units. TG measurements with missing fasting status will be excluded from the summaries.

4.7.3. Other Variables

Other assessment endpoints are listed and defined below.

- The change in hemoglobin A1c (HbA1c [%]) from baseline to post-baseline visits.
- The percent change in hs-CRP from baseline over time
- Post heparin LPL activity
- Apolipoproteins: APOC2, APOA5
- Metabolic parameters (fasting blood glucose, insulin, C-peptide, NEFA)

4.7.4. PET Variable(s)

The F-FDG PET endpoints are listed below:

- Percent change in pancreatic 18F-FDG standardized uptake values SUVmax and SUVmean from baseline at week 12
- Percent change in 18F-FDG-PET target to background ratio [TBR] in carotids and/or aorta atherosclerotic plaques at week 12
- The change in pancreatic ^{18}F-FDG Ki or Kpatlak from baseline at week 12

4.7.5. MRI Variable(s)

The MRI endpoints are listed below:

- The change in apparent diffusion coefficient (ADC) in the pancreas from baseline to post-baseline visits
- The change in T2 signal in the pancreas from baseline to post-baseline visits
- The change in hepatic fat fraction from baseline to post-baseline visits

The baseline value is defined as the mean of two measurements prior to the date of the first double-blind study treatment administration (applicable to measurement derivations during both DBTP and SBTP)

4.8. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, and ECG. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of double-blind study treatment.

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 double-blind study treatment administration.
- The double-blind treatment-emergent adverse event (TEAE) period is defined from the day of the first dose of double-blind study treatment administration to the day of the last dose of double-blind study treatment administration + 168 days (24 weeks) for those patients not proceeding into the SBTP, or up to the day before the first dose of single-blind study treatment administration for those patients proceeding into the SBTP.
- The single-blind treatment-emergent adverse event (TEAE) period is defined from the day of the first single-blind study treatment administration to the day of the last single-blind study treatment administration + 168 days (24 weeks).
- The POST-TREATMENT period is defined from the day after the end of the respective TEAE periods to the last study visit.

4.8.1.1. Adverse Events and Serious Adverse Events

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

All AEs will be 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.
- Double-blind and single-blind TEAEs are AEs that developed or worsened or became serious during the respective TEAE periods.
- 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, and/or identified using standard MedDRA queries (SMQ), and/or company MedDRA queries (CMQ), and/or applicable laboratory assessments. Appendix 10.2 contains the definitions used to identify AESIs:

The AESIs include the following:

- Anaphylactic reactions (CRF)
- General allergic events (SMQ)

- Infusion reactions (CRF)
- Pregnancy (CRF)
- Symptomatic overdose with investigational medicinal product (CRF)
- Neurocognitive events (CMQ)
- New onset of diabetes (NOD) (lab data)
- Pancreatitis (CRF)

4.8.1.3. Events Causing Death

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

- Death on-treatment: deaths occurring during the respective TEAE period (double-blind or single-blind),
- Death post-treatment: deaths occurring during the post-treatment period.

4.8.1.4. Incidence of Recurrent Acute Pancreatitis

Acute pancreatitis events are recorded in e-CRF as an AESI with event details captured in the complimentary e-CRF page.

4.8.1.5. Hospitalizations

Hospitalizations for abdominal pain, hospitalizations for pancreatitis, and hospitalizations for cardiovascular disease are recorded in AE e-CRF.

4.8.2. Laboratory Safety Variables

Clinical laboratory tests will consist of blood analyses (including hematology, clinical chemistry and other) and urinalysis. 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.

In addition, local laboratory tests for hematology will be summarized in the same manner as the central lab results.

The laboratory parameters will be classified as follows:

Hematology:

- Red blood cells and platelets: hemoglobin, hematocrit, erythrocytes count, red blood cells, platelets count, reticulocyte count, red blood indices

- White blood cells: white blood cells, neutrophils, lymphocytes, monocytes, basophils, eosinophils

Clinical chemistry:

- Metabolism: glucose, total protein, albumin, creatine phosphokinase
- 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

Urinalysis

Urinalysis will include the following parameters: color, clarity, pH, specific gravity, ketones, protein, glucose, blood, bilirubin, leukocyte esterase, nitrite, WBC, RBC, hyaline and other casts, bacteria, epithelial cells, crystals, and yeast.

4.8.3. Vital Signs

Vital signs parameters will include 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. 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)

Electrocardiograms will be recorded in the supine position after the patient has rested for at least 10 min. Electrocardiogram assessments will be described as normal or abnormal.

4.8.5. Physical Examination Variables

Physical examination will be conducted at the protocol scheduled visits (See Appendix 10.4 for schedule of event). The result is an outcome of clinically significant (Yes/No, not examined).

4.9. Pharmacokinetic Variables

Pharmacokinetic (PK) variables include total evinacumab and total ANGPTL3 concentrations at each time point specified in the protocol (See Appendix 10.4 for schedule of event).

4.10. Anti-Drug (evinacumab) Antibody Variables (ADA)

Anti-drug antibody variables will include ADA status (positive or negative), titer and neutralizing antibody (NAb) status for samples analyzed at each time point specified in the protocol (See Appendix 10.4 for schedule of event).

