Clinical Development and Regulatory Affairs
Biostatistics and Data Management

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STATISTICAL ANALYSIS PLAN
VERSION: 1.0

A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia

Compound:	Evinacumab
Protocol Number:	R1500-CL-1629 Version 3B
Clinical Phase:	Phase 3
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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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
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
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-1629 study. The content of this SAP is inclusive of both the first and second step analyses as described in the protocol.

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

1.1. Background/Rationale

Homozygous familial hypercholesterolemia (HoFH) is a rare and serious genetic condition resulting in severely elevated low-density lipoprotein cholesterol (LDL-C) and accelerated cardiovascular disease (CVD). Familial hypercholesterolemia results from mutations in the low-density lipoprotein receptor (LDLR), or in 3 associated genes: proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (Apo B), and LDLR adaptor protein 1 (LDLRAP1).

Homozygous FH is frequently caused by mutations in both alleles of the LDLR gene and results in the decreased clearance of LDL particles from plasma. Patients with HoFH have severe hypercholesterolemia which can lead to an exceedingly high risk of developing premature atherosclerosis, as well as valvular and supravalvular stenosis. In children as young as 7 years of age, mild coronary atherosclerosis can be evident even without any clinically apparent coronary artery disease. This accelerated atherosclerosis results in premature CVD and an increased risk of a cardiovascular (CV) event.

Angiopoietin-like 3 (ANGPTL3) has recently emerged as a potential target for the treatment of elevated levels of triglycerides (TGs) and for the treatment of elevated levels of LDL-C, both risk factors for the development of CVD. ANGPTL3 acts as a natural inhibitor of lipoprotein lipase, an endothelial-bound enzyme involved in the hydrolysis of the TG content of very-low-density lipoproteins and chylomicron lipoproteins. Patients who are homozygous for loss-of-function (LOF) mutations in ANGPTL3 have lower levels of LDL-C (mean difference of 48% versus control family members).

Evinacumab (REGN1500) is a fully human mAb, 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 demonstrate the reduction of LDL-C by evinacumab 15 mg/kg intravenously (IV) in comparison to placebo after 24 weeks in patients with HoFH.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the effect of evinacumab 15 mg/kg IV on other lipid parameters (i.e., apolipoprotein [Apo B], non-high-density lipoprotein cholesterol [non-HDL-C, total cholesterol [TC]) in patients with HoFH)
- To evaluate the effect of evinacumab on LDL-C goal attainment
- To assess the effect of evinacumab on patients meeting eligibility criteria for apheresis (using German and US apheresis criteria)
- To evaluate the safety and tolerability of evinacumab 15 mg/kg IV in patients with HoFH
- To determine concentrations of evinacumab in patients with HoFH
- To evaluate the potential development of anti-evinacumab antibodies

1.2.3. Other Objectives

- Genotyping will be performed for all patients to identify mutations causing HoFH and to explore potential differences in efficacy and safety based on type of LDLR function variant.
- To assess the effect of evinacumab on quality of life using the EQ-5D and HADS QOL questionnaires.

1.2.4. Modifications from the Statistical Section in the Final Protocol

The summary of modifications is listed in the following table.

Item	Protocol Section	Description
1	10.3.2.1 Double-Blind Safety Analysis Set	SAP Section 3.2: The second item for determining the as-treated treatment group will be changed from "For patients receiving study drug from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be the one in which the patient was treated with the highest number of infusions." **to** For patients receiving study drug from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be evinacumab.

1.2.5. Revision History for Statistical Analysis Plan Amendments

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

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia (HoFH).

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a 2:1 ratio to receive evinacumab 15 mg/kg IV every 4 weeks (Q4W) or matching placebo IV Q4W for the 24-week double-blind treatment period (DBTP). The randomization will be stratified by apheresis treatment (Yes, No) and by region (Japan, Rest of World). After completion of the DBTP, all patients will enter a 24-week open-label treatment period (OLTP) and receive open-label evinacumab 15 mg/kg IV Q4W.

After completion of the 24-week OLTP, all patients who have successfully completed this study may have the opportunity to participate in a separate open-label (OL) study. All patients that enroll in the separate OL study will continue to receive open-label evinacumab at a dose of 15 mg/kg IV Q4W. Those patients who do not participate in the separate open-label study will undergo a 24-week follow-up after the last dose of study treatment.

The analyses will be conducted in 2 steps. The first analysis will be conducted as soon as all patients have been randomized and all data through week 24 (double-blind treatment period) has been collected and validated; this first analysis will consist of the final analysis of the double-blind primary and secondary efficacy endpoints. The safety analysis will be performed on all safety data collected and validated at the time of the first step analysis database lock. Since the double-blind primary efficacy measure data collection will have been concluded at the time of this first analysis, the significance level for the study remains at 0.05.

The second analysis will be performed with the data from the open-label treatment period and will consist of the final analysis for the safety and efficacy measures beyond week 24-time point.

The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. 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.

2.2. Sample Size and Power Considerations

For the primary efficacy hypothesis during the DBTP, a total sample size of 57 patients (38 on evinacumab and 19 on placebo) will have 90% power based on a two sample t-test to detect a treatment group difference in mean percent change LDL-C of 38% with a 0.05 two-sided significance level and assuming a common standard deviation of 35% using nQuery 7.0. This

sample size has been adjusted for a 5% non-evaluable patient rate for the primary efficacy endpoint, and a 15% dropout rate.

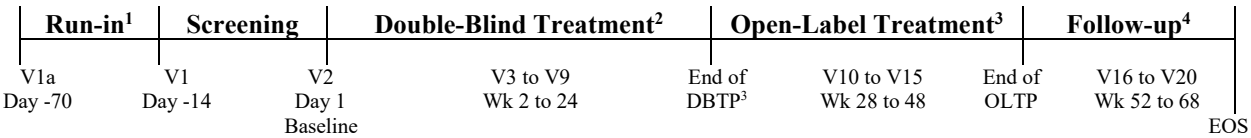
To gain experience with evinacumab in the population of Japanese patients, this study will plan to enroll up to 9 patients in Japan. Due to the rare patient population planned for evaluation, the sample size of 9 patients (15% of the planned study sample size) was chosen for practical reasons, centered on the feasibility to identify and enroll these patients into the trial. Based on the Ministry of Health, Labor, and Welfare 2007 "Basic Principles on Global Clinical Trials" method 1, a sample size of 12 (21%) will be needed to achieve 80% probability that the effect in Japan is at least ½ of the global effect. A sample size of 9 provides approximately 77% probability.

2.3. Study Plan

This study consists of the following periods: up to an 8-week run-in period (for patients who may require HoFH genotyping, for patients whose background medical lipid modifying therapy (LMT) has not been stable prior to screening or whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a 2-week screening period, a 24-week double-blind treatment period (DBTP), and a 24-week open-label treatment period (OLTP), and a 24-week follow-up period after the last dose of study drug for those patients who choose not to enter the open-label study (See Figure 1.)

