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REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN

VERSION: FINAL

AN OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF EVINACUMAB IN PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Compound:	Evinacumab
Protocol Number:	R1500-CL-1719 Amendment 5A and 5B
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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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
Apo A-1	Apolipoprotein A-1
Apo B	Apolipoprotein B
Apo CIII	Apolipoprotein CIII
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

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Lp(a)	Lipoprotein a
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed-effect model with repeated measures
NAb	Neutralizing Antibody
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

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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-1719 study.

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 data review, and a final plan will be issued prior to the 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

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism that predisposes a person to premature severe cardiovascular disease (CVD). Familial hypercholesterolemia can be either an autosomal dominant or an autosomal recessive disease that results from mutations in the low-density lipoprotein receptor (LDLR), or in 3 associated genes: proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (APOB), and low-density lipoprotein (LDL) receptor adaptor protein 1 (LDLRAP1) with a similar phenotype and varying severity.

Homozygous familial hypercholesterolemia (HoFH) is a rare, serious condition that is frequently caused by loss-of-function mutations in both alleles of the LDL receptor gene, resulting in the decreased clearance of LDL particles from plasma. Patients with HoFH have severe hypercholesterolemia (500-1000 mg/dL), resulting in lifelong exposure to high levels of plasma LDL and increased risk of developing atherosclerosis.

Accelerated atherosclerosis results in premature CVD and an increased risk of a cardiovascular event. Although double-blind cardiovascular outcome data in this rare population do not exist, observational studies suggest that lowering low-density lipoprotein cholesterol (LDL-C) with statin therapy may reduce the risk of coronary heart disease by 50% to 80% in patients with familial hypercholesterolemia.

Angiopoietin-like 3 (ANGPTL3) has recently emerged as a potential target for the treatment of elevated levels of triglycerides, and for the treatment of elevated levels of LDL-C, both factors in the development of CVD. Angiopoietin-like 3 (ANGPTL3) acts as a natural inhibitor of lipoprotein lipase (LPL), an endothelial-bound enzyme involved in the hydrolysis of the triglycerides (TG) content of very-low-density lipoproteins (VLDL) 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.

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1.2. Study Objectives

1.2.1. Primary Objectives

The primary objectives of the study are:

- To evaluate the long-term safety and tolerability of evinacumab 15 mg/kg IV administered Q4W in patients with HoFH.
- To evaluate the long-term safety and tolerability of evinacumab 15 mg/kg IV administered Q4W in adolescent 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 lipid parameters (i.e., LDL-C, Apo B, non-HDL-C, total cholesterol [TC], and triglycerides [TG]) in patients with HoFH
- To evaluate the effect of evinacumab 15 mg/kg IV on lipid parameters (ie, LDL-C, Apo B, non-HDL-C, total cholesterol [TC], and TG) in adolescent patients with HoFH
- To assess immunogenicity to evinacumab

1.2.3. Modifications from the Statistical Section in the Final Protocol

N/A.

1.2.4. Revision History for Statistical Analysis Plan Amendments

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

2. INVESTIGATION PLAN

2.1. Study Design

This is an open-label, single armed study designed to evaluate the long-term safety and efficacy of evinacumab in patients with HoFH.

Eligible patients for this study are male and female patients with HoFH, receiving LMT, as applicable. Lipid modifying therapies may include maximally tolerated statin, ezetimibe, PCSK9 inhibitor antibody, or other lipid lowering therapies, including lipoprotein apheresis. Patients include those who have participated in a previous evinacumab study (i.e., R1500-CL-1331 and R1500-CL-1629) and evinacumab-naïve patients with HoFH.

2.2. Sample Size and Power Considerations

Since this study is an open-label single treatment arm study for patients with HoFH, no calculation for sample size was performed. Approximately 120 patients will be enrolled.

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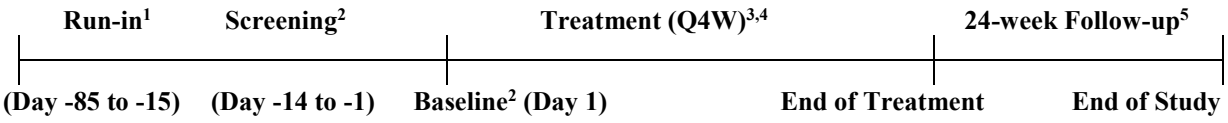
To gain experience with evinacumab in the subpopulation of adolescent patients, this study will plan to enroll approximately 14 patients in the age range of 12 years to < 18 years old. Due to the rare patient population planned for evaluation, the sample size of 14 patients was chosen for practical reasons, centered on the feasibility to identify and enroll these patients into the trial and regulatory precedent.

2.3. Study Plan

This study consists of 4 periods: a run-in period (for patients who may require HoFH genotyping, patients whose background medical LMT has not been stable prior to screening, or those whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a 2-week screening period, an open-label treatment period, and a 24-week follow-up period after the last dose of study drug (See Figure 1 below)

Study duration will vary for each patient in this open-label study designed to evaluate the long-term safety and efficacy of evinacumab in patients with HoFH. It will range from months up to approximately 4 years, depending on conditions met in protocol Section 5.1, including IP regulatory approval.

Figure 1: Study Flow Diagram



1. Patients who may require HoFH genotyping and patients whose background LMT/apheresis settings and/or schedule has not been stable prior to baseline (day 1) will enter an up to 10-week run-in period.
2. All patients who are on a stable background LMT will enter a 2-week screening period except for those from a previous evinacumab study who completed an end of study visit within 7 days prior to the baseline/day 1 visit for this open-label study.
3. Patients who completed an end of study visit in a previous evinacumab study within 7 days of the baseline/day 1 visit for this open-label study do not have to undergo the screening visit and may enroll directly into this study. The EOS visit from the previous study can serve as the baseline/day 1 visit for this open-label study and overlapping assessments do not need to be repeated in this study. Only those assessments and procedures not done in the previous study must be conducted at the baseline visit. These specific assessments to be administered to all patients are identified in the Schedule of Events. The Study event table is presented in Appendix 10.5 in protocol.
4. Starting on day 1 (baseline), patients will receive evinacumab 15 mg/kg IV administered Q4W.
5. Patients will be followed for 24 weeks after receiving the last dose of study drug.

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3. ANALYSIS POPULATIONS

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

3.1. Safety Analysis Set

The safety analysis set (SAF) includes all patients who was enrolled and received at least 1 dose or part of a dose of open-label study treatment in this study. The SAF will be the main analysis set for exposure/compliance, clinical safety and efficacy.

3.2. Efficacy Analysis Set

The SAF will be the main analysis set for efficacy.

3.3. Pharmacokinetic (PK) Analysis Set

The PK analysis set includes all treated patients who received any study drug and who had at least 1 non-missing result of evinacumab concentration following the first dose of study drug.

3.4. The Immunogenicity Analysis Sets

3.4.1. The Anti-evinacumab Antibody Analysis (ADA) Set

The anti-evinacumab antibody (ADA) analysis set includes all treated patients who received any study drug and who had at least 1 non-missing ADA result following the first dose of study drug.