4.11. PRO Variables

The baseline value is defined as the last available measurement prior to the date of the first double-blind study treatment administration (applicable to measurement derivations during both DBTP and SBTP).

The patient experience of symptoms and the impact on dietary behavior will be assessed with two de novo PRO measures: the Hypertriglyceridemia and Acute Pancreatitis Symptoms Scale (HAP-SS) and the Hypertriglyceridemia and Acute Pancreatitis Dietary Behavior questionnaire (HAP-DB).

- Hypertriglyceridemia and Acute Pancreatitis Symptom Scale (HAP-SS)

The HAP-SS is a 19-item measure of symptoms that has a 24-hour recall period. Four pain items are captured on a 0-10-point severity NRS, each scored 0=’No pain’ to 10=’Worst possible pain’, while the 15 non-pain items are captured on a 5-point frequency Likert scale, each scored from 1=’None of the time’ to 5=’All of the time’. The proposed structure of the measure is currently being tested and is yet to be finalized but currently consists of a total score and four domain scores: pain; abdominal symptoms; physical symptoms; other symptoms, each scored 0 (no symptoms) to 100 (severe symptoms).

The Pain domain includes the four items: item 1 - stomach pain average, item 2 - stomach pain at worst, item 3 - back pain at worst, item 4 - stomach pain after eating (possible score range: 0 to 40).

The Abdominal symptoms domain includes the 6 items: item 5 – bloated or swollen stomach, item 6 – nausea/feeling sick, item 7 – vomiting, item 8 – passed excessive gas, item 9 – loose stools/diarrhoea, item 10 – foul smelling, light-coloured or greasy stool (possible score range: 6 to 30).

The Physical symptoms domain includes 5 items: item 11 – fever or flu like symptoms, item 12 - insomnia, item 13 – excessive sweating, item 14 – dizziness (light/headedness), item 15 - racing heart rate (felt like your heart was racing) (possible score range 5 to 25).

The Other symptoms domain includes 4 items: item 16 – fatigue, item 17 – loss of appetite, item 18 – been hungry after eating, item 19 – felt full after eating a small amount (possible score range 4 to 20).

Each item will be calculated at each evaluation/visit as the mean of the item scores over the seven days previous to the visit; each domain score at each evaluation/visit will be calculated as the sum of the mean component item scores. Each domain score will then be transformed onto a 0-100 scale, with the total score being the sum of the four domain scores (0-400), also then transformed to a 0-100 scale.

To transform to a 0-100 scale the following algorithm will be applied:

Transformed score = 100 x (score – minimum possible score) / (maximum – minimum possible score).

- Dietary behavior questionnaire (HAP-DB)

The HAP-DB is a 6-item measure of dietary behavior that has a 24-hour recall period. The items in the measure are all captured on a 5-point frequency Likert scale, each scored from 1=’None of

the time' to 5='All of the time'. The proposed structure of the measure is currently being tested and is yet to be finalized but currently consists of a dietary impact total score, ranging from 6 (no impact) to 30 (severe impact).

The six HAP-DB items are: item 1 – amount of food eaten, item 2 – fatty or greasy food, item 3 – carbohydrates, item 4 – sugar or sugary foods, item 5 – alcohol intake, item 6 – skipped meal.

Each item will be calculated at each evaluation/visit as the mean of the item scores over the seven days previous to the visit. The total score will be calculated as the sum of the six item scores and then transformed to a 0-100 score.

To transform to a 0-100 scale the following algorithm will be applied:

Transformed score = 100 x (score – minimum possible score) / (maximum – minimum possible score).

4.11.1. Number of pain and abdominal symptom free days and days where meals are avoided

Exploratory endpoints of the frequency of stomach pain (on average, and at its worse), pain (stomach pain, back pain, stomach pain at its worst after eating), and abdominal symptom free days at each evaluation/visit will be defined as the number and percentage of stomach pain free days, number and percentage of pain free days, and the number and percentage of abdominal symptom free days over the seven days prior to the visit, as assessed by the HAP-SS:

- A stomach pain free day will be determined if the patient scores 0 - 'No Pain' on both of the HAP-SS stomach pain items 1 and 2.
- A pain free day will be determined if the patient scores 0 - 'No Pain' on all of the HAP-SS pain items 1, 2, 3 and 4.
- An abdominal symptom free day will be determined if the patient scores 1 - 'None of the time' to all the HAP-SS abdominal symptoms items 5-10.

An additional exploratory endpoint of the number of days where meals are avoided will be assessed as the number of days where all meals are skipped as assessed by the HAP-DB:

- A day where all meals are avoided will be determined if the patient scores 5 - 'All of the time' to item 6 in HAP-DB, skipped meals.

4.12. Biomarker Variable(s)

The biomarker endpoints include the following:

- Biochemical markers (amylase, lipase, IL-1, IL-6, IL-8 and TNFa)
- LPL concentration, Hepatic Lipase activity and concentration, Endothelial Lipase activity and concentration
- Lipoprotein subfraction composition after ultracentrifugation: chylomicrons (CM), VLDL, IDL, LDL (low-density lipoprotein), HDL (high-density lipoprotein) and TG content.