The Study event table is presented in Appendix 10.9 .

Figure 1: Study Flow Diagram



[1] Patients who are undergoing apheresis therapy with a schedule and/or apheresis settings that have not been stable for at least 8 weeks before the screening visit will enter a run-in period before the screening period. Patients who are on background LMT that has not been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies) before the screening visit will enter the run-in period to stabilize their LMT before entering the screening period. Patients who have completed the R727-CL-1628 study and meet all the eligibility criteria for this study can be enrolled directly. The end of the open-label treatment visit from the R727-CL-1628 study can serve as the baseline/day 1 visit for this study.

[2] Patients will receive study drug IV Q4W starting at day 1.

[3] The open-label treatment period begins at week 24 (day 169) when all patients will receive evinacumab 15 mg/kg IV Q4W. The last dose of evinacumab will be at week 44.

[4] Follow-up only for patients who do not enter a separate, optional OL study, R1500-CL-1719 or prematurely discontinue study treatment in this study.

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), quality-of-life, 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 more than once in this trial, safety data from the first randomization will be included in the safety population, with safety data associated with the later randomization reported separately. Inclusion of efficacy data from the patient randomized more than once 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 is defined as all randomized patients who received at least one 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 (i.e., as randomized patient 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 as 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 24. The efficacy treatment period is defined as the time from the first double-blind study drug administration up to 35 days after the last double-blind study drug administration, 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 or evinacumab). In addition:

- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized.
- For patients receiving study drug from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be evinacumab.

3.3. Open-Label Safety Analysis Set

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).

3.5. The Anti-evinacumab Antibody Analysis Set

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

3.6. Quality-of-life Analysis Set

The analyses for quality of life in the respective treatment period (DBTP and OLTP) will be performed on all randomized patients who received any study treatment with a baseline and at least 1 post-baseline evaluation. Further for each scale:

- For EQ-5D, patients will be included when at least 1 post-baseline utility score is available.

- For HADS, patients will be included for each sub-scale (anxiety and depression) when at least 1 post-baseline sub-scale is available, and included for the total score when at least one post-baseline total score is available.

Treatment assignments for the DBTP are based on the treatment received (placebo or evinacumab).

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

For each patient, demographic and baseline characteristics will be obtained from the last available value up to the date of the first study treatment administration (i.e. baseline definition). For R727-CL-1628 patients who were immediately randomized into R1500-CL-1629, demographic and baseline characteristic measurements will be collected from the last assessment obtained in R727-CL-1628. For patients randomized and not treated in R1500-CL-1629, 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: ≥12 to <18, ≥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
- Randomization strata as reported from the e-CRF
- Current apheresis treatment (yes/no)

- If apheresis occurring: schedule from the e-CRF (i.e. QW, Q2W, Q3W)

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
- LDL-C: <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: <150, ≥150 to <200, ≥200 mg/dL, and category ≥150 mg/dL for mixed dyslipidaemia (<1.7, ≥1.7 to <2.3, ≥2.3 mmol/L, and category ≥ 1.7 mmol/L),
- Lp(a): <30, ≥30 to <50, ≥50 mg/dL, and category ≥30 mg/dL (<75, ≥75 to <125, and ≥125 nmol/L, and category ≥ 75 nmol/L)
- Mutation type (e.g. homozygous [defective/defective or negative/negative mutations], compound heterozygous [defective/defective, defective/negative or negative/negative mutations], and double heterozygous [defective/defective, defective/negative or negative/negative])

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, patient medical allergic history, and family medical allergic history. Primary and secondary CVD prevention, CV risk factors categorized by high and very high risk, hyperlipoproteinemia disease history (including LMT therapies), and apheresis history (as applicable) 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
5. Patient's allergies (described using all pre-printed terms collected in the medical allergic history e-CRF page).

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.

Hyperlipoproteinemia disease history will be assessed through diagnosis of HoFH, time from diagnosis to study randomization (years), method of diagnosis of HoFH (genotyping, clinical

diagnosis), lipid modifying therapies history reported in the "History of Hypercholesterolemia/Statin Use" e-CRF page.

Apheresis history information will include the procedure frequency, and treatment technique.

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).

- 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); **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; o**r**
  - 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).

The concomitant medication treatment emergent periods are defined as:

- For concomitant medications in the DBTP, the treatment emergent period is defined from the first day of double-blind study treatment administration to the last day of double-blind study treatment +168 days (for patients who do not continue into the OLTP) or to the day before the first open-label study treatment administration (for patients who enter the OLTP).
- For concomitant medications in the OLTP, 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). For patients entering the OL study R1500-CL-1719, post-treatment medications period will be truncated at the day before study treatment administration in R1500-CL-1719.

4.4. Prohibited Medications and Procedures During Study

The definitions of prohibited medications and procedures are described in the section 7.8.1 of the protocol. They will be reviewed and identified by the study clinician and reported in protocol deviations.

4.5. Patient Disposition

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

For patient study status, patient double-blind treatment period milestone categories are defined below. As applicable, percentages will be calculated using the number of randomized patients in the denominator, with two exceptions. Specifically, the two exceptions will be for the screened and non-randomized categories, which will not have associated percentages shown.

- The total number of screened patients, defined as originally having met the inclusion criteria and signed the ICF.
- The total number of randomized patients, defined as all screened patients with a double-blind treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used.
- The total number of patients randomized but not receiving study treatment.
- The total number of patients randomized and receiving study treatment.
- The total number of patients who completed the DBTP as collected on the end of double-blind treatment e-CRF.
- The total number of patients who completed the DBTP, defined as at least 20 weeks of study treatment exposure and visit week 24 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 who do not proceed into OLTP and complete the last study follow-up visit (i.e. Follow-up week 20).

Patient OLTP milestone categories 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 OLTP, defined as at least 44 weeks of study treatment exposure and week 48 visit 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 choosing to proceed into R1500-CL-1719.

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
- Quality-of-life analysis set

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

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

4.6. Study Treatment Exposure and Compliance Variables

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

- Patient duration of double-blind study treatment exposure in weeks defined as: (last double-blind study treatment administration date +28 – first double-blind study treatment administration date+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.
- The total number of double-blind study treatment infusions by patient.

- The following categories will be used for treatment exposure intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks.

Study treatment exposure variables for infusions administered during the OLTP 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.
- The total number of open-label evinacumab treatment infusions by patient.
- The following categories will be used for treatment exposure intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks.