3.4.2. The Neutralizing Antibody (NAb) Analysis Set

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

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

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

According to the protocol, patients who completed the EOS visit in the previous evinacumab study within 7 days of the baseline/day 1 visit for this open label study do not have to undergo the screening visit and may enroll directly into this study if they fulfill all of the inclusion criteria and none of the exclusion criteria. Therefore, the EOS visit from the previous study can serve as

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the baseline/day 1 visit for this open-label study and overlapping assessments do not need to be repeated in this study. Such data will be rolled into the R1500-CL-1719 database and will be used in the calculation of the baseline assessments.

Baseline assessments and procedures that do not overlap with assessments at the EOS visit of the previous study will be performed after all EOS assessments and procedures have been completed in the previous evinacumab study.

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)
- Current apheresis treatment (yes/no)
- If apheresis occurring: schedule from the e-CRF (i.e. QW, Q2W, Q3W)
- Tanner staging (for adolescent patients)

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),

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- 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])
- LDLR activity status (null/null [LDLR activity ≤15%], not null/null [LDLR activity >15%]

4.2. Medical History

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

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

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

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

5. 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)
6. 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:

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- 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 the first open-label evinacumab treatment administration date (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.

- Prior medications are defined as medications for which the stop date is before the date of the first study treatment administration.

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- Concomitant medications are defined as medications that are administered to the patients during the study treatment period. Specifically:
  - Start date of the concomitant medication is on or after the first study treatment administration in study treatment period (≥ OLTP Day 1); **or**
  - Start date of the concomitant medication is before the first study treatment administration in study treatment period and is "Ongoing" during the treatment emergent period; o**r**
  - Start date of the concomitant medication is before the first study treatment administration in study treatment period, and the end date is on or after the first study treatment administration in study treatment period (≥ OLTP Day 1).

The concomitant medication treatment emergent period is defined as:

- 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).

4.4. Prohibited Medications and Procedures During Study

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

4.5. Patient Disposition

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

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

- The total number of screened patients: defined as originally having met the inclusion criteria and signed the ICF
- The total number of patients failed screening
- The total number of patients enrolled, defined as all screened patients with a treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used.

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- The total number of patients enrolled but not receiving study treatment.
- The total number of patients enrolled and receiving study treatment.
- The total numbers of patients who have participated in a previous evinacumab study (i.e., R1500-CL-1331 and R1500-CL-1629), or evinacumab-naïve patients with HoFH.
- The total number of patients who completed the OLTP as collected on the End of Treatment - Evinacumab e-CRF.
- The total number of patients who prematurely discontinued study treatment during the OLTP, and the reasons for discontinuation collected on the End of Treatment - Evinacumab e-CRF.
- The total number of patients ongoing in OLTP (applicable for the interim analyses)
- The total number of patients who complete the last study follow-up visit (i.e. Follow-up week 24).

The following patient populations for analyses are listed below:

- Safety (SAF) Analysis Set
- Efficacy Analysis Set (same as SAF)
- Pharmacokinetic (PK) Analysis Set
- Immunogenicity (ADA and NAb) Analysis Sets

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

- A listing of patients treated but not enrolled, patients enrolled but not treated.
- 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 study 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 in the study +28 – first open-label evinacumab treatment administration date in the study +1)/7. Unplanned intermittent discontinuations in study treatment will be addressed on a case-by-case basis, since this is expected to be a rare occurrence.
- Patient duration of open-label study treatment exposure in patient-years is calculated as the patient duration in weeks multiplied by 7/365.
- The following categories will be used for treatment exposure intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks and <24 weeks, ≥24 weeks and <28 weeks,

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≥28 weeks and <32 weeks, ≥32 weeks and <36 weeks, ≥36 weeks and <40 weeks, ≥40 weeks and <44 weeks, ≥44 weeks and <48 weeks, etc.

- The total number of open-label evinacumab treatment infusions by patient.

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

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

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

4.7. Primary and Secondary Endpoints

4.7.1. Primary Endpoint

The primary endpoint is the incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables during the open-label treatment period in patients treated with evinacumab 15 mg/kg IV Q4W.

4.7.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The percent change in LDL-C from baseline over time
- The absolute change in LDL-C from baseline over time
- The percent change in Apo B from baseline over time
- The absolute change in Apo B from baseline over time
- The percent change in non-HDL-C from baseline over time
- The absolute change in non-HDL-C from baseline over time
- The percent change in TC from baseline over time
- The absolute change in TC from baseline over time
- The percent change in TGs from baseline over time
- The absolute change in TGs from baseline over time

The definition of the baseline value for computation of the change from baseline can be found in Section 6.1.

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

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The baseline lipid value will be the last value obtained according to the definition of baseline specified in Section 6.1. The lipid value at each post-baseline time point will be the lipid value obtained within the global analysis window, regardless of adherence to treatment and subsequent therapies.

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

- Only fasting TG measurements will be included in the analysis. TG measurements with missing fasting status will be excluded from the analyses.
- 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. 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 according to the definition of baseline specified in Section 6.1.

4.8. Other Safety Variables

The other safety variables include clinical laboratory data, vital signs, and ECG. Unless otherwise noted, the baseline value is defined according to the definition of baseline specified in Section 6.1.

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 open-label study treatment administration.
- 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).
- The POST-TREATMENT period is defined from the day after the end of the TEAE period to the last study visit.

4.8.1.1. Adverse Events and Serious Adverse Events

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

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

Adverse Event Observation Period

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

4.8.1.2. Adverse Events of Special Interest

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

The AESIs include:

- Anaphylactic reactions (e-CRF)
- General allergic events (SMQ)
- Infusion reactions (e-CRF)
- Hepatic Disorder (SMQ, lab data)
- Pregnancy (e-CRF)
- Symptomatic overdose with investigational medicinal product (e-CRF)
- Neurocognitive events (CMQ)
- Neurologic events (e-CRF)
- New onset of diabetes (NOD) (lab data, MedDRA 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 open-label TEAE period,
- Death post-treatment: deaths occurring during the post-treatment period.

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4.8.2. Laboratory Safety Variables

Clinical laboratory tests will consist of blood analyses (including hematology, clinical chemistry and other) and urinalysis. Clinical laboratory values will be converted and analyzed in both international units and US conventional units, with associated normal ranges provided by the central laboratory. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries. Potentially clinically significant values (PCSV) ranges will be applied to the laboratory test values as applicable (see Appendix 10.4 for PCSV definitions). For those laboratory tests that do not have PCSV ranges, central laboratory normal ranges will be applied to identify out-of-range values. All laboratory test samples will be collected before study treatment administration during the protocol scheduled visits.

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

Hematology:

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

Clinical chemistry:

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

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 height (cm), weight (kg), heart rate (bpm), respiration (rpm), temperature (C or F), systolic and diastolic blood pressure (mmHg) after resting at least five minutes. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be provided for protocol specified visits and visits will be assigned to the Global Analysis Windows (See Appendix 10.2). Potentially clinically significant

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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 performed before blood samples are collected at visits requiring blood draws. A standard 12-lead ECG will be performed at specified time points according to Appendices 10.5 and 10.6. The ventricular rate, PR, QRS, RR, QT, QTcF, and QTcB intervals will be recorded. Electrocardiogram assessments will be described as normal or abnormal, and visits will be assigned to the Global Analysis Windows (See Appendix 10.2).

4.8.5. Physical Examination Variables

Physical examination will be conducted at the protocol scheduled visits (See Appendices 10.5 and 10.6 for schedule of events). 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).

