Clinical Development and Regulatory Affairs
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Varying Doses and Dose Regimens of Evinacumab in Patients with Persistent Hypercholesterolemia Despite Maximally Tolerated Lipid Modifying Therapy

Compound:	Evinacumab
Protocol Number:	R1500-CL-1643 Version 4
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
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
Apo A-1	Apolipoprotein A-1
Apo B	Apolipoprotein B
Apo CIII	Apolipoprotein CIII
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CEC	Clinical Events Committee
CI	Confidence interval
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CV	Cardiovascular
CVD	Cardiovascular disease
DBTP	Double-blind treatment period
ECG	Electrocardiogram
EOT	End of treatment
FH	Familial hypercholesterolemia
FSH	Follicle stimulating hormone
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolemia
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-treat
IV	Intravenously
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor

LMT	Lipid modifying therapy
Lp(a)	Lipoprotein a
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed-effect model with repeated measures
OLTP	Open-label treatment period
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PMM	Pattern Mixture Model
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
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMT	Safety Monitoring Team
SOC	System organ class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
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-CL-1643 study. The content of this SAP is inclusive of the first, second, and third 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 step database lock (i.e. before treatment assignments become known for Group B). For the purposes of this document, REGN1500 will be referred to as "evinacumab".

1.1. Background/Rationale

Angiopoietin-like 3 (ANGPTL3) has recently emerged as an attractive target for the treatment of elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs), both factors for the development of cardiovascular disease (CVD). Importantly, population genetic studies indicate that patients heterozygous for Angiopoietin-like 3 (ANGPTL3) protein loss-of-function (LOF) mutations have reduced cardiovascular (CV) risk. These data suggest that inhibiting ANGPTL3 may be a meaningful strategy for lowering serum lipids in patients whose elevated LDL-C levels place them at significant residual CV risk, despite otherwise optimized lipid-lowering therapy.

Evinacumab (REGN1500) is a fully human monoclonal antibody, created with Regeneron's VelocImmune technology platform, which specifically binds to ANGPTL3. 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 evaluate the reduction of LDL-C by evinacumab in comparison to placebo after 16 weeks in patients with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [HeFH], or non-HeFH with a history of clinical atherosclerotic cardiovascular disease [ASCVD]) with persistent hypercholesterolemia despite receiving maximally-tolerated LMT. Persistent hypercholesterolemia is defined as LDL-C ≥70 mg/dL (1.81 mmol/L) for those patients with clinical ASCVD and LDL-C ≥100 mg/dL (2.59 mmol/L) for those patients without clinical ASCVD.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the dose-response effect of evinacumab on other lipid parameters (ie, Apolipoprotein B [ApoB], non-high-density lipoprotein cholesterol [non-HDL-C], total cholesterol [TC], Lipoprotein(a) [Lp (a)], triglycerides [TGs], ApoCIII), and total ANGPTL3 in patients with primary hypercholesterolemia
- To evaluate the safety and tolerability of subcutaneous (SC) and intravenous (IV) doses of evinacumab in patients with primary hypercholesterolemia
- To assess systemic concentrations of evinacumab in serum in patients with primary hypercholesterolemia
- To evaluate the potential development of anti-evinacumab antibodies

1.2.3. Modifications from the Statistical Section in the Final Protocol

The summary of modifications is listed in the following table.

Item	Protocol Section	Description
1	10.3.1.1 Intent-to-Treat (ITT)	SAP Section 3.1.1 Evaluable primary endpoint requirement for the primary analysis population was removed per FDA request.
2	10.3.2.1 Double-Blind Safety Analysis Set/second item "For patients receiving study drug from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be the one in which the patient was treated with the highest number of injections (Group A) or infusions (Group B)."	SAP Section 3.2: The second item for determining the as-treated treatment group will be conservatively changed to: "For randomized patients receiving both evinacumab and placebo study treatment during the trial, the treatment group allocation for as-treated analysis will be evinacumab.
3	10.4.3.1 Primary Efficacy Analysis "Each model will include the fixed categorical effects of treatment group (placebo and evinacumab dose regimens), randomization strata, time point (weeks 4, 8, 12, 16 for the Group B treatment groups; weeks 2, 4, 6, 8, 12, 16 for the Group A treatment groups)"	SAP Section 5.7.1 Timepoints in the MMRM model are updated: "Each model will include the fixed categorical effects of treatment group (evinacumab dose regimens versus placebo), randomization strata (high-intensity statin [Yes/No] and HeFH status

Item	Protocol Section	Description
		[Yes/No]), time point (weeks 2, 4, 6, 8, 12, 16 for the Group B treatment groups; weeks 2, 4, 6, 8, 10, 12, 14, 16 for the Group A treatment groups)"
4	4.2.2. Secondary Efficacy Analysis • Proportion of patients with calculated LDL-C < 100 mg/dL (2.59 mmol/L) at week 16 • Proportion of patients with calculated LDL-C < 70 mg/dL (1.81 mmol/L) at week 16	SAP Section 4.7.2 These two secondary endpoints were removed due to the protocol amendment for changes to the inclusion criteria. Specifically, the LDL-C threshold was lowered to aid patient enrollment, potentially allowing patients to achieve one or both of the secondary endpoints at baseline.

1.2.4. Revision History for Statistical Analysis Plan Amendments

The following modification has been made in this SAP version 2, as compared to version 1.

Item	SAP Section	Description
1	Appendix 10.2	The upper bound for Week 16 in Table 1 and 2 (analysis windows for Group B) was increased by 2 days (from study day 126 to 128). These extra 2 days in the week 16 analysis window will reduce the missing data rate for the primary efficacy endpoint.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to assess varying doses of SC and IV regimens of evinacumab in patients diagnosed with primary hypercholesterolemia (HeFH, or non-HeFH with a history of clinical ASCVD) who have an LDL-C ≥70 mg/dL (1.81 mmol/L) for those patients with clinical ASCVD and LDL-C ≥100 mg/dL (2.59 mmol/L) for those patients without clinical ASCVD, despite receiving a stable maximally-tolerated LMT. The LMT should include a stable, maximally-tolerated statin and stable PCSK9 inhibitor antibody for patients who are HeFH, or non-HeFH with a history of clinical ASCVD. Patients with HeFH not on a statin are eligible if there is documentation of

inability to tolerate at least 2 statins (see Protocol Section 7.3) Background Treatments for further information).

Patients who meet all inclusion criteria and who meet none of the exclusion criteria will be randomized within either Group A (1:1:1:1) or Group B (1:1:1) to receive:

Group A

- Evinacumab 300 mg SC QW for 16 weeks, or
- Evinacumab 300 mg SC Q2W, for 16 weeks (alternating with placebo on opposite weeks), or
- Evinacumab 450 mg SC QW, for 16 weeks, or
- Placebo SC QW, for 16 weeks

Group B

- Evinacumab 5 mg/kg IV Q4W, for 24 weeks, or
- Evinacumab 15 mg/kg IV Q4W, for 24 weeks, or
- Placebo IV Q4W, for 24 weeks

Enrollment of IV cohorts will occur before enrollment of SC cohorts, accordingly, enrollment of Group A will not begin until Group B enrollment is completed.

Patients enrolled to the SC (Group A) and IV (Group B) treatment groups will have different visit schedules because of the differences in dosing frequency.

Randomization will be stratified by high-intensity statin (Yes/No) and HeFH (Yes/No) at baseline. High-intensity statin is defined as rosuvastatin 20 mg or 40 mg daily, atorvastatin 40 mg or 80 mg daily, or simvastatin 80 mg daily (if already on this dose for >1 year). To ensure an adequate number of patients with HeFH are included in this study and exposed to each dose, randomization will be stratified 2:1 (HeFH:non-HeFH; 24:12) within each treatment group.

2.2. Sample Size and Power Considerations

Four pairwise comparisons of evinacumab to a placebo control arm corresponding to the route of administration (Group A or Group B) are hypothesized for the primary efficacy analysis of this study. A total of 216 patients are planned for assessing the primary measure at week 16. Specifically, a sample size of 36 patients per treatment arm will have 90% power to detect a treatment group difference in mean percent change LDL-C of 20% in any 1 pairwise comparison (ie, evinacumab mean = 27% and control mean = 7%), assuming that the common standard deviation (SD) is 25 using an independent group t-test. This sample size has been adjusted for a 5% dropout rate. The alpha level for each of the 4 pairwise comparisons is 0.05 (2-sided), and assumes control of the overall type-1 error rate using a pre-specified hierarchical inferential approach.

Further, the evinacumab 5 mg/kg IV Q4W regimen has been added to Group B, allowing for an assessment of dose-response in the IV route of administration. The additional 36 patients for this second IV dose regimen culminate in a total of 252 patients planned for the study.

With the intent to gain evinacumab experience across these dose regimens for future study planning in patients with HeFH, a subgroup analysis is planned for the stratified sub-population of patients diagnosed with HeFH. To ensure an adequate number of patients are randomized into the HeFH strata level, a total of 175 patients are planned for assessing the percent change LDL-C from baseline at week 16. Specifically, a sample size of 36 patients per treatment arm will have 90% power to detect a treatment group difference in mean percent change LDL-C of 20% in any 1 pairwise comparison (ie, evinacumab mean = 27% and Control mean = 7%), assuming that the common SD is 20 using an independent group t-test. This sample size has been adjusted for a 5% dropout rate.

Blinded Sample Size Adjustment

Referencing the ICH E9 regulatory guidance, the study sample size may be re-estimated after approximately 75% of the patients reach the week 8 visit in the double-blind period, to ensure adequate power in the case of a larger-than-expected variability in the data. This sample size re-estimation process may be performed twice; once for Group A and again for Group B. The sample size re-estimation will be based on the actual blinded pooled SD (adjusted as described in Keiser 2003) for the primary efficacy measure. Since the patients' post-baseline LDL-C levels are masked to all study participants (patients, site personnel, and sponsor staff), the blinded pooled SD will be calculated by a designated statistician external to Regeneron who has access to the lipid data. As mentioned in Keiser 2003, the blinded sample size re-estimation does not affect type-I error materially for continuous endpoints.

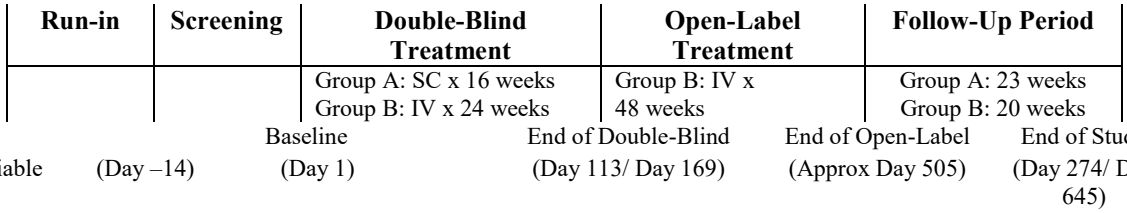
This re-estimation procedure will assess the need for an increase or decrease in sample size (unrestricted recalculation). The result of this procedure is non-binding, since the decision to increase the sample size will also take into account other study execution factors (for example, availability of patients). In the case the re-estimated sample size is implemented, a protocol amendment will document the modification.