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

- Cumulative patient duration of evinacumab exposure in weeks defined as: double-blind treatment exposure plus open-label treatment exposure, regardless of unplanned intermittent discontinuations.
- Cumulative total number of evinacumab treatment infusions by patient defined as: total number of double-blind infusions plus total number of open-label infusions.
- The following categories will be used for cumulative patient treatment exposure intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks and <24 weeks, ≥24 weeks 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.

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

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

1. Only fasting TG measurements will be included in the analysis. TG measurements with missing fasting status will be excluded from the analyses.
2. On the day of apheresis, any lipid values collected after apheresis for the respective visit will be excluded from the efficacy analyses.

All 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 4 to week 24 time points. 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 endpoint is the percent change in calculated LDL-C from baseline to week 24. The primary endpoint is defined as: 100x (calculated LDL-C value at week 24 - calculated LDL-C value at baseline)/calculated LDL-C value at baseline.

The baseline LDL-C value will be the last calculated LDL-C value obtained before the first dose of double-blind-study drug. The calculated LDL-C at week 24 will be the LDL-C value obtained within the week 24 efficacy analysis window, regardless of adherence to treatment and subsequent therapies (intent-to-treat [ITT] estimand).

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. Key Secondary Efficacy Variable(s)

The key secondary efficacy variables include:

- The percent change in Apo B from baseline to week 24 (ITT estimand)
- The percent change in non-HDL-C from baseline to week 24 (ITT estimand)
- The percent change in TC from baseline to week 24 (ITT estimand)

- The proportion of patients with ≥ 30% reduction in calculated LDL-C at week 24 (ITT estimand)
- The proportion of patients with ≥ 50% reduction in calculated LDL-C at week 24 (ITT estimand)
- The change in calculated LDL-C from baseline to week 24 (ITT estimand)
- The proportion of patients who meet US apheresis eligibility criteria (see US [National Lipid Association] Lipid Apheresis Criteria (Goldberg 2011)) at week 24 (ITT estimand)
  - A patient is considered as meeting US apheresis eligibility criteria if LDL-C ≥ 300 mg/dL (7.77 mmol/L).
- The proportion of patients with LDL-C <100 mg/dL [2.59 mmol/L] at week 24 (ITT estimand)
- The proportion of patients who meet EU apheresis eligibility criteria (see German Apheresis Working Group (Schettler 2012)) at week 24 (ITT estimand)
  - A patient with primary CVD prevention is considered as meeting German apheresis eligibility criteria if LDL-C > 160 mg/dL (4.2 mmol/L).
  - A patient with secondary CVD prevention is considered as meeting German apheresis eligibility criteria if LDL-C > 120 mg/dL (3.1 mmol/L).

4.7.3. Other Secondary Efficacy Variables

- The percent change in TG from baseline to week 24 (ITT estimand)
- The change in Apo B from baseline to week 24 (ITT estimand)
- The change in non-HDL-C from baseline to week 24 (ITT estimand)
- The change in TC from baseline to week 24 (ITT estimand)
- The percent change in lipoprotein a [Lp(a)] from baseline to week 24 (ITT estimand)
- The proportion of patients with LDL-C <70 mg/dL [1.81 mmol/L] at week 24 (ITT estimand)
- The percent change in apolipoprotein CIII (Apo CIII) from baseline to week 24 (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) for those patients not proceeding into the OLTP, or up to the day before the first dose of open-label study treatment administration for those patients proceeding into the OLTP

  The double-blind TEAE period will include:

  – The TREATMENT period is defined from the day of first double-blind study treatment administration up to the day of last double-blind study treatment administration + 35 days. For patients entering into the OLTP, the treatment period will be truncated at the day before the first dose of open-label study treatment administration.

  – The RESIDUAL TREATMENT period is defined from the day of last double-blind study treatment administration + 36 days up to the day of last double-blind study treatment administration + 168 days (24 weeks), or up to the day before first dose of open label study treatment administration, whichever is earlier.
- The open-label treatment-emergent adverse event (TEAE) period 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). For patients entering the open-label study R1500-CL-1719, the TEAE period will be truncated at the day before first study treatment administration in R1500-CL-1719.

  The open-label TEAE period will include:

  – The TREATMENT period is defined from the day of first open-label study treatment administration up to the day of last open-label study treatment administration + 35 days.

  – The RESIDUAL TREATMENT period is defined from the day of last open-label study treatment administration + 36 days up to the day of 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. For patients entering the open-label study R1500-CL-1719, the post-treatment period will be truncated at the day before first study treatment administration in R1500-CL-1719.

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 periods.
- Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period.

4.8.1.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner. AESIs will be recorded on the adverse event e-CRF using dedicated tick boxes, and/or identified using standard MedDRA queries (SMQ), company MedDRA queries (CMQ), 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, concomitant medications) for patients without diabetes mellitus at baseline
- Diabetic complication (CMQ, concomitant medications) for patients with diabetes mellitus at baseline
- Pancreatitis (e-CRF)

- Cataracts (MedDRA HLT)
- Immune complex diseases (SMQ)
- Muscle events/CK elevation (MedDRA SOC, 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 10.9). 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

Other Laboratory Tests

High sensitivity C-reactive protein (hs-CRP), HbA1c.

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. 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 10.9 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 over time
- The percent change in hs-CRP from baseline over time
- The percent change in HDL-C from baseline over time
- The percent change in Apo A1 from baseline over time
- The percent change in Apo B/Apo A1 ratio from baseline over time

4.10. Pharmacokinetic Variables

Pharmacokinetic (PK) variables include total evinacumab concentrations, Total ANGPTL3 concentrations, alirocumab concentrations, total PCSK9 concentrations, and statins concentrations (rosuvastatin, atorvastatin, simvastatin) at each time point.

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

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

4.12. Quality-of-Life Variables

EQ-5D

EQ-5D is a standardized and generic instrument for measuring the health status and health related quality of life for clinical and economic assessment (Dolan 1997). The EQ-5D instrument includes 5 items corresponding to the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item can take one of three responses: (1.) "no problem", (2.) "some problems", and (3.) "severe problems". Overall health state is defined as a 5-digit number and will be converted into a standard utility score ranging between - 0.594 (representing severe problems) and 1 (representing no problem): the single index utility score, using a regression model (Dolan 1997) (Appendix 10.5). If response to one or more dimensions is missing, the utility score will be missing.

Quality of life endpoints include response to each EQ-5D items at week 0 and week 24. The change in utility score from baseline will also be evaluated at each post-baseline week. Protocol schedule visits will be assigned to the Global Analysis Windows (See Appendix 10.2).