Tanner assessments for boy and girl will be conducted at the protocol scheduled visits (See Appendices 10.5 and 10.6 for schedule of event).

4.9. Other Variables

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

- The change in hemoglobin A1c (HbA1c [%]) from baseline to post-baseline visits.
- The percent change in hs-CRP from baseline over time.
- The percent change in HDL-C from baseline over time
- The percent change in Apo A1 from baseline over time
- The percent change in Apo B/Apo A1 ratio from baseline over time
- The percent change in Lp(a) from baseline over time
- The percent change in Apo CIII from baseline over time

4.10. Pharmacokinetic Variables

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

4.11. Immunogenicity Variables

Anti-drug antibody variables will include ADA status, titer and neutralizing antibody (NAb) status and time-point/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendices 10.5 and 10.6.

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5. STATISTICAL METHODS

In general, data will be summarized and presented in three patient groups, depending on the status of previous evinacumab treatment exposure:

- Continue Evinacumab: Patients who received evinacumab in a previous study (eg, R1500-CL-1331 or R1500-CL-1629);
- New Evinacumab: Patients without previous exposure to evinacumab (ie, evinacumab naïve);
- Total: All patients, regardless of previous (or not) evinacumab exposure.

These 3 evinacumab exposure groups will be provided for all patients in the respective patient analysis sets. Assuming there are enough adolescent patients (age ranging from 12 years to < 18 years old) to perform an evaluation, the three evinacumab treatment exposure groups will be provided again for the subpopulation of adolescent patients [yes/no]. The subpopulation of adolescent patients has two categories, specifically the patient is an adolescent defined as ranging in age from 12 years to < 18 years old, or the patient is not an adolescent (i.e. an adult) defined as ≥ 18 years of age. Unless otherwise noted, data from both adolescent and adult patient subgroups will be summarized.

Continuous data will be summarized descriptively using the number of patients with data, mean, SD, median, minimum and maximum for each patient group for the study. 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 for each patient group for the study.

5.1. Demographics and Baseline Characteristics

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

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

The summary of demographic and baseline characteristics will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

5.2. Medical History

Medical history will be descriptively summarized by patient group for the study in the safety analysis set, and again for the subpopulation of adolescent patients [yes/no].

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.

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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 and alcohol consumption 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 patient groups. Categorical and ordinal data will be summarized using the number and percentage of patients in the study and for each of the patient groups.

5.3. Prior and Concomitant Medications

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

All concomitant medications during the study, dictionary coded by WHO-DD, will be descriptively summarized by patient group for the study. 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 anatomical or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication. Additionally, concomitant 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.

The summary of prior and concomitant medications will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

5.4. Prohibited Medications

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

5.5. Patient Disposition

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

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

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

The incidence of premature study treatment discontinuation (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically by patient group for the study in the safety analysis set using the Kaplan-Meier method.

The summary of patient disposition will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

5.6. Extent of Study Treatment Exposure and Compliance

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

5.6.1. Exposure to Investigational Product

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

5.6.2. Study Treatment Compliance

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 symptomatic overdose will be reported in the AE e-CRF page and will be described in the adverse event analysis.

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

5.7. Analyses of Efficacy Variables

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

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Descriptive analyses for the efficacy endpoints will be conducted as described below.

5.7.1. Analyses of Efficacy Variables

The observed percent and absolute change in lipid parameters (e.g., LDL-C, Apo B, TG, etc.) will be descriptively summarized for each visit, and by patient group for the study for patients in the SAF, and again for the subpopulation of adolescent patients for patients in the SAF. A within-patient t-test (lipids with a normal distribution) or Wilcoxon signed-rank test (non-parametric test for lipids with a non-normal distribution such as TG) will be provided for secondary efficacy endpoints to descriptively compare each patient's week 24 assessment to their baseline assessment. Missing data will not be imputed.

Unless otherwise specified, the baseline value used for determining percent and absolute change for each patient is defined as follows (also see in Section 6.1).

- For patients who participated in previous evinacumab study R1500-CL-1629, baseline is defined as the last obtained value before the first dose of double-blind study drug in R1500-CL-1629.
- For patients who participated in previous evinacumab study R1500-CL-1331 or did not participate in any previous evinacumab study, baseline is defined as the last obtained value before the first dose of study drug in R1500-CL-1719 (Note: Baseline for patients who participated in R1500-CL-1331 is defined as the baseline from the R1500-CL-1719 study due to the long time between the last study treatment in R1500-CL-1331 and the first study treatment in R1500-CL-1719).

For patients who participated in previous evinacumab study R1500-CL-1629 and received evinacumab in the DBTP, a combined summary of LDL-C including both the DBTP and OLTP assessments in R1500-CL-1629 study and the assessments in R1500-CL-1719 study (i.e., with DBTP first dose date in R1500-CL-1629 study as starting point) will be considered, referencing the double-blind baseline for variable calculations.

For patients who participated in previous evinacumab study R1500-CL-1629 and received placebo in the DBTP but received evinacumab in the OLTP, a combined summary of LDL-C including OLTP assessments in R1500-CL-1629 study and the assessments in R1500-CL-1719 study (i.e., with OLTP first dose date in R1500-CL-1629 study as starting point) will also be considered, referencing the double-blind baseline for variable calculations.

A combined summary of LDL-C assessments when receiving study R1500-CL-1629 evinacumab in the DBTP and OLTP for the above two groups of patients will also be considered.

Prolonged time between last dose of DBTP treatment and first dose of OLTP treatment in R1500-CL-1629 study, or between last dose of OL TP treatment in R1500-CL-1629 study and first dose of open-label treatment in R1500-CL-1719 study will need to be taken into consideration when combining longitudinal efficacy data. Formal statistical testing is not planned.

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5.7.2. Subgroup Analyses of Efficacy Variables

The percent change in LDL-C from baseline over time will be summarized by the following subgroups of interest, assuming there are enough patients in each subgroup level to perform the evaluation:

- Gender (Female, Male)
- Geriatric (No: Age < 65, Yes: Age ≥ 65)
- Adolescent (Yes: Age < 18, No: Age ≥ 18)
- Race
- Ethnicity
- Baseline LDL-C (<130, ≥130 mg/dL)
- HoFH genotyping (homozygous, compound heterozygous, and double heterozygous)
- Receptor-negative mutation in both LDLR alleles (Yes, No)
- LDLR activity (null/null [LDLR activity ≤15%], not null/null [LDLR activity > 15%])
- Apheresis patients (Yes, No)

5.8. Analysis of Safety Data

Safety summaries for the study will be presented by patient group for the study in the safety analysis set, and again for the subpopulation of adolescent patients. No formal inferential testing will be performed. Summaries will be descriptive in nature.

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

General common rules

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

- Safety data in patients who do not belong to the safety analysis set (e.g., exposed but not enrolled) will be listed separately.
- The potentially clinically significant value (PCSV) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (PCSV version dated January 2009 [Appendix 10.4]).

  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).