- Apolipoprotein composition per lipid subfraction by ultra-centrifugation
- Lipoprotein concentration parameters determined by Nuclear Magnetic Resonance (NMR)

5. STATISTICAL METHODS

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the study, as well as by treatment group and overall within each cohort in the FAS population.

Continuous data will be summarized using the number of patients with data, mean, SD, median, Q1, Q3, minimum and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

For the single-blind safety population, demographic and baseline characteristics will be summarized by all patients and by treatment group of the DBTP (i.e., evinacumab, placebo).

5.2. Medical History

Medical history will be descriptively summarized by treatment group and overall for the study, as well as by treatment group and overall within each cohort in the FAS population.

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, all medical history of specific interest, primary and secondary CVD prevention including corresponding criteria, as described in Section 4.2, will be summarized by patient incidence and percentage.

The number (%) of patients will be summarized by CVD prevention status (i.e. primary and secondary CVD prevention status).

In addition, smoking status will be summarized in patients with primary CVD prevention status.

For patient disease characteristics, as described in Section 4.2, continuous data will be summarized using the number of patients with data, mean, SD, median, Q1, Q3, minimum and maximum for the study. Categorical and ordinal data will be summarized using the number and percentage of patients in the study.

5.3. Prior and Concomitant Medications

All prior medications, dictionary coded by WHO-DD, will be descriptively summarized by treatment group and overall for the study, as well as by treatment group and overall within each cohort for patients in the double-blind safety population. 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 anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category

(anatomic or therapeutic) linked to the medication but may be counted several times for the same medication.

All concomitant medications during the DBTP, dictionary coded by WHO-DD, will be descriptively summarized by treatment group, for patients in the double-blind safety population. Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications, by decreasing frequency of the evinacumab group incidence of ATC followed by therapeutic class. In case of equal frequency across anatomic 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. Post-treatment medications will be summarized as described above for all medications.

For the SBTP, concomitant and post-treatment medications will be dictionary coded by WHO-DD and will be descriptively summarized as described for the DBTP. Medications will be summarized for all patients and by treatment group of the DBTP (i.e., evinacumab, placebo) for patient in the single-blind safety population. Summaries will present patient counts (and percentages).

5.4. Prohibited Medications

Listing of prohibited medications will be provided for the patients in the double-blind safety analysis set for the DBTP and SBTP.

5.5. Patient Disposition

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

Patient study status for the DBTP will be summarized by treatment group and overall for the study, as well as by treatment group and overall within each cohort (screened patients, screen failures, and non-randomized 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 randomized, randomized but not treated, and treated differently than randomized.

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

For the SBTP, the patient study status and patient analysis populations will be summarized by all patients and by treatment group of the DBTP (i.e., evinacumab, placebo) on the single-blind safety population for the variables described in Section 4.5

For both the DBTP and SBTP, the incidence of premature study treatment discontinuation (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically by treatment group in the respective safety analysis set using the Kaplan-Meier method.

5.6. Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure for the DBTP described in Section 4.6 will be assessed and summarized by treatment group, for patients in the double-blind safety analysis set. The extent of study treatment exposure for the SBTP described in Section 4.6 will be assessed and summarized for all patients and by treatment group of the DBTP (i.e., evinacumab, placebo) for patients in the single-blind safety analysis set.

5.6.1. Exposure to Investigational Product

Study treatment exposure in the DBTP and SBTP will be descriptively summarized for treatment duration and total number of infusions as described in Section 4.6. Treatment duration and total number of infusions will be summarized using the number of patients with data, mean, SD, Q1, Q3, median, minimum and maximum.

Additionally, evinacumab dosing exposure will be summarized cumulatively across the study, combining DBTP and SBTP for patients who received evinacumab in the DBTP.

5.6.2. Study Treatment Compliance

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.

Descriptive statistics of the infusion frequency will be summarized. A patient listing will be provided for those patients with incomplete or interrupted infusions. Cases of study treatment overdose will be reported in the AE e-CRF page and will be described in the adverse event analysis.

5.7. Analyses of Efficacy Variables

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

Statistical analyses for the primary efficacy endpoint will be conducted as described below and will be completed during the final efficacy analysis (Section 7). Only measurements collected at the protocol scheduled time point (as defined by e-CRF visit label) will be used for the analyses.

5.7.1. Analysis of Primary Efficacy Variable

The primary efficacy analysis will assess within-patient percent change in TG over 12 weeks of evinacumab treatment (double-blind period for patients randomized to evinacumab and single-blind period for patients randomized to placebo).