Hospital Anxiety and Depression Scale (HADS)

HADS is a validated, widely used questionnaire designed to identify anxiety disorders and depression in patients at non-psychiatric medical institutions. Repeated administration also provides information about changes in a patient's emotional state (Bjelland 2002, Herrmann 1997, Zigmond 1983). The HADS questionnaire consists of 14 items that assess symptoms experienced in the previous week, with 7 items that are related to anxiety and 7 that are related to depression (See Appendix 10.6 for the details). Patients provided responses to each item based on a 4-point Likert scale. Each item on the questionnaire is scored from 0 (the best) to 3 (the worst); thus, a person can score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 8 or more on the HADS-Anxiety or the HADS-Depression subscale are considered to be indicative of anxiety or depression, respectively (Bjelland 2002).

The HADS total score is the sum of the two sub-scores, anxiety and depression. In the case a sub-score is missing, the HADS total score is considered missing. Similarly, in the case questionnaire items are missing, the applicable sub-score is considered also missing.

Both the HADS total score and the total score change from baseline will be provided. Change in HADS total score from baseline over time will be derived. Protocol schedule visits will be assigned to the Global Analysis Windows (See Appendix 10.2).

5. STATISTICAL METHODS

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the study, as well as by treatment group and overall for the study within each of the stratification factors (IVRS/IWRS defined yes/no of apheresis treatment status and geographical region [Japan, Rest of World]).

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 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 two 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 open-label safety population, demographic and baseline characteristics will be summarized by all patients and by treatment group of the DBTP (i.e., 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 in 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. In addition, all medical history of specific interest, primary and secondary CVD prevention including corresponding criteria, as described in Section 4.2, will be summarized by patient incidence and percentage.

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

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

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

All concomitant medications during the DBTP, dictionary coded by WHO-DD, will be descriptively summarized by treatment group, for patients in the double-blind safety population. Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications (including statin, LMT, CV), by decreasing frequency of the evinacumab group incidence of ATC followed by therapeutic class. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication. 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. Post-treatment medications will be summarized as described above for all medications.

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. Medications will be summarized for all patients and by treatment group of the DBTP (i.e., evinacumab, placebo) for patient in the open-label safety population. Summaries will present patient counts (and percentages).

5.4. Prohibited Medications

Listing of prohibited medications will be provided for the patients in the 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). 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., 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 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., 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 as described in Section 4.6. Treatment duration and total number of infusions will be summarized using the number of patients with data, mean, SD, Q1, Q3, median, minimum and maximum.

Additionally, evinacumab dosing exposure will be summarized cumulatively across the study, combining DBTP and 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 deviations (counts of deviations), patients (incurring a deviation by count and percentage), and by type of important deviation (patient count and percentage). A patient listing of all important and minor protocol deviations will be provided.

Descriptive statistics of the infusion frequency will be summarized. 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, key secondary endpoints, and other secondary efficacy endpoints will be conducted in the DBTP as described below, and will be completed during the step 1 efficacy analyses (Section 7). Remaining descriptive efficacy analyses will be completed during step 2. The definition for baseline is applicable to derived variables (e.g., percent change from baseline) in both DBTP and OLTP.

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 24 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 24 efficacy analysis windows will be used and missing data are accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group (evinacumab versus placebo), randomization strata (apheresis [Yes/No] and region [Japan, Rest of World]), time point (weeks 2, 4, 8, 12, 16, 20, and 24), 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.

This model will be run using Statistical Analysis System (SAS) Mixed Procedure 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. This model will provide baseline adjusted least-squares (LS) means estimates at week 24 for both treatment groups with their corresponding standard errors.

Let $\mu 0$ and $\mu 1$ be the population means of the percent change from baseline in calculated LDL-C at week 24 under placebo and evinacumab, respectively. The hypothesis that will be tested is "H_0: $\mu_0 = \mu_1$" versus "H_1: $\mu_0 \neq \mu_1$". Therefore, the evinacumab group will be compared to the placebo group using an appropriate contrast statement tested at the 2-sided 0.05 level, with corresponding least square estimate of mean difference, SE and 95% confidence interval.

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 across the study population (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 24 (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 Sec 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 (Sec 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:
  1. Calculated LDL-C available at week 24 (i.e. primary efficacy endpoint available),
  2. Calculated LDL-C available at week 20 but missing at week 24,
  3. Calculated LDL-C available at week 16 but missing from week 20,
  4. Calculated LDL-C available at week 12 but missing from week 16,
  5. Calculated LDL-C available at week 8 but missing from week 12,
  6. Calculated LDL-C available at week 4 but missing from week 8,
  7. Calculated LDL-C available at week 2 but missing from week 4,
  8. Calculated LDL-C missing from week 2.

  A graph of mean percent change from baseline calculated LDL-C levels ± SE at baseline, and at weeks 2, 4, 8, 12, 16, 20, and 24 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.

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 10.8 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) 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) based on the following assumptions:

- Patients within 35 days 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 24 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. 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. LS mean difference versus placebo at week 24 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 24 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 apheresis status (Yes, No) per IVRS,
- Geographical region (Japan, Rest of World) per IVRS,
- Gender (Female, Male),
- Age (<65, ≥65),
- Race
- Ethnicity
- Baseline LDL-C (<130, ≥130 mg/dL),
- HoFH genotyping (homozygous, compound heterozygous, and double heterozygous)
- Receptor-negative mutation in both LDLR alleles (i.e. receptor-negative defined as a mutation resulting in termination codons, splice site mutations, frame shifts and large insertion/deletions) (Yes, No)

Subgroup analysis for Japanese patients

With respect to the subgroup analysis for Japan, the primary efficacy analysis MMRM model will be used to evaluate treatment effect in Japanese patients (as recorded in the electronic data capture [EDC] system) by adding the variables of treatment-by-region strata and treatment-by time point-by region strata interaction terms to the model. With this subgroup specific MMRM model, the primary efficacy endpoint LS mean at week 24 for the evinacumab treatment group will be provided for the Japanese patients, along with the corresponding SE and 95% CI. Due to the few Japanese patients expected to be randomized to the placebo group, the evinacumab group LS mean point estimate will be used to access consistency of evinacumab effect between the Japanese patients and all evinacumab treated patients in this global study (provided by the primary efficacy analysis described in Section 5.7.1). The evinacumab primary efficacy endpoint LS mean point estimate for the Japanese patients is considered to show consistent efficacy results with the global study point estimate when the ratio of the Japanese LS mean point estimate over the global study point estimate is ≥ 0.5.

5.7.2. Analysis of Secondary Efficacy Variables

Statistical analyses for the key secondary efficacy endpoints (defined in Section 4.7.2) and other secondary efficacy endpoints (described in Section 4.7.3) will be performed in the ITT population using the ITT estimand.

For descriptive summaries, percent change, and when appropriate, absolute change from baseline in LDL-C, Apo B, total-C, TG, non-HDL-C, Lp(a), and Apo CIII will be provided at each time point for each treatment group. All measurements, scheduled or unscheduled, will be assigned to efficacy analysis windows defined in Appendix 10.2 in order to provide an assessment for these time points. For TGs, measurements on not-fasting patients will be excluded. The time profile of each parameter will be plotted by treatment group with the corresponding standard errors. Similar tables (with either percent change from baseline or absolute change from baseline for the ratio) and plots will be provided for other efficacy parameters: Apo A-1 and ratio Apo B/Apo A-1.