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- PCSV criteria will determine which patients had at least 1 PCSV during the TEAE period, taking into account all evaluations including unscheduled or repeated evaluations.
- The treatment-emergent PCSV denominator by patient group for a given parameter will be based on the number of patients assessed for that given parameter at least once during the TEAE period.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to Global Analysis Windows defined in Appendix 10.2 /Table 1 in order to provide an assessment for the screening visit through follow-up visit time points.
- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize observed values and change from baseline values by visit.
- Open-label treatment period (OLTP): The treatment period used for quantitative analysis of laboratory and vital signs data in the open-label study period is defined from the day after the first dose of open-label study treatment to the day of the last dose of open-label study treatment + 28 days.
- 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 TEAE period. Post-treatment AEs will be summarized separately.

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

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

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

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The event rate per patient-year (the number of patients with an event divided by total patient-years) will be provided in the table for all TEAEs by SOC and PT. For a patient with an event, patient-year is censored at time of first event. For a patient without an event, patient-year corresponds to the length of the TEAE period.

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 patient 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

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- 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

Patient Deaths

The following summaries of deaths will be generated.

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

5.8.2. Analysis of Adverse Events of Special Interest

- Treatment-emergent adverse events of special interest (AESI), as listed in Section 4.8.1.2, will be presented by SOC and PT as applicable. AESI are defined by SMQ, CMQ, and/or 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 treatment period;
- Time from first study treatment to first infusion reaction;

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5.8.3. Clinical Laboratory Measurements

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

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

Individual patient laboratory parameter measurements will be additionally evaluated by PCSV criteria (See Appendix 10.4), specifically identifying patients with at least one post-baseline measurement that meets the PCSV criteria within the TEAE period. These laboratory parameters will be presented by the biological functions defined in Section 4.8.2. The incidence of PCSVs at any time during the TEAE period will be summarized regardless of the baseline level, and again according to the following baseline categories:

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

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

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

Drug-induced liver injury

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

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

The summary of clinical laboratory parameter measurements will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

5.8.4. Analysis of Vital Signs

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

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

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

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

The summary of vital signs will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

5.8.5. Analysis of 12-Lead ECG

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

- Normal/missing;
- Abnormal

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

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

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

The summary of ECG data will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

5.8.6. Physical Exams

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

The summary of physical exams will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

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5.9. Analysis of Other Variables

Summaries for the treatment period will be presented by patient group for the study in the safety analysis set. No formal inferential testing will be performed. 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, Lp(a), Apo CIII 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, Lp(a), Apo CIII. Applying the PCSV criteria at any time during the TEAE period, the number of patients (and percentages) meeting the criteria will be summarized.

The summary of other variables will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

5.10. Analysis of Pharmacokinetic Variables

Descriptive statistics of concentrations of total evinacumab, total ANGPTL3 will be presented. Mean concentrations of each analyte will be tabulated by visit for the study in the PK analysis set, 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 comparison of concentrations of evinacumab and total ANGPTL3 between Caucasian patients and Japanese patients may be performed if sufficient data are collected.

Concentrations of evinacumab measured before and post apheresis procedure will be summarized descriptively. Other descriptive sub-group analyses may be performed as appropriate, including concomitant medications, parent studies, previous treatment with evinacumab, adolescents, renal impairment, etc.

When appropriate, relationship between concentrations of evinacumab and LDL-C or other biomarkers may be evaluated descriptively.

The summary of pharmacokinetic variables will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

5.11. Analysis of Immunogenicity Variables

The summary of immunogenicity variables will be provided for all patients in the study in the safety analysis set, and again for the subpopulation of adolescent patients.

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

The ADA variables described in Section 4.11 will be summarized using descriptive statistics by patient group for the study in the ADA analysis set. Listings of ADA positivity and titers

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presented by patient, time point, and study treatment received will be provided. Incidence of treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (N) and percent of patients (%), summarized by patient group. The baseline ADA status in the parent study will be considered as the baseline ADA status of the patient.

Anti-drug antibody status and titer over the study duration may be classified as follows:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-first dose ADA results negative, or a positive assay response at baseline, with all post-first dose ADA assay responses less than 9-fold over baseline titer levels.
- Treatment emergent - defined as any post- first dose ADA positive response when baseline results are negative or missing.
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post-first dose samples separated by at least a 16-week [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 collected and analyzed time point
  - Transient - Not persistent or indeterminate
- Treatment boosted - defined as any post- first dose ADA response that is at least 9-fold over baseline titer levels when baseline results are positive

Samples positive in the ADA assay will be further characterized for ADA titers and for the presence of neutralizing antibody (NAb) response.

- 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)

  NAb status (positive or negative) will be reported in the NAb analysis set. The impact of NAb on concentrations of evinacumab, safety and efficacy will be evaluated.

5.11.2. Association of Immunogenicity with Exposure, Safety and Efficacy

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

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

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

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline value used for determining percent and absolute change for each patient is defined as follows:

- For patients who participated in previous evinacumab study R1500-CL-1629, baseline is defined as the last obtained value before the first dose of double-blind study drug in R1500-CL-1629
- For patients who participated in previous evinacumab study R1500-CL-1331 or did not participate in any previous evinacumab study, baseline is defined as the last obtained value before the first dose of study drug in R1500-CL-1719 (Note: Baseline for patients who participated in R1500-CL-1331 is defined as the baseline from the R1500-CL-1719 study due to the long time between the last study treatment in R1500-CL-1331 and the first study treatment in R1500-CL-1719).

6.2. Data Handling Convention for Efficacy Variables

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

6.3. Data Handling Convention for Missing Data

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

Date of First/Last Study Treatment

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

Adverse Event

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

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

Medication/Procedure

No imputation of medication/procedure start/end dates will be performed. If a medication date is missing or partially missing and it cannot be determined whether it was taken prior or

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concomitantly or stopped prior to the first study treatment administration, it will be considered as concomitant medication/procedure.

Potentially Clinically Significant Value (PCSV)

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

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

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

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

6.4. Visit Windows

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

6.5. Unscheduled Assessments

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

6.6. Pooling of Centers for Statistical Analyses

Not applicable.

6.7. Statistical Technical Issues

Not applicable.

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7. TIMING OF STATISTICAL ANALYSES

In order to provide information from this study, data may be analyzed on an ongoing basis. The results will not be used to change the conduct of the ongoing study in any aspect.

Additionally, an interim analysis is planned for the subpopulation of adolescent patients. This planned interim analysis will be conducted as soon as all adolescent patients have been enrolled and all their data through week 24 has been collected and validated. For adolescent patients, the analysis will consist of the final analysis of the primary (safety) and secondary (lipids) endpoints collected during the initial 24 weeks of study treatment exposure. The safety and lipids analyses will be performed on all data collected and validated at the time of this adolescent subpopulation interim analysis.

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized.

8. SOFTWARE

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

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9. REFERENCES

1. ICH. (1996, July 30). ICH Harmonized tripartite guideline: Structure and content of clinical study reports (E3). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
2. ICH. (1997, July 17). ICH Harmonized tripartite guideline: General considerations for clinical trials (E8). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
3. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
4. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003 Jan 28;107(3):499-511.
5. Zigmond AS, Snaith RP: The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica 1983, 67:361-70.
6. Bjelland I, Dahl AA, Haug TT et al. Review: The validity of the hospital anxiety and depression scale, an updated literature review. J Psychosom Res 2002;52:69-77.
7. Herrmann C. International Experiences with the Hospital Anxiety and Depression Scale – A Review of Validation Data and Clinical Results; Journal of Psychosomatic Research, Vol. 42, No. 1, pp 17-41, 1997
8. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997 Nov; 35(11):1095-108.
9. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012 Oct 4;367(14):1355-60. doi: 10.1056/NEJMsr1203730.
10. Mehrotra DV, Li X, Liu J, Lu K. Analysis of longitudinal clinical trials with missing data using multiple imputation in conjunction with robust regression. Biometrics. 2012 Dec;68(4):1250-9. doi: 10.1111/j.1541-0420.2012.01780.x.
11. Goldberg AC, Hopkins PN, Toth PP et al., Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011; 5(3):133-40

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10. APPENDIX

10.1. Summary of Statistical Analyses

All safety and efficacy data will be summarized descriptively.