2.3. Study Plan

The study consists of 4 (for Group A [SC treatment groups]) or 5 (for Group B [IV treatment groups]) periods: a run-in period (for patients whose background LMT has not been stable prior to screening, who are not already receiving a PCSK9 inhibitor antibody, or whose background LMT is not optimized), a 2-week screening period, a 16-week double-blind treatment period for the SC dose groups or 24-week double-blind treatment period for the IV dose groups, an approximately 48-week open-label treatment period for the IV dose groups, and a follow-up period lasting 24 weeks after the last dose of study drug (Figure 1).

The Study event table is presented in Appendix 10.7 .

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. Two efficacy populations are planned for this study, specifically the Intent-to-Treat (ITT) population and the Modified Intent-to-Treat population (mITT). The primary efficacy analysis population is the ITT population. Additional patient populations are defined for safety, anti-drug (evinacumab) anti-body (ADA), pharmacokinetic (PK), pharmacodynamic (PD), and open-label 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 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 and treated more than once in this trial, safety data from the first randomization and treatment will be included in the safety population, with safety data associated with the later randomization and treatment reported separately. Inclusion of efficacy data from the patient randomized and treated more than once in the two efficacy populations 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 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. Efficacy Analysis Sets

3.1.1. Intent-to-Treat (ITT)

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

3.1.2. Modified Intent-to-Treat (mITT)

The modified ITT (mITT) population is defined as the all randomized population who took at least 1 dose or part of a dose of study drug and have an evaluable primary endpoint. The endpoint is considered evaluable when both of the following conditions are met:

- Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (i.e., baseline).
- Availability of at least 1 calculated LDL-C value during the efficacy treatment period and within one of the efficacy analysis windows in the DBTP up to week 16. The group A (SC dose regimens) efficacy treatment period is defined as the time from the first study drug administration up to 14 days after the last double-blind study drug injection. The Group B (IV dose regimens) efficacy treatment period is defined as the time from the first study drug administration up to 35 days after the last double-blind study drug infusion, or up to the first dose of the open-label study drug, whichever is earlier.

Patients in the mITT population will be analyzed according to the treatment group allocated by randomization.

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 IV, evinacumab 5 mg/kg or 15 mg/kg IV Q4W, placebo SC, evinacumab 300 mg SC QW or Q2W, evinacumab 450 mg SC QW). Actual treatment received is defined as follows:

- For Group A, each study drug administration visit is assigned 3 kits with 150 mg IP concentration in each kit, and each kit contains either evinacumab or placebo. Different combinations of evinacumab or placebo kits determine the actual dosage as follows:
  - For the evinacumab 450 mg SC QW treatment group, the 3 kits at all weekly visits contain evinacumab as recorded in eCRF “Study Drug Administration- Evinacumab/Placebo SC”
  - For the 300 evinacumab mg SC QW treatment group, 2 kits contain evinacumab and 1 kit contains placebo at all weekly visits as recorded in eCRF “Study Drug Administration- Evinacumab/Placebo SC”
  - For the 300 evinacumab mg SC Q2W treatment group, 2 kits contain evinacumab and 1 kit contains placebo at all even-numbered weekly visits (Day 1, Week 2, Week 4, etc.) as recorded in eCRF “Study Drug Administration- Evinacumab/Placebo SC.” All odd-numbered weekly visits (Week 1, Week 3, etc.) contain 3 kits of placebo as recorded in eCRF “Study Drug Administration- Evinacumab/Placebo SC”
  - For the placebo SC QW treatment group, the 3 kits at all weekly visits contain placebo as recorded in eCRF “Study Drug Administration- Evinacumab/Placebo SC”
- For Group B, each study drug administration visit is assigned 1 kit, and it contains either evinacumab or placebo (regardless of evinacumab dose). The actual study

treatment received (placebo, evinacumab 5mg/kg IV, or evinacumab 15 mg/kg IV) is defined as follows:

- Active study treatment (evinacumab or placebo) is defined from the kit number in eCRF "Study Drug Administration- IV"
- Evinacumab study treatment dose (5 mg/kg or 15 mg/kg) is defined as "active study treatment = evinacumab" and the dose is defined in the "Total IP Dose Administration – IV Double-blind (Unblinded)" eCRF page.

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 randomized patients receiving both evinacumab and placebo study treatment during the trial, the treatment group allocation for as-treated analysis will be evinacumab.
- If a randomized patient receives both evinacumab doses (300 mg SC and 450 mg SC for Group A; 5 mg/kg IV and 15 mg/kg IV for Group B), the treatment group allocation for as-treated analysis will be the most frequently administered evinacumab dose.

3.3. Open-Label Safety Analysis Set

For Group B, the open-label SAF considered for safety analyses will be the randomized population who received at least 1 dose or part of a dose of open-label 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 post-baseline measurement of evinacumab concentration. 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.

3.5. The Immunogenicity Analysis Set

The anti-evinacumab antibody (ADA) analysis set is defined as all randomized patients who received any study treatment, and have at least 1 non-missing ADA result following the first dose of study treatment. Patients will be analyzed according to a treatment actually received.

The neutralizing antibody (NAb) analysis set includes all subjects/patients who received any study drug and who are negative in the REGN1500 ADA assay or with at least one non-missing result in the REGN1500 NAb assay after first dose of the study drug. Patients who are ADA negative are set to negative in the NAb analysis set. Patients will be analyzed according to the treatment actually received.

3.6. Pharmacodynamic (PD) Analysis Set

The PD population includes all treated patients who received any study drug (safety population) and had at least one non-missing protocol defined PD marker (as defined in Protocol/Section 8.2.5) following the first dose of study drug.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

For each patient, demographic and baseline characteristics will be obtained from the last available value up to the date of the first study treatment administration (i.e. baseline definition). For patients randomized and not treated in R1500-CL-1643, 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, ≥65 to <75, and ≥75 years; and <65, and ≥65 years)
- 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)
- Randomization strata as reported in the IVRS
  - High intensity statin (Yes/No)
  - HeFH status (Yes/ No)
- Randomization strata as reported from the e-CRF

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
- Calculated LDL-C categories: <70, ≥ 70 to <100, ≥100 to <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL (<1.81, ≥1.81, <2.59, ≥2.59 to <3.37, ≥3.37 to <4.14, ≥4.14 to <4.91, ≥4.91 mmol/L)
- Fasting TG categories: <150, ≥150 to <200, ≥200 mg/dL, and category ≥150 mg/dL for mixed dyslipidemia (<1.7, ≥1.7 to <2.3, ≥2.3 mmol/L, and category ≥ 1.7 mmol/L),
- Lp(a) categories: <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)

4.2. Medical History

As applicable, patient medical history, pre-listed or not in the e-CRF will be dictionary coded by primary system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), specifically the MedDRA version in effect at the time of the first database lock. The medical history of interest collected on dedicated and pre-listed e-CRFs is: cardiovascular history and risk factors, Primary and secondary CVD prevention, CV risk factors categorized by high and very high risk, hypercholesterolemia disease history (including LMT therapies) 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.

Hypercholesterolemia disease history will be assessed through diagnosis of HeFH, time from diagnosis to study randomization (years), method of diagnosis of HeFH (genotyping, clinical diagnosis), lipid modifying therapies history reported in the "History of Hypercholesterolemia /Statin Use" e-CRF page.

4.3. Prior and Concomitant Medications

All medications (including statin, non-statin LMT, and CV) 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 OLTP for Group B only).

- 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 ≥ OLTP Week 24 for Group B only); **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 ≥ OLTP Week 24 for Group B only).

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 Group A patients or Group B patients who do not continue into the OLTP) or to the day before the first open-label study treatment administration (for Group B patients who enter the OLTP).
- For concomitant medications in the OLTP (Group B only), the treatment emergent period is defined from the first day of open-label study treatment administration to the last day of open-label study treatment +168 days.

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

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

4.4. Prohibited Medications and Procedures During Study

The definitions of prohibited medications and procedures are described in the section 7.8.1 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 milestone categories for the DBTP 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 screen failure (SF) patients:
  - if a SF patient's first informed consent date is before randomization date of the last IV patient, this patient will be included in Group B; otherwise this patient will be included in Group A
- 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 double-blind treatment e-CRF.
- The total number of patients who completed the DBTP, defined for Group A as at least 15 weeks of study treatment administration and week 16 visit performed; and defined for Group B as at least 20 weeks of study treatment administration and week 24 visit performed
- The total number of Group B patients who completed week 16 visit, defined as at least 12 weeks of study treatment administration and week 16 visit 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 Double-blind Treatment e-CRF
- The total number of patients in Group B who do not proceed into OLTP and complete the last study follow-up visit (i.e. Follow-up week 20).
- The total number of patients in Group A who complete the last study follow-up visit (i.e. Follow-up week 20).
- The total number of patients who did not complete the study follow-up period, defined as the last visit performed less than 23 weeks after the last study treatment administration. Patients who died during the study are excluded. (For Group B this applies only to patients who did not proceed to OLTP).

Patient milestone categories for the OLTP (Group B only) are defined below. As applicable, percentages will be calculated using a denominator of the number of patients administer open-label study treatment.

- The total number of patients receiving open-label study treatment.

- The total number of patients ongoing in OLTP (applicable for the first step analysis)
- The total number of patients who completed the OLTP as collected on the end of open-label treatment e-CRF.
- The total number of patients who completed the open-label treatment period, defined as at least 44 weeks of open-label study treatment administration and visit week 72 performed.
- The total number of patients who prematurely discontinued study treatment during the OLTP, and the reasons for discontinuation collected on the End of Open-label Treatment e-CRF.
- The total number of patients from OLTP who complete the last study follow-up visit (i.e. Follow-up week 20).
- The total number of patients who did not complete the study follow-up period, defined as the last visit performed less than 23 weeks after the last study treatment administration. Patients who died during the study are excluded

The following patient populations for analyses are defined below:

- Randomized population
- Efficacy populations: ITT and mITT populations
- Double-blind safety analysis set
- Open-label safety analysis set
- Anti-evinacumab antibody (ADA) analysis set
- Pharmacokinetic (PK) analysis set
- Pharmacodynamic (PD) 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 injections administered during the DBTP for Group A patients are listed below with associated definitions:

- Patient duration of double-blind study treatment exposure in weeks defined as: (last study drug dosing date +7 – first study drug dosing date + 1 day)/7. Unplanned intermittent discontinuations in study treatment will be addressed on a case-by-case basis, since this is expected to be a rare occurrence.
- The total number of injections by patient

- The following categories will be used for treatment exposure at 1 week intervals: ≥1 day and <1 week, ≥1 weeks and <2 weeks, ≥2 weeks and <3 weeks, ≥3 weeks and <4 weeks, ≥4 weeks and <5 weeks, ≥5 weeks and <6 weeks, ≥6 weeks and <7 weeks, ≥7 weeks and <8 weeks, ≥8 weeks and <9 weeks, ≥9 weeks and <10 weeks, ≥10 weeks and <11 weeks, ≥11 weeks and <12 weeks, ≥12 weeks and <13 weeks, ≥13 weeks and <14 weeks, ≥14 weeks and <15 weeks, ≥15 weeks and <16 weeks, ≥16 weeks.

Study treatment exposure variables for infusions administered during the DBTP for Group B patients 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 + 1)/7. Unplanned intermittent discontinuations in study treatment will be addressed on a case-by-case basis, since this is expected to be a rare occurrence. 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 at 4 week 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.