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 and 4.7.3 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 24, 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 and 4.7.3 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 10.7, 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 and 4.7.3 will be analyzed using the multiple imputation approach for handling of missing values as described in Appendix 10.7.

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 24 efficacy analysis window to impute the missing week 24 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 Key Secondary Endpoint Variables

In order to assess the robustness of more clinically relevant between group comparisons for the analysis of the key secondary efficacy endpoint, 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 key secondary efficacy endpoints values collected during the efficacy treatment period (Sec 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, Apo CIII, Lp(a), Apo-A1, and ratio Apo-B/Apo-A1. Summaries will include both the ITT and mITT populations. 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 and SD for each treatment group at all planned time points.

During the OLTP, efficacy variables 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., 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 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.

Adjustment for Multiple Comparison

In order to handle multiple key secondary endpoints during the DBTP for the comparison of the evinacumab group and the placebo group, the overall type-I error will be controlled by the use of a hierarchical inferential approach. Statistical significance of the primary parameter at the 0.05 alpha level is required before drawing inferential conclusions about first key secondary parameter. Inferential conclusions about successive key secondary parameters require statistical significance of the prior one. The hierarchy testing sequence is the order of endpoints as presented in Sections 4.7.1 and 4.7.2.

This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.05 level.

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

No adjustment will be made for the first step and second-step statistical analyses (Section 7), since the primary and key secondary endpoints testing will have been concluded at the time of the first step analysis.

5.8. Analysis of Safety Data

The summary of safety results will be presented separately for the DBTP and OLTP, unless otherwise noted. Safety summaries for the DBTP will be presented by treatment groups (evinacumab, placebo) containing patients from the double-blind safety analysis set. Safety summaries for the OLTP will be presented by all patients and by treatment group in DBTP (i.e.,

evinacumab, placebo), for patients in the open-label safety analysis set. No formal inferential testing will be performed for either period. Summaries will be descriptive in nature.

General common rules

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

- Safety data in patients who do not belong to the safety analysis set (i.e., exposed but not randomized) will be listed separately.
- PCSV values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (PCSV version dated January 2009 [Appendix 10.4]). 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 /Table 1 in order to provide an assessment for the screening visit through follow-up visit time points.
- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize observed values and change from baseline values by visit.
- Analyses performed according to diabetes status will be done considering diabetic patients as patients with either type 1 or type 2 diabetes in the medical history e-CRF page (regardless of the ongoing status).

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. Post-treatment AEs will be summarized separately.

If an AE onset date (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine pre-treatment or

post-treatment status. Details on classification of AEs with missing or partial onset dates are provided in Section 6.3.

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

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

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE;
  - Serious TEAE;
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, 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)
- 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.

Post-treatment adverse events

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

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

Analysis of all treatment-emergent adverse event(s) by status of negative mutation in both LDLR alleles (Yes, No) – receptor-negative/negative vs not receptor-negative/negative

- All TEAEs by primary SOC and PT
- All Serious TEAEs by primary SOC and PT
- All TEAEs leading to permanent treatment discontinuation, by primary SOC and PT
- All TEAEs leading to death by primary SOC and PT

Patient Deaths

The following summaries of deaths will be generated.

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

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. AESI are defined by SMQ, CMQ, and dedicated e-CRF as described in Appendix 10.3 .

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

- Intensity of the event (mild, moderate, severe or very 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;

5.8.3. Clinical Laboratory Measurements

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 (collected up to the day of last dose of study treatment +28 days) by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum. Clinical laboratory parameters mean changes from baseline, with the corresponding SE, can be plotted at each visit in the case results warrant further investigation. These parameters will be presented by the biological functions defined in Section 4.8.2. For glucose, only fasting samples will be included in the summaries.

Individual patient laboratory parameter measurements will be additionally evaluated by PCSV criteria (See Appendix 10.4), 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

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 (collected up to the day of last dose of study treatment +28 days) by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum. Vital sign mean changes from baseline, with the corresponding SE, can be plotted at each visit in the case results warrant further investigation.

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

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

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

5.8.5. Analysis of 12-Lead ECG

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

5.8.6. Physical Exams

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

5.9. Analysis of Other Variables

The summary of results for other variables will be presented separately for the DBTP and OLTP, unless otherwise noted. Summaries for the DBTP will be presented by treatment groups (evinacumab, placebo) containing patients from the double-blind safety analysis set. Summaries for the OLTP will be presented by all patients and by treatment group in DBTP (i.e., evinacumab, placebo), for patients in the open-label safety analysis set. 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, HDL-C, Apo A1, and Apo B/Apo A1 ratio 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, and means (+/- SE) for HbA1c, HDL-C, Apo A1, and Apo B/Apo A1 ratio. Applying the PCSV criteria at any time during the TEAE period, the number of patients (and percentages) meeting the criteria will be summarized.

Correlations between HoFH genotype status and lipid parameters will be explored (e.g., plot of mean percent change from baseline ±SE in lipids over time by genotype).

5.10. Analysis of Pharmacokinetic Variables

Descriptive statistics of concentrations of total evinacumab, total ANGPTL3, total alirocumab and total PCSK9 will be presented. Mean concentrations of each analyte will be tabulated by visit and treatment group, with concentrations below the LLOQ set to zero.

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

Descriptive statistics will be provided for concentrations of statins at each sampling time. The ratio of concentration at week 24 over baseline will be presented for individual patient, when available.

Descriptive comparison of concentrations of evinacumab and total ANGPTL3 between Caucasian patients and Japanese patients may be performed, if sufficient data are collected.

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 using descriptive statistics by dose/cohort group in the ADA analysis set. Listings of ADA positivity and titers presented by patient, time point, and study treatment received will be provided. 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 (negative or positive) 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. Treatment emergent ADA responses will be further classified into persistent, indeterminate and transient.
  - 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

A second ad-hoc analysis set may also be generated that employs definitions as outlined in the Shankar et. al publication. Two sets of results will be presented in the Clinical Pharmacology report for the study, one using our definitions as provided in the SAP (Primary results) and one using the Shankar et. al definitions (Secondary or ad-hoc results). The primary results will be reported in the CSR.

- 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)
- Subgroup analysis of ADA data may be performed for Japanese patients when appropriate.

