Clinical Development and Regulatory Affairs
Biostatistics and Data Management

REGENERON
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STATISTICAL ANALYSIS PLAN
VERSION: FINAL

A THREE-PART, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF EVINACUMAB IN PEDIATRIC PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Compound:	REGN1500 (Evinacumab)
Protocol Number:	R1500-CL-17100
Clinical Phase:	Phase 1b/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Version/Date:	1.0 / February 16, 2021

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

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

LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LMT	Lipid modifying therapy
Lp(a)	Lipoprotein a
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed-effect model with repeated measures
OLTP	Open-label treatment period
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PMM	Pattern Mixture Model
PT	Preferred term
Q4W	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMT	Safety Monitoring Team
SOC	System organ class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. 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 R1500-CL-17100 study. The content of this SAP is inclusive of all analyses (the first, second, and third step analyses) as described in the protocol.

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

1.1. Background/Rationale

Familial hypercholesterolemia (FH), a primary hyperlipidemia driven by genetic mutation(s) primarily in the low-density lipoprotein (LDL) receptor (LDLR), is the most common monogenic hypercholesterolemia condition in children. The most rare and severe form of FH is homozygous familial hypercholesterolemia (HoFH). It is an inherited autosomal dominant disorder primarily resulting from mutations in the LDLR or, less frequently, from mutations in 3 associated genes: proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (APOB), and LDL receptor adaptor protein 1 (LDLRAP1). Depending on the genes affected and the mutations that are present, patients are categorized as either true homozygotes, compound heterozygotes, or double heterozygotes. True homozygotes have the same mutation on both alleles. Compound heterozygotes have different mutations on the 2 alleles. Double heterozygotes have mutations in 2 different genes. The resulting phenotype includes deficient or defective LDL receptors on the surface of hepatocytes causing impaired clearance of circulating low-density lipoprotein cholesterol (LDL-C). This leads to severe hypercholesterolemia, often 3 to 6 times normal (≥500 mg/dL), starting in infancy, which results in an exceedingly high risk of developing premature atherosclerosis, as well as valvular and supravalvular stenosis.

Evinacumab (also referred to as REGN1500) is a fully human monoclonal antibody that specifically binds to and inhibits angiopoietin-like 3 (ANGPTL3). Evinacumab inhibition of ANGPTL3 leads to reductions in LDL-C, high-density lipoprotein cholesterol (HDL-C), and TGs, mirroring the lipid phenotype observed in humans with ANGPTL3 loss of function (LOF). Evinacumab reduces LDL-C independent of the presence of LDL receptor (LDLR) by promoting very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation. Evinacumab blockade of ANGPTL3 lowers TGs and HDL-C by rescuing lipoprotein lipase and endothelial lipase activities, respectively.

Treatment with evinacumab in adult and adolescent patients with HoFH resulted in an approximately 50% mean reduction in LDL-C in the pivotal phase 3 study, R1500-CL-1629.

The primary purpose of this current study is to demonstrate the efficacy, safety and tolerability of evinacumab in pediatric patients, aged 5 through 11 years, with HoFH. Additional background

information on the study drug and development program can be found in the Investigator's Brochure.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective for Part A of the study is:

- To assess the PK of evinacumab in pediatric patients with HoFH

The primary objective for Part B of the study is:

- To demonstrate a reduction of LDL-C by evinacumab in pediatric (5 to 11 years of age) patients with HoFH

1.2.2. Secondary Objectives

The secondary objective for Part A of the study is:

- To evaluate the safety and tolerability of evinacumab administered IV in pediatric patients with HoFH

The secondary objectives for Part B of the study are:

- To evaluate the effect of evinacumab on other lipid parameters (i.e., Apo B, non-HDL C, total cholesterol (TC), lipoprotein a [Lp(a)]) in pediatric patients with HoFH
- To evaluate the safety and tolerability of evinacumab administered IV in pediatric patients with HoFH
- To assess the PK of evinacumab in pediatric patients with HoFH
- To assess the immunogenicity of evinacumab in pediatric patients with HoFH over time
- To evaluate patient efficacy by mutation status.

1.2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate the efficacy of evinacumab in the extension of the study (Part C) in patients with HoFH
- To explore vascular changes using imaging techniques

1.2.4. Modifications from the Statistical Section in the Final Protocol

The content of this SAP reflects the content of the statistical section of Protocol R1500-CL-17100 Amendment 1.

1.2.5. Revision History for Statistical Analysis Plan Amendments

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

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This study consists of 3 parts: Part A, Part B, and Part C

- Part A: phase 1B single arm, single dose PK/PD analysis
- Part B: phase 3, single-arm, 24-week, open-label efficacy and safety study
- Part C: phase 3 48-week treatment period and 20-week follow-up period

Part A is a phase 1B single-dose, open-label study to determine the safety, PK and PD of evinacumab 15 mg/kg IV in approximately 6 patients ages 5 to 11 years with HoFH. To ensure a distribution of body weight within Part A of the study, every effort will be made to enroll 3 patients <25 kg and 3 patients ≥25 kg. Additionally, to ensure a distribution of ages, every effort will be made to enroll 2 patients <10 years of age. All patients who successfully complete Part A may continue receiving evinacumab in Part C. Initially, patients from Part A who enter Part C will receive evinacumab 15 mg/kg IV Q4W. When concentrations of total evinacumab in serum from all patients in Part A have been sufficiently analyzed, the dose for Part B will be determined using the cumulative data to date with evinacumab and data from Part A. If data from 6 patients are insufficient, up to 4 more patients may be enrolled to confirm the dose in Part B. The dose for Part B will also be the final dose in Part C. The dose for Part B (and final dose in Part C) will likely remain at 15 mg/kg IV Q4W. However, due to the nonlinear relationship between body weight and exposure, it is possible that increased dose may be required to match the exposures observed in adults. As such, the dose in Part B (and final dose in Part C) could be between 15 and 20 mg/kg IV Q4W. A maximum dose of 20 mg/kg is selected as the top dose because it is the highest dose evaluated in prior evinacumab studies.

Part B is a phase 3 single-arm, open-label study to assess the efficacy and safety of evinacumab in pediatric patients (age 5 to 11 years) with HoFH. Part B will begin once dose-selection for Part B has been completed. Part B will enroll approximately 18 pediatric patients. Patients enrolled into Part B will not include patients from Part A. Upon completion of Part B, patients will have the opportunity to continue into Part C.

Part C is an extension for patients from both Part A and Part B.

The analyses will be conducted in 3 steps. The first step will be an analysis of PK data and safety data from all patients in Part A when at least 8 weeks of concentrations of total evinacumab in serum have been collected and analyzed for these patients. The second analysis will be conducted as soon as all patient data through week 24 in Part B have been collected and validated; this will consist of the final analysis of the primary and secondary efficacy endpoints up to week 24 for Part B patients. The safety analysis will be performed on all safety data collected and validated at the time of the second analysis for Part B patients. The results of the second analysis will not be used to change the conduct of the ongoing study in any aspect. This second analysis may be used for the submission dossier to health authorities. The third analysis will be conducted at the end of the study and will consist of the final safety analysis.

2.2. Sample Size and Power Considerations

Since this is an open-label single treatment arm study, formal statistical testing is not planned, Therefore, a calculation for patient sample size is not applicable.

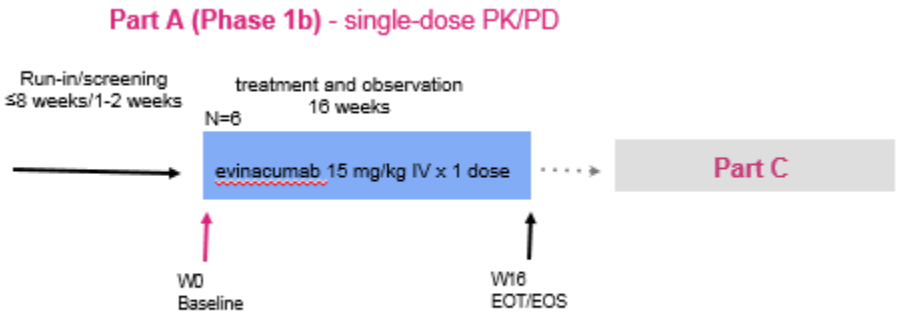
Six patients are planned to be enrolled for Part A and 18 pediatric patients are planned to be enrolled for Part B, considering the recruitment constraints in this rare patient population.

2.3. Study Plan

Part A and Part B are the two main study parts. Part C is an extension for patients from both Part A and Part B.

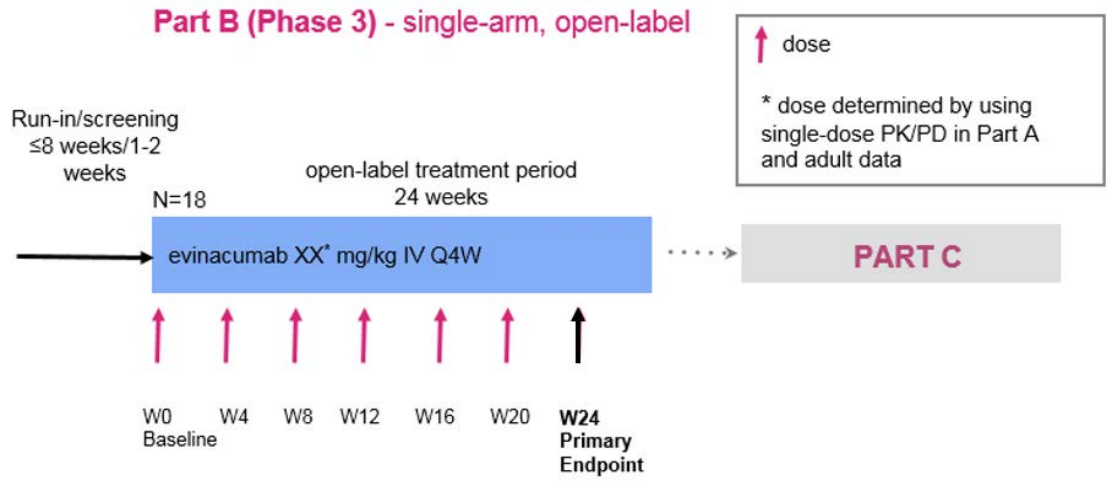
Part A consists of up to 4 periods: run-in; screening; single-dose open-label treatment and 16-week observation, and a 8-week follow-up period (for patients who do not enter Part C). Upon completion of Part A, patients will have the opportunity to continue into Part C (See Figure 1).