Study treatment exposure variables for infusions administered during the OLTP for Group B patients are listed below with associated definitions:

- Patient duration of open-label study treatment exposure in weeks defined as: (last open-label evinacumab treatment administration date +28 – first open-label evinacumab treatment administration date)/7. Unplanned intermittent discontinuations in study treatment will be addressed on a case-by-case basis, since this is expected to be a rare occurrence. Values will be rounded to one decimal place.
- Patient duration of open-label study treatment exposure in patient-years defined as: (last open-label evinacumab treatment administration date +28 – first open-label evinacumab treatment administration date)/365, regardless of unplanned intermittent discontinuations.
- The total number of open-label evinacumab treatment infusions by patient.
- The following categories will be used for treatment exposure at 4 week intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks and <24 weeks, ≥24 weeks and <28 weeks, ≥28 weeks and <32 weeks, ≥32 weeks and <36 weeks, ≥36 weeks and <40 weeks, ≥40 weeks and <44 weeks, ≥44 weeks and <48 weeks, ≥48 weeks

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

- Cumulative patient duration of evinacumab exposure in weeks defined as: double-blind treatment exposure plus open-label treatment exposure, regardless of unplanned intermittent discontinuations.

- Cumulative patient duration of evinacumab exposure in patient-years defined as: double-blind treatment exposure in patient-years plus open-label treatment exposure in patient-years, 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 open-label infusions.
- The following categories will be used for cumulative patient treatment exposure at 4 week intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks and <24 weeks, ≥24 weeks and <28 weeks, ≥28 weeks and <32 weeks, ≥32 weeks and <36 weeks, ≥36 weeks and <40 weeks, ≥40 weeks and <44 weeks, ≥44 weeks and <48 weeks, ≥48 weeks and <52 weeks, ≥52 weeks and <56 weeks, ≥56 weeks and <60 weeks, ≥60 weeks and <64 weeks, ≥64 weeks and <68 weeks, ≥68 weeks and <72 weeks, ≥72 weeks, etc.

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/injection frequency for respective treatment periods, specifically:

- DBTP: The mean infusion/injection frequency for study treatment will be defined for each patient as the average number of days between 2 consecutive infusions/injections: (last double-blind dose date – first double-blind dose date) / (number of infusions/injections in DBTP -1), for patients receiving at least 2 infusions/injections.
- OLTP (Group B only): for each patient as the average number of days between 2 infusions: (last open-label dose date – first open-label dose date) / (number of infusions in OLTP -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 Variable

Efficacy will be assessed through the following lipid parameters: calculated LDL-C (using the Friedewald formula), total-C, TG, non-HDL-C (calculated by subtracting HDL-C from Total-C), Apo B, and Lp(a). All lipid parameters will be collected over the course of the study and sent to a central laboratory for evaluation, including scheduled and unscheduled blood draws.

All lipid values obtained during the study (scheduled or unscheduled), regardless of fasting status (fasting or not fasting), can be used to provide a value for the primary and secondary efficacy endpoints, with the following exceptions:

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

All efficacy measurements will be assigned to efficacy analysis windows defined in Appendix 10.2 of this SAP, with the intent to provide an assessment for week 2 to week 16 timepoints for Group A and 2 to week 24 timepoints for Group B. For all time points post-baseline, the value used for the analyses at a given time point (e.g. at week 24) is the value obtained within the corresponding efficacy analysis window. 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 OLTP). 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 (s)

The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to week 16 in the intent-to-treat (ITT) population, using the intent-to-treat [ITT] estimand (defined as all LDL-C values regardless of adherence to treatment and subsequent therapies).

The primary endpoint is defined as: 100 x (calculated LDL-C value at week 16 - calculated LDL-C value at baseline)/calculated LDL-C value at baseline. The baseline calculated LDL-C value will be the last LDL-C level obtained before the first dose of study drug. The calculated LDL-C at week 16 will be the LDL-C level obtained within the week 16 analysis window.

All calculated LDL-C values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the primary efficacy endpoint, if appropriate, according to the above definition.

4.7.2. Secondary Efficacy Variable(s)

The secondary efficacy variables include:

- The percent change in Apo B from baseline to week 16 (ITT estimand)
- The percent change in non-HDL-C from baseline to week 16 (ITT estimand)

  The percent change in TC from baseline to week 16 (ITT estimand)
- The proportion of patients with ≥ 30% reduction in calculated LDL-C at week 16 (ITT estimand)

  The proportion of patients with ≥ 50% reduction in calculated LDL-C at week 16 (ITT estimand)
- Percent change in TGs from baseline to week 16 (ITT estimand)
- Percent change in Lp(a) from baseline to week 16 (ITT estimand)
- Proportion of patients with calculated LDL-C < 50 mg/dL (1.30 mmol/L) at week 16 (ITT estimand)
- Percent change in calculated LDL-C, Apo B, non-HDL-C, TC, TG, and Lp(a) from baseline to week 24 (only applicable to those patients receiving IV route of study treatment administration) (ITT estimand)

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) (based on PK considerations, residual effect of study treatment might be observed until 24 weeks after the last dose of study drug) for those patients not proceeding into the OLTP (ie, Group A patients and Group B patients who prematurely discontinue study treatment), or up to the day before the first dose of open-label study treatment administration for those patients proceeding into the OLTP
- The open-label treatment-emergent adverse event (TEAE) period (Group B only) is defined from the day of the first open-label study treatment administration to the day of the last open-label 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 causing permanent treatment discontinuation, deaths, and AEs of special interest) are recorded from the time of signed informed consent until the end of study. All AEs diagnosed by the Investigator will be reported and described.

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

Adverse Event Observation Period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.
- Double-blind and open-label TEAEs are AEs that developed or worsened or became serious during the respective TEAE period.
- Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period.

4.8.1.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner. AESIs will be recorded on the adverse event e-CRF using dedicated tick boxes, and/or identified using standard MedDRA queries (SMQ), company MedDRA queries (CMQ), MedDRA terms, and/or applicable laboratory assessments. Appendix 10.3 contains the definitions used to identify AESIs:

The AESIs include:

- Anaphylactic reactions (e-CRF)
- General allergic events (SMQ)
- Infusion reactions (e-CRF)
- Hepatic Disorder (SMQ, lab data)
- Pregnancy (e-CRF)
- Symptomatic overdose with investigational medicinal product (e-CRF)
- Neurocognitive events (CMQ)
- Neurologic events (e-CRF)
- New onset of diabetes (NOD) (lab data, HLT, and concomitant medications)
- Diabetes mellitus or diabetic complication (CMQ, concomitant medications)
- Pancreatitis (e-CRF)
- Cataracts (MedDRA HLT)
- Immune complex diseases SMQ
- Muscle events/CK elevation (MedDRA SOC, MedDRA SMQ, lab data)

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 open-label),
- Death post-treatment: deaths occurring during the post-treatment period.

4.8.2. Laboratory Safety Variables

Clinical laboratory tests will consist of blood analyses (including hematology, clinical chemistry and other) 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 10.4 for PCSV definitions). For those laboratory tests that do not have

PCSV ranges, central laboratory normal ranges will be applied to identify out-of-range values. All laboratory test samples will be collected before study treatment administration during the protocol scheduled visits.

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

Hematology:

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

Non-Efficacy Lipid Panel

Apo A-1, Apo CIII, and ratio Apo B/Apo A-1.

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 and visits will be assigned to the Global Analysis Windows (See Appendix 10.2). Potentially clinically significant values (PCSV) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.4 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. A standard 12-lead ECG will be performed at specified time points according to Appendix 10.2. The ventricular rate, PR, QRS, RR, QTcF, QTcB, and QT intervals will be

recorded. Electrocardiogram assessments will be described as normal or abnormal, and visits will be assigned to the Global Analysis Windows (See Appendix 10.2).

4.8.5. Physical Examination Variables

Physical examination will be conducted at the protocol scheduled visits (See Appendix 10.7 for schedule of event). The result is an outcome of clinically significant (Yes/No, not examined) and visits will be assigned to the Global Analysis Windows (See Appendix 10.2).

4.9. Other Variables

Other assessment endpoints are listed and defined below. Protocol schedule visits will be assigned to the Global Analysis Windows (See Appendix 10.2).

- The change in hemoglobin A1c (HbA1c [%]) from baseline to post-baseline visits.
- The percent change in hs-CRP from baseline over time.
- The percent change in HDL-C from baseline over time

4.10. Pharmacokinetic and Pharmacodynamic Variables

Pharmacokinetic (PK) and pharmacodynamic (PD) variables include total evinacumab concentrations and total ANGPTL3 concentrations at each time point.

Pharmacodynamic variables include lipid profile and total PCSK9.

4.11. Immunogenicity Variables (ADA and NAb)

Anti-drug antibody variables will include ADA status, titer and neutralizing antibody (NAb) status for analyzed samples collected at each time point.

5. STATISTICAL METHODS

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be descriptively summarized by treatment group and overall for the study within each route of administration (Group A or B). In addition, the same descriptive statistics will be provided by treatment group and overall for each stratification factor level (IVRS/IWRS defined high intensity statin [yes/no] and HeFH [yes/no]), within each route of administration. Parameters described in Section 4.1 will be summarized for those patients in the ITT population.

Continuous data will be summarized using the number of patients with data, mean, SD, median, minimum and maximum for each treatment group and for each of the strata. First quartile (Q1) and third quartile (Q3) will be also provided for baseline lipid parameters, HbA1c, and hs-CRP. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Treatment group comparisons within each route of administration for demographic characteristics and disease characteristics will be provided for descriptive purposes (i.e.,

confirmation of the randomization process to equally distribute relevant patient background profiles among the treatment groups) using the Fisher exact test for categorical data and the asymptotic one-way ANOVA test for Wilcoxon scores (Kruskal-Wallis test) for continuous data. As applicable, other safety baseline data not listed in Section 4.1 will be presented collectively in the descriptive statistics summary tables containing respective post-baseline data.

For the Group B open-label safety population, demographic and baseline characteristics will be summarized for all patients and by treatment group of the DBTP (i.e., 5 mg/kg IV evinacumab, 15 mg/kg IV evinacumab, placebo). Parameters listed in Section 4.1 will be summarized as described for the DBTP, except for treatment group comparison testing.

5.2. Medical History

Medical history will be descriptively summarized by treatment group and overall for the study within each route of administration (Group A or Group B) for patients in the ITT 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.

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, minimum and maximum for the study and for each of the strata. Categorical and ordinal data will be summarized using the number and percentage of patients in the study and for each stratum.

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 within each route of administration (Group A or Group B) 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. Prior LMT (statins and non-statin) and CV medication use will also be summarized.

For patients in the double-blind safety population, all concomitant medications during the DBTP, dictionary coded by WHO-DD, will be descriptively summarized by treatment group. Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications (including statin, LMT, CV), by decreasing frequency of the evinacumab highest dose 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. Additionally, concomitant medications pre-specified from e-CRF as statin, LMT, and CV will be summarized by patient counts (and percentages) for the standardized medication names.

For the OLTP, concomitant and post-treatment medications will be dictionary coded by WHO-DD and will be descriptively summarized as described for the DBTP. For patient in the open-label safety population, medications will be summarized for all patients and by treatment group of the DBTP (i.e., 5 mg/kg IV evinacumab, 15 mg/kg IV evinacumab, placebo). Summaries will present patient counts (and percentages).

5.4. Prohibited Medications

Listing of prohibited medications will be provided for the patients in the safety analysis set for the DBTP and OLTP.

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 (screened patients, screen failures, and non-randomized but treated patients only) within each route of administration (Group A or Group B). 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 OLTP, the patient study status and patient analysis populations will be summarized by all patients and by treatment group of the DBTP (i.e., 5 mg/kg IV evinacumab, 15 mg/kg IV evinacumab, placebo) on the open-label safety population for the variables described in Section 4.5.