5.12. Analysis of Quality-of-life Variables

The summary of results for quality-of-life variables will be presented separately for the DBTP and OLTP, unless otherwise noted. Summaries for the DBTP will be presented by treatment groups (evinacumab, placebo) containing patients from the quality-of-life analysis set. Summaries for the OLTP will be presented by all patients and by treatment group in DBTP (i.e.,

evinacumab, placebo), for patients in the quality-of-life analysis set. No formal inferential testing will be performed for either period. Summaries will be descriptive in nature.

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).

EQ-5D

Individual EQ-5D items

Responses for each one of the 5 EQ-5D items will be summarized by patient frequency and percentage at baseline and each post-baseline visit. Responses are defined by 4 levels, specifically reporting level 1 (no problems), level 2 (some problems) and level 3 (extreme problems), and level 4 (not answered).

EQ-5D utility score

The observed value and the change from baseline of the utility score will be summarized using mean, median, Q1, Q3, SD, minimum and maximum for each post-baseline visit. Cumulative distribution functions for the change in utility score from baseline will be displayed at post-baseline visits.

HADS

The analysis of data from HADS instrument will be performed on the HADS quality-of-life analysis set.

The total score is the sum of the two sub-scores of anxiety and depression. Descriptive statistics (mean, median, Q1, Q3, SD, minimum and maximum) of the observed total scores and the change from baseline observed total scores will be summarized by visit.

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 5.7.2.

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, ECG, quality of life, drug concentration and ADA) 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, ECG, ED-5D, and HADS, 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

Efficacy and safety analyses for this study will be performed in two steps, specifically for patient data collected up to the time the last patient completes efficacy assessments at week 24 (step 1 consisting of the DBTP) and at the end of the study (step 2 for the OLTP). No formal interim analysis for efficacy is planned since analyses of primary and key secondary efficacy endpoints will be final at the time of first step analysis. Therefore, no multiplicity adjustment for multiple analyses is needed (see Section 5.7.2.5). The timing for patient data to be reported is defined below for each step:

- First step: efficacy analyses up to week 24 and interim safety analysis
  - This analysis will be conducted on all randomized patients when all patients will have all their lipid data up to week 24 efficacy analysis window collected and validated.
  - The efficacy analyses will be performed up to week 24 visit. Analyses of endpoints up to week 24 visit will correspond to the final analyses for these endpoints. Analysis of lipid parameters beyond week 24 visit will be descriptive.
  - The safety analyses will be performed on all safety data (double-blind and open-label) collected up to the common cut-off date. For this analysis, the common cut-off date is defined as date of the last week 24 visit.
- Second-step: final analysis
  - This analysis will be conducted at the end of the study and will consist of the final analysis of efficacy data at time points beyond the week 24 visit and final safety analysis.

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. The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect.

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 step analysis:

- Any lipid assessments within efficacy analysis windows up to the week 24 visit 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 cut-off date.
  - Their treatment duration will be derived by considering date of cut-off as last administration date.
- Analyses of number of administrations, and mean administration frequency will be performed up to the last administration reported in the e-CRF up to the cut-off date.
- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an adverse event starting prior to the cut-off date will be taken into account. Medications, treatment discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.
- Post-treatment period, and post-study period are not applicable for ongoing patients. Analyses of post-treatment AEs, post-study deaths and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.
- Analysis of status at last study contact and proportion of patients with insufficient follow-up will be provided for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.

8. SOFTWARE

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

9. REFERENCES

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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 24	ITT	ITT estimand: The calculated LDL-C at week 24 will be the LDL-C value obtained within the week 24 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
2. Study Day 1.
3. Open-label study day is defined as the number of days since the first open-label study treatment administration+1
4. 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.
5. For randomized but not treated patients, Day 1 is the day of randomization.

Table 1: Global Analysis Windows

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 42
Week 8	57	N/A	43 to 70
Week 12	85	N/A	71 to 98
Week 16	113	N/A	99 to 126
Week 20	141	N/A	127 to 154
Week 24	169	Day 1	155 to 182 for patients not entering OLTP or 155 to first OL treatment day for patients entering OLTP
Week 28	197	29	first OL treatment day+1 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
Week 48	337	169	323 to 350
FU – W4	For patients prematurely discontinued trt: last study trt to 28 days after last study trt For patients completed OLTP: 365	For patients prematurely discontinued trt: last study trt to 28 days after last study trt For patients completed OLTP: 197	For patients prematurely discontinued trt: Last study trt day +1 to 56 days after last study trt For patients completed OLTP:351 to 392
FU – W12	For patients prematurely discontinued trt: last study trt to 84 days after last study trt For patients completed OLTP: 421	For patients prematurely discontinued trt: last study trt to 84 days after last study trt For patients completed OLTP: 253	For patients prematurely discontinued trt: 57 days after last study trt to 112 days after last study trt

Visit label	Targeted Study Day	Targeted Open-Label Study Day	Analysis Window in Study Day
FU – W20	For patients prematurely discontinued trt: last study trt to 140 days after last study trt For patients completed OLTP: 477	For patients prematurely discontinued trt: last study trt to 140 days after last study trt For patients completed OLTP: 309	For patients prematurely discontinued trt: 113 days after last study trt to 168 days after last study trt For patients completed OLTP:449 to 504
FU > W20	N/A	N/A	For patients prematurely discontinued trt: >168 days after last study trt For patients completed OLTP:>504

Study days are calculated from the day of first double-blind IMP administration, the day of first double-blind IMP administration being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

Table 2: Efficacy Analysis Windows – Statistical Testing

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 42
Week 8	57	43 to 70
Week 12	85	71 to 98
Week 16	113	99 to 126
Week 20	141	127 to 154
Week 24	169	155 to 182 for patients not entering OLTP or 155 to first OL treatment day for patients entering OLTP

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 defined based on Regulatory Agency request for another lipid lowering program (See Table 4 in Appendix 10.3 for the list of terms)
Neurologic events	Yes	No

New onset of diabetes (NOD) for patients without diabetes mellitus at baseline	No	No medical history of diabetes as specified in Cardiovascular History and Cardiovascular Risk Factors and Medical History CRF pages AND one of the following: 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 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 (including subtypes) OR Initiation of any new concomitant medication for hyperglycemia during the treatment period
Diabetic complication for patients	No	For patients with medical history of diabetes as specified in Cardiovascular History and Cardiovascular Risk

with diabetes mellitus at baseline		Factors and Medical History CRF pages, each of the following criteria will be considered, respectively: • Diabetes mellitus or diabetic complication TEAEs using HLGT Diabetic complications, HLT Diabetes mellitus (incl subtypes), and PTs Blood glucose increases, Glycosylated haemoglobin increased, Hyperglycaemia, Hyperglycaemic unconsciousness, and Hyperglycaemic seizure • 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
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
Hs-CRP	> 2 ULN or >10 mg/L, if ULN not provided
Hematology	
WBC	< 3.0 Giga/L (3000/ mm^3) (Non-Black) < 2.0 Giga/L (2000/ mm^3) (Black) ≥16.0 Giga/L (16000/ mm^3)
Lymphocytes	>4.0 Giga/L
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. EQ-5D Utility Score Algorithm

EQ-5D Utility Score Algorithm

Algorithm: UK based

```
/*=====================================================================*/
;

/*  Aim                        : Derive the EQ5-D index (utility)
*/;

/*  Source for the algorithm : scoring EQ-5D health states (Rosalind Rabin
*/;

/*            (cf. G:\_HE\PRO questionnaire\EQ5D\scoring\YorkTariffx.doc)
*/;

/*  Note                       : UK based population (Dolan, 1997)
*/;

/*=====================================================================*/
;
```

Answer to questions in numeric format, from 1 (no problem) to 3 (severe problem); Q1 (mobility), Q2 (self-care), Q3 (usual activities), Q4 (pain/discomfort), Q5 (anxiety/depression)

Result of the algorithm: Utility (EQ-5D utility score).