10.2. Windows for Analysis Time Points

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

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

1. Study day is defined as the number of days since the first study treatment administration +1. The first study treatment occurs on
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 enrolled but not treated patients, Day 1 is the day of enrollment.

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Table 1: Global Analysis Windows

Visit label	Targeted Study Day	Analysis Window in Study Day
Screening	< Day 1	Measurement obtained prior to first study treatment, and not defined as baseline visit
Day 1	1	Measurement obtained closest to first study treatment, while remaining prior to first study treatment
Week 4	29	15 to 42
Week 4K, where K=2,3,…	28K+1	15+28*(K-1) to 42+28*(K-1)
FU – W4	last study trt to 28 days after last study trt	Last study trt to 56 days after last study trt
FU – W12	last study trt to 84 days after last study trt	57 days after last study trt to 112 days after last study trt
FU – W24	last study trt to 168 days after last study trt	113 days after last study trt to 196 days after last study trt
FU > W24	N/A	>196 days after last study trt
Study days are calculated from the day of first study treatment administration, the day of first study treatment administration being Day 1.		

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

Table 2: 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	Yes	• CMQ for neurocognitive events as defined based on Regulatory Agency request for another lipid lowering program (See Table 3 in Appendix 10.3 for the list of terms)
Neurologic events	Yes	No

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AESI	Using an e-CRF specific tick box on AE page	Using Standard MedDRA Query (SMQ)/company MedDRA Query (CMQ) or lab data
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 Hb1Ac < 6.5% at baseline 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 with diabetes mellitus at baseline	No	For patients with medical history of diabetes as specified in Cardiovascular History and Cardiovascular Risk Factors and Medical History CRF pages, each of the following criteria will be considered, respectively:

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AESI	Using an e-CRF specific tick box on AE page	Using Standard MedDRA Query (SMQ)/company MedDRA Query (CMQ) or lab data
		• 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)

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Table 3: 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

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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)

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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

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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

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10.5. Schedule of Time and Events for Protocol Amendment 5A

Table 4: Schedule of Events – Run-In and Screening

Study Procedure	Run-in[7]	Screening[1]
Visit	**-1**	**1A**
Day	**-85 to -15**	**-14 to -1**
Visit Window (Day)		
Week	**-12 to -2**	**-2 to -1**
Screening:		
Informed Consent	X	
Inclusion/Exclusion		X
Medical/Surgical History	X	X
Alcohol/Smoking Habits		X
Medication History	X	X
Demographics		X
Treatment:		
Concomitant Medications and Procedures (including LMT and apheresis)[2]	X	X
Efficacy:		
Lipid Panel[3]		X
Specialty Lipid Panel[3]		X
Safety:		
Adverse Events	X	X
Physical Examination		X
Measured Height		X
Body Weight		X
Vital Signs	X	X
Electrocardiogram[4]		X
Contraception Use Reminder		X
Remind Male Patients to Use Condoms		X
Laboratory Testing:		
Hematology		X
Blood Chemistry		X
Serum Pregnancy Test[5]		X
Urine Pregnancy Test[5]	X	
Urinalysis		X
hs-CRP		X
FSH[5]	X	
TSH[6]		X
Hepatitis B Surface Antigen[6]		X
Hepatitis C Antibody[6]		X
Research Samples		X
DNA Sample for HoFH Genotyping[8]	X	
Other:		
Review of Diet	X	X
Reminder of LMT Compliance	X	X

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Table 5: Schedule of Events – Screening for Patients with No Run-In

Study Procedure	**Screening[1]**
Visit	**1A**
Day	**-14 to -1**
Visit Window (Day)	
Week	**-2 to -1**
Screening:	
Informed Consent	X
Inclusion/Exclusion	X
Medical/Surgical History	X
Alcohol/Smoking Habits	X
Medication History	X
Demographics	X
Treatment:	
Concomitant Medications and Procedures (including LMT and apheresis)[2]	X
Efficacy:	
Lipid Panel[3]	X
Specialty Lipid Panel[3]	X
Safety:	
Adverse Events	X
Physical Examination	X
Measured Height	X
Body Weight	X
Vital Signs	X
Electrocardiogram[4]	X
Contraception Use Reminder	X
Remind Male Patients to Use Condoms	X
Laboratory Testing:	
Hematology	X
Blood Chemistry	X
Serum Pregnancy Test[5]	X
Urine Pregnancy Test[5]	
Urinalysis	X
hs-CRP	X
FSH[5]	X
TSH[6]	X
Hepatitis B Surface Antigen[6]	X
Hepatitis C Antibody[6]	X
Research Samples	X
DNA sample for HoFH Genotyping[7,8]	X
Other:	
Review of Diet	X
Reminder of LMT Compliance	X

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Table 6: Schedule of Events – Open-Label Treatment Period and Follow-Up

Study Procedure	Baseline[1]	Open-Label Treatment Period						Q4-Week Visit Sequence[11]	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**A**	**B**
Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**±7 days**	**±7 days**
Visit Window (Day)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**		
Baseline:									
Informed Consent	X								
Treatment:									
Administer IV Open-Label Study Drug[3,4]	X	X	X	X	X	X	X	X	X
Concomitant Medications and Procedures (including LMT and apheresis)[3]	X	X	X	X	X	X	X	X	X
Efficacy:									
Lipid Panel[3,5]	X		X	X	X		X		X
Specialty Lipid Panel[3,5]	X		X		X		X		X
Safety:									
Adverse Events	X	X	X	X	X	X	X	X	X
Physical Examination	X								
Body Weight	X	X	X	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X
Electrocardiogram[6]	X						X		
Contraception Use Reminder	X	X	X	X	X	X	X	X	X
Remind Male Patients to Use Condoms	X	X	X	X	X	X	X	X	X
Laboratory Testing[2]:									
Hematology	X		X		X		X		X
Blood Chemistry	X		X		X		X		X
Serum Pregnancy Test[7]									
Urine Pregnancy Test[7]	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X
hs-CRP	X		X		X		X		X
HbA1C	X			X			X		
Research Samples	X		X				X		X

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Study Procedure	Baseline[1]	Open-Label Treatment Period						Q4-Week Visit Sequence[11]	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**A**	**B**
Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**±7 days**	**±7 days**
Visit Window (Day)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**		
ADA Samples[8]	X						X		
Pharmacokinetics (PK) of Evinacumab [9,10]	X[10]			X[10]			X[10]		
Optional DNA sample[14]									
Other:									
Review of Diet	X	X	X	X	X	X	X	X	X
Reminder of LMT Compliance	X	X	X	X	X	X	X	X	X