Figure 1: Study Flow Diagram Part A



Part B consists of up to 4 periods: run-in; screening; 24-week open-label treatment period; 20-week follow-up (for patients who do not enter Part C) (See Figure 2)

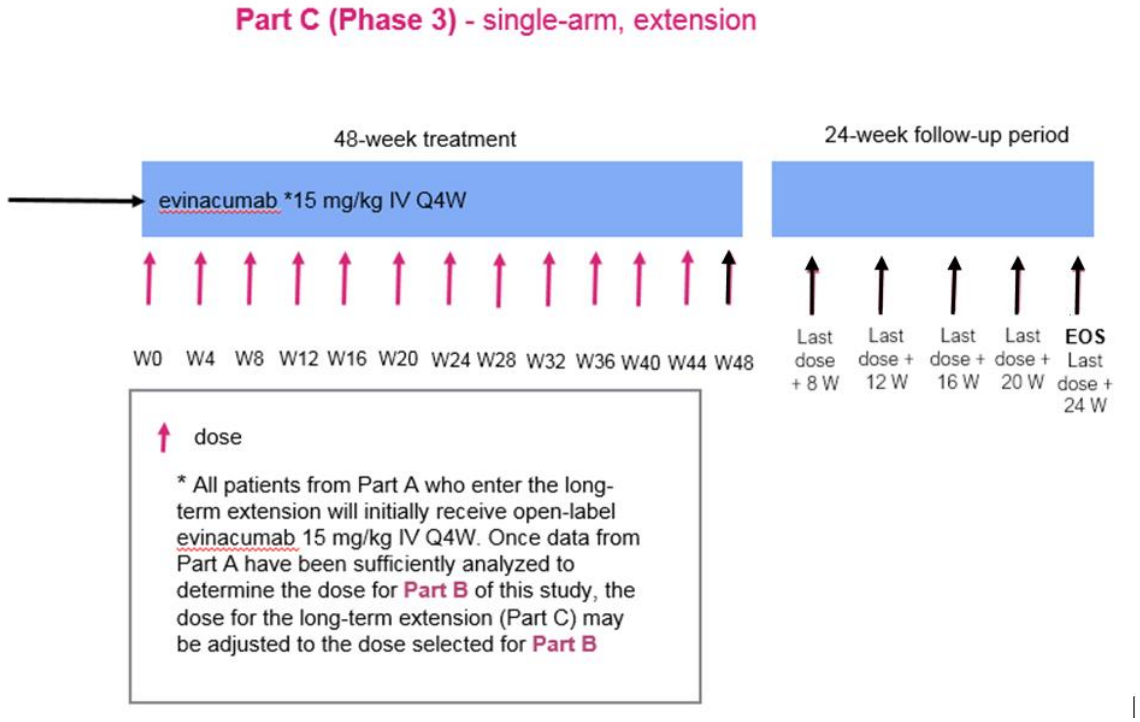
Figure 2: Study Flow Diagram Part B



Part C consists of 2 periods: a 48-week treatment period and a 20-week follow-up period (See Figure 3). Patients who participate in Part C should enter directly from Part A or Part B. The first visit (visit 1) in Part C can occur on the same day as the EOT visit in Part A (visit 11)/Part B (visit 11). Overlapping assessments completed at the EOT visit do not need to be duplicated during visit 1 in Part C.

All patients from Part A who enter Part C will initially receive open-label evinacumab 15 mg/kg IV Q4W. The final dose in Part C will be the same as the dose in Part B; therefore, the dose in Part C for patients entering from Part A may need to be adjusted to align with the dose in Part B.

Figure 3: Study Flow Diagram – Extension



The Study event table is presented in Appendix 10.7 .

2.4. Combining Data Across Study Parts

This section describes the integrated data pool and the data pooling strategy for analysis. By combining the individual data across study parts into an integrated data pool, there is a better chance for detecting a safety signal, for example, in uncommon adverse events (AEs), and a more accurate estimation of the rate for common AEs.

2.4.1. Data Pooling Strategy for Statistical Analyses

All post-baseline visit data from Part B and Part C will be included in the pool. Data in Part A will not be integrated into the data pool, since the safety profile for the single treatment administration in Part A can be different from the multiple study treatment administrations in Parts B and C. Patients enrolled in Part A will only contribute Part C data to the pool.

The following safety and efficacy parameters will be included in the pooled datasets: selected demographics and baseline characteristics, evinacumab exposure, AEs (including all TEAEs, SAEs, TEAE leading to permanent treatment discontinuation, death, AESIs), laboratory data, vital signs, ECGs, and lipid parameters (calculated LDL-C, Apo B, non-HDL-C, TC, Lp(a)).

The integration of evinacumab data includes study treatment period and follow-up data collected during Part B and Part C. Patients participating in multiple Parts of the study will have their individual data (within a patient) chronologically combined across those parts as follows:

A. Patients treated in Part A who proceed to be treated in Part C: Common reference point for pooled study treatment Day 1 is Part C Study Day 1. Note: Part A data will not be included in the pool.

B. Patients treated in Part B: A Part B patient will have the Part B assessments combined with Part C, if applicable, to assess longer term evinacumab exposure. Specifically, Part C visits will be chronologically appended to the last Part B visit, so all patients in Part B will have a common reference for first study treatment, defined as Part B first study treatment (Study Day 1). Operationally, Extension Study Day will be defined for Part C visits as Part C visit date – Part B first study treatment date +1.

Using the redefined Study Day structure above, individual patient data will be pooled. Specifically, patients in Bullet A + Bullet B above will be pooled, using the structure of redefined Study Day definitions (common reference for first study treatment) also described above for evinacumab treatment duration. A pooled analysis visit window label will be defined using the evinacumab treatment duration (see Appendix 10.2). Following the overlay of the pooled data visit windows to each patient's data, the data are pooled by visit, as well as assessment date, for repeated study assessments (example: laboratory assessments).

The integrated data will be summarized by the following types of patient groups.

- Part A Patients: Patients who were enrolled to Part A and received any IV dose of evinacumab in Part C.
- Part B Patients: Patients who were enrolled and treated with at least one IV dose of evinacumab in Part B.
- Total: Combined patients in the above two groups.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), below are the patient populations defined for statistical analysis. Two efficacy populations are planned for this study, specifically the Intent-to-Treat (ITT) population and the Modified Intent-to-Treat population (mITT). The primary efficacy analysis population is the ITT population. Additional patient populations are defined for safety, anti-drug (evinacumab) anti-body (ADA), and pharmacokinetic (PK).

3.1. Efficacy Analysis Sets for Part B

3.1.1. Intent-to-Treat (ITT)

The intent-to-treat (ITT) population is defined as all patients who received at least 1 dose or part of a dose of study drug in Part B.

3.1.2. Modified Intent-to-Treat (mITT)

The modified ITT (mITT) population is defined as all patients who received at least 1 dose or part of a dose of open-label study drug in Part B and have an evaluable primary efficacy endpoint. The endpoint is considered as evaluable when both of the following conditions are met:

1. Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (i.e., baseline).
2. Availability of at least 1 calculated LDL-C value during the efficacy treatment period and within one of the analysis windows up to week 24. The efficacy treatment period is defined as the time from the first study drug administration up to 35 days after the last study drug administration in Part B.

3.2. Safety Analysis Set

The safety analysis set (SAF) includes all patients in Part A or Part B who received at least 1 dose or part of a dose of study drug in the respective study treatment period.

3.3. Part C Safety Analysis Set

The Part C safety analysis set includes all patients who received at least 1 dose or part of a dose of study drug in Part C.

3.4. Pooled Safety Analysis Set

The pooled safety analysis set includes all Patients in Part A who received at least 1 or part of a dose of study drug in Part C and all patients in Part B who received at least 1 dose or part of a dose of study drug in Part B.

3.5. Pharmacokinetic (PK) Analysis Set

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

3.6. The Immunogenicity Analysis Set

3.6.1. ADA Analysis Set

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

Samples positive in the ADA assay may be further analyzed in neutralizing antibody assay.

3.6.2. NAb Analysis Set

The NAb analysis set includes all patients who received any study drug and who are either negative in the ADA assay or positive for ADA with at least 1 non-missing result in the NAb assay following the first dose of the study drug. Patients and samples that are ADA negative are set to negative in the NAb analysis set.

3.7. The Target Analysis Set

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

3.8. The Concentration-Response (C-R) Analysis Set

The concentration-response (C-R) analysis set consists of the PK analysis set and at least one non-missing baseline and one non-missing post dose response assessment for LDL-C and/or any other relevant lipid parameter.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

For each patient, demographic and baseline characteristics will be obtained from the last available value up to the date of the first study treatment administration (i.e. baseline definition), regardless of the study treatment period.

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: ≥5 to <10, and ≥10 to <12 years)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)

Baseline Characteristics

- Baseline Weight (kg) (quantitative and categorical variable: <25 kg, and ≥25 kg)
- Baseline Height (cm)
- Body mass index (BMI) in kg/m² (quantitative and categorical variable: <P5: Underweight, ≥P5 to <P85: Healthy weight, ≥P85 to <P95: Overweight and ≥P95: Obesity, using the World Health Organization [WHO] growth reference 5-19 years (Cole, 1992;WHO, 2006; Rigby, 2004).

- Current apheresis treatment (yes/no)
- If apheresis occurring, schedule from the e-CRF (i.e. QW, Q2W)

Baseline Disease Characteristics

- Lipid parameters (pre-apheresis, if applicable) - quantitative variables for all efficacy parameters
- Mutation type (e.g. homozygous, compound heterozygous, and double heterozygous)
- Receptor-negative mutation in both LDLR or LDLRAP1 alleles (i.e. receptor-negative defined as a mutation resulting in termination codons, splice site mutations, frame shifts and large insertion/deletions) (Yes, No)
- LDLR activity (null/null [LDLR activity ≤15%], not null/null [LDLR activity > 15%])

4.2. Medical History

As applicable, patient medical history 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.

Hypercholesterolemia disease history will be assessed through diagnosis of HoFH, time from diagnosis to first study treatment administration (years), method of diagnosis of HoFH (genotyping, clinical diagnosis), lipid modifying therapies history reported in the "History of HoFH/LMT" e-CRF page.