For both the DBTP and OLTP, 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 OLTP described in Section 4.6 will be assessed and summarized for all patients and by treatment group of the DBTP (i.e., 5 mg/kg IV evinacumab, 15 mg/kg IV evinacumab, placebo) for patients in the open-label safety analysis set.

5.6.1. Exposure to Investigational Product

Study treatment exposure in the DBTP and OLTP will be descriptively summarized for treatment duration and total number of infusions/injections 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, median, minimum and maximum.

Additionally, evinacumab dosing exposure for Group B will be summarized cumulatively across the study, combining DBTP and OLTP 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 deviation categories by count (percentage), and again 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 or injection frequency of study treatment will be summarized. Further, study treatment infusion interruptions and incomplete infusions with reason will be summarized by patient count (percentage) and a patient listing will be provided for those patients with incomplete 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, statistical testing for both percent and absolute 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 endpoints and secondary endpoints will be conducted in the DBTP as described below, and will be completed during the step 1 and 2 efficacy analyses (Section 7). Remaining descriptive efficacy analyses will be completed during step 3. The definition for baseline is applicable to derived variables (e.g., percent change from baseline) in both DBTP and OLTP.

Within each study treatment route of administration (Group A or B), HeFH diagnosis (Yes/No), and high-intensity statin (Yes/No) (high-intensity statin defined as rosuvastatin 20 mg to 40 mg daily, atorvastatin 40 mg to 80 mg daily, or simvastatin 80 mg daily) will be the 2 stratification factors for patient randomization. Stratification factors HeFH diagnosis and high-intensity statin will be accounted for in the statistical modeling for efficacy.

5.7.1. Analysis of Primary Efficacy Variable

For the double-blind primary comparison of the evinacumab group to the placebo group, the percent change from baseline in calculated LDL-C at week 16 will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 2 to week 16 efficacy analysis windows will be used and missing data are accounted for by the MMRM model. Each model will include the fixed

categorical effects of treatment group (evinacumab dose regimens versus placebo), randomization strata (high-intensity statin [Yes/No] and HeFH status [Yes/No]), time point (weeks 2, 4, 6, 8, 12, 16 for the Group B treatment groups; weeks 2, 4, 6, 8, 10, 12, 14, 16 for the Group A treatment groups), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction. Contrast and estimate statements will be used to assess the treatment effects (LS means with confidence intervals) and each dose regimen pairwise comparison to placebo (mean difference and p-values).

This model will be run separately for each route of administration (Group A or Group B, with Group B consisting of 3 dose regimens for the variability estimate) with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation.

Let $\mu 0$ and $\mu 1$ be the population means of the percent change from baseline in calculated LDL-C at week 16 under each of 2 placebo control arms and the 4 evinacumab treatment arms, respectively. The hypothesis that will be tested is "H_0: $\mu_0 = \mu_1$" versus "H_1: $\mu_0 \neq \mu_1$".

The 4 primary treatment group comparisons will evaluate at week 16 each evinacumab dose regimen to the placebo group corresponding to the route of administration (IV or SC).

1. Evinacumab 15 mg/kg IV Q4W compared to Placebo IV
2. Evinacumab 450 mg SC QW compared to Placebo SC
3. Evinacumab 300 mg SC QW compared to Placebo SC
4. Evinacumab 300 mg SC Q2W compared to Placebo SC

The statistical testing of the 4 pairwise comparisons for the primary measure will be evaluated at a 2-sided significance level of 0.05 per pair wise comparison, with corresponding least square estimate of mean difference, SE and 95% confidence interval. The overall study α level will be controlled by the use of a hierarchical inferential approach for the testing of the 4 pairwise comparisons, thereby adjusting for multiplicity.

Within treatment group least-square means and standard errors will be adjusted using weights equal to the observed proportion of patients in strata variable levels (i.e. "population weight"), rather than equal weights. Population weights are considered more appropriate than equal coefficients due to potential imbalances observed in the study population between levels of the randomization stratification factors.

Prior to performing the primary efficacy analysis, statistical analysis method assumptions will be checked for baseline homogeneity of calculated LDL-C levels between treatment groups, normality of the percent change calculated LDL-C distribution for each treatment group, and homogeneity of variances between treatment groups using residual plot.

5.7.1.1. Sensitivity of the Primary Efficacy Analysis

Robustness of the primary analysis statistical methods will be assessed through sensitivity analyses, including a different methodology for missing data (e.g., pattern mixture model to assess the potential violation of the missing at random assumption) and on-treatment analysis for

more clinically relevant treatment comparisons of the percent change in calculated LDL-C from baseline to week 16 (i.e., mITT patient population using calculated LDL-C values collected during the efficacy treatment period [on-treatment estimand]).

Sensitivity to Stratification at Randomization

To assess the robustness of the primary analysis to stratification mistakes made at the time of randomization (i.e. the stratum recorded in IVRS/IWRS differs from the actual stratum recorded in the e-CRF), the MMRM model will be re-run replacing the IVRS/IWRS strata with the e-CRF actual strata.

Sensitivity to On-treatment Calculated LDL-C Values

To assess the robustness of more clinically relevant between group comparisons for the analysis of the primary efficacy endpoint, the same statistical analysis method approach as described above in Section 5.7.1 will be applied in the mITT population. The intent-to-treat estimand will be replaced by the on-treatment estimand, which is defined as all LDL-C values collected during the efficacy treatment period (Section 3.1.2).

Sensitivity to Non-Good Clinical Practice (GCP) Compliant Sites

To assess the impact of non-GCP compliance sites on the primary efficacy endpoint, the primary efficacy analysis will be performed excluding non-GCP compliant sites. Sites known to be non-GCP compliant at the time of database lock will be identified for this analysis before database lock. Any additional sites determined to be non-GCP compliant post-database lock will be separately identified.

Sensitivity to the Handling of Missing Data

Sensitivity analyses will be conducted to assess the robustness of primary efficacy analysis with regards to the handling of missing data (Little RJ 2012).

Visual examination

- In order to explore the missing data pattern, post-baseline calculated LDL-C observations (in the ITT population) will be described according to the following groups:
- Group A
    1. Calculated LDL-C available at week 16 (i.e. primary efficacy endpoint available),
    2. Calculated LDL-C available at week 14 but missing at week 16,
    3. Calculated LDL-C available at week 12 but missing at week 14,
    4. Calculated LDL-C available at week 10 but missing at week 12,
    5. Calculated LDL-C available at week 8 but missing at week 10,
    6. Calculated LDL-C available at week 6 but missing at week 8,
    7. Calculated LDL-C available at week 4 but missing at week 6,
    8. Calculated LDL-C available at week 2 but missing at week 4

9. Calculated LDL-C missing at week 2.

- Group B

10. Calculated LDL-C available at week 16 (i.e. primary efficacy endpoint available),
11. Calculated LDL-C available at week 12 but missing at week 16,
12. Calculated LDL-C available at week 8 but missing at week 12,
13. Calculated LDL-C available at week 6 but missing at week 8
14. Calculated LDL-C available at week 4 but missing at week 6
15. Calculated LDL-C available at week 2 but missing at week 4
16. Calculated LDL-C missing at week 2.

A graph of mean percent change from baseline calculated LDL-C levels ± SE at baseline, and at time points (weeks 4, 8, 12, 16 for the Group B treatment groups; weeks 2, 4, 6, 8, 12, 16 for the Group A treatment groups) will be provided by missing data pattern, for each treatment group.

- In the ITT population, demographic and baseline lipids will be described within the missing data pattern number 1 above versus the remaining missing data patterns above. P-values from Fisher exact test for categorical data and from asymptotic one-way ANOVA test for Wilcoxon scores (Kruskal-Wallis test) for continuous data, will be also provided, for descriptive purposes.

Tipping point analysis

Robustness of the primary analysis results to departure from the MAR assumption will be explored in the ITT population using the tipping point approach. For the tipping point approach, missing calculated LDL-C will be imputed using the multiple imputation method described in Appendix 10.5. All observed LDL-C values up to and including week 16 will be used, regardless of adherence to treatment and subsequent therapies (ITT estimand).

For missing calculated LDL-C values at visits subsequent to permanent treatment discontinuation (Appendix 10.5, Step 2), a sequence of shift parameters, δ, will adjust the imputed calculated LDL-C values in the evinacumab treatment group. Each of the 100 imputed datasets will be analyzed using the MMRM model described for the primary efficacy analysis. For each δ, the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formula. By progressively increasing δ, this sensitivity analysis will explore the tipping point, e.g., δ value when the p-value for a treatment comparison is above 0.05. Results will be summarized in a table and graph.

Pattern mixture model (PMM)

The MMRM model relies on the "missing-at-random" (MAR) assumption. Because the possibility for a not-missing-at-random (NMAR) missingness mechanism can never be excluded, sensitivity analysis to explore the impact of non-ignorable missingness on the primary efficacy analysis will be conducted using the PMM approach as described below (see Appendix 10.6 for more details).

In the PMM approach, different imputation strategies will be applied to calculated LDL-C values missing during the double-blind on-treatment period (i.e. within the time period from the first double-blind study treatment administration up to the day of last double-blind administration +35 days for Group B or +14 days for Group A) versus calculated LDL C values missing due to treatment discontinuation after the on-treatment period (i.e. after the day of last double-blind administration +35 days for Group B or +14 days for Group A) based on the following assumptions:

- Patients within 35 days for Group B (14 days for Group A) of their last double-blind study treatment administration would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, LDL-C values missing during the on-treatment period (e.g., samples obtained out-side the specified window, no blood sample available although visit was performed, etc.) should be considered "Missing at Random" and imputed based on other observed measurements in the on-treatment period.
- Patients who stopped taking their study treatment no longer benefited from it after discontinuation, and thus tended to have LDL-C values returning to baseline. Therefore, LDL-C values missing after the on-treatment period should be imputed based on patient's own baseline value.

Missing data from the randomized population will be imputed 100 times to generate 100 complete data sets, using the SAS MI procedure (using Markov Chain Monte Carlo). The 100 completed datasets of observed and imputed LDL-C data will be used for the sensitivity analysis of the primary efficacy analysis method.

For the percent change from baseline calculated LDL-C endpoint, the 100 complete datasets of observed and imputed LDL-C data at week 16 will be analyzed using an ANCOVA model with treatment group and randomization strata as fixed effect, and the baseline LDL-C value as continuous covariate. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae.

5.7.1.2. Dose-Response Analysis

Within each route of administration (Group A or Group B), a dose-response descriptive analysis is planned for the evinacumab dose regimens, with the placebo group in the role of the null dose, for patients in the ITT population. Summary tables will provide descriptive statistics (at least mean, median, SD, min/max) for percent change from baseline in LDL-C at each protocol planned visit in the double-blind period, by treatment group. A graph will provide mean and standard error bars for percent change from baseline in calculated LDL-C at each protocol planned visit, by treatment group.

In addition to the analyses results for each evinacumab dose regimen comparison to placebo, the comparisons among the evinacumab dose regimens will be assessed in the ITT population for the percent change from baseline in calculated LDL-C at week 16. This analysis will employ the same statistical methodology as described for the primary comparisons, specifically the MMRM approach, for evaluating effects among the evinacumab dose regimens. P-values will be provided for descriptive purposes to aid in interpretation of the dose-response.