Study Procedure	Q4-Week Visit Sequence[10]				End of Treatment (4 weeks post last dose)/ Early Termination Visit[12]	24-Week Follow-up Period				
Visit	**C**	**D**	**E**	**F**		**PV 8 weeks post last dose[13]**	**12 weeks post last dose**	**PV 16 weeks post last dose[13]**	**20 weeks post last dose**	**24 weeks post last dose/ End of Study Visit**
Visit Window (Day)	±7	±7	±7	±7		**F/U** ±5	**F/U** ±5	**F/U** ±5	**F/U** ±5	**F/U** ±5
Treatment:										
Administer IV Open-Label Study Drug[3]	X	X	X	X						
Concomitant Medications and Procedures including LMT and apheresis)[3]	X	X	X	X	X	X	X	X	X	X
Efficacy:										
Lipid Panel[3,5]	X	X		X	X		X			X
Specialty Lipid Panel[3,5]		X		X	X		X			X
Safety:										
Adverse Events	X	X	X	X	X	X	X	X	X	X
Physical Examination										X

Study Procedure	Q4-Week Visit Sequence[10]				End of Treatment (4 weeks post last dose)/ Early Termination Visit[12]	24-Week Follow-up Period				
Visit	C	D	E	F		PV 8 weeks post last dose[13]	12 weeks post last dose	PV 16 weeks post last dose[13]	20 weeks post last dose	24 weeks post last dose/ End of Study Visit
Visit Window (Day)	±7	±7	±7	±7		F/U ±5	F/U ±5	F/U ±5	F/U ±5	F/U ±5
Body Weight	X	X	X	X	X					X
Vital Signs[4]	X	X	X	X	X		X		X	X
Electrocardiogram[6]				X	X					X
Contraception Use Reminder	X	X	X	X	X	X	X	X	X	X
Remind Male Patients to Use Condoms	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[2]:										
Hematology		X		X	X		X		X	X
Blood Chemistry		X		X	X		X		X	X
Serum Pregnancy Test[7]					X					X
Urine Pregnancy Test[7]	X	X	X	X		X	X	X	X	X
Urinalysis		X		X	X					X
hs-CRP		X		X	X					X
HbA1C	X			X	X		X			X
Research Samples				X	X					X
ADA Samples[8]				X	X					X
Pharmacokinetics (PK) of Evinacumab[9,10]	X[10]			X[10]	X					X
Optional DNA Sample[14]	X									
Other:										
Review of Diet	X	X	X	X	X	X	X	X	X	X
Reminder of LMT Compliance	X	X	X	X	X	X	X	X	X	X

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10.5.1. Footnotes for Schedule of Events Table 4

1. All evinacumab-naïve patients will enter the screening period. Patients who participated in a previous evinacumab study and who completed an end of study visit in the previous evinacumab study within 7 days prior to the baseline/day 1 visit for this open label study do not have to enter the screening period and may enroll directly in this study. Patients from previous evinacumab studies who do not enter this study within 7 days of completing the EOS visit of the previous study, must undergo screening.
2. For patients undergoing apheresis: Study assessments should be performed and blood samples should be collected immediately before the lipoprotein apheresis procedure.
3. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, and non-HDL-C, and the specialty lipid panel: Apo B, ratio of Apo B/Apo A-1, Lp(a), and ApoCIII.
4. Electrocardiograms should be performed before blood samples are collected at visits requiring blood draws.
5. WOCBP only, confirm required contraception use and reminder of pregnancy reporting.
6. For evinacumab treatment naïve patients only.
7. Only for patients who require HoFH genotyping, stabilization of their lipoprotein apheresis schedule or stabilization on their background medical LMT
8. DNA sample for HoFH genotyping should be taken only for patients who have not been enrolled in a previous evinacumab or alirocumab clinical study

10.5.2. Footnotes for the Schedule of Events Table 5

1. All evinacumab-naïve patients will enter the screening period. Patients who participated in a previous evinacumab study and who completed an end of study visit in the previous evinacumab study within 7 days prior to the baseline/day 1 visit may enroll directly and do not have to enter a run-in or screening period. Patients from previous evinacumab studies who do not enter this study within 7 days of completing the EOS visit of the previous study, must undergo screening.
2. For patients undergoing apheresis: Study assessments should be performed and blood samples should be collected immediately before the lipoprotein apheresis procedure.
3. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, and non-HDL-C, and the specialty lipid panel: Apo B, ratio of Apo B/Apo A-1, Lp(a), and ApoCIII.
4. Electrocardiograms should be performed before blood samples are collected at visits requiring blood draws.
5. WOCBP only, confirm required contraception use and reminder of pregnancy reporting.
6. For evinacumab-naïve patients only

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7. DNA sample for HoFH genotyping should be taken only for patients who have not been enrolled in a previous evinacumab or alirocumab clinical study

10.5.3. Footnotes for Schedule of Events Table 6

1. For patients directly transitioning from a previous evinacumab study: all assessments and procedures should be performed after end of study assessments and procedures have been completed in the previous study, if applicable. Only assessments not performed at the previous end of study visit need to be performed-at the baseline visit.
2. All laboratory samples should be collected before administration of study drug.
3. Study assessments should be performed and blood samples should be collected before study drug administration. For patients undergoing apheresis: Study assessments should be performed and blood samples should be collected immediately before the lipoprotein apheresis procedure. Every effort should be made for the patient to receive study drug immediately after completion of the apheresis procedure, but patients can receive study drug 1 day before 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 apheresis procedure and sample collection, the visit window may not apply.
4. Vital signs (temperature, sitting blood pressure, pulse, and respiration rate) should be measured before study drug administration on days when study drug is administered. On dosing days, patients should remain in the clinic for 60 minutes after the end of the IV infusion for monitoring. Pulse and blood pressure should be measured 30 and 60 minutes after the end of the IV infusion.
5. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, and non-HDL-C, and the specialty lipid panel: Apo B, ratio of Apo B/Apo A-1, Lp(a), and ApoCIII.
6. Electrocardiograms should be performed before blood samples are collected at visits requiring blood draws.
7. All patients will be reminded of protocol-specified contraception use and pregnancy reporting.
8. The ADA sample should be drawn before study drug administration or immediately prior to the apheresis procedure, if applicable.
9. Including assay of total ANGPTL3.
10. PK sample collected in all patients. For patients undergoing apheresis, a PK sample should be collected immediately before the apheresis procedure. For patients who are not undergoing the apheresis procedure, the PK sample should be drawn before the dose of study drug.

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11. After the week 24 visit, visits are in a strict sequence of A through F and should occur every 4 weeks. After visit F, the sequence repeats (visits A through F) until the end of treatment visit.
12. The end of treatment visit should occur 4 weeks post the last dose. Patients who prematurely discontinue from study drug should return to the clinic within 5 days if possible for end of treatment visit assessments. At this visit, WOCBP will be provided with urine pregnancy tests with instructions to test for pregnancy at home every 4 weeks after this visit and Q4W when phone visits are scheduled (weeks 8 and 16 post last dose). Urine pregnancy testing will be done during clinic visits at week 12, week 20, and week 24.
13. At weeks 8 and 16 of the follow-up period all patients will be contacted by phone to query LMT compliance, to inquire about AEs or changes to concomitant medications, confirm required contraception use, and remind patients of pregnancy reporting. Women of childbearing potential will report the results of their home pregnancy test.
14. Should be collected at the baseline visit or at any study visit for patients who have not previously been enrolled in an evinacumab or alirocumab clinical study.