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

4.3. Prior and Concomitant Medications

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

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

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

- Concomitant medications are defined as medications that are administered to the patients during the respective study treatment periods. Specifically:
  - Start date of the concomitant medication is on or after the first study treatment administration in respective study treatment periods (≥ Day 1 for Part A, or Part B, or ≥ Week 0 of Part C for Part C); **or**
  - Start date of the concomitant medication is before the first study treatment administration in respective study treatment periods and is "Ongoing" during the treatment emergent period; **or**
  - Start date of the concomitant medication is before the first study treatment administration in respective study treatment periods, and the end date is on or after the first study treatment administration in respective study treatment periods (≥ Day 1 for Part A, or Part B, or ≥ Week 0 of Part C for Part C).

The concomitant medication treatment emergent periods are defined as:

- For concomitant medications in the Part A or Part B, the treatment emergent period is defined from the first day of study treatment administration to the last day of study treatment +168 days (for patients who do not continue into the Part C) or to the day before the first Part C study treatment administration (for patients who enter the Part C).
- For concomitant medications in the Part C, the treatment emergent period is defined from the first day of Part C study treatment administration to the last day of Part C 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 8.9.1 of the protocol. They will be reviewed and identified by the study clinician and reported in protocol deviations.

4.5. Patient Disposition

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

For patient study status, patient milestone categories for Part A are defined below. As applicable, percentages will be calculated using the number of enrolled patients in the denominator, 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 screen failure (SF) patients.
- The total number of enrolled patients, 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.
- The total number of patients enrolled but not receiving study treatment.
- The total number of patients enrolled and receiving study treatment.
- The total number of patients who completed the Part A observation period.
- The total number of patients who prematurely discontinued the Part A observation period, and the reasons for discontinuation
- The total number of patients in Part A who do not proceed into Part C and who complete the 8-week follow-up visit.
- The total number of patients in Part A who do not proceed into Part C and who do not complete the 8-week follow-up visit. Patients who died during the study are excluded.

For patient study status, patient milestone categories for Part B are defined below. As applicable, percentages will be calculated using the number of enrolled patients in the denominator, 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 screen failure (SF) patients:
- The total number of enrolled patients, 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.
- The total number of patients enrolled but not receiving study treatment.
- The total number of patients enrolled and receiving study treatment.
- The total number of patients who completed Part B treatment period as collected on the End of Treatment e-CRF.

- The total number of patients who completed Part B treatment period, defined as at least 20 weeks of study treatment administration and visit week 24 performed.
- The total number of patients who prematurely discontinued Part B treatment, and the reasons for discontinuation collected on the End of Treatment e-CRF
- The total number of patients in Part B who do not proceed into Part C and complete the last study follow-up visit (i.e. Follow-up Week 20).
- The total number of patients in Part B who do not proceed into Part C and do not complete the study follow-up period, defined as the last visit performed less than 22 weeks after the last study treatment administration. Patients who died during the study are excluded.

Patient milestone categories for Part C are defined below. As applicable, percentages will be calculated using a denominator of the number of patients receiving Part C study treatment.

- The total number of patients receiving Part C study treatment.
- The total number of patients ongoing in Part C (applicable for the first step and second step analyses)
- The total number of patients who completed Part C treatment period as collected on the End of Treatment e-CRF.
- The total number of patients who completed Part C treatment period, defined as at least 44 weeks of Part C study treatment administration and Part C visit week 48 performed.
- The total number of patients who prematurely discontinued study treatment during Part C, and the reasons for discontinuation collected on the End of Treatment e-CRF.
- The total number of patients in Part C who complete the last study follow-up visit (i.e. Follow-up week 24).
- The total number of patients who did not complete the study follow-up period, defined as the last visit performed less than 22 weeks after the last study treatment administration. Patients who died during the study are excluded.

The following patient populations for analyses are defined in Section 4.2:

- Efficacy populations (for Part B only): ITT and mITT populations
- Safety analysis set
- Part C safety analysis set
- Pooled safety analysis set
- Anti-evinacumab antibody (ADA) analysis set
- Neutralizing anti-evinacumab antibody (NAb) analysis set
- Pharmacokinetic (PK) analysis set
- Target analysis set

- Concentration-Response (C-R) analysis set

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

- A listing of patients treated but not enrolled, and 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 in Part A are listed below with associated definitions:

- The total number of Part A study treatment infusions by patient.
- Patient duration of Part A observation treatment period in weeks defined as: (last visit date during the Part A observation period - first study treatment administration date in Part A)/7.

Study treatment exposure variables for infusions administered in Part B are listed below with associated definitions:

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

Study treatment exposure variables for infusions administered in Part C are listed below with associated definitions:

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

Study treatment exposure variables on the integrated data pool (Section 2.4) are listed below with associated definitions:

- Cumulative patient duration of study treatment exposure in weeks defined as: Part C treatment exposure for Part A patients, and Part B treatment exposure plus Part C treatment exposure for Part B patients.
- Cumulative total number of study treatment infusions by patient defined as: total number of Part C infusions for Part A patients, and total number of Part B infusions plus total number of Part C infusions for Part B patients.
- The following categories will be used for cumulative patient treatment exposure at 4 week intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks and <24 weeks, ≥24 weeks and <28 weeks, ≥28 weeks and <32 weeks, ≥32 weeks and <36 weeks, ≥36 weeks and <40 weeks, ≥40 weeks and <44 weeks, ≥44 weeks and <48 weeks, ≥48 weeks and <52 weeks, ≥52 weeks and <56 weeks, ≥56 weeks and <60 weeks, ≥60 weeks and <64 weeks, ≥64 weeks and <68 weeks, ≥68 weeks and <72 weeks, ≥72 weeks, etc.

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

- The mean infusion/injection frequency for study treatment will be defined for each patient as the average number of days between 2 consecutive infusions: (last study treatment administration date – first study treatment administration date) / (number of infusions -1), for patients receiving at least 2 infusions.

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

4.7. Efficacy Variable

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

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

1. On the day of apheresis, any lipid values collected after apheresis for the respective visit will be excluded from the efficacy analyses.

All efficacy measurements will be assigned to efficacy analysis windows defined in Appendix 10.2 of this SAP, with the intent to provide an assessment for week 1 to week 24 timepoints for Part B. For all time points post-baseline, the value used for the analyses at a given

time point (e.g. at week 24) is the value obtained within the corresponding efficacy analysis window. The baseline value is defined as the last available measurement prior to the date of the first study treatment administration regardless of the study treatment period.

4.7.1. Primary Efficacy Variable (s)

The primary efficacy endpoint for Part B is:

- The percent change in calculated LDL-C from baseline to week 24 (intent-to-treat [ITT] estimand) in Part B. The primary endpoint is defined as: 100x (calculated LDL C value at week 24 - calculated LDL-C value at baseline)/calculated LDL-C value at baseline.

The baseline LDL-C value is defined as the last calculated LDL-C value obtained before the first dose of study treatment in Part B. The calculated LDL-C at week 24 will be the LDL-C value obtained within the week 24 analysis window.

The intent-to-treat estimand used for the primary efficacy analysis is the treatment policy strategy, specifically the occurrence of the intercurrent events is irrelevant; the value for the primary efficacy endpoint is used regardless of whether or not the intercurrent events occur. The intent-to-treat estimand for the primary efficacy analysis is defined as:

A. The patient population is defined as the Intent-to-treat population (Section 3.1.1).
B. The primary efficacy endpoint is defined above.
C. The intercurrent events of interest are the administration of study treatment and the administration of subsequent therapies. The interruption of study treatment and the change in subsequent therapies are ignored, and the value for the primary efficacy endpoint is used regardless of adherence to study treatment and subsequent therapies.
D. The population-level summary for the primary efficacy endpoint is evinacumab mean value, SE and 95% confidence interval.

4.7.2. Secondary Efficacy Variable(s)

The secondary continuous efficacy endpoints in Part B are provided below, applying the ITT estimand described for primary efficacy endpoint (Section 4.7.1 definitions A, C and D).

- The percent change in Apo B from baseline to week 24 (ITT estimand)
- The percent change in non-HDL-C from baseline to week 24 (ITT estimand)
- The percent change in TC from baseline to week 24 (ITT estimand)
- The percent change in calculated LDL-C from baseline to week 24 in patients who have negative/negative and null/null mutations (ITT estimand)
- The percent change in Lp(a) from baseline to week 24 (ITT estimand)
- The absolute change in LDL-C at week 24 (ITT estimand)

The secondary binary efficacy endpoint in Part B is provided below, applying the ITT estimand described for primary efficacy endpoint (Section 4.7.1 definitions A and C). The definition for the population-level summary (definition D) is evinacumab proportion and 95% confidence interval.

- The proportion of patients with ≥50% reduction in calculated LDL-C at week 24 (ITT estimand)

4.8. Safety Variables

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

4.8.1. Adverse Events Variables

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

- The PRE-TREATMENT period is defined from the day the ICF is signed to the day before the first dose of study treatment administration.
- The treatment-emergent adverse event (TEAE) period (Part A or Part B) is defined from the day of the first dose of study treatment administration to the day of the last dose of study treatment administration in Part A or Part B respectively + 168 days (24 weeks). For patients entering Part C, the TEAE period is truncated at the day before the first study treatment administration in Part C.
- The Part C TEAE period is defined from the day of the first study treatment administration in Part C to the day of the last study treatment administration in Part C + 168 days (24 weeks).
- The pooled TEAE period is defined below:
  - Part A Patients: defined as the Part C TEAE period.
  - Part B Patients: defined from the day of the first study treatment administration in Part B to the day of the last study treatment administration in Part C + 168 days (24 weeks) or to the last study treatment administration in Part B + 168 days (24 weeks) for patients not entering into Part C.
- The POST-TREATMENT period is defined from the day after the end of the respective TEAE periods to the last study visit.