5.7.1.3. 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 for each route of administration (Group A or Group B). LS mean difference versus placebo at week 16 will be provided, as well as the corresponding SE and 95% CI, within each subgroup. The significance level of the treatment-by-subgroup factor interaction term at week 16 will be also provided for each factor for descriptive purpose. Forest plots will be provided. In order to handle imbalances between randomization stratification factors levels, population weights will be used as for the primary analysis model.

The following subgroups of interest will be evaluated, assuming there are enough patients in each subgroup level to perform the evaluation. For the subgroup factors that are also randomization stratification factors, the IVRS strata will be used.

- The baseline high-intensity statin (Yes, No) per IVRS,
- The baseline HeFH status (Yes, No) per IVRS,
- Gender (Female, Male),
- Age (<65, ≥65),
- Race
- Ethnicity
- Baseline LDL-C (<100, ≥100 mg/dL),
- Baseline LDL-C (<130, ≥130 mg/dL).

Subgroup analysis for HeFH patients

To assess the evinacumab treatment effect during the double-blind treatment period on the stratification variable HeFH (Yes/No), specifically the strata level containing patients diagnosed with HeFH (Yes), a subgroup analysis is planned for the percent change from baseline LDL-C in the ITT population for each route of administration (Group A or Group B). Specifically, the primary MMRM model used to assess the treatment group pairwise comparisons will have the additional variables of treatment-by-HeFH strata, time point-by-HeFH strata, treatment-by time point-by HeFH strata interaction terms, and a HeFH factor term. For each dose regimen versus placebo at week 16, the LS mean treatment group difference will be provided for the HeFH (Yes) strata level, along with the corresponding SE, 95% CI and p-value (p-value is provided for descriptive purposes only). The HeFH (Yes/No) stratification factor to be used for this subgroup analysis will be as recorded in the electronic data capture system.

5.7.1.4. Multiplicity Considerations

To control the 5% overall type-I error for the 4 pairwise comparisons in the primary analysis, the overall study α level will be controlled by the use of a hierarchical inferential approach. Statistical significance of the first pairwise treatment comparison is required before drawing inferential conclusions about the second pairwise treatment comparison at the 0.05 alpha level. Inferential conclusions about successive pairwise treatment comparisons require statistical

significance of the prior treatment comparison. The hierarchy testing sequence is the order of treatment comparisons as presented in Section 5.7.1. This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.05 level for each evinacumab dose regimen comparison.

No further adjustments will be made for secondary efficacy endpoints collected during the double-blind treatment period, nor for the comparison of the evinacumab 5 mg/kg IV Q4W patient treated group to the Placebo IV group on any efficacy endpoint collected during the double-blind treatment period. P-values will be provided for descriptive purposes only.

5.7.2. Analysis of Secondary Efficacy Variables

Statistical analyses for the secondary efficacy endpoints (defined in Section 4.7.2) collected in the double-blind treatment period will be performed in the ITT population using the ITT estimand for each of the 5 pairwise treatment group comparisons, including the comparison of evinacumab 5 mg/kg IV Q4W patient treated group to the Placebo IV group. P-values will be provided for descriptive purposes only.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (example: percent change in LDL-C), continuous measurements expected to have a non-normal distribution (example: TG), and binary measurements (example: proportion of patients with at least 30% reduction in LDL-C).

5.7.2.1. Continuous Endpoints Anticipated to have a Normal Distribution

Continuous secondary variables defined in Section 4.7.2 anticipated to have a normal distribution (i.e. lipids other than TG and Lp(a)) will be analyzed using the same MMRM model as described for the primary endpoint. Specifically, the model will contain the fixed categorical effects of treatment group, randomization strata (as per IVRS/IWRS), planned time points up to week 16 or week 24 (depending on the time point of interest), strata-by-time point, and treatment-by-time point interaction, as well as, the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

5.7.2.2. Continuous Endpoints Anticipated to have a Non-Normal Distribution

Continuous secondary efficacy variables defined in Section 4.7.2 anticipated to have a non-normal distribution (i.e. TG and Lp(a)) will be analyzed using the multiple imputation approach for handling of missing values as described in Appendix 10.5, with data log-transformed before imputation process and then back transformed to create the imputed data sets using the TRANSFORM statement of SAS MI procedure.

The percent change from baseline at time point of interest will be derived from observed and imputed lipid values at this time point. Multiple imputation will be followed by robust regression model (Mehrotra, 2012) to compare treatment group differences, with the endpoint of interest as the response variable using M-estimation (using SAS ROBUSTREG procedure) with treatment group, randomization strata (as per IVRS/IWRS) and corresponding baseline value(s). Combined means estimates for both treatment groups, as well as the differences of these

estimates, with their corresponding SEs, 95% CIs and p-value will be provided through the SAS MIANALYZE procedure.

5.7.2.3. Binary Endpoint Variables

Binary secondary efficacy endpoints defined in Section 4.7.2 will be analyzed using the multiple imputation approach for handling of missing values as described in Appendix 10.5.

The binary endpoint at time point of interest will be derived from observed and imputed lipid values at this time point. Multiple imputation will be followed by stratified logistic regression, (with strata defined as randomized in the IVRS/IWRS) using the strata option of the SAS logistic procedure. The logistic regression procedure will be used to compare treatment group differences, with the model containing treatment group and corresponding baseline value(s) as covariate, stratified by randomization strata defined as per IVRS/IWRS. Combined estimates of odds ratio versus placebo, 95% CI, and p-value will be obtained through the SAS MIANALYZE procedure.

In the data dependent case such logistic regression is not applicable (e.g. the response rate is zero in one treatment arm and thus the maximum likelihood estimate may not exist), the last observation carried forward (LOCF) approach would be used for handling of missing values. Treatment effects would be compared using the stratified exact conditional logistic regression method, specifically using the strata option of the SAS logistic procedure (with strata defined as randomized in the IVRS/IWRS). In case the model would not converge with stratification variables, an unstratified exact logistic regression will be performed. The LOCF imputation method will consist of using the last value obtained up to the week 16 efficacy analysis window to impute the missing week 16 value.

In case of computing issues with exact logistic regression, the baseline level(s) will be entered in the model as a categorical variable(s) using quartiles. Exact odds ratio versus placebo, 95% CI, and p-value will be provided.

5.7.2.4. Sensitivity Analysis of Secondary Endpoint Variables

In order to assess the robustness of more clinically relevant between group comparisons for the analysis of the secondary efficacy endpoints, the same statistical analysis method approach as described above in Sec 5.7.2 will be applied in the mITT population. The intent-to-treat estimand will be replaced by the on-treatment estimand, which is defined as all secondary efficacy endpoints values collected during the efficacy treatment period (Section 3.1.2).

5.7.2.5. Summary of Results by Time Point

Central laboratory values (in conventional (US) and international units), percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units) will be summarized at protocol scheduled visits by treatment group for calculated LDL-C, Total-C, fasting TG, non-HDL-C, Apo B, and Lp(a). Summaries will include both the ITT and mITT populations. The time profile of each parameter will be plotted by treatment group with the corresponding standard errors. Further details are described below:

- For lipids other than TG and Lp(a): LS mean and SE for each treatment group, obtained from the same MMRM models as used for endpoints above and including

planned time points (see Section 5.7.2.1) and with raw values, changes from baseline, and percent change from baseline as response variable in the model as appropriate.

- For lipids other than TG and Lp(a): Observed data raw values, change from baseline (as applicable), and percent change from baseline response variables will be summarized by patient counts, mean and SD for each treatment group at all planned time points.
- For TG and Lp(a): mean and SE for each treatment group obtained from multiple imputation approach followed by the robust regression models as used for endpoints above and including planned time points (see Section 5.7.2.2) and with raw values or percent changes from baseline as response variable in the model as appropriate.
- For TG and Lp(a): Observed data raw values and percent change from baseline response variables will be summarized by patient counts, mean, SD, median, Q1, and Q3 for each treatment group at all planned time points.

During the OLTP, efficacy variables for Group B will be explored through descriptive statistics at each protocol scheduled visit for the total patients administered open-label study treatment (total), as well as by the patient subgroups of study treatment received in the double-blind treatment period (i.e., 5 mg/kg IV evinacumab, 15 mg/kg IV evinacumab, placebo). Formal statistical testing is not planned. Descriptive statistics will include the observed values of the same parameters as described for each variable in the DBTP, for patients in the open-label safety analysis set.

For Group B patients receiving evinacumab in the DBTP, a combined summary including both the DBTP and OLTP 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 open-label treatment will need to be taken into consideration when combining longitudinal efficacy data. Formal statistical testing is not planned. 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.

5.8. Analysis of Safety Data

In general, for the double-blind period, the summary of safety results for patients in the double-blind SAF population will be presented by route of administration (Group A or Group B) and pooling the evinacumab dose regimens within each route of administration (Group A or Group B), with the intent to maximize efforts to identify potential safety signals. The treatment group data (individual evinacumab dose regimens and placebo) will also be presented with the intent to support the pooled dose regimens. No formal inferential testing will be performed. Summaries will be descriptive in nature.

For Group B, summaries of safety results for the open-label period will be presented for patients in the open-label SAF, by the total number of patients administered open-label study treatment (i.e.,15 mg/kg IV), as well as by the patient subgroups of study treatment received in the DBTP (i.e., 5 mg/kg IV, 15 mg/kg IV, or placebo). Summaries will be descriptive in nature.

General common rules

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

- For DBTP, safety data in patients who do not belong to the double-blind 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 10.4]). 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.
- 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.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to Global Analysis Windows defined in Appendix 10.2 in order to provide an assessment for the screening visit through follow-up visit time points.
- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize observed values and change from baseline values by visit.

5.8.1. Adverse Events

In general, the primary focus of AE reporting will be on TEAEs summarized in respective TEAE periods, specifically the DBTP and OLTP.

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

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by SOC and PT. In addition, incidence tables by SOC, HLGT, HLT, and PT will be provided for all TEAEs, serious TEAEs, and TEAE leading to permanent treatment discontinuation. Multiple occurrences of the same event in the same patient will be counted only once in a table. 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 pooled 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, HLGT, HLT, and PT
- All TEAEs by primary SOC and PT
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC and PT (PT incidence ≥ 5 % in any treatment group)
- All TEAEs relationship (related/not related) to evinacumab
- All TEAEs by maximum severity (i.e., mild, moderate or severe)
- For the OLTP only, the event rate per patient-year (the number of patients with an event in question divided by total patient-years) will be provided for all TEAEs by SOC and PT. For a patient with an event, patient-year is censored at time of first event. For a patient without an event, patient-year corresponds to the length of the TEAE period.
- A common TEAE related to any clinically significant signal will be further characterized as appropriate. The characterization of the clinically significant signal can include Kaplan-Meier curves for time from first dose to first occurrence of selected TEAE, time to resolution, and event duration. Patients without any event will be censored at the end of the respective TEAE period.

Analysis of all treatment emergent serious adverse event(s)

- All Serious TEAEs by primary SOC, HLGT, HLT, and PT
- All Serious TEAEs by primary SOC and PT
- Patient listings of serious TEAEs will be provided in the report appendix.
- All Serious TEAEs relationship (related/not related) to evinacumab
- A serious TEAE related to any clinically significant signal will be further characterized as appropriate. The characterization of the clinically significant signal can include Kaplan-Meier curves for time from first dose to first occurrence of

selected TEAE, time to resolution, and event duration. Patients without any event will be censored at the end of the respective TEAE period.