The point estimates of TG percent changes between the placebo period and each observation week will be calculated using a Mixed-effect Model for Repeated Measures (MMRM) method in the FAS population. A natural log transformation will be applied to the TG levels prior to

analysis, aiming to provide a relatively normal data distribution (residuals will be examined for normality prior to proceeding with the analysis). The MMRM model will assess within-patient treatment comparisons (using an unstructured covariance matrix), while accounting for baseline TG, study visit, and baseline TG by study visit interaction. Note that study visits will be adjusted to start of evinacumab in order to pool data from both randomized groups of patients for this analysis. Since the comparison of study visits yields the within-patient comparisons of study treatments (ie, week 12 [after 12 weeks of treatment with evinacumab] compared to baseline at week 0 [after 4 weeks of treatment with placebo] for patients randomized to evinacumab and week 24 [after 12 weeks of treatment with evinacumab] compared to baseline at week 12 for those randomized to placebo), contrast and estimate statements will be used to assess treatment effects (least squares [LS] means with confidence intervals) and comparisons (LS mean ratio with CI). Within-patient comparisons will include all patients. In the event the MMRM model covariance matrix does not converge or normality is not achieved with the natural log transformation, then other transformations will be explored, including ranks.

To reduce variability of TG baseline measurements, baseline at week 0 for patients randomized to active treatment is the mean of the 3 log-transformed measurements at day -28, day -14, and week 0. Baseline at week 12 for patients switching from placebo to active is the mean of 3 log-transformed measurements at weeks 6, 8, and 12. Additional exploratory analyses may be carried out using the average of all available TG observations prior to first dose of active treatment, if no trend over time in those measurements is discernable.

The estimate of the log TG mean ratio (week 12/baseline at week 0 for patients randomized to evinacumab and week 24/baseline at week 12 for those randomized to placebo) and the log of the standard deviation derived from the MMRM model (ie., LS mean ratio with CI) based on observed results from the patients without LOF mutations in genes in the LPL pathway will be reviewed for 40% reduction.

5.7.1.1. Sub-group Analyses

To assess the homogeneity of the treatment effect across various subgroups, treatment-by-subgroup factor, time point-by-subgroup factor and treatment-by time point-by subgroup factor interaction terms and a subgroup factor term will be added in the primary MMRM model. Within-patient contrast and estimate statements will be used to assess treatment effects (least squares [LS means with confidence intervals) and comparisons (LS mean ratio with CI). In order to handle imbalances between subgroup factors levels, population weights will be used in the analysis model.

The following subgroups of interest will be evaluated, assuming there are enough patients in each subgroup level to perform the evaluation.

- Cohort assignment (1,2 and 3) as defined at the time of the analysis

A graph will depict the mean (+/- SE) TG concentrations over time for each genotype subgroup.

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

5.7.2. Analyses of Lipids Variables

Descriptive statistical analyses for the lipids defined in Section 4.7.2 will be summarized by treatment group and overall for the study, as well as by treatment group and overall within each cohort in the FAS population.

For descriptive summaries, percent change, and/or when appropriate, absolute change from baseline in conventional (US) and international units will be provided for lipids (LDL-C, Apo B, total-C, TG, non-HDL-C, Lp(a), Apo CIII, Apo A-1, and ratio Apo B/Apo A-1) at each protocol scheduled time point (as defined by e-CRF visit label) for each treatment group. For TGs, measurements on not-fasting patients will be excluded. Observed lipid values will be used, ie, imputation of missing values is not planned. For the evinacumab treated group, within-patient testing of endpoints with a non-normal distribution will use the Wilcoxon signed-rank test and endpoints with a normal distribution will use the paired t-test to evaluate the mean differences between baseline and each protocol visit. The p-value will be provided for descriptive purposes only.

Figures will be produced to support the summary tables for percent change and/or when appropriate absolute change from baseline. The plot will contain mean percent change +/- standard error (SE) through the study visits for each lipid variable (except TG and Lp(a)) by treatment group. For TG and Lp(a), plots will contain the median percent and /or absolute change from baseline along with quartiles (Q1 and Q3) over time by treatment group.

In addition, all lipids measurements (scheduled and unscheduled) will be included in patient listing.

During the SBTP, efficacy variables will be explored through descriptive statistics at each protocol scheduled visit for the total patients administered single-blind study treatment (total), as well as by the patient subgroups of study treatment received in the double-blind treatment period (i.e., evinacumab, placebo). Descriptive statistics will include the observed values of the same parameters as described for each variable in the DBTP, for patients in the single-blind safety analysis set.

For patients receiving evinacumab in the DBTP, a combined summary including both the DBTP and SBTP assessments may be considered, referencing the double-blind baseline for variable calculations. Prolonged time between last dose of double-blind treatment and first dose of single-blind treatment will need to be taken into consideration when combining longitudinal efficacy data. Descriptive statistics will include the observed values of the same parameters as described for each variable in the DBTP, for patients in the double-blind safety analysis set.

5.7.3. Analysis of Other Variables

Descriptive statistical analyses for other endpoints (described in Section 4.7.3) will be summarized by treatment group and overall for the study, as well as by treatment group and overall in the FAS population. For summary tables, only protocol scheduled measurements (as defined by e-CRF visit label) will be included. Patient listings will include all measurements, scheduled and unscheduled.