4.8.1.1. Adverse Events and Serious Adverse Events

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

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

Adverse Event Observation Period

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

4.8.1.2. Adverse Events of Special Interest

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

The AESIs include:

- Anaphylactic reactions (e-CRF)
- General allergic events (SMQ)
- Moderate or severe infusion reactions (e-CRF)
- Hepatic Disorder (SMQ, lab data)
- Pregnancy (e-CRF)
- Symptomatic overdose with investigational medicinal product (e-CRF)
- Neurocognitive events (CMQ)
- New onset of diabetes (NOD) (lab data, HLT, and concomitant medications)
- Pancreatitis (e-CRF)

4.8.1.3. Events Causing Death

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

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

4.8.2. Laboratory Safety Variables

Clinical laboratory tests will consist of blood analyses (including hematology, clinical chemistry and other) and urinalysis. Clinical laboratory values will be converted and analyzed in both international units and US conventional units, with associated normal ranges provided by the

central laboratory. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries. Potentially clinically significant values (PCSV) ranges will be applied to the laboratory test values as applicable (see Appendix 10.4 for PCSV definitions). For those laboratory tests that do not have PCSV ranges, central laboratory normal ranges will be applied to identify out-of-range values. All laboratory test samples will be collected before study treatment administration during the protocol scheduled visits.

Unless otherwise specified below, blood samples for clinical laboratories will be collected at the protocol scheduled visits. The laboratory parameters (excluding those considered as efficacy parameters) will be classified as follows:

Hematology:

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

Clinical chemistry:

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

Non-Efficacy Lipid Panel

HDL-C, TG, Apo A-1, Apo CIII, Apo E, and ratio Apo B/Apo A-1.

Urinalysis

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

Other

TSH, sex hormones (luteinizing hormone, follicle stimulating hormone, estradiol, and total testosterone).

4.8.3. Vital Signs

Vital signs parameters will include weight (kg or lb), height (cm or in), BMI (kg/m^2), 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 used in the result summaries. Potentially clinically significant values (PCSV) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.4 for PCSV definitions).

BMI and height percentiles will be calculated (Cole, 1992; WHO, 2006; Rigby, 2004).

4.8.4. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at specified time points according to Appendix 10.7. The ventricular rate, PR, QRS, RR, QTcF, QTcB, and QT intervals will be recorded. Electrocardiogram assessments will be described as normal or abnormal.

4.8.5. Tanner stages

Tanner stage assessments will be performed at specified time points according to Appendix 10.7. Tanner stages (1, 2, 3, 4, 5) will be recorded.

4.8.6. Physical Examination Variables

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

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 change in carotid intima-media thickness (cIMT in mm) from baseline over time

4.10. Pharmacokinetic Variables

The PK variables are the concentrations of total evinacumab at each time point.

Total ANGPTL3 concentration in serum is a measure of target engagement by evinacumab and will be determined in the samples obtained to evaluate evinacumab concentration.

4.11. Immunogenicity Variables (ADA and NAb)

The immunogenicity variables are ADA status, titer, and neutralizing antibody (NAb) status for analyzed samples at time-point/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.2.

5. STATISTICAL METHODS

In general, patient data collected in Part A will be summarized for all patients (i.e., Part A Total). For Part B, data will be summarized again for all patients (i.e., Part B Total). Part C data summaries will show three columns, specifically, patients treated in Part A, patients treated in Part B, and Total. The baseline value is defined as the last available measurement prior to the date of the first study treatment administration regardless of the study treatment period.

In addition, pooled analyses will summarize data in three columns, specifically, Part A Patients, Part B Patients, and Total. The baseline value for the pooled analyses is defined as the last available measurement prior to the date of the first study treatment administration regardless of the study treatment period. Note: Although Part A patients only contributed data from Part C for the pooled analyses, Part A patient's baseline is defined as Part A baseline for variable derivations.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be descriptively summarized by total patients within each main study part (Part A or Part B). Parameters described in Section 4.1 will be summarized for patients in the SAF for Part A, and for patients in the ITT population for Part B.

Continuous data will be summarized using the number of patients with data, mean, SD, median, minimum and maximum. 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.

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

For Part C safety analysis set, demographic and baseline characteristics will be summarized by total patients in Part C and by main study part (Part A or Part B) in which patients are originally enrolled at the beginning of the study.

Selected demographic and baseline characteristics will also be summarized for the pooled data in the pooled safety analysis set, by patient groups defined in Section 2.4.1.

5.2. Medical History

Medical history will be descriptively summarized by total patients within each main study part (Part A or Part B) and Part C. Parameters described in Section 4.2 will be summarized for patients in the SAF for Part A and C, and for patients in the ITT population for Part B. 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 each main study part.

For patient disease characteristics, continuous data will be summarized using the number of patients with data, mean, SD, median, minimum and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients.

5.3. Prior and Concomitant Medications

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

For patients in the safety analysis set, all concomitant medications during the respective treatment period, dictionary coded by WHO-DD, will be descriptively summarized by total patients within each main study part (Part A or Part B). Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications, by decreasing frequency of the incidence of ATC followed by therapeutic class. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication. Additionally, concomitant medications for LMT will be summarized by patient counts (and percentages) for the standardized medication names.

For Part C treatment period, concomitant medications will be dictionary coded by WHO-DD and will be descriptively summarized as described above. For patient in the Part C safety analysis set, medications will be summarized for all patients and by main study part (Part A or Part B) in which patients are originally enrolled at the beginning of the study. Summaries will present patient counts (and percentages).

Post-treatment medications will be dictionary coded by WHO-DD and will be provided in the study datasets.

5.4. Prohibited Medications

Listing of prohibited medications will be provided for the patients in the safety analysis set within main study part (Part A or Part B) and in the Part C safety analysis set during the extension (Part C).

5.5. Patient Disposition

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

Patient study status for the main study part (Part A or Part B) will be summarized by total patients 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, and enrolled but not treated.

Patient analysis populations will be summarized by total patients within main study part (Part A or Part B), depicting frequencies (and percentages) of patients that met the criteria for each population described in Section 3.

For Part C treatment period, the patient study status and patient analysis populations will be summarized for all patients and by main study part (Part A or Part B) in which patients are originally enrolled at the beginning of the study on the Part C safety population for the variables described in Section 4.5.

The incidence of premature study treatment discontinuation (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically by total patients within Part B, or Part C in the respective safety analysis set using the Kaplan-Meier method.

5.6. Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure for the main study part (Part A or Part B) described in Section 4.6 will be assessed and summarized for all patients in the safety analysis set.

The extent of study treatment exposure for Part C described in Section 4.6 will be assessed and summarized for patients in the Part C safety analysis set, specifically for all patients and again by main study part (Part A or Part B) in which patients are originally enrolled at the beginning of the study.

The extent of study treatment exposure on the pooled data described in Section 4.6 will be assessed and summarized in the pooled safety analysis set by patient groups.

5.6.1. Exposure to Investigational Product

Study treatment exposure in the respective treatment period will be descriptively summarized for treatment duration, total number of infusions, and observation period duration (Part A) as described in Section 4.6. Treatment duration and total number of infusions will be summarized using the number of patients with data, mean, SD, median, minimum and maximum.

5.6.2. Study Treatment Compliance

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

Descriptive statistics of the infusion frequency of study treatment will be summarized. Further, study treatment infusion interruptions and incomplete infusions with reason will be summarized by patient count (percentage) and a patient listing will be provided for those patients with incomplete infusions. Cases of study treatment overdose will be reported in the AE e-CRF page and will be described in the adverse event analysis.

5.7. Analyses of Efficacy Variables

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

Statistical analyses for the primary efficacy endpoint and secondary efficacy endpoints will be conducted in Part B as described below, and will be completed during the step 2 efficacy analyses (Section 7). Remaining descriptive efficacy analyses will be completed during step 3.

5.7.1. Analysis of Primary Efficacy Variable for Part B

While applying the ITT estimand, the percent change from baseline in calculated LDL-C at week 24 will be descriptively summarized for all patients in the ITT population using mean, SE, and 95% CI. Missing data will be imputed using a pattern mixture model (PMM) approach as described below (see Appendix 10.6 for more details).

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

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

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

For the percent change from baseline calculated LDL-C endpoint, the 100 complete datasets of observed and imputed calculated LDL-C data at week 24 will be analyzed using the SAS MEANS procedure. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae. Combined estimate for mean at Week 24 will be provided with the standard error (SE) and 95% confidence interval (CI). Formal statistical testing is not planned.

5.7.1.1. Sensitivity of the Primary Efficacy Analysis

Robustness of the primary analysis statistical method will be assessed through sensitivity analyses, including an ITT analysis and an on-treatment analysis of the percent change in calculated LDL-C from baseline to week 24 using a mixed-effect model with repeated measures (MMRM) approach.

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

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

Sensitivity to the Handling of Missing Data

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

Mixed-effect Model with Repeated Measures (MMRM) Approach

The percent change from baseline in calculated LDL-C at week 24 will be analyzed in the ITT population using a mixed effect model with repeated measures (MMRM) approach. All post-baseline data available within week 1 to week 24 analysis windows regardless of adherence to treatment and subsequent therapies will be used and missing data are accounted for by the MMRM model. The MMRM model assumes "missing-at-random" (MAR). The model will include the fixed categorical effect of time point (weeks 1, 2, 4, 8, 12, 16, 20, and 24), as well as the continuous fixed covariates of baseline calculated LDL-C value.

This model will be run using Statistical Analysis Software (SAS) mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least-squares mean estimate at week 24 with their corresponding standard error.

Sensitivity to On-treatment Calculated LDL-C Values

To assess the robustness of the more clinically relevant data for the analysis of the primary efficacy endpoint, the same statistical analysis method approach as described above for the MMRM approach will be applied in the mITT population. The intent-to-treat estimand will be replaced by the on-treatment estimand.

The on-treatment estimand used for the primary efficacy sensitivity analysis is the "while on treatment strategy" estimand. The on-treatment estimand for the primary efficacy sensitivity analysis is defined as:

A. The patient population is defined as the Modified Intent-to-treat (mITT) population (Section 3.1.2).
B. Same definition as the treatment policy estimand described for primary efficacy analysis.
C. The intercurrent events of interest are the administration of study treatment and the administration of subsequent therapies. The discontinuation of study treatment impacts the primary efficacy endpoint values used in the analysis, specifically including those values collected during the efficacy treatment period (Section 3.1.2). For subsequent therapies, any changes are ignored in the analysis.
D. The population-level summary for the primary efficacy sensitivity analysis is the least square estimate of mean calculated using the mixed effect model with repeated measures (MMRM) approach.