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

- All TEAEs leading to permanent treatment discontinuation, by primary SOC, HLGT, HLT, and PT
- All TEAEs leading to permanent treatment discontinuation, by primary SOC and PT
- Patient listings of TEAEs leading to permanent treatment discontinuation will be provided in the report appendix.
- A TEAE leading to permanent treatment discontinuation and related to any clinically significant signal will be further characterized as appropriate. The characterization of the clinically significant signal can include Kaplan-Meier curves for time from first dose to first occurrence of selected TEAE, time to resolution, and event duration. Patients without any event will be censored at the end of the respective TEAE period.

Analysis of Cardiovascular events

- TEAEs suspected of being CV events by primary SOC and PT
- TEAEs suspected of being CV events categorized by adjudicated outcome of positive, negative, or in-process (as applicable)
- Number of patients with adjudication positive by outcome categories, specifically CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, ischemia driven coronary revascularization procedure
- Patient listing of positively adjudicated TEAE CV events

Patient Deaths

The following summaries of deaths will be generated.

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

5.8.2. Analysis of Adverse Events of Special Interest

Treatment-emergent adverse events of special interest (AESI), as listed in Section 4.8.1.2, will be presented by SOC and PT as applicable. AESI are defined by SMQ, CMQ, lab data, and/or dedicated e-CRF as described in Appendix 10.3.

For Group B, the following variables will also be tabulated for infusion reactions TEAEs:

- Intensity of the event (mild, moderate, or 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 OLTP depending on the analysis) to first infusion reaction;

For Group A, the following variables will also be tabulated for injection reactions TEAEs:

- Intensity of the event (mild, moderate, or severe);
- Number of events divided by the number of study treatment administrations received in DBTP treatment period;
- Time from first study treatment administration to first injection reaction;
- Description of the highest intensity of each symptom recorded in the specific e-CRF page with table and bar chart.

5.8.3. Clinical Laboratory Measurements

The following definitions will be applied to laboratory parameters:

- Double-blind treatment period: The treatment period used for quantitative analysis in the double-blind period is defined as the day after the first study drug administration to the day of the last double-blind study drug injection + 7 days for Group A. For Group B, the treatment period is defined from the day after the first administration of double-blind study treatment to the day of the last administration of double-blind study treatment + 28 days for those patients not proceeding into the open-label treatment period, or up to the day of the first open-label study treatment administration for those patients proceeding into the open-label treatment period.
- Open-label treatment period: The treatment period used for quantitative analysis in the open-label study period is defined from the day after the first dose of open-label study treatment to the day of the last dose of open label study treatment + 28 days.

For respective treatment period (DBTP and OLTP), clinical laboratory parameter actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit 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 10.4), 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 OLTP), 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.

5.8.4. Analysis of Vital Signs

The following definitions will be applied to vital signs parameters:

- Double-blind treatment period: The treatment period used for quantitative analysis in the double-blind period is defined as the day after the first study drug administration to the day of the last double-blind study drug injection + 7 days for Group A. For Group B, the treatment period is defined from the day after the first administration of double-blind study treatment to the day of the last administration of double-blind study treatment + 28 days for those patients not proceeding into the open-label treatment period, or up to the day of the first open-label study treatment administration for those patients proceeding into the open-label treatment period.
- Open-label treatment period: The treatment period used for quantitative analysis in the open-label study period is defined from the day after the first dose of open-label study treatment to the day of the last dose of open label study treatment + 28 days.

For respective treatment period (DBTP and OLTP), the vital sign actual values and change from baseline values obtained while sitting will be descriptively summarized at baseline and each post-baseline visit 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.

5.8.5. Analysis of 12-Lead ECG

The following definitions will be applied to ECG parameters:

- Double-blind treatment period: The treatment period used for quantitative analysis in the double-blind period is defined as the day after the first study drug administration to the day of the last double-blind study drug injection + 7 days for Group A. For Group B, the treatment period is defined from the day after the first administration of double-blind study treatment to the day of the last administration of double-blind study treatment + 28 days for those patients not proceeding into the open-label treatment period, or up to the day of the first open-label study treatment administration for those patients proceeding into the open-label treatment period.
- Open-label treatment period: The treatment period used for quantitative analysis in the open-label study period is defined from the day after the first dose of open-label study treatment to the day of the last dose of open label study treatment + 28 days.

For respective treatment period (DBTP and OLTP), 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

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

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

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

5.8.6. Physical Exams

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

5.9. Analysis of Other Variables

In general, for the double-blind period, the summary of results for other variables for patients in the double-blind SAF population will be presented by route of administration (Group A or Group B) and pooling the evinacumab dose regimens within each route of administration (Group A or Group B), with the intent to maximize efforts to identify potential safety signals. The treatment group data (individual evinacumab dose regimens and placebo) will also be presented with the intent to support the pooled dose regimens. No formal inferential testing will be performed. Summaries will be descriptive in nature.

For Group B, summaries of safety results for the open-label period will be presented for patients in the open-label SAF, by the total number of patients administered open-label study treatment (ie.,15 mg/kg IV), as well as by the patient subgroups of study treatment received in the DBTP (ie., 5 mg/kg IV, 15 mg/kg IV, or placebo). No formal inferential testing will be performed for either period. Summaries will be descriptive in nature.

All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to Global Analysis Windows (Appendix 10.2) in order to provide an assessment for all post-baseline visit.

Hs-CRP, HbA1c, and HDL-C parameters will be summarized for the number of patients with data, mean, SD, median, minimum, maximum, Q1 and Q3 by analysis visit during the treatment period. The medians (with Q1-Q3) will be plotted for hs-CRP. The means (+/-SE) will be plotted for HbA1c and HDL-C. In addition, HbA1C will be summarized at each visit by diabetic status as recorded in the medical history e-CRF page (regardless of the ongoing status). Applying the

PCSV criteria to HbA1c at any time during the TEAE period, the number of patients (and percentages) meeting the criteria will be summarized.

5.10. Analysis of Pharmacokinetic and Pharmacodynamic Variables

Descriptive statistics of concentrations of total evinacumab and total ANGPTL3 will be presented. For the determination of arithmetic means and descriptive statistics, individual concentration values below the LLOQ, will be set to zero. If geometric means are determined, individual concentrations values below the LLOQ will be imputed as LLOQ/2.

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 LDL-C or other biomarkers may be evaluated descriptively.

5.11. Analysis of Anti-evinacumab Antibody Variables

The ADA variables described in Section 4.11 will be summarized by dose/cohort group in the ADA analysis set. Listings of ADA results and titers values presented by patient, time point, and study treatment received will be provided. Prevalence 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 and titer over the study duration may be classified as follows:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 9-fold over baseline titer levels.
- Treatment emergent - defined as any post-dose ADA positive response when baseline results are negative or missing.
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point analyzed only, regardless of any missing samples
  - Transient - Not persistent or indeterminate regardless of any missing samples
- Treatment boosted - defined as any post-dose ADA response 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)

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 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. Data Handling Convention for Efficacy Variables

Rules for handling missing data for primary and secondary efficacy variables are described in Section 5.7.1 and Section 5.7.1.4.

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. Visit Windows

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

6.5. Unscheduled Assessments

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

6.6. Pooling of Centers for Statistical Analyses

The randomization scheme was not stratified by center because the primary efficacy variable is centrally assessed and expected not to be influenced by the center when other factors such as diet are already controlled. Therefore, the center will not be added as factor in the primary analysis model.

6.7. Statistical Technical Issues

Not Applicable.

7. TIMING OF STATISTICAL ANALYSES

7.1. First Step: Group B Main Efficacy and Safety Analysis

The first analysis will be conducted when all Group B patients have been randomized and all data through week 24 has been collected and validated for these patients. This will consist of the final efficacy analysis of the primary and secondary endpoints for the Group B patients. The Group B safety analysis will be performed on all double-blind safety data and any open-label safety data collected and validated at the time of the first step analysis.

The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. This first analysis may be used for submission to health authorities.

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

7.2. Second Step: Group A Main Efficacy and Safety Analysis

The second analysis will be conducted when all Group A patients have been randomized and all data through week 16 has been collected and validated for these patients. This will consist of the final efficacy analysis of the primary and secondary endpoints for the Group A patients. The Group A and Group B (open-label period) safety analyses will be performed on all safety data collected and validated at the time of the second step analysis.

Results of the second analysis will not be used to change the conduct of the ongoing study in any aspect. This second analysis may be used for submission to health authorities.

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

7.3. Third Step: Final Safety Analysis

The third analysis will be conducted at EOS and will consist of the final safety analysis through the follow-up period (week 39 for Group A and week 92 for Group B).

7.4. Additional Rules

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 first and second step analyses:

- Any lipid assessments within efficacy analysis windows up to the week 24 visit for Group B and week 16 visit for Group A will be taken into account (may include few unscheduled lipid data soon after the cut-off date).

- 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 respective data 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-study deaths and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the data 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 data cut-off date.

8. SOFTWARE

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

9. REFERENCES

1. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
2. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012 Oct 4;367(14):1355-60. doi: 10.1056/NEJMsr1203730.
3. Mehrotra DV, Li X, Liu J, Lu K. Analysis of longitudinal clinical trials with missing data using multiple imputation in conjunction with robust regression. Biometrics. 2012 Dec;68(4):1250-9. doi: 10.1111/j.1541-0420.2012.01780.x.
4. Kieser M, Friede T. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. Stat Med. 2003; 22(23): 3571-81.

10. APPENDIX

10.1. Summary of Statistical Analyses

Primary Efficacy Analysis:

Endpoint	Analysis Populations	Estimand	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
Percent change from baseline in calculated LDL-C at week 16	ITT	ITT estimand: The calculated LDL-C at week 16 will be the LDL-C value obtained within the week 16 efficacy analysis window, regardless of adherence to treatment and subsequent therapies.	MMRM	Yes	Yes	1. mITT 2. PMM (randomized population) 3. MMRM using strata based on observed data

10.2. Windows for Analysis Time Points

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

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

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

Table 1 Global Analysis Windows for Group B (IV)

Visit label	Targeted Study Day	Targeted Open-Label Study Day	Analysis Window in Study Day
Screening	< Day 1	N/A	Measurement obtained prior to first study treatment, and not defined as baseline visit
Baseline	1	N/A	Measurement obtained closest to first study treatment, while remaining prior to first study treatment
Week 2	15	N/A	2 to 21
Week 4	29	N/A	22 to 35
Week 6	43	N/A	36 to 49
Week 8	57	N/A	50 to 70
Week 12	85	N/A	71 to 98
Week 16	113	N/A	99 to 128
Week 20	141	N/A	129 to 154
Week 24	169	Day 1	155 to 182
Week 28	197	29	183 to 210
Week 32	225	57	211 to 238
Week 36	253	85	239 to 266
Week 40	281	113	267 to 294
Week 44	309	141	295 to 322

Visit label	Targeted Study Day	Targeted Open-Label Study Day	Analysis Window in Study Day
Week 48	337	169	323 to 350
Week 52	365	197	351 to 378
Week 56	393	225	379 to 406
Week 60	421	253	407 to 434
Week 64	449	281	435 to 462
Week 68	477	309	463 to 490
Week 72	505	337	491 to 518
FU – W4	For patients prematurely discontinued trt: last study trt + 28 days For patients completed OLTP: 533	For patients prematurely discontinued trt: last study trt + 28 days For patients completed OLTP: 365	For patients prematurely discontinued trt: last study trt to 56 days after last study trt For patients completed OLTP: 519 to 560
FU – W12	For patients prematurely discontinued trt: last study trt + 84 days For patients completed OLTP: 589	For patients prematurely discontinued trt: last study trt + 84 days For patients completed OLTP: 421	For patients prematurely discontinued trt: 57 days after to 112 days after last study trt For patients completed OLTP: 561 to 616
FU – W20	For patients prematurely discontinued trt: last study trt + 140 days For patients completed OLTP: 645	For patients prematurely discontinued trt: last study trt + 140 days For patients completed OLTP: 477	For patients prematurely discontinued trt: 113 days after to 168 days after last study trt For patients completed OLTP: 617 to 672
FU > W20	N/A	N/A	For patients prematurely discontinued trt: >168 days after last study trt For patients completed OLTP: > 672
Study days are calculated from the day of first double-blind IMP infusion, the day of first double-blind IMP infusion being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.			