The summary of results for other variables will be presented separately for the DBTP and SBTP, unless otherwise noted. Summaries for the DBTP will be presented by treatment groups

(evinacumab, placebo) containing patients from the double-blind safety analysis set. Summaries for the SBTP will be presented by all patients and by treatment group in DBTP (i.e., evinacumab, placebo), for patients in the single-blind safety analysis set. No formal inferential testing will be performed for either period. Summaries will be descriptive in nature.

Hs-CRP and HbA1c parameters will be summarized at each protocol-scheduled visit. The medians (with Q1-Q3) will be plotted for hs-CRP and HbA1c. Applying the PCSV criteria at any time during the TEAE period, the number of patients (and percentages) meeting the criteria will be summarized.

Similar tables, except PCSV criteria, will be provided for post heparin LPL activity, APOC2, APOA5, and metabolic parameters.

5.7.4. Analysis of PET Variables

Descriptive statistical analyses for the PET variables defined in Section 4.7.4 will be summarized by treatment group and overall for the study, as well as by treatment group and overall within each cohort in the PET population.

For descriptive summaries, raw values, percent change, and/or when appropriate, absolute change from baseline will be provided for PET variables at each protocol scheduled time point (as defined by e-CRF visit label) for each treatment group. Missing values will not be imputed. For the evinacumab treated group, within-patient testing of endpoints with a non-normal distribution will use the Wilcoxon signed-rank test and endpoints with a normal distribution will use the paired t-test to evaluate the mean differences between baseline and each protocol visit. The p-value will be provided for descriptive purposes only

5.7.5. Analysis of MRI Variables

Descriptive statistical analyses for the MRI variables defined in Section 4.7.5 will be summarized by treatment group and overall for the study, as well as by treatment group and overall within each cohort in the MRI population.

For descriptive summaries, raw values, percent change, and/or when appropriate, absolute change from baseline will be provided for MRI variables at each protocol scheduled time point (as defined by e-CRF visit label) for each treatment group. Missing values will not be imputed. For the evinacumab treated group, within-patient testing of endpoints with a non-normal distribution will use the Wilcoxon signed-rank test and endpoints with a normal distribution will use the paired t-test to evaluate the mean differences between baseline and each protocol visit. The p-value will be provided for descriptive purposes only

5.8. Analysis of Safety Data

The summary of safety results will be presented separately for the DBTP and SBTP, unless otherwise noted. Safety summaries for the DBTP will be presented by treatment groups (evinacumab, placebo), as well as by treatment group within each cohort containing patients from the double-blind safety analysis set. Safety summaries for the SBTP will be presented by all patients and by treatment group in DBTP (i.e., evinacumab, placebo), for patients in the single-blind safety analysis set. No formal inferential testing will be performed for either period. Summaries will be descriptive in nature.

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 (i.e., exposed but not randomized) will be listed separately.
- 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 respective TEAE periods, taking into account all evaluations including unscheduled or repeated evaluations.
- For summary tables, only protocol scheduled measurements (as defined by e-CRF visit label) will be included. Patient listings will include all measurements, scheduled and unscheduled.
- 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 respective TEAE periods.
- 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 respective TEAE periods, specifically the DBTP and SBTP. 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 6.2.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by SOC and PT. 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 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 respective 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 evinacumab treated group 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 and PT
- Number (%) of patients experiencing any TEAE(s) presented by primary SOC and PT
- 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 and PT
- Patient listings of serious TEAEs will be provided in the report appendix
- All Serious TEAEs relationship (related/not related) to evinacumab

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

- 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

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.

Hepatic Disorder

Hepatic disorder events will be defined using the SMQ drug-related hepatic disorder (comprehensive search).

- All hepatic disorder TEAEs by 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, if applicable. AESI are defined by SMQ, CMQ, dedicated e-CRF, or lab data as described in Appendix 10.2.

The following variables will also be tabulated for infusion reactions TEAEs:

- Intensity of the event (mild, moderate, and severe);
- Number of events divided by the number of study treatment administrations received in respective treatment periods;
- Time from first study treatment administration (DBTP or SBTP depending on the analysis) to first infusion reaction;

5.8.3. Analysis of Incidence of Recurrent Acute Pancreatitis

Acute pancreatitis event incidence table will present the number (n) and percentage (%) of patients experiencing such event. 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). The denominator for computation of percentages is the respective safety analysis set within each treatment group.

5.8.4. Analysis of Hospitalizations

Hospitalizations event (defined in Section 4.8.1.5) incidence table will present the number (n) and percentage (%) of patients experiencing such event. 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). The denominator for computation of percentages is the respective safety analysis set within each treatment group.

5.8.5. Clinical Laboratory Measurements

For respective treatment period (DBTP and SBTP), clinical laboratory parameter actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit (collected up to the day of last dose of study treatment +28 days) 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 respective TEAE periods. 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 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 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 respective treatment period (DBTP and SBTP), 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 respective TEAE periods. 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.

5.8.6. Analysis of Vital Signs

For respective treatment period (DBTP and SBTP), the vital sign actual values and change from baseline values obtained while sitting will be descriptively summarized at baseline and each post-baseline visit (collected up to the day of last dose of study treatment +28 days) by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum. Vital sign 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 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 vital sign measurements that meet PCSV criteria will be provided for the report appendix.