5.7.1.2. Sub-group Analyses

To assess the homogeneity of the treatment effect across various subgroups, the percent change in LDL-C from baseline at Week 24 will be summarized by the following subgroups of interest, assuming there are enough patients in each subgroup level to perform the evaluation, using the same ITT estimand and PMM approach for missing data as for the primary endpoint:

- Gender (Female, Male)
- Age (≥5 to <10, ≥10 to <12 years)

- Race
- Ethnicity
- The baseline apheresis status (Yes, No)
- Receptor-negative mutation in both LDLR or LDLRAP1 alleles (i.e. receptor-negative defined as a mutation resulting in termination codons, splice site mutations, frame shifts and large insertion/deletions) (Yes, No)
- LDLR activity (null/null [LDLR activity ≤15%], not null/null [LDLR activity > 15%])

5.7.1.3. Multiplicity Considerations

Not applicable.

5.7.2. Analysis of Secondary Efficacy Variables for Part B

For the secondary efficacy endpoints (defined in Section 4.7.2), descriptive summaries and analyses will be performed in the ITT population, using values obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand).

For descriptive summaries, percent change, and when appropriate change from baseline, in calculated LDL-C, total-C, non-HDL-C, Apo B, and Lp(a) will be provided at each time point during the 24-week treatment period. All measurements, scheduled or unscheduled, will be assigned to efficacy analysis windows defined in Appendix 10.2 in order to provide an assessment for these time points. Lipid assessments other than the ones provided by the central laboratory will be excluded. The time profile of each parameter will be plotted with the corresponding SEs.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (e.g., percent change in calculated LDL-C), continuous measurements expected to have a non-normal distribution [e.g., Lp(a)], and binary measurements (e.g., proportion of patients with ≥50% reduction in calculated LDL-C).

5.7.2.1. Continuous Endpoints Anticipated to have a Normal Distribution

Continuous secondary variables defined in Section 4.7.2 anticipated to have a normal distribution (i.e. lipids other than Lp(a)) will be analyzed using the same ITT estimand and PMM approach for missing data as described for the primary efficacy endpoint.

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

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

The percent change from baseline at time point of interest will be derived from observed and imputed lipid values at this time point. Multiple imputation will be followed by robust regression model (Mehrotra, 2012), with the endpoint of interest as the response variable using M-estimation (using SAS ROBUSTREG procedure) with corresponding baseline value(s). Combined means estimates with their corresponding SEs and 95% CIs will be provided through the SAS MIANALYZE procedure.

5.7.2.3. Binary Endpoint Variables

Binary secondary efficacy endpoints defined in Section 4.7.2 will be descriptively summarized using the ITT estimand for all patients in the ITT population with the proportion and 95% CI. Missing data will be imputed using the same PMM approach as described for the primary efficacy endpoint.

5.7.3. Summary of Results by Time Point

For Part B, central laboratory values (in conventional (US) and international units), percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units) will be summarized at protocol scheduled visits by total patients for calculated LDL-C, Total-C, non-HDL-C, Apo B, and Lp(a). The time profile of each parameter will be plotted with the corresponding standard errors. Further details are described below:

- For lipids other than Lp(a): observed and imputed values, change from baseline (as applicable), and percent change from baseline, will be summarized using the same ITT estimand and PMM approach for missing data for all patients in the ITT population as described for endpoints above by mean and SE at all planned time points (see Section 5.7.2.1).
- For Lp(a): observed and imputed values, and percent change from baseline, will be summarized using the same ITT estimand and multiple imputation approach for missing data for all patients in the ITT population as described above by mean and SE at all planned time points (see Section 5.7.2.1).
- Observed data raw values, change from baseline (as applicable), and percent change from baseline response variables will be descriptively summarized using the ITT estimand for all patients in the ITT population by patient counts, mean, SD, median, Q1, Q3, minimum, and maximum at all planned time points.
- Observed data raw values, change from baseline (as applicable), and percent change from baseline response variables will be descriptively summarized using the on-treatment estimand for all patients in the mITT population by patient counts, mean, SD, median, Q1, Q3, minimum, and maximum at all planned time points. On-treatment estimand is defined as all secondary efficacy endpoints values collected during the efficacy treatment period (Section 3.1.2).

5.7.4. Analysis of Efficacy Variables for Part A and Part C

For Part A treatment and observation period, observed central laboratory values (in conventional (US) and international units), percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units) will be descriptively summarized

at protocol scheduled visits by total patients in the safety analysis set within Part A for calculated LDL-C, Total-C, non-HDL-C, Apo B, and Lp(a). Descriptive statistics include patient counts, mean, SD, median, Q1, Q3, minimum, and maximum.

For Part C treatment period, similar analyses will be performed for all patients in the Part C safety analysis set and by main study part (Part A or Part B) in which patients are originally enrolled at the beginning of the study. The time profile of each parameter may be plotted with the corresponding standard errors.

5.7.5. Pooled Analysis of Efficacy Variables

Lipids analyses will also be performed on the pooed data in the pooled safety analysis set by patient groups. Observed central laboratory values (in conventional (US) and international units), percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units) will be descriptively summarized over time by patient groups for calculated LDL-C, Total-C, non-HDL-C, Apo B, and Lp(a). Descriptive statistics include patient counts, mean, SD, median, Q1, Q3, minimum, and maximum.

5.8. Analysis of Safety Data

In general, for main study part (Part A or Part B), the summary of safety results for patients in the safety analysis set will be presented by each study part. No formal inferential testing will be performed. Summaries will be descriptive in nature.

For Part C, the summary of safety results for patients in the Part C safety analysis set will be presented for all patients and by main study part (Part A or Part B) in which patients are originally enrolled at the beginning of the study.

In addition, the safety analyses will be performed on the pooled data in the pooled safety analysis set. The summary of safety results will be presented by patient groups defined in Section 2.4.1.

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 (i.e., exposed but not enrolled) will be listed separately.
- PCSV values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (PCSV version dated January 2009 [Appendix 10.4]). Considering that the threshold defined in the PCSV list for monocytes and basophils can be below the ULN, the following PCSV criterion will be used for the PCSV analysis of monocytes and basophils:
  - PCSV criterion for monocytes: >0.7 Giga/L or >ULN (if ULN ≥0.7 Giga/L).
  - PCSV criterion for basophils: >0.1 Giga/L or >ULN (if ULN ≥0.1 Giga/L).

- PCSV criteria will determine which patients had at least 1 PCSV during the respective TEAE periods, taking into account all evaluations including unscheduled or repeated evaluations.
- The treatment-emergent PCSV denominator for a given parameter will be based on the number of patients assessed for that given parameter at least once during the respective TEAE periods.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to Global Analysis Windows defined in Appendix 10.2 in order to provide an assessment for the screening visit through follow-up visit time points.
- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize observed values and change from baseline values by visit.

5.8.1. Adverse Events

In general, the primary focus of AE reporting will be on TEAEs summarized in respective TEAE periods, specifically the Part A, Part B, Part C, and pooled treatment periods.

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

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

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

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE;
  - Serious TEAE;
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT
- All TEAEs by primary SOC and PT
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC and PT (PT incidence $\geq$ 2 patients)
- All TEAEs relationship (related/not related) to evinacumab
- All TEAEs by maximum severity (i.e., mild, moderate or severe)
- A common TEAE related to any clinically significant signal will be further characterized as appropriate. The characterization of the clinically significant signal can include Kaplan-Meier curves for time from first dose to first occurrence of selected TEAE, time to resolution, and event duration. Patients without any event will be censored at the end of the respective TEAE period.

Analysis of all treatment emergent serious adverse event(s)

- All Serious TEAEs by primary SOC, HLGT, HLT, and PT
- All Serious TEAEs by primary SOC and PT
- Patient listings of serious TEAEs will be provided in the report appendix
- All Serious TEAEs relationship (related/not related) to evinacumab
- A serious TEAE related to any clinically significant signal will be further characterized as appropriate. The characterization of the clinically significant signal can include Kaplan-Meier curves for time from first dose to first occurrence of selected TEAE, time to resolution, and event duration. Patients without any event will be censored at the end of the respective TEAE period.

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

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

- A TEAE leading to permanent treatment discontinuation and related to any clinically significant signal will be further characterized as appropriate. The characterization of the clinically significant signal can include Kaplan-Meier curves for time from first dose to first occurrence of selected TEAE, time to resolution, and event duration. Patients without any event will be censored at the end of the respective TEAE period.

Patient Deaths

The following summaries of deaths will be generated.

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

5.8.2. Analysis of Adverse Events of Special Interest

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

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

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

5.8.3. Clinical Laboratory Measurements

The following definitions will be applied to laboratory parameters:

- Part A treatment and observation period: the period used for quantitative analysis for Part A is defined from the day after the first study treatment administration to the day of last visit during the Part A observation period.
- Part B treatment period: the treatment period used for quantitative analysis is defined from the day after the first study treatment administration to the day of the last study treatment administration + 28 days for those patients not proceeding into Part C, or up to the day of the first study treatment administration in Part C for those patients proceeding into Part C.
- Part C treatment period: the treatment period used for quantitative analysis is defined from the day after the first study treatment administration in Part C to the day of the last study treatment administration in Part C + 28 days.
- Pooled treatment period: for Part A patients, the treatment period used for quantitative analysis is defined from the day after the first study treatment administration in Part C to the day of the last study treatment administration in Part C + 28 days. For Part B patients, the treatment period used for quantitative analysis is

defined from the day after the first study treatment administration in Part B to the day of the last study treatment administration in Part C + 28 days or to last study treatment administration in Part B + 28 days for patients not entering into the Part C.

For respective treatment period, clinical laboratory parameter actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum. Clinical laboratory parameters mean changes from baseline, with the corresponding SE, can be plotted at each visit in the case results warrant further investigation. These parameters will be presented by the biological functions defined in Section 4.8.2. For glucose, only fasting samples will be included in the summaries.

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

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

Patient listings of laboratory measurements that meet PCSV criteria will be provided for the report appendix. For those laboratory parameters that don't have an associated PCSV criteria, similar summary tables can be provided based on measurements outside the central laboratory normal ranges, if applicable.

Drug-induced liver injury

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

Patient listing of possible Hy's law cases identified (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.

Sex hormones

For respective treatment period, the sex hormones will be described separately by gender.