Table 2 Efficacy Analysis Windows – Statistical Testing for Group B (IV)

Visit Label	Targeted study day	Analysis window in study days
Screening	< Day 1	Measurement obtained prior to first study treatment, and not defined as baseline visit
Baseline	1	Measurement obtained closest to first study treatment, while remaining prior to first study treatment
Week 2	15	2 to 21
Week 4	29	22 to 35
Week 6	43	36 to 49
Week 8	57	50to 70
Week 12	85	71 to 98
Week 16	113	99 to 128
Week 20	141	129 to 154
Week 24	169	155 to 182

Table 3 Global Analysis Windows for Group A (SC)

Visit label	Targeted Study Day	Analysis Window in Study Day
Screening	< Day 1	Measurement obtained prior to first study treatment, and not defined as baseline visit
Baseline	1	Measurement obtained closest to first study treatment, while remaining prior to first study treatment
Week 1	8	2 to 11
Week 2	15	12 to 18
Week 3	22	19 to 25
Week 4	29	26 to 32
Week 5	36	33 to 39
Week 6	43	40 to 46
Week 7	50	47 to 53
Week 8	57	54 to 60
Week 9	64	61 to 67
Week 10	71	68 to 74
Week 11	78	75 to 81
Week 12	85	82 to 88
Week 13	92	89 to 95

Visit label	Targeted Study Day	Analysis Window in Study Day
Week 14	99	96 to 102
Week 15	106	103 to 109
Week 16	113	110 to 140
FU – W8	For patients prematurely discontinued trt: last study trt + 56 days For patients completed DBTP: 169	For patients prematurely discontinued trt: last study trt to 84 days after last study trt For patients completed DBTP: 141 to 196
FU – W16	For patients prematurely discontinued trt: last study trt + 112 days For patients completed DBTP: 225	For patients prematurely discontinued trt: 85 days after last study trt to 137 days after last study trt For patients completed DBTP: 197 to 249
FU – W23	For patients prematurely discontinued trt: last study trt + 161 days For patients completed DBTP: 274	For patients prematurely discontinued trt: 138 days after last study trt to 186 days after last study trt For patients completed DBTP: 250 to 298
FU > W23	N/A	For patients prematurely discontinued trt: >186 days after last study trt For patients completed DBTP: > 298

Table 4 Efficacy Analysis Windows – Statistical Testing for Group A (SC)

Visit label	Targeted Study Day	Analysis Window in Study Day
Screening	< Day 1	Measurement obtained prior to first study treatment, and not defined as baseline visit
Baseline	1	Measurement obtained closest to first study treatment, while remaining prior to first study treatment
Week 2	15	12 to 21
Week 4	29	22 to 35
Week 6	43	36 to 49
Week 8	57	50 to 63
Week 10	71	64 to 77
Week 12	85	78 to 91
Week 14	99	92 to 106
Week 16	113	107 to 126

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

Table 3 Summary of AESIs and the Methods of Data Collections and Derivations

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
Hepatic Disorders	No	• SMQ Drug-related hepatic disorder • Potentially clinically significant value (PCSV) in Appendix 10.4, • Hy's law eDISH plot,
Pregnancy	Yes	No
Symptomatic overdose with investigational medicinal product	Yes	No
Neurocognitive events	No	CMQ for neurocognitive events as define based on Regulatory Agency request for another lipid lowering program (See Table 4

AESI	Using an e-CRF specific tick box on AE page	Using Standard MedDRA Query (SMQ)/company MedDRA Query (CMQ) or lab data
		in Appendix 10.3 for the list of terms)
Neurologic events	Yes	No
New onset of diabetes (NOD)	No	No medical history of diabetes as specified in "Cardiovascular History and Cardiovascular Risk Factors" CRF page AND one of the following criteria: • Lab criteria: 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*** • Lab criteria: 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

AESI	Using an e-CRF specific tick box on AE page	Using Standard MedDRA Query (SMQ)/company MedDRA Query (CMQ) or lab data
		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. ***OR*** • HLT Diabetes mellitus (incl subtypes) ***OR*** • Initiation of any new concomitant medication for hyperglycemia during the treatment period
Diabetes mellitus or diabetic complications	No	• HLGT "diabetes complications" (including PTs pertaining to the secondary SOC included in the HLGT), HLT "diabetes mellitus", and HLT "carbohydrate tolerance analyses (incl diabetes)" excluding PTs "blood glucose decreased" and "Glycosylated haemoglobin decreased" and including the PTs "hyperglycaemia", "Hyperglycaemic unconsciousness" and "Hyperglycaemic seizure" from the HLT "Hyperglyceamic conditions NEC"

AESI	Using an e-CRF specific tick box on AE page	Using Standard MedDRA Query (SMQ)/company MedDRA Query (CMQ) or lab data
		• Changes in diabetic medication dosage (specifically increases in dosage) or initiation of additional diabetic medication
Pancreatitis	Yes	No
Cataracts	No	HLT Cataract conditions
Immune complex diseases	No	SMQ (Narrow) Systemic lupus erythematous SMQ (Narrow) Vasculitis SMQ (Narrow) Guillain-Barre syndrome
Muscle events/CK elevation	No	• Lab data analyses (e.g. PCSV) • All preferred terms under system organ class (SOC): Musculoskeletal and connective tissue disorders • Rhabdomyolysis/myopathy (Narrow SMQ)

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
PTCD	Confusional State

MedDRA level	MedDRA Term Label
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
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

10.4. 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
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)

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
Orthostatic Hypotension	SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg
Weight	≥5% increase versus baseline ≥5% decrease versus baseline
ECG parameters	
HR	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
PR	≥220 ms and increase from baseline ≥20 ms
QRS	≥ 120 ms
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Borderline 431-450 ms (Male) 451-470 ms (Female) Prolonged* > 450 ms (Male) > 470 ms (Female) QTc ≥500 ms <u>Increase versus baseline</u> (Males and Females) Borderline Δ 30-60 ms Prolonged * Δ > 60 ms

10.5. Detailed Description of the Multiple Imputation Procedure

The following is a detailed description of the multiple imputation procedure which will be used for analysis of the secondary efficacy endpoints.

In general, the missing pattern is anticipated to be not monotone, a two-step approach will be used:

- Step 1: the MCMC method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern. Set the SEED=1643 option in SAS MI procedure
- Step 2: Using the monotone data set from step 1, missing data will be imputed using the regression method. Set the SEED=3461 option in SAS MI procedure

The imputation model for step 1 will include the treatment group and the values of the analyzed parameter at baseline and planned time-points up to week 24/week 16.

The imputation model for step 2 will include the same variables as in step 1 with the following additional variables:

- the randomization strata;
- age, BMI, and gender (age and BMI included as continuous variables).

Non-continuous variables included in the imputer's model (i.e., treatment group, randomization strata and gender) are not expected to be missing.

In addition, for continuous efficacy variables anticipated to have a non-normal distribution (i.e. TG and Lp(a)), data will be log-transformed before imputation process and then back-transformed to create the imputed data sets using the TRANSFORM statement of SAS MI procedure.

For variables other than those continuous efficacy variables anticipated to have a non-normal distribution (i.e. TG and Lp(a)), for each simulation leading to negative imputed value, another value will be redrawn using MINIMUM option of SAS MI procedure.

The number of imputations (100) will be informally verified by replicating sets of 100 imputations and checking whether the combined results are stable. If not stable, the number of imputations will be increased and informally checked as above, and thus continued until stable estimates are obtained.

10.6. Detailed Description of Pattern Mixture Model

As a sensitivity analysis of the primary efficacy endpoint (i.e. percent change from baseline to Week 16 in LDL-C), a pattern-mixture model approach will be used, with a different imputation strategy applied for missing LDL-C values during the on-treatment period (i.e. within the time period from the first double-blind study treatment administration up to the day of the last double-blind study treatment administration +35 days or to the day before the first open-label study treatment administration, whichever comes first for Group B or +14 days for Group A) and missing LDL-C values after treatment discontinuation (i.e. after the day of last study treatment

administration +35 days for Group B or +14 days for Group A) based on the following assumptions:

- Patients within 35 days for Group B or 14 days for Group A of their last study treatment administration would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, LDL-C values missing during the on-treatment period will be considered "Missing at Random" and imputed using a model estimated using all samples collected on treatment.
- Patients who stopped taking their study treatment no longer benefited from it in the future, and thus tended to have LDL-C values returning to baseline. Thus LDL-C values missing after treatment discontinuation will be imputed based on patient's own baseline value.

The assumptions for this approach are based on the following considerations:

- Missing values during the on-treatment period are mostly consecutive to:
  - Visits performed outside of the pre-specified time-window
  - No blood sample available although visit was done
  - LDL-C not measurable due to technical reasons

  In addition, these missing data are often intermittent, i.e. followed by LDL-C values collected at subsequent visits. It is therefore considered reasonable to assume that these missing data were "At Random".

Missing LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to Week 16 will be derived from observed and imputed LDL-C at this time point. The completed data sets will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and randomization strata as fixed effects, and the baseline LDL-C value as continuous covariate. The results from the 100 analyses will be combined using Rubin's formulae. If necessary, the number of imputations (100) will be increased until stable estimates are obtained.

Imputation of missing data during the on-treatment period

Missing LDL-C values during the on-treatment period will be imputed from other on-treatment measurements assuming Missing At Random, using SAS® MI procedure.

Only LDL-C values collected during the on-treatment period will be included in the imputation model. This way, missing LDL-C values during the on-treatment period will be imputed based solely on observed on-treatment LDL-C values.

The imputation model will include the treatment arm, baseline LDL-C value, and all LDL-C values at pre-specified visits. Since the pattern of missing data will necessarily be non-monotone, a Monte-Carlo Markov Chain (MCMC) method will be used. A minimum value of 0 will be specified in order to avoid negative imputed LDL-C values.

A sample SAS code is provided below:

```
proc mi data=DATAIN out=DATAOUT nimpute=100 minimum=. 0 0 0 0 0 0 0 0 SEED=1643;
```

```
mcmc impute=monotone;
var ARM LDL_BASE LDL_W2 LDL_W4 LDL_W8 LDL_W12 LDL_W16;
run;
```

As stated above, the input dataset DATAIN will include only LDL-C values collected during the on-treatment period. Any LDL-C values collected during the post-treatment period will be excluded from the input dataset. In practice, the MI procedure will generate imputed values for all missing values (whether on-treatment or post-treatment), but only imputed values during the-on-treatment period will be kept in the final datasets that will be analyzed using ANCOVA. Imputed values during the post-treatment period will be discarded and replaced by imputed values described in the next paragraph.