5.8.7. Analysis of 12-Lead ECG

For respective treatment period (DBTP and SBTP), 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 respective TEAE period will be summarized according to the following baseline status categories:

- Normal/missing;
- Abnormal

5.8.8. Physical Exams

A list of patients with any clinically significant abnormality results will be generated.

5.9. Analysis of Pharmacokinetic Variables

Descriptive statistics for concentrations of total evinacumab and total ANGPTL3 will be presented. Mean concentrations of each analyte will be tabulated by visit and treatment group, with concentrations below the LLOQ set to zero.

Plots of the mean concentrations (linear and log scales) will be presented by nominal sampling time. Plots of the individual concentrations (linear and log scales) will be presented by actual sampling time. In the linear-scaled plots, concentrations below the LLOQ will be set to zero; in the log-scaled plots, concentrations below the LLOQ will be imputed as LLOQ/2.

When appropriate, relationship between concentrations of evinacumab and concentration of total ANGPTL3 (target engagement), percentage of TG reduction or other biomarkers may be evaluated descriptively.

5.10. Analysis of Anti-evinacumab Antibody Variables

The ADA variables described in Section 4.10 will be summarized using descriptive statistics by dose/cohort group in the ADA analysis set. Listings of ADA positivity and titers presented by patient, time point, and study treatment received will be provided. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study treatment received.

The influence of ADA on drug concentrations will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.
Anti-drug antibody status (negative or positive) and titer over the study duration may be classified as follows:

- Negative - negative in the ADA assay at all time points
- Pre-existing immunoreactivity - a positive response in the ADA assay at baseline with all post first double-blind dose results negative in the ADA assay, or a positive response at baseline with all post-first dose responses less than 9-fold of the baseline titer levels

- Treatment emergent response is defined as a positive response in the ADA assay post first double-blind dose when baseline results are negative or missing. The treatment emergent responses will be further characterized as Persistent, Indeterminate or Transient and further categorized as follows:
  - Persistent - Treatment emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate - A positive result in the ADA assay at the last collection time point analyzed only, regardless of any missing samples
  - Transient - a treatment emergent ADA positive assay response that is not considered persistent or indeterminate regardless of any missing samples
- Treatment boosted response - defined as a positive response in the ADA assay post first dose, that is at least 9-fold over baseline titer levels when baseline results are positive
- Titer category for subjects, by maximum ADA titer value:
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- NAb status (positive or negative)

5.11. Analysis of PRO Variables

Descriptive statistical analyses for the PRO variables defined in Section 4.11 will be summarized by treatment group and overall for the study, as well as by treatment group and overall within each cohort in the PRO population.

Only measurements collected within 14 days prior to the protocol scheduled time point (as defined by e-CRF visit label) will be assigned to that visit and used for the analyses. If more than 7 days of data are collected during this period, only 7 days of the data (closest to the visit date) will be used. PRO evaluation at the visit is considered non-missing if a patient completes the questionnaire for at least four days for this visit. Missing PRO evaluations will not be imputed.

A cross-sectional analysis will be performed for each available PRO variable for the SBTP and the DBTP. The HAP-SS and HAP-DB domains and total scores including change from baseline will be reported at each time point. The number of patients with non-missing values, mean, standard deviation, median, Q1, Q3, minimum value, and maximum value will be reported. Summaries for the DBTP will be presented by treatment groups (evinacumab, placebo). Summaries for the SBTP will be presented by all patients and by treatment group in DBTP (i.e., evinacumab, placebo).

During the DBTP the difference in change score from baseline between the treatment groups will be calculated and presented as the number of patients with non-missing values, mean, 95%

confidence interval (if data is normally distributed), standard error, median, Q1, Q3, minimum value, and maximum value at each time point. No formal inferential testing will be performed. Summaries will be descriptive in nature.

The number and percentage of stomach pain, pain, and abdominal symptom free days, and avoidance of meals, at each evaluation/visit (calculated over the seven days prior to the visit), will be presented at each time point for all patients (SBTP) and for each treatment arm (DBTP). To take account of varying numbers of completed HAP-SS and HAP-DB scores over the seven days prior to each visit (minimum number = 4, maximum number = 7), percentage scores will be calculated using both a denominator of 7 and a denominator of the number of days of available data.

5.12. Analysis of Biomarker Variables

Descriptive statistical analyses for the biomarker variables defined in Section 4.12 will be summarized by treatment group and overall for the study, as well as by treatment group and overall within each cohort in the FAS population.

For descriptive summaries, percent change, and/or when appropriate, absolute change from baseline will be provided for biomarker variables at each protocol scheduled time point (as defined by e-CRF visit label) for each treatment group. Missing values will not be imputed.

In addition, all biomarker measurements (scheduled and unscheduled) will be included in patient listing.

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 last available measurement prior to the date of the first double-blind study treatment administration. For patients randomized and not treated, the baseline value is defined as the last available value prior to the date of randomization.