- For girls
  - Values and changes from baseline will be descriptively summarized by time point for estradiol, FSH and LH.
  - Similar table as for PCSA will be provided using normal range during the respective TEAE period. The number (%) of patients with at least one estradiol

value <LLN and LH >ULN, estradiol value<LLN and FSH >ULN, estradiol value <LLN and LH>ULN and FSH >ULN) during the TEAE period.

- For boys
  - Values and changes from baseline will be descriptively summarized by time point for testosterone, FSH and LH.
  - Similar table as for PCSA will be provided using the normal range. The number (%) of patients with at least one testosterone value <LLN and LH >ULN, testosterone value<LLN and FSH >ULN, testosterone value<LLN and LH>ULN and FSH >ULN) during the respective TEAE period.

5.8.4. Analysis of Vital Signs

For respective treatment period as defined for clinical laboratory measurements (Section 4.8.2), the vital sign actual values and change from baseline values obtained while sitting will be descriptively summarized at baseline and each post-baseline visit by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum. Mean changes from baseline, with the corresponding SE, can be plotted at each visit in the case results warrant further investigation.

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

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

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

5.8.5. Analysis of 12-Lead ECG

For respective treatment period as defined for clinical laboratory measurements (Section 5.8.3), ECG parameters will be described through an overall interpretation of ECG status (e.g. normal, abnormal [clinically significant (Yes/No)]).

The count and percentage of patients with at least 1 abnormal post-baseline ECG during the respective TEAE period will be summarized according to the following baseline status categories:

- Normal/missing;
- Abnormal

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

- Normal (according to PCSV criterion/criteria)/missing
- Abnormal according to PCSV criterion or criteria
- Patient listings of ECG measurements that meet PCSV criteria will be provided for the report appendix.
- administration in Part B for patients not entering into the Part C + 28 days.

5.8.6. Tanner Stages

For respective treatment period as defined for clinical laboratory measurements (Section 5.8.3), tanner stages (outcome categories of 1, 2, 3, 4, 5) will be summarized by patient frequency and percentage at baseline and each post-baseline visit. The change from baseline in tanner stage by visits will be assessed (No change in Tanner stage, change in Tanner stage ≥1).

5.8.7. Physical Exams

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

5.9. Analysis of Other Variables

In general, for main study part (Part A or Part B), the summary of results for other variables for patients in the safety analysis set will be presented by each study part. No formal inferential testing will be performed. Summaries will be descriptive in nature.

For Part C, the summary of results for other variables for patients in the Part C safety analysis set will be presented for all patients and by main study part (Part A or Part B) in which patients are originally enrolled at the beginning of the study.

In addition, the analyses for other variables will be performed on the pooled data in the pooled safety analysis set. The summary of results will be presented by patient groups defined in Section 2.4.1.

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

5.10. Analysis of Pharmacokinetic Variables

PK parameters for Part A may include, but are not limited to:

- C_{max}
- AUC_{last}

- AUC_{inf}
- CL
- Vss
- MRT

PK parameters for Part B may include, but are not limited to:

- $C_{max.ss}$
- $C_{trough.ss}$

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

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

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

5.11. Analysis of Immunogenicity Data

5.11.1. Analysis of ADA data

The ADA variables described in Section 4.11 will be summarized using descriptive statistics.

Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA analysis set. ADA response categories and titer categories are defined as follows:

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

- ADA Negative, defined as ADA negative response in the assay at all timepoints, regardless of any missing samples.
- 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 of baseline titer levels
- Treatment-emergent ADA response, defined as any post-first dose positive ADA assay response when the baseline results are negative
  - For Part B and Part C of the study, treatment-emergent ADA response will be further characterized as persistent, transient, or indeterminate:
  - Persistent Response – Treatment-emergent ADA positive response with 2 or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.

  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate.
- Treatment boosted ADA response, defined as any post-first dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories
- Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
- Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
- Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

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

5.11.2. Analysis of Neutralizing Antibody (NAb) Data

The absolute occurrence (n) and percent of subjects/patients (%) with NAb status in the NAb analysis set will be provided by treatment groups.

5.11.3. Association of Immunogenicity with Exposure, Safety and Efficacy

5.11.3.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to REGN1500 will be explored. Plots of REGN1500 concentration may be provided for analyzing the potential impact of ADA response status, titer and NAb on the concentration time profiles.

5.11.3.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Potential association immunogenicity variables and efficacy endpoints may be explored (e.g. scatter plot or spaghetti plot).
The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response.
- ADA negative patients, that is subjects/patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.
- Patients with persistent treatment-emergent ADA response
- NAb positive patients, that is ADA positive patients who were positive in the NAb assay at any time point analyzed.
- Maximum post-baseline titer in treatment-emergent or treatment-boosted ADA positive patients:
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment is programmatically defined as the last available measurement prior to the date of the first study treatment administration, regardless of the study treatment period.

6.2. Data Handling Convention for Efficacy Variables

Rules for handling missing data for primary and secondary efficacy variables are described in Section 5.7.1 and Section 5.7.1.3.

6.3. Data Handling Convention for Missing Data

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

Date and Time of First/Last Study Treatment

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

Adverse Event

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

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

Medication/Procedure

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

Potentially Clinically Significant Value (PCSV)

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

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

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

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

6.4. Visit Windows

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

6.5. Unscheduled Assessments

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

6.6. Pooling of Centers for Statistical Analyses

Not applicable.

6.7. Statistical Technical Issues

Not applicable.

7. TIMING OF STATISTICAL ANALYSES

7.1. First Step: PK and Safety Analysis for Part A

The first step will be an analysis of PK data and safety data from all patients in Part A to determine the dose for Part B. The analysis will be performed when at least 8 weeks of concentrations of total evinacumab in serum have been collected and analyzed for all patients in Part A. Subsequent analyses may be conducted using additional accrued PK, LDL-C or safety data if needed to confirm the dose selection for Part B and Part C.

7.2. Second Step: Efficacy and Safety Analysis for Part B

The second analysis will be conducted as soon as all Part B patient data through week 24 have been collected and validated; this will consist of the final analysis of the primary and secondary efficacy endpoints up to week 24 for Part B patients. The safety analysis will be performed on all safety data collected and validated at the time of the second analysis for Part B patients.

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

7.3. Third Step: Final Safety Analysis

The third analysis will be conducted at the end of the study when all Part B and Part C patients have concluded the study, and will consist of the final efficacy and safety analyses.

7.4. Additional Rules

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

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

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

8. SOFTWARE

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

9. REFERENCES

1. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
2. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. Stat Med. 1992;11(10):1305-19.
3. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization; 2006.
4. Rigby RA, Stasinopoulos DM. Smooth centile curves for skew and kurtotic data modelled using the Box-Cox power exponential distribution. Stat Med. 2004;23(19):3053-76.
5. 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.
6. 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.

10. APPENDIX

10.1. Summary of Statistical Analyses

Primary Efficacy Analysis – Part B:

Endpoint	Analysis Populations	Estimand	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
Percent change from baseline in calculated LDL-C at Week 24	ITT	ITT estimand: The calculated LDL-C at week 24 will be the LDL-C value obtained within the week 24 efficacy analysis window, regardless of adherence to treatment and subsequent therapies.	PMM	Yes	Yes	1. MMRM - ITT 2. MMRM - mITT

10.2. Windows for Analysis Time Points

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

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

1. Study day is defined as the number of days since the first study treatment administration +1. The first study treatment occurs on Study Day 1.
2. Part C study day is defined as the number of days since the first Part C study treatment administration+1
3. Since the protocol specifies that measurements be collected before study treatment is administered on a given day, it is appropriate that baseline include Day 1.

Table 1: Global Analysis Windows for Part A

Visit label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	Measurement obtained closest to first study treatment, while remaining prior to first study treatment
Week 1	8	2 to 11
Week 2	15	12 to 18
Week 3	22	19 to 25
Week 4	29	26 to 35
Week 6	43	36 to 49
Week 8	57	50 to 63
Week 10	71	64 to 77
Week 12	85	78 to 98
Week 16	113	99 to 140
FU- W8	For patients prematurely discontinued Part A: EOT visit study day + 56 days For patients completed Week 16 visit: 169	For patients prematurely discontinued Part A: EOT visit to 84 days after EOT visit For patients completed Week 16 visit: 141 to 196
Study days are calculated from the day of first IMP infusion, the day of first IMP infusion being Day 1.		

Table 2: Global Analysis Windows for Part B

Visit label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	Measurement obtained closest to first study treatment, while remaining prior to first study treatment
Week 1	8	2 to 11
Week 2	15	12 to 21
Week 4	29	22 to 35
Week 6	43	36 to 49
Week 8	57	50 to 70
Week 12	85	71 to 98
Week 16	113	99 to 126
Week 20	141	127 to 154
Week 24	169	155 to 196
FU- W8	For patients prematurely discontinued trt: last study trt + 84 days For patients completed Part B trt period: 225	For patients prematurely discontinued trt: 56 to 97 days after last trt For patients completed Part B trt period: 197 to 238
FU-W12	For patients prematurely discontinued trt: last study trt + 112 days For patients completed Part B trt period: 253	For patients prematurely discontinued trt: 98 to 125 days after last trt For patients completed Part B trt period: 239 to 266
FU-W16	For patients prematurely discontinued trt: last study trt + 140 days For patients completed Part B trt period: 281	For patients prematurely discontinued trt: 126 to 153 days after last trt For patients completed Part B trt period: 267 to 294
FU-W20	For patients prematurely discontinued trt: last study trt + 168 days For patients completed Part B trt period: 309	For patients prematurely discontinued trt: 154 to 181 days after last trt For patients completed Part B trt period: 295 to 322
Study days are calculated from the day of first IMP infusion, the day of first IMP infusion being Day 1.		