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10.6. Schedule of Time and Events for Protocol Amendment 5B

Table 7: Schedule of Events – Run-In and Screening

Study Procedure	Run-in[9]	Screening[1]
Visit	**-1**	**1A**
Day	**-85 to -15**	**-14 to -1**
Visit Window (Day)		
Week	**-12 to -2**	**-2 to -1**
Screening:		
Informed Consent	X	
Inclusion/Exclusion		X
Medical/Surgical History	X	X
Alcohol/Smoking Habits		X
Medication History	X	X
Demographics		X
Treatment:		
Concomitant Medications and Procedures (including LMT and apheresis)[2]	X	X
Efficacy:		
Lipid Panel[3]		X
Specialty Lipid Panel[3]		X
Safety:		
Adverse Events	X	X
Physical Examination		X
Measured Height		X
Body Weight		X
Vital Signs	X	X
Electrocardiogram[4]		X
Tanner Stage[5]		X
Contraception Use Reminder		X
Remind male patients to use condoms		X
Laboratory Testing:		
Hematology		X
Blood Chemistry		X
Sex Hormones[5,6]		X
Serum Pregnancy Test[7]		X
Urine Pregnancy Test[7]	X	
Urinalysis		X
hs-CRP		X
FSH[7]	X	
TSH[8]		X
Hepatitis B Surface Antigen[8]		X
Hepatitis C Antibody[8]		X

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Study Procedure	Run-in[9]	Screening[1]
Visit	**-1**	**1A**
Day	**-85 to -15**	**-14 to -1**
Visit Window (Day)		
Week	**-12 to -2**	**-2 to -1**
Research Samples		X
DNA Sample for HoFH Genotyping[10]	X	
Other:		
Review of Diet	X	X
Reminder of LMT Compliance	X	X

Table 8: Schedule of Events – Screening for Patients with No Run-In

Study Procedure	Screening[1]
Visit	**1A**
Day	**-14 to -1**
Visit Window (Day)	
Week	**-2 to -1**
Screening:	
Informed Consent	X
Inclusion/Exclusion	X
Medical/Surgical History	X
Alcohol/Smoking Habits	X
Medication History	X
Demographics	X
Treatment:	
Concomitant Medications and Procedures (including LMT and apheresis)[2]	X
Efficacy:	
Lipid Panel[3]	X
Specialty Lipid Panel[3]	X
Safety:	
Adverse Events	X
Physical Examination	X
Measured Height	X
Body Weight	X
Vital Signs	X
Electrocardiogram[4]	X
Tanner Stage[5]	X
Contraception Use Reminder	X
Remind male patients to use condoms	X
Laboratory Testing:	
Hematology	X

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Study Procedure	**Screening[1]**
Visit	**1A**
Day	**-14 to -1**
Visit Window (Day)	
Week	**-2 to -1**
Blood Chemistry	X
Sex Hormones[5,6]	X
Serum Pregnancy Test[7]	X
Urine Pregnancy Test[7]	
Urinalysis	X
hs-CRP	X
FSH[7]	X
TSH[8]	X
Hepatitis B Surface Antigen[8]	X
Hepatitis C Antibody[8]	X
Research Samples	X
DNA sample for HoFH Genotyping[9]	X
Other:	
Review of Diet	X
Reminder of LMT Compliance	X

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Table 9: Schedule of Events – Open-Label Treatment Period and Follow-Up

Study Procedure	Baseline[1]	Open-Label Treatment Period						Q4-Week Visit Sequence[13]	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**A**	**B**
Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**±7 days**	**±7 days**
Visit Window (Day)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**		
Baseline:									
Informed Consent	X								
Treatment:									
Administer IV Open-Label Study Drug[3,4]	X	X	X	X	X	X	X	X	X
Concomitant Medications and Procedures (including LMT and apheresis)[3]	X	X	X	X	X	X	X	X	X
Efficacy:									
Lipid Panel[3,5]	X		X	X	X		X		X
Specialty Lipid Panel[3,5]	X		X		X		X		X
Safety:									
Adverse Events	X	X	X	X	X	X	X	X	X
Physical Examination	X								
Measured Height[6]	X						X		
Body Weight	X	X	X	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X
Electrocardiogram[7]	X						X		
Tanner Stage[6]							X		
Contraception Use Reminder	X	X	X	X	X	X	X	X	X
Remind male patients to use condoms	X	X	X	X	X	X	X	X	X
Laboratory Testing[2]:									
Hematology	X		X		X		X		X

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Study Procedure	Baseline[1]	Open-Label Treatment Period						Q4-Week Visit Sequence[13]	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**A**	**B**
Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**±7 days**	**±7 days**
Visit Window (Day)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**		
Blood Chemistry	X		X		X		X		X
Sex Hormones[6,8]							X		
Serum Pregnancy Test[7]									
Urine Pregnancy Test[9]	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X
hs-CRP	X		X		X		X		X
HbA1C	X			X			X		
Research Samples	X		X				X		X
ADA Samples[10]	X						X		
Pharmacokinetics (PK) of Evinacumab [11,12]	X[12]	X[12,17]	X[12,17]	X[12]	X[12,17]	X[12,17]	X[12]	X[12,17]	
Optional DNA sample[16]									
Other:									
Review of Diet	X	X	X	X	X	X	X	X	X
Reminder of LMT Compliance	X	X	X	X	X	X	X	X	X

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Study Procedure	Q4-Week Visit Sequence[10]				End of Treatment (4 weeks post last dose)/ Early Termination Visit[14]	24-Week Follow-up Period				
Visit	C	D	E	F		PV 8 weeks post last dose[15]	12 weeks post last dose	PV 16 weeks post last dose[15]	20 weeks post last dose	24 weeks post last dose/ End of Study Visit
Visit Window (Day)	**±7**	**±7**	**±7**	**±7**		**F/U** ±5	**F/U** ±5	**F/U** ±5	**F/U** ±5	**F/U** ±5
Treatment:										
Administer IV Open-Label Study Drug[3]	X	X	X	X						
Concomitant Medications and Procedures including LMT and apheresis)[3]	X	X	X	X	X	X	X	X	X	X
Efficacy:										
Lipid Panel[3,5]	X	X		X	X		X			X
Specialty Lipid Panel[3,5]		X		X	X		X			X
Safety:										
Adverse Events	X	X	X	X	X	X	X	X	X	X
Physical Examination										X
Measured Height[6]				X	X					X
Body Weight	X	X	X	X	X					X
Vital Signs[4]	X	X	X	X	X		X		X	X
Electrocardiogram[7]				X	X					X
Tanner Stage[6,8]				X	X					X
Contraception Use Reminder	X	X	X	X	X	X	X	X	X	X
Remind male patients to use condoms	X	X	X	X	X	X	X	X	X	X