6.2. Definition of Cohort Assignment

Cohort assignment (1,2, and 3) as defined at the time of the analysis will be used for all statistical 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 and Time of First/Last Study Treatment

Since the study drug is administered at the site, the date and time of study drug administration are 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/time 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 or times will be performed. If a medication date or time 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. 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.

6.5. Statistical Technical Issues

Not Applicable.

7. TIMING OF STATISTICAL ANALYSES

The analyses will be conducted in 2 steps:

- First step: Main Efficacy and Safety Analysis

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

- Second-step: Final Efficacy and Safety analysis

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

Interim Analyses

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

- The interim analysis will be conducted when the first 9 randomized patients have been administered study treatment in cohort 1 and have completed the double-blind period (i.e., week 12 visit). This will consist of the final data contributing to the analysis of the applicable variables up to week 12 for these 9 patients. In general, interim analysis will include only limited number of outputs applicable for the small sample size. For lipid variables, only descriptive summaries (without within-patient tests) in conventional units will be provided. Other variables (defined in Section 4.7.3) biomarkers, ECG, and PRO variables will not be included. Imaging and PK/ADA may be included in the analyses depending on the availability. For general labs and vital signs only PCSV summary tables will be included. The safety analysis will be performed for these 9 patients on all safety data collected and validated at the time of the first interim analysis. The interim analysis results will be used for the future program development.

  The results of the interim analyses will not be used to change the conduct of the ongoing study in any aspect. Individuals involved in the interim 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 interim analysis processes, the measures used to protect the blind and the integrity of the study, the communication plan, and the confidentiality agreement will be described in separate documents.

  Additional interim analyses may be conducted if decided by the study team.

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply for analyses performed at interim and first step analyses:

- Patients without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:
  - Patients who did not complete the respective treatment period nor prematurely discontinued the study treatment at cut-off date will be analyzed as "ongoing" in the disposition summary.
  - Their TEAE period and treatment period will end at the cut-off date.
  - Their treatment duration will be derived by considering date of cut-off as last administration date.
- Analyses of number of administrations, and mean administration frequency will be performed up to the last administration reported in the e-CRF up to the cut-off date.
- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an adverse event starting prior to the cut-off date will be taken into account. Medications, treatment discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.
- Post-treatment period, and post-study period are not applicable for ongoing patients. Analyses of post-treatment AEs, post-study deaths and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.
- Analysis of status at last study contact and proportion of patients with insufficient follow-up will be provided for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.

8. SOFTWARE

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

9. REFERENCES

1. ICH. (1996, July 30). ICH Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
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4. Klauss M, Maier-Hein K, Tjaden C, Hackert T, Grenacher L, Stieltjes B. IVIM DW-MRI of autoimmune pancreatitis: therapy monitoring and differentiation from pancreatic cancer. Eur Radiol. 2015 DOI 10.1007/s00330-015-4041-4.
5. Shigekawa M, Yamao K, Sawaki A, Hara K, Takagi T, Bhatia V, Nishio M, Tamaki T, El-Amin H, Sayed Zel A, Mizuno N. Is (18)F-fluorodeoxyglucose positron emission tomography meaningful for estimating the efficacy of corticosteroid therapy in patients with autoimmune pancreatitis? J Hepatobiliary Pancreat Sci. 2010 17(3): 269-274.

10. APPENDIX

10.1. Summary of Statistical Analyses

Primary Efficacy Analysis:

Endpoint	Analysis Population	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Percent lowering of TG levels from baseline following 12 weeks of repeated IV doses of evinacumab in the subset of patients with a documented history of sHTG (TG ≥1000 mg/dL [11.3 mmol/L]), a TG level of at least 500 mg/dL (5.6 mmol/L) at screening, a history of acute pancreatitis, and without LOF mutations in genes in the LPL pathway.	FAS	MMRM	No	Yes	No

10.2. List of AESIs with Data Sources and Definitions of SMQ/CMQ

AESI	Using an e-CRF specific tick box on AE page	Using Standard MedDRA Query (SMQ)/company MedDRA Query (CMQ) or lab data
Anaphylactic reactions	Yes	No
General allergic events	No	SMQ "hypersensitivity" (broad and narrow) excluding the following preferred terms linked to local injection site reactions ("infusion site dermatitis", "infusion site hypersensitivity", "infusion site rash", "infusion site urticaria", "injection site dermatitis", "injection site hypersensitivity", "injection site rash", "injection site urticaria", "injection site vasculitis") plus "idiopathic angioedema"
Infusion reactions	Yes	No
Pregnancy	Yes	No
Symptomatic overdose with investigational medicinal product	Yes	No
Neurocognitive events	No	CMQ for neurocognitive events as defined based on Regulatory Agency request for another lipid lowering program (See Table 4 in Appendix 10.2 for the list of terms)

New onset of diabetes (NOD)	No	• At least 2 values of HbA1c ≥6.5% during the TEAE period. **NOTE**: For patients with only a single measurement available during the TEAE period, a single value ≥6.5% will be considered and qualify the patient as NOD by default. For patients with several HbA1c measurements but only with the last one ≥6.5%, this single value ≥6.5% will be considered and qualify the patient as NOD by default. OR • At least 2 values of fasting glucose ≥126 mg/dL (7.0 mmol/L). NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD. For patients with several fasting glucose measurements but only with the last one ≥126 mg/dL (7.0 mmol/L), this single value ≥ 126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD.
Pancreatitis	Yes	No