Table 3: Efficacy Analysis Windows for Part B

Visit Label	Targeted study day	Analysis window in study days
Baseline	1	Measurement obtained closest to first study treatment, while remaining prior to first study treatment
Week 1	8	2 to 11
Week 2	15	12 to 21
Week 4	29	22 to 42
Week 8	57	43 to 70
Week 12	85	71 to 98
Week 16	113	99 to 126
Week 20	141	127 to 154
Week 24	169	155 to 196

Table 4: Global Analysis Windows for Part C

Visit label	Targeted Study Day	Analysis Window in Study Day
Week 0	1	1
Week 4	29	15 to 42
Week 8	57	43 to 70
Week 12	85	71 to 98
Week 16	113	99 to 126
Week 20	141	127 to 154
Week 24	169	155 to 182
Week 28	197	183 to 210
Week 32	225	211 to 238
Week 36	253	239 to 266
Week 40	281	267 to 294
Week 44	309	295 to 322
Week 48	337	323 to 364
FU – W8	For patients prematurely discontinued trt: last study trt + 56 days For patients completed Part C trt period: 365	For patients prematurely discontinued trt: 28 to 69 days after last trt For patients completed Part C trt period: 337 to 378
FU – W12	For patients prematurely discontinued trt: last study trt + 84 days For patients completed Part C trt period: 393	For patients prematurely discontinued trt: 70 to 97 days after last trt For patients completed Part C trt period: 379 to 406

Visit label	Targeted Study Day	Analysis Window in Study Day
FU – W16	For patients prematurely discontinued trt: last study trt + 112 days For patients completed Part C trt period: 421	For patients prematurely discontinued trt: 98 to 139 days after last trt For patients completed Part C trt period: 407 to 448
FU – W24	For patients prematurely discontinued trt: last study trt + 168 days For patients completed Part C trt period: 477	For patients prematurely discontinued trt: 140 to 195 days after last trt For patients completed Part C trt period: 449 to 504
Study days are calculated from the day of first Part C IMP infusion, the day of first Part C IMP infusion being Day 1.		

Table 5: Pooled Analysis Windows for the Integrated Data Pool

Patients	Part A Patients	Part B Patients	
Visit Label	**Targeted Study Day from Part C Day 1**	**Targeted Study Day from Part B Day 1**	**Analysis Window in Study Day in Combine Open-Label Treatment Period**
Baseline	N/A	1	Part A patients: measurement obtained closest to first Part A study treatment, while remaining prior to first Part A study treatment. Part B patients: measurement obtained closest to first Part B study treatment, while remaining prior to first Part B study treatment.
Week 4	29	29	15 to 42
Week 8	57	57	43 to 70
Week 12	85	85	71 to 98
Week 16	113	113	99 to 126
Week 20	141	141	127 to 154
Week 24	169	169	155 to 182
Week 28	197	197	183 to 210
Week 32	225	225	211 to 238
Week 36	253	253	239 to 266
Week 40	281	281	267 to 294
Week 44	309	309	295 to 322
Week 48	337	337	323 to 350
Week 52	N/A	365	351 to 378
Week 56	N/A	393	379 to 406

Patients	**Part A Patients**	**Part B Patients**	
Visit Label	**Targeted Study Day from Part C Day 1**	**Targeted Study Day from Part B Day 1**	**Analysis Window in Study Day in Combine Open-Label Treatment Period**
Week 60	N/A	421	407 to 434
Week 64	N/A	449	435 to 462
Week 68	N/A	477	463 to 490
Week 72	N/A	505	491 to 518
FU – W12	Last study trt + 84 days	Last study trt + 84 days	70 to 97 days after last trt
FU – W16	Last study trt + 112 days	Last study trt + 112 days	98 to 139 days after last trt
FU – W24	Last study trt + 168 days	Last study trt + 168 days	140 to 195 days after last study trt
Study days for Part A patients are calculated from the day of first Part C IMP infusion, the day of first Part C IMP infusion being Day 1. Study days for Part B patients are calculated from the day of first Part B IMP infusion, the day of first Part B IMP infusion being Day 1.			

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

Table 6: Summary of AESIs and the Methods of Data Collections and Derivations

AESI	Using an e-CRF specific tick box on AE page	Using Standard MedDRA Query (SMQ)/company MedDRA Query (CMQ) or lab data
Anaphylactic reactions	Yes	No
General allergic events	No	SMQ "hypersensitivity" (broad and narrow) excluding the following preferred terms linked to local injection site reactions ("infusion site dermatitis", "infusion site hypersensitivity", "infusion site rash", "infusion site urticaria", "injection site dermatitis", "injection site hypersensitivity", "injection site rash", "injection site urticaria", "injection site vasculitis") plus "idiopathic angioedema"
Infusion reactions	Yes	No
Hepatic Disorders	No	• SMQ Drug-related hepatic disorder • Potentially clinically significant value (PCSV) in Appendix 10.4, • Hy's law eDISH plot,
Pregnancy	Yes	No
Symptomatic overdose with investigational medicinal product	Yes	No
Neurocognitive events	No	CMQ for neurocognitive events as define based on Regulatory Agency request for another lipid lowering program (See Table 5 in Appendix 10.3 for the list of terms)
New onset of diabetes (NOD)	No	No medical history of diabetes as specified in "Cardiovascular History and Cardiovascular Risk Factors" CRF page AND one of the following criteria: • Lab criteria: At least 2 values of HbA1c ≥6.5% during the TEAE period. **NOTE**: For patients with only a single measurement available during the TEAE period,

AESI	Using an e-CRF specific tick box on AE page	Using Standard MedDRA Query (SMQ)/company MedDRA Query (CMQ) or lab data
		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 (incl subtypes) ***OR*** • Initiation of any new concomitant medication for hyperglycemia during the treatment period
Pancreatitis	Yes	No

Table 7: 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

MedDRA level	MedDRA Term Label
PTCD	Cognitive Disorder
LLTCD	Confusion
LLTCD	Confusion Aggravated
PTCD	Confusional State
PTCD	Delirium
PTCD	Dementia
PTCD	Dementia Alzheimer's type
LLTCD	Dementia Nos
LLTCD	Dementia Nos Aggravated
LLTCD	Dementia of the Alzheimer's type NOS
PTCD	Dementia with Lewy Bodies
PTCD	Disorientation
PTCD	Disturbance in attention
PTCD	Executive dysfunction
PTCD	Frontotemporal Dementia
LLTCD	Global Amnesia
PTCD	Illogical Thinking
PTCD	Impaired reasoning
PTCD	Incoherent
PTCD	Judgement impaired
PTCD	Memory Impairment
PTCD	Mental Impairment
LLTCD	Mental Impairment Nos
LLTCD	Mental State Abnormal Aggravated
PTCD	Mental Status Changes
PTCD	Mini Mental Status Examination Abnormal
PTCD	Presenile Dementia
PTCD	Retrograde Amnesia
PTCD	Senile Dementia
LLTCD	Senile Dementia Nos
LLTCD	Short-term Memory Loss
PTCD	Thinking Abnormal
LLTCD	Thinking Slowed
PTCD	Transient Global Amnesia
PTCD	Vascular Dementia

10.4. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV
Clinical chemistry	
ALT	By distribution analysis: >2 ULN and baseline ≤ 2 ULN >3 ULN and baseline ≤ 3 ULN >5 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN
AST	By distribution analysis: >2 ULN and baseline ≤ 2 ULN >3 ULN and baseline ≤ 3 ULN >5 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN
Alkaline Phosphatase	> 1.5 ULN and baseline ≤ 1.5 ULN
Total Bilirubin	> 1.5 ULN and baseline ≤ 1.5 ULN > 2 ULN and baseline ≤ 2 ULN
Conjugated bilirubin	> 35% total bilirubin (when total bilirubin >1.5 ULN)
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN and baseline ALT≤3 ULN or Total bilirubin ≤ 2 ULN
CPK	> 3 ULN and ≤ 5 ULN and baseline ≤ 3ULN >5 ULN and ≤ 10 ULN and baseline ≤ 5 ULN >10 ULN and baseline ≤ 10 ULN
Creatinine	≥ 150 µmol/L (adults) ≥ 30% from baseline ≥ 100% from baseline
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)

Parameter	PCSV
Uric Acid Hyperuricemia: Hypouricemia:	 >408 µmol/L <120 µmol/L
Blood Urea Nitrogen	≥17 mmol/L
Chloride	<80 mmol/L >115 mmol/L
Sodium	≤129 mmol/L ≥ 160 mmol/L
Potassium	< 3 mmol/L ≥ 5.5 mmol/L
Glucose Hypoglycaemia Hyperglycaemia	 ≤ 3.9 mmol/L and < LLN ≥ 7 mmol/L (fasted); ≥ 11.1 mmol/L (unfasted)
HbA1c	>8%
Albumin	≤25 g/L
CRP	> 2 ULN or >10 mg/L, if ULN not provided
Hematology	
WBC	< 3.0 Giga/L (3000/ mm^3) (Non-Black) < 2.0 Giga/L (2000/ mm^3) (Black) ≥16.0 Giga/L (16000/ mm^3)
Lymphocytes	>4.0 Giga/L
Neutrophils	< 1.5 Giga/L (1500/ mm^3) (Non-Black) < 1.0 Giga/L (1000/ mm^3) (Black)
Monocytes	>0.7 Giga/L
Eosinophils	> 0.5 Giga/L (500/ mm^3) or > ULN if ULN ≥ 0.5 Giga/L
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥15 g/L Decrease from Baseline ≥20 g/L
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)
RBC	≥6 Tera/L

Parameter	PCSV
Platelets	< 100 Giga/L (100 000/mm^3) ≥700 Giga/L (700000/mm^3)
Urinalysis	
pH	≤4.6 ≥8
Vital signs	
HR	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
SBP	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg ≥ 160 mmHg and increase from baseline ≥ 20 mmHg
DBP	Young and elderly patients ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg ≥ 110 mmHg and increase from baseline ≥ 10 mmHg
Orthostatic Hypotension	SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg
Weight	≥5% increase versus baseline ≥5% decrease versus baseline
ECG parameters	
HR	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
PR	≥220 ms and increase from baseline ≥20 ms
QRS	≥ 120 ms
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Borderline 431-450 ms (Male) 451-470 ms (Female) Prolonged* > 450 ms (Male) > 470 ms (Female) QTc ≥500 ms <u>Increase versus baseline</u> (Males and Females) Borderline Δ 30-60 ms Prolonged * Δ > 60 ms

10.5. Detailed Description of the Multiple Imputation Procedure

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

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

- Step 1: the MCMC method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern. Set the SEED=17100 option in SAS MI procedure
- Step 2: Using the monotone data set from step 1, missing data will be imputed using the regression method. Set the SEED=34200 option in SAS MI procedure

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

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

- age, BMI, and gender (age and BMI included as continuous variables).