Imputation of missing data after treatment discontinuation

Missing LDL-C values during the post-treatment period will be imputed assuming LDL-C values would on average return to baseline values.

For each patient, missing post-treatment LDL-C values will be imputed 100 times, using a random draw from a normal distribution (SEED=3461), with mean equal to patient's own baseline value and variance equal to the conditional variance at the specific time-point, given the baseline value.

Let Y_0 and Y_1 denote the LDL-C at baseline and at the specific time-point respectively. Since Y_0 and Y_1 are assumed to have a bivariate normal distribution, the conditional variance of Y_1 given Y_0 is:

$$Var(Y_1 | Y_0 = y_0) = \sigma_1^2(1-\rho^2)$$

Where σ_1^2 denotes the variance of Y1 and ρ the coefficient of correlation between Y_0 and Y_1.

The conditional variance will be estimated from observed data within the same treatment arm at the specific time-point.

During the random generation process, a minimum value of 0 will also be applied in order to avoid negative imputed LDL-C values.

10.7. Schedule of Time and Events

Table 1: Screening Schedule of Events – Patients Requiring Medication Change or Daily Statin Stabilization at Study Entry

Visit Number	Visit 1a Pre-Screening	Visit 1 Full Screening Visit
Visit Window (Day)		**Day -14 to -1**
Week		**-2**
Screening/Baseline:		
Informed Consent	X	
[redacted]	X	
Medication Adjustment	X	
Inclusion/Exclusion	X	X
Medical History/Surgical History, Alcohol Habits, Smoking Habits		X
Demographics		X
Treatment:		
Concomitant Medications	X	X
Query LMT compliance	X	X
Safety:		
Height		X
Weight		X
Vital Signs		X
Physical Examination		X
Electrocardiogram[3]		X
Contraception Use Reminder[1]	X	X
Adverse Events	X	X
Laboratory Testing[2]:		
Hematology		X
Chemistry		X
Urinalysis		X
Core Lipid Panel (8-hour fasting sample)	X	X
HbA1c	X	X
Pregnancy Test	Urine	Serum
Hepatitis B and C serology		X
TSH		X
FSH		X
PK and Ab Samples:		
Research Samples (biomarkers)		X
Other:		
Review of diet	X	X

Table 2: Screening Schedule of Events – Patients on Stable Statin, PCSK9 Inhibitor Antibody and Lipid Modifying Therapy Regimen at Study Entry

Visit Number	Visit 1 Screening Visit
	Day-14 to -1
Screening/Baseline:	
Informed Consent	X
[redacted]	X
Inclusion/Exclusion	X
Medical/Surgical History, Alcohol habits, Smoking habits	X
Demographics	X
Treatment:	
Concomitant Medications	X
Query LMT compliance	X
Safety:	
Height	X
Weight	X
Vital Signs	X
Physical Examination	X
Electrocardiogram[3]	X
Contraception Use Reminder[1]	X
Adverse Events	X
Laboratory Testing[2]:	
Hematology	X
Chemistry	X
Urinalysis	X
Core Lipid Panel (8-hour fasting sample)	X
HbA1c	X
Pregnancy Test	Serum
Hepatitis B and C serology	X
TSH	X
FSH	X
PK and Ab Samples:	
Research samples (biomarkers)	X
Other:	
Review of diet	X

Table 3: Schedule of Events for SC Treatment Group A

	Double-Blind Treatment Period																
	Visit 2	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18/ EOT**
Day	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**
Visit Window (Day)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Screening/Baseline:																	
Randomization	X																
Treatment:																	
Administer SC Study Drug[4, 7, 8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Query LMT compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety:																	
Weight	X								X								X
Vital Signs[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination																	X
Electrocardiogram[3]																	X
Contraception Use Reminder[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[2]:																	
Hematology	X		X		X				X				X				X
Chemistry	X		X		X				X				X				X
Urinalysis	X		X		X				X				X				X
Core Lipid Panel	X		X		X		X		X		X		X		X		X
Specialty Lipid Panel	X				X				X				X				X

	Double-Blind Treatment Period																
	Visit 2	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18/ EOT**
Day	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**
Visit Window (Day)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
HbA1c																	X
hs-CRP	X								X								X
Pregnancy Test	U				U				U				U				U
PK and Research Samples:																	
PK (evinacumab, alirocumab)[4], ANGPTL3, PCSK9 sample	X	X	X		X				X		X		X				X
Anti-evinacumab antibody sample	X				X												X
Research samples (biomarkers)	X						X						X				X
LDL-R function sample[5]	X																
[redacted]	X		X														
[redacted]	X																
Other:																	
Review of low fat diet	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4: Schedule of Events for IV Treatment Group B

	Double Blind Treatment Period									Open-Label Treatment Period					
	Visit 2	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**End of DBTP Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**
Day	**1**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (Day)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Week	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Screening/Baseline:															
Randomization	X														
Treatment:															
Administer Double-Blind IV Study Drug[4,7]	X		X		X	X	X	X							
Administer Open-Label IV Study Drug[4,7]									X#	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Query LMT compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety:															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination									X						
Electrocardiogram[3]									X						X
Contraception Use Reminder[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[2]:															
Hematology	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Core Lipid Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Specialty Lipid Panel	X		X		X	X	X	X	X	X	X	X	X	X	X
HbA1c						X			X			X			X
hs-CRP	X					X			X			X			X
Pregnancy Test	U		U		U	U	U	U	U	U	U	U	U	U	U

	Double Blind Treatment Period									Open-Label Treatment Period					
	Visit 2	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**End of DBTP Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**
Day	**1**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (Day)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Week	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
PK and Research Samples:															
PK (evinacumab, alirocumab)[4], ANGPTL3, and PCSK9	X	X	X	X	X		X		X			X			X
Anti-evinacumab antibody sample	X		X			X			X			X			X
Research samples (biomarkers)	X			X		X			X			X			X
LDL-R function sample[5]	X														
[redacted]	X	X													
[redacted]	X														
Other:															
Review of low fat diet	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5: Schedule of Events for IV Treatment Group B (Continued for Open-Label)

	Open-Label Treatment Period - Continued (Group B)					
	Visit 17	**Visit 18**	**Visit 19**	**Visit 20**	**Visit 21**	**End of Open-Label Visit 22**
Day	**365**	**398**	**421**	**449**	**477**	**505**
Visit Window (Day)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Week	**52**	**56**	**60**	**64**	**68**	**72**
Treatment:						
Administer Open-Label IV Study Drug[4, 7]	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X
Query LMT compliance	X	X	X	X	X	X
Safety:						
Weight	X	X	X	X	X	X
Vital Signs[11]	X	X	X	X	X	X
Contraception Use Reminder[1]	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X
Laboratory Testing[2]:						
Hematology			X			X
Chemistry			X			X
Urinalysis			X			X
Core Lipid Panel	X	X	X	X	X	X
Specialty Lipid Panel			X			X
HbA1c			X			X
hs-CRP			X			X
Pregnancy Test	U	U	U	U	U	U
PK and Research Samples:						
PK (evinacumab, alirocumab)[4], ANGPTL3, and PCSK9			X			X
Anti-evinacumab antibody sample			X			X
Research samples (biomarkers)			X			X
Other:						
Review of low fat diet	X	X	X	X	X	X

Table 6: Follow-up Schedule of Events for SC Treatment Group A

	Follow-up Period					
	Phone[10] Visit 19	**Visit 20**	**Phone[10] Visit 21**	**Visit 22**	**Phone[10] Visit 23**	**Visit 24/ EOS**
Day	**141**	**169**	**197**	**225**	**253**	**274**
Visit Window (Day)	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Week	**20**	**24**	**28**	**32**	**36**	**39**
Treatment:						
Concomitant Medications	X	X	X	X	X	X
Query LMT compliance	X	X	X	X	X	X
Safety:						
Weight						X
Vital Signs		X		X		X
Physical Examination						X
Electrocardiogram						X
Contraception Use Reminder[1]	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X
Laboratory Testing:						
Hematology		X		X		X
Chemistry		X		X		X
Urinalysis		X		X		X
Core Lipid Panel		X		X		X
Specialty Lipid Panel		X		X		X
HbA1c		X		X		X
hs-CRP						X
Pregnancy Test	U (home)[9]	U	U (home)[9]	U	U (home)[9]	S
PK and Research Samples:						
PK (evinacumab, alirocumab), ANGPTL3, PCSK9 sample		X		X		X
Anti-evinacumab antibody sample						X
Research samples (biomarkers)						X
Other:						
Review of low fat diet	X	X	X	X	X	X

Table 7: Follow-up Schedule of Events for IV Treatment Group B

	Follow-up Period				
	Visit 23	**Phone[10] Visit 24**	**Visit 25**	**Phone[10] Visit 26**	**EOS Visit 27**
Day	**533**	**561**	**589**	**617**	**645**
Visit Window (Day)	**±7**	**±7**	**±7**	**±7**	**±7**
Week	**76**	**80**	**84**	**88**	**92**
Treatment:					
Concomitant Medications	X	X	X	X	X
Query LMT compliance	X	X	X	X	X
Safety:					
Weight					X
Vital Signs	X		X		X
Physical Examination					X
Electrocardiogram					X
Contraception Use Reminder[1]	X	X	X	X	X
Adverse Events	X	X	X	X	X
Laboratory Testing:					
Hematology	X		X		X
Chemistry	X		X		X
Urinalysis	X		X		X
Core Lipid Panel	X		X		X
Specialty Lipid Panel	X		X		X
HbA1c			X		X
hs-CRP					X
Pregnancy Test	U	U (home)[9]	U	U (home) [9]	S
PK and Research Samples:					
PK (evinacumab, alirocumab), ANGPTL3, and PCSK9	X		X		X
Anti-evinacumab antibody sample					X
Research samples (biomarkers)					X
Other:					
Review of low fat diet	X	X	X	X	X

Footnotes for the Schedule of Events Tables

EOS = end of study; EOT = end of treatment; U = urine; Core lipid panel = TC, calculated LDL-C, HDL-C, TGs, and non-HDL-C; Specialty lipid panel = ApoB, ApoA-1, ratio ApoB/ApoA-1, and Lp(a).

1. All patients will be reminded of protocol-specified contraception use and pregnancy reporting.
2. All laboratory samples should be collected before the administration of study drug. All samples should be collected following at least an 8-hour fast.
3. Electrocardiograms should be performed before blood is drawn during visits requiring blood draws.
4. On dosing days, PK collection should occur pre-dose for group A and prior to IV infusion and at the end of the IV infusion for group B.
5. LDL-R function samples will be collected from a sub-set of patients based on enrollment and will be determined by IWRS.

[redacted]

7. For SC dosing, patients will be observed at the clinical site for at least 30 minutes following each SC study drug administration. For IV dosing, patients will be monitored for at least 60 minutes following the end of each IV study drug administration.
8. Starting at W1 and every odd visit week (ie, W3, W5, W7, etc) thereafter, visiting home nurses may administer study drug for those patients randomized to Group A.
9. WOCBP will be provided urine pregnancy tests with instructions to test for pregnancy at home.
10. All subjects will be contacted by phone to query LMT compliance, inquire about AEs or changes to concomitant medications, confirm required contraception use and remind patients of pregnancy reporting. Women of childbearing potential will report the results of their home urine pregnancy test. All patients will also be queried regarding their low fat diet.
11. Vital signs should be recorded prior to SC injection or IV infusion, and 30 minutes and 60 minutes post-IV infusion.

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