Table 4 CMQ "Neurocognitive disorders – FDA's recommendation"

MedDRA level	**MedDRA Term Label**
PTCD	Amnesia
PTCD	Amnestic disorder
PTCD	Anterograde Amnesia
PTCD	Behavioural and Psychiatric Symptoms of Dementia
PTCD	Change in sustained attention
LLTCD	Cognitive Deterioration
PTCD	Cognitive Disorder
LLTCD	Confusion
LLTCD	Confusion Aggravated

MedDRA level	MedDRA Term Label
PTCD	Confusional State
PTCD	Delirium
PTCD	Dementia
PTCD	Dementia Alzheimer's type
LLTCD	Dementia Nos
LLTCD	Dementia Nos Aggravated
LLTCD	Dementia of the Alzheimer's type NOS
PTCD	Dementia with Lewy Bodies
PTCD	Disorientation
PTCD	Disturbance in attention
PTCD	Executive dysfunction
PTCD	Frontotemporal Dementia
LLTCD	Global Amnesia
PTCD	Illogical Thinking
PTCD	Impaired reasoning
PTCD	Incoherent
PTCD	Judgement impaired
PTCD	Memory Impairment
PTCD	Mental Impairment
LLTCD	Mental Impairment Nos
LLTCD	Mental State Abnormal Aggravated
PTCD	Mental Status Changes
PTCD	Mini Mental Status Examination Abnormal

MedDRA level	MedDRA Term Label
PTCD	Presenile Dementia
PTCD	Retrograde Amnesia
PTCD	Senile Dementia
LLTCD	Senile Dementia Nos
LLTCD	Short-term Memory Loss
PTCD	Thinking Abnormal
LLTCD	Thinking Slowed
PTCD	Transient Global Amnesia
PTCD	Vascular Dementia

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
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
CrCl (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)

Parameter	PCSV
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
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
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

Parameter	PCSV
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
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
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 1: Schedule of Events

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

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

	Screening Period			Placebo run-in[1]/ Baseline		Double-Blind Treatment Period[2]						Single-Blind Treatment Period[3]		
Study Procedure	**Visit 1**	**Visit 1b[4]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10[5]**	**Visit 11**	**Visit 12**	**End of Treat-ment Visit 13**
Day	**-66 to -59**	**-58 to -52**	**-51 to -39**	**-28 +4d**	**-14 ± 4d**	**1 ± 4d**	**15 ± 4d**	**29 ± 4d**	**43 ± 4d**	**57 ± 4d**	**85 ± 4d**	**113 ± 4d**	**141 ± 4d**	**169 ± 5d**
Week						**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**
APOC2, APOC3, APOA5, NEFA[11]						X					X			X
Inflammation Panel (eg, IL-1, IL-6, IL-8, TNFα)				X		X					X			X
hs-CRP				X		X					X			X
Lipid sub-fractions by UC						X					X			X
Genomic DNA sample:														
Whole blood DNA sample				X										

Schedule of Events (continued)

	Off-Drug Treatment Follow-Up Period				
Study Procedure	**Visit 14**	**Phone Call**	**Visit 16**	**Phone Call**	**End of Study Visit 18**
Day	**197± 5d**	**225± 5d**	**253± 5d**	**281± 5d**	**309± 5d**
Week(s)	**28**	**32**	**36**	**40**	**44**
Treatment:					
Concomitant Medications and treatment	X	X	X	X	X
Efficacy:					
Lipids and lipoproteins[11,12]	X		X		X
HbA1c, Insulin, C-peptide, and Homa[11]					X
Daily Symptom Questionnaire (Hypertriglyceridemia and Acute Pancreatitis Signs and Symptoms)[15]	X[16]		X[16]		X[16]
Symptom/Dietary Impact Questionnaire (Hypertriglyceridemia and Acute Pancreatitis Dietary Behavior)[15]	X		X		X
Site review of responses to questionnaires	X		X		X
Safety:					
Vital Signs	X		X		X
Physical Examination					X
Weight	X		X		X
Electrocardiogram[17]					X
Adverse Events	X	X	X	X	X
Confirm required contraception use and reminder of pregnancy status reporting in women of child bearing potential and female partners of male patients[19]	X	X	X	X	X
Laboratory Testing:					
Hematology[11]	X		X		X
Blood Chemistry[11]	X		X		X
Pregnancy Test[19]	Urine	Urine	urine	urine	serum
Urinalysis					X
Imaging and Other Assessments:					
Amylase, lipase[11]	X		X		X
PK/Drug Concentration and ADA Samples:					
PK/Drug conc. Sample[21]	X		X		X
ADA sample 23					X
Biomarkers:					
Inflammation Panel (eg, IL-1, IL-6, IL-8, TNFα)					X
hs-CRP					X

10.4.1. Footnotes for the Schedule of Events Table

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

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

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