If at least one of the answer to questions is missing then the utility score is missing.

Start with Utility =**1** and apply the following sequential algorithm.

**********Mobility*********
if Q1=**2** then Utility = Utility - **0.069**
if Q1=**3** then Utility = Utility - **0.314**

********Self-care**********
if Q2=**2** then Utility = Utility - **0.104**
if Q2=**3** then Utility = Utility - **0.214**

******Usual activities*****
if Q3=**2** then Utility = Utility - **0.036**
if Q3=**3** then Utility = Utility - **0.094**

*****Pain/discomfort******

if Q4=**2** then Utility = Utility - **0.123**
if Q4=**3** then Utility = Utility - **0.386**

*****Anxiety/depression*****
if Q5=**2** then Utility = Utility - **0.071**
if Q5=**3** then Utility = Utility - **0.236**

if (Q1 ≠ **1** or Q2 ≠ **1** or Q3 ≠ **1** or Q4 ≠ **1** or Q5 ≠ **1**) then Utility = Utility - **0.081**
if (Q1=**3** or Q2=**3** or Q3=**3** or Q4=**3** or Q5=**3**) then Utility = Utility - **0.269**
End of the sequential algorithm

10.6. Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Note: Questions with response scoring under column header D are depression related questions. Otherwise, those are depression related questions.

10.7. 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=1629 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=9261 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.

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

- the randomization strata (apheresis treatment status 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.

10.8. Detailed Description of Pattern Mixture Model

As a sensitivity analysis of the primary efficacy endpoint (i.e. percent change from baseline to Week 24 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) and missing LDL-C values after treatment discontinuation (i.e. after the day of last study treatment administration +35 days) based on the following assumptions:

- Patients within 35 days of their last study treatment administration would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, LDLC 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 24 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=1629;

  mcmc impute=monotone;

  var ARM LDL_BASE LDL_W2 LDL_W4 LDL_W8 LDL_W12 LDL_W16 LDL_W20
LDL_W24;

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=9261), 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.

10.9. Schedule of Time and Events

Schedule of Events – Run-in and Screening

Study Procedure	Run-in[7]	Screening
Visit	**1a**	**1**
Day	**-70 to -14**	**-14 to -1**
Visit Window (Day)		
Week	**-10 to -2**	**-2 to -1**
Screening/Baseline:		
Informed Consent	X	
[redacted]		X
Inclusion/Exclusion		X
Medical/Surgical History, Alcohol/Smoking Habits		X
Medication History		X
Demographics		X
Treatment:		
Concomitant Medications (including LMT and apheresis)	X	X
Query LMT Compliance	X	X
Efficacy:		
Lipid Panel[1,2]		X
Safety:		
Adverse Events	X	X
Physical Examination		X
Measured Height		X
Body Weight		X
Vital Signs (pulse rate, BP)	X	X
Electrocardiogram[3]		X
Tanner stage[4]		X
Laboratory Testing[5]:		
Hematology		X
Blood Chemistry		X
Creatine Phosphokinase		X
Hepatitis B Surface Antigen		X
Hepatitis C Antibody		X
Serum Pregnancy Test[6]		X
Urine Pregnancy Test[6]	X	
FSH	X	
Sex Hormones[4]		X
Urinalysis		X
TSH		X
DNA sample for HoFH genotyping	X	
Other:		
Review of diet	X	X

Footnotes for Schedule of Events – Run-in Period

1. Study assessments will be performed and blood samples will be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments will be performed and blood samples will be collected immediately before the lipid-apheresis procedure; study drug will be administered after the apheresis procedure.

2. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, non-HDL-C
3. ECG should be performed before blood samples are collected at visits requiring blood draws.
4. Assessment of Tanner Stage and sex hormones (includes luteinizing hormone, follicle stimulating hormone, estradiol, total testosterone) only applicable to patients <18 years old.
5. All laboratory samples should be collected before administration of study drug.
6. WOCBP only, confirm required contraception use and reminder pregnancy reporting
7. For patients who require HoFH genotyping, stabilization of their lipid-apheresis schedule or stabilization of their background medical LMT, i.e., stable lipid-apheresis for at least 8 weeks before screening and stable background medical LMT for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies)

Schedule of Events – Screening for Patients with No Run-in

Study Procedure	Screening
Visit	**1**
Day	**-14 to -1**
Visit Window (Day)	
Week	**-2 to -1**
Screening/Baseline:	
Informed Consent	X
[redacted]	X
Inclusion/Exclusion	X
Medical/Surgical History, Alcohol/Smoking Habits	X
Medication History	X
Demographics	X
Treatment:	
Concomitant Medications (including LMT and apheresis)	X
Query LMT Compliance	X
Efficacy:	
Lipid Panel[1,2]	X
Safety:	
Adverse Events	X
Physical Examination	X
Measured Height	X
Body Weight	X
Vital Signs (pulse rate, BP)	X
Electrocardiogram[3]	X
Tanner stage[4]	X
Laboratory Testing[5]:	
Hematology	X
Blood Chemistry	X
Creatine Phosphokinase	X
Hepatitis B Surface Antigen	X
Hepatitis C Antibody	X
Serum Pregnancy Test[6]	X
Urine Pregnancy Test[6]	
Sex Hormones[4]	X
FSH	X
Urinalysis	X
TSH	X
DNA sample for HoFH genotyping	X
Other:	
Review of diet	X

Footnotes for Schedule of Events – Screening for Patients with No Run-in

1. Study assessments will be performed and blood samples will be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments will be performed and blood samples will be collected immediately before the lipid-apheresis procedure; study drug will be administered after the apheresis procedure.
2. Fasting sample will be collected for the lipid panel: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C