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Study Procedure	Q4-Week Visit Sequence[10]				End of Treatment (4 weeks post last dose)/ Early Termination Visit[14]	24-Week Follow-up Period				
Visit	C	D	E	F		PV 8 weeks post last dose[15]	12 weeks post last dose	PV 16 weeks post last dose[15]	20 weeks post last dose	24 weeks post last dose/ End of Study Visit
Visit Window (Day)	**±7**	**±7**	**±7**	**±7**		**F/U ±5**	**F/U ±5**	**F/U ±5**	**F/U ±5**	**F/U ±5**
Laboratory Testing[2]:										
Hematology		X		X	X		X		X	X
Blood Chemistry		X		X	X		X		X	X
Serum Pregnancy Test[9]					X					X
Urine Pregnancy Test[9]	X	X	X	X		X	X	X	X	X
Urinalysis		X		X	X					X
hs-CRP		X		X	X					X
HbA1C	X			X	X		X			X
Research Samples				X	X					X
ADA Samples[10]				X	X					X
Pharmacokinetics (PK) of Evinacumab[11,12]	X[12]			X[12]	X					X
Optional DNA Sample[16]	X									
Other:										
Review of Diet	X	X	X	X	X	X	X	X	X	X
Reminder of LMT Compliance	X	X	X	X	X	X	X	X	X	X

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10.6.1. Footnotes for Schedule of Events Table 7

1. All evinacumab-naïve patients will enter the screening period. Patients who participated in a previous evinacumab study and who completed an end of study visit in the previous evinacumab study within 7 days prior to the baseline/day 1 visit for this open label study do not have to enter the screening period and may enroll directly in this study. Patients from previous evinacumab studies who do not enter this study within 7 days of completing the EOS visit of the previous study, must undergo screening.
2. For patients undergoing apheresis: Study assessments should be performed and blood samples should be collected immediately before the lipoprotein apheresis procedure.
3. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, and non-HDL-C, and the specialty lipid panel: Apo B, ratio of Apo B/Apo A-1, Lp(a), and ApoCIII.
4. Electrocardiograms should be performed before blood samples are collected at visits requiring blood draws.
5. Assessment of Tanner Stage, sex hormones, and post-baseline height only applicable to patients < 18 years old.
6. Sex hormones include luteinizing hormone, FSH , estradiol, and total testosterone.
7. WOCBP only, confirm required contraception use and reminder of pregnancy reporting. For adolescent patients not of childbearing potential at Screening, confirm whether the patient is of childbearing potential at every visit. If an adolescent patient becomes of childbearing potential during the course of the study, exclusion criterion #14 applies and administer pregnancy tests administered every 4 weeks.
8. For evinacumab treatment naïve patients only.
9. Only for patients who require HoFH genotyping, stabilization of their lipoprotein apheresis schedule or stabilization on their background medical LMT.
10. DNA sample for HoFH genotyping should be taken only for patients who have not been enrolled in a previous evinacumab or alirocumab clinical study.

10.6.2. Footnotes for the Schedule of Events Table 8

1. All evinacumab-naïve patients will enter the screening period. Patients who participated in a previous evinacumab study and who completed an end of study visit in the previous evinacumab study within 7 days prior to the baseline/day 1 visit may enroll directly and do not have to enter a run-in or screening period. Patients from previous evinacumab studies who do not enter this study within 7 days of completing the EOS visit of the previous study, must undergo screening.
2. For patients undergoing apheresis: Study assessments should be performed and blood samples should be collected immediately before the lipoprotein apheresis procedure.

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3. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, and non-HDL-C, and the specialty lipid panel: Apo B, ratio of Apo B/Apo A-1, Lp(a), and ApoCIII.
4. Electrocardiograms should be performed before blood samples are collected at visits requiring blood draws.
5. Assessment of Tanner Stage, sex hormones, and post-baseline height only applicable to patients < 18 years old.
6. Sex hormones include luteinizing hormone, FSH , estradiol, and total testosterone
7. WOCBP only, confirm required contraception use and reminder of pregnancy reporting. For adolescent patients not of childbearing potential at Screening, confirm whether the patient is of childbearing potential at every visit. If an adolescent patient becomes of childbearing potential during the course of the study, exclusion criterion #14 applies and administer pregnancy tests administered every 4 weeks.
8. For evinacumab-naïve patients only.
9. DNA sample for HoFH genotyping should be taken only for patients who have not been enrolled in a previous evinacumab or alirocumab clinical study.

10.6.3. Footnotes for Schedule of Events Table 9

1. For patients directly transitioning from a previous evinacumab study: all assessments and procedures should be performed after end of study assessments and procedures have been completed in the previous study, if applicable. Only assessments not performed at the previous end of study visit need to be performed-at the baseline visit.
2. All laboratory samples should be collected before administration of study drug.
3. Study assessments should be performed and blood samples should be collected before study drug administration. For patients undergoing apheresis: Study assessments should be performed and blood samples should be collected before the lipoprotein apheresis procedure; Every effort should be made for the patient to receive study drug immediately after completion of the apheresis procedure, but patients can receive study drug 1 day before 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 apheresis procedure and sample collection, the visit window may not apply.
4. Vital signs (temperature, sitting blood pressure, pulse, and respiration rate) should be measured before study drug administration on days when study drug is administered. On dosing days, patients should remain in the clinic for 60 minutes after the end of the IV infusion for monitoring. Pulse and blood pressure should be measured 30 and 60 minutes after the end of the IV infusion.

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5. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, and non-HDL-C, and the specialty lipid panel: Apo B, ratio of Apo B/Apo A-1, Lp(a), and ApoCIII.
6. Assessment of Tanner Stage, sex hormones, and post-baseline height only applicable to patients < 18 years old.
7. Electrocardiograms should be performed before blood samples are collected at visits requiring blood draws.
8. Sex hormones include luteinizing hormone, FSH, estradiol, and total testosterone.
9. All patients will be reminded of protocol-specified contraception use and pregnancy reporting. For adolescent patients not of childbearing potential at Screening, confirm whether the patient is of childbearing potential at every visit. If an adolescent patient becomes of childbearing potential during the course of the study, exclusion criterion #14 applies and administer pregnancy tests administered every 4 weeks.
10. The ADA sample should be drawn before study drug administration or immediately prior to the apheresis procedure, if applicable.
11. Including assay of total ANGPTL3.
12. PK sample collected in all patients. For patients undergoing apheresis, a PK sample should be collected immediately before the apheresis procedure. For patients who are not undergoing the apheresis procedure, the PK sample should be drawn before the dose of study drug.
13. After the week 24 visit, visits are in a strict sequence of A through F and should occur every 4 weeks. After visit F, the sequence repeats (visits A through F) until the end of treatment visit.
14. The end of treatment visit should occur 4 weeks post the last dose. Patients who prematurely discontinue from study drug should return to the clinic within 5 days if possible for end of treatment visit assessments. At this visit, WOCBP will be provided with urine pregnancy tests with instructions to test for pregnancy at home every 4 weeks after this visit and Q4W when phone visits are scheduled (weeks 8 and 16 post last dose). Urine pregnancy testing will be done during clinic visits at week 12, week 20, and week 24.
15. At weeks 8 and 16 of the follow-up period all patients will be contacted by phone to query LMT compliance, to inquire about AEs or changes to concomitant medications, confirm required contraception use, and remind patients of pregnancy reporting. Women of childbearing potential will report the results of their home pregnancy test.
16. Should be collected at the baseline visit or at any study visit for patients who have not previously been enrolled in an evinacumab or alirocumab clinical study.
17. PK sample (including ANGPTL3) only for evinacumab-naïve adolescent patients.

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