3. ECG should be performed before blood samples are collected at visits requiring blood draws.
4. Assessment of Tanner Stage and sex hormones (includes luteinizing hormone, follicle stimulating hormone, estradiol, total testosterone) only applicable to patients <18 years old.
5. All laboratory samples should be collected before administration of study drug.
6. WOCBP only, confirm required contraception use and reminder pregnancy reporting

Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period

Study Procedure	**Double-Blind Treatment Period**								**Open-Label Treatment Period**					
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 End DBTP[14]**	**10**	**11**	**12**	**13**	**14**	**15 End of OLTP**
Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (Day)	**±1**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±1**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Baseline:														
Informed Consent	X[1]													
[redacted]	X[1]													
Treatment:														
Randomization	X[1]													
Administer IV Double-Blind Study Drug	X[1]		X	X	X	X	X							
Administer IV Open-Label Study Drug								X[10]	X	X	X	X	X	
Concomitant Medications (including LMT and apheresis)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Query LMT Compliance	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:														
Lipid Panel[2,3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Specialty Lipid Panel[2,4]	X		X	X	X	X		X		X		X		X
Safety:														
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination								X				X		X
Measured Height														X
Body Weight	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (pulse rate, BP)[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[6]								X						X
Tanner stage[7]								X						X
Confirm contraception use and reminder of pregnancy reporting	X[1]		X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Double-Blind Treatment Period								Open-Label Treatment Period					
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 End DBTP[14]**	**10**	**11**	**12**	**13**	**14**	**15 End of OLTP**
Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (Day)	**±1**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±1**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Laboratory Testing[8]:														
Hematology	X		X	X	X	X		X		X		X		X
Blood Chemistry	X		X	X	X	X		X		X		X		X
Creatine Phosphokinase	X		X	X	X	X		X		X		X		X
Serum Pregnancy Test[9]														X
Urine Pregnancy Test[9]	X		X	X	X	X	X	X	X	X	X	X	X	
Sex Hormones[7]								X						X
Urinalysis	X		X	X	X	X		X		X		X		X
hs-CRP	X							X						X
HbA1C	X[1]				X			X			X			X
LDLR function	X[1]													
Research Samples	X[1]		X	X		X		X	X					
PK and PD Samples														
ADA Sample[10]	X[1]		X		X			X						X
PK (evinacumab, alirocumab), ANGPTL3, PCSK9 Samples[11,12]	X[1]	X	X	X	X	X	X	X			X			X
PK of statin[11]	X[1]					X								
DNA sample for HoFH genotyping	X[1]													
[redacted]	X[1]													
Other:														
EQ-5D	X							X						
HADS	X[1]							X				X[15]		X[15]
Review of diet	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes for Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period

1. For those patients enrolling directly from the R727-CL-1628 study and do not complete the R1500-CL-1629 run-in or screening period, the informed consent forms should be signed at the baseline visit. Overlapping assessments completed at the R727-CL-1628 open-label EOT visit do not need to be duplicated during the R1500-CL-1629 baseline visit; only assessments footnoted will need to be performed.
2. Study assessments will be performed and blood samples will be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments will be performed and blood samples will be collected immediately before the lipid-apheresis procedure; study drug will be administered after the apheresis procedure. The timing between the baseline sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen should match the timing of the week 24 sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen. Depending on the duration between the LDL apheresis procedure and sample collection, the visit window may not apply.
3. Fasting sample will be collected for the lipid panel: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C
4. Fasting sample will be collected for specialty lipid panel: Apo B, Apo A-1, and Lp(a)
5. On dosing days, vital signs should be recorded prior to IV infusion, and 30 minutes and 60 minutes post-IV infusion
6. ECG should be performed before blood samples are collected at visits requiring blood draws.
7. Assessment of Tanner Stage and sex hormones (includes luteinizing hormone, follicle stimulating hormone, estradiol, total testosterone) only applicable to patients <18 years old.
8. All laboratory samples should be collected before administration of study drug.
9. WOCBP only, confirm required contraception use and reminder pregnancy reporting
10. The ADA sample should be drawn before study drug administration
11. For patients who are not undergoing apheresis, the PK sample should be drawn before the dose of study drug and at the end of the infusion. For patients undergoing apheresis, a PK sample should be collected immediately before the apheresis procedure and a PK sample should be collected immediately after the apheresis procedure, prior to administration of study drug, and, again at the end of the infusion of study drug.
12. Including assay of total ANGPTL3.
13. Should be collected at the baseline visit, or at any study visit
14. All end of treatment (EOT) assessments will be performed and blood samples will be collected before the dose of open-label study drug in all patients. For patients undergoing

apheresis: Study assessments will be performed and blood samples will be collected immediately before the lipid-apheresis procedure; open-label study drug will be administered after the apheresis procedure.

15. In the OLTP, the HADS should be administered after the patients have been informed of their lipid results.

Schedule of Events – Follow-up Period

Study Procedure	**Follow-up Period[5]**				
Visit	**16[5]**	**PV17[5,6]**	**18[5]**	**PV19[5,6]**	**EOS 20**
Day	**365**	**393**	**421**	**449**	**477**
Visit Window (Day)	**±5**	**±5**	**±5**	**±5**	**±5**
Week	**52**	**56**	**60**	**64**	**68**
Treatment:					
Concomitant Medications (including LMT and apheresis)	X	X	X	X	X
Query LMT Compliance	X	X	X	X	X
Safety:					
Adverse Events	X	X	X	X	X
Physical Examination					X
Measured Height					
Body Weight					X
Vital Signs (pulse rate, BP)					X
Electrocardiogram[1]					X
Tanner stage[2]					X
Confirm contraception use and reminder of pregnancy reporting	X	X	X	X	X
Laboratory Testing:					
Lipid Panel	X		X		X
Specialty Lipid Panel	X		X		X
Hematology	X		X		X
Blood Chemistry	X		X		X
Creatine Phosphokinase	X		X		X
Serum Pregnancy Test[3]					X
Urine Pregnancy Test[3]	X	X	X	X	
Sex Hormones[2]					X
Urinalysis					X
hs-CRP					X
HbA1C			X		X
PK and PD Samples					
ADA Sample					X
PK (evinacumab, alirocumab), ANGPTL3 Samples[4]					X
Other:					
Review of diet					X

Footnotes for Schedule of Events –Follow-up Period

1. ECG should be performed before blood samples are collected at visits requiring blood draws.
2. Assessment of Tanner Stage and sex hormones (includes luteinizing hormone, follicle stimulating hormone, estradiol, total testosterone) only applicable to patients <18 years old.
3. WOCBP only, confirm required contraception use and reminder pregnancy reporting.
4. Including assay of total ANGPTL3.
5. For patients who discontinue prematurely or who opt out of the OL study.
6. Phone visits (PV) at weeks 56 and 64 to confirm required contraception use and obtain results of the home urine pregnancy test. Adverse events and concomitant medications will be collected.

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