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

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

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

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

10.6. Detailed Description of Pattern Mixture Model

As the primary analysis of the primary efficacy endpoint (i.e., percent change from baseline to week 24 in calculated LDL-C for Part B), a pattern-mixture model approach will be used with a different imputation strategy applied for missing calculated LDL-C values during the on-treatment period (i.e., within the time period from the first study treatment administration up to the day of the last study treatment administration +35 days or to the day before the first long-term extension treatment administration, whichever comes first for Part B) and missing LDL-C values after treatment discontinuation (i.e., after the day of last study treatment administration +35 days in Part B) based on the following assumptions:

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

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

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

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

Missing LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to week 24 will be derived from observed and imputed LDL-C at this time point. The completed data sets will be analyzed using the SAS MEANS procedure. The results from the 100 analyses will be combined using Rubin's formulae. If necessary, the number of imputations (100) will be increased until stable estimates are obtained.

Imputation of missing data during the on-treatment period

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

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

The imputation model will include baseline LDL-C value, and all LDL-C values at pre-specified visits. Since the pattern of missing data will necessarily be non-monotone, a Monte-Carlo

Markov Chain (MCMC) method will be used. A minimum value of 0 will be specified in order to avoid negative imputed LDL-C values.

A sample SAS code is provided below:

```
proc mi data=DATAIN out=DATAOUT nimpute=100 minimum=. 0 0 0 0 0 0 0 0 0
SEED=17100;

 var LDL_BASE LDL_W1 LDL_W2 LDL_W4 LDL_W8 LDL_W12 LDL_W16 LDL_W20
LDL_W24;

run;
```

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

Imputation of missing data after treatment discontinuation

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

For each patient, missing post-treatment LDL-C values will be imputed 100 times, using a random draw from a normal distribution (SEED=34200), with mean equal to patient's own baseline value and variance equal to the conditional variance at the specific time-point, given the baseline value.

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

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

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

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

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

10.7. Schedule of Time and Events

Schedule of Events – Part A, PK and PD Portion

	Run-in[13]	Screening	Open-Label Treatment and Observation Period										Follow-up[16]
Study Procedure	**Visit 1**	**Visit 1a**	**Baseline Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[17] Visit 11**	**EOS Visit 12**
Day	-70 to -14	-14 to -1	1	8	15	22	29	43	57	71	85	113	169
Week	-10 to -2	-2 to -1	0	1	2	3	4	6	8	10	12	16	24
Visit Window (day)			±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Screening/Baseline:													
Inclusion/Exclusion	X	X											
Informed Consent and Assent	X[14]	X											
Pharmacogenomics consent		X											
Future Biomedical Research Consent		X											
Medical/Surgical History		X											
Medication History		X											
Demographics		X											
Treatment:													
Administer Study Drug			X										
Concomitant Meds and Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:													
Lipid Panel (fasting): total C, LDL-C, HDL-C, TG, non-HDL-C[1]		X	X	X	X		X		X		X	X	X
Specialty Lipid Panel (fasting): Apo B, Apo A-1, ApoCIII, ApoE, Lp(a)[1]			X				X		X		X	X	X
Safety:													
Vital Signs	X	X	X[15]	X	X	X	X	X	X	X	X	X	X
Physical Examination		X										X	X

	Run-in[13]	Screening	Open-Label Treatment and Observation Period										Follow-up[16]
Study Procedure	**Visit 1**	**Visit 1a**	**Baseline Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[17] Visit 11**	**EOS Visit 12**
Day	-70 to -14	-14 to -1	1	8	15	22	29	43	57	71	85	113	169
Week	-10 to -2	-2 to -1	0	1	2	3	4	6	8	10	12	16	24
Visit Window (day)			±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Electrocardiogram[2]		X										X	X
Tanner Stage		X										X	
Height		X										X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[3]:													
Hematology		X	X	X			X		X		X	X	X
Blood Chemistry		X	X	X			X		X		X	X	X
HbA1c			X									X	X
Sex Hormones[4]			X									X	
Urine Pregnancy Test[5]		X	X				X		X		X	X	X
Urinalysis		X	X	X			X		X		X	X	X
TSH		X											
Hs-CRP			X									X	
PK/Drug Concentration and ADA Samples:													
PK/Drug conc. Sample[6,7,8]			X	X	X		X		X		X	X	X
ADA sample[9]			X									X	X
Biomarkers:													
Future Biomedical Research Serum[10]			X		X				X			X	
Future Biomedical Research Plasma[10]			X		X				X			X	
Pharmacogenomics:													
Blood sample for HoFH genotyping (mandatory)		X											
Whole Blood for DNA (optional)[11]		X											

	Run-in[13]	Screening	Open-Label Treatment and Observation Period										Follow-up[16]
Study Procedure	**Visit 1**	**Visit 1a**	**Baseline Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[17] Visit 11**	**EOS Visit 12**
Day	-70 to -14	-14 to -1	1	8	15	22	29	43	57	71	85	113	169
Week	-10 to -2	-2 to -1	0	1	2	3	4	6	8	10	12	16	24
Visit Window (day)			±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Other													
Review of Diet/ compliance with LMT	X	X	X	X	x	X	X	X	X	X	X	X	X
Carotid Ultrasound Imaging[12]	X											X	

Footnotes for Schedule of Events – Part A, PK and PD Portion

1. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients.
1. ECG should be performed before blood samples are collected at visits requiring blood draws.
2. All laboratory samples should be collected before administration of study drug.
3. Sex hormones include luteinizing hormone, FSH, estradiol, and total testosterone.
4. Pregnancy test with a local urine pregnancy test should be done on sexually active females who have experienced menarche and are of childbearing potential.
5. Including assay of total ANGPTL3. Extra samples may be used to assess the concentration of concomitant medications, e.g., statins.
6. The PK sample should be drawn predose and at the end of the IV infusion on days when study drug is administered
7. If apheresis is administered on a dosing day, it is preferred to administer apheresis before the evinacumab infusion. The PK sample should be collected prior to apheresis and at the end of the evinacumab infusion. In the event apheresis is administered after evinacumab administration, the PK sample should be collected prior to and at the end of evinacumab infusion, prior to apheresis.
8. The ADA sample should be drawn before study drug administration.

9. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent prior to collection of Future Biomedical Research samples. Patients are still eligible to enroll in the study if they do not wish to participate in the Future Biomedical Research.
10. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent to participate in the optional genomics sub-study prior to collection of whole blood DNA samples. Patients are still eligible to enroll in the study if they do not wish to participate in the genomics sub-study
11. Carotid ultrasound imaging will be performed only at sites with this capability. Every effort should be made for patients to undergo 2 carotid ultrasound imaging assessments before the first dose of study drug. The assessments should be separated by at least 1 day.
12. For patients who require stabilization of their background LMT (including apheresis) or need to undergo genotyping to confirm diagnosis of HoFH.
13. If the patient requires a run-in the ICF should be signed at that time; otherwise ICF should be signed at screening visit.
14. On dosing days, vital signs consisting of blood pressure and pulse rate will also be collected pre-dose and 30 minutes and 60 minutes after completion of the IV infusion
15. For patients who do not enter Part C, there will be an 8-week follow-up period (visit 12).
16. If continuing to Part C, this visit can occur on the same day as visit 1 of Part C.

Schedule of Events – Part B, 24-Week Efficacy and Safety Portion

	Run-In[14]	Screening	Baseline	Treatment Period								
Study Procedure	**Visit 1**	**Visit 1a**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**EOT[16] Visit 11**
Day	-70 to -14	-14 to -1	1	8	15	29	43	57	85	113	141	169
Week	-10 to -2	-2 to -1	0	1	2	4	6	8	12	16	20	24
Visit Window (day)			±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Screening/Baseline:												
Inclusion/Exclusion	X	X										
Informed Consent and Assent	X[17]	X										
Pharmacogenomics consent		X										
Future Biomedical Research Consent		X										
Medical/Surgical History		X										
Medication History		X										
Demographics		X										
Treatment:												
Administer Study Drug			X			X		X	X	X	X	
Concomitant Meds and Treatment	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:												
Lipid Panel (fasting): total C, LDL-C, HDL-C, TG, non-HDL-C[1]		X	X	X	X	X		X	X	X	X	X
Specialty Lipid Panel (fasting): Apo B, Apo A-1, ApoCIII, ApoE, Lp(a)[1]			X			X		X	X			X
Safety:												
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X										X
Electrocardiogram[3]		X										X
Tanner Stage		X										X
Height		X										X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Run-In[14] Visit 1	Screening Visit 1a	Baseline Visit 2	Treatment Period Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	EOT[16] Visit 11
Day	-70 to -14	-14 to -1	1	8	15	29	43	57	85	113	141	169
Week	-10 to -2	-2 to -1	0	1	2	4	6	8	12	16	20	24
Visit Window (day)			±1	±1	±1	±1	±3	±3	±3	±3	±3	±3
Laboratory Testing[4]:												
Hematology		X	X					X	X	X		X
Blood Chemistry		X	X					X	X	X		X
HbA1c			X						X			X
Sex Hormones[5]		X	X									X
Urine Pregnancy Test[6]		X	X			X		X	X	X	X	X
Urinalysis		X	X					X	X	X		X
TSH		X										
Hs-CRP			X									X
PK/Drug Concentration and ADA Samples:												
PK/Drug conc. Sample[7,8,9]			X			X		X	X			X
ADA sample[10]			X									X
Biomarkers:												
Future Biomedical Research Serum[11]			X			X			X			X
Future Biomedical Research Plasma[11]			X			X			X			X
Pharmacogenomics:												
Blood sample for HoFH genotyping (mandatory)			X									
Whole Blood for DNA (optional)[12]			X									
Other												
Review of Diet, compliance with LMT	X	X	X	X	X	X	X	X	X	X	X	X
Carotid Ultrasound Imaging[13]	X											X

Schedule of Events – Part B (cont'd)

	Follow-Up Period[15]			
Study Procedure	**Phone Visit 12**	**Visit 13**	**Phone Visit 14**	**Visit 15 EOS**
Day	225	253	281	309
Week	32	36	40	44
Visit Window (day)	±5	±5	±5	±5
Treatment:				
Administer Study Drug				
Concomitant Meds and Treatment	X	X	X	X
Efficacy:				
Lipid Panel (fasting): total C, LDL-C, HDL-C, TG, non-HDL-C[1]		X		X
Specialty Lipid Panel (fasting): Apo B, Apo A-1, ApoCIII, ApoE, Lp(a)[1]				
Safety:				
Vital Signs[2]		X		X
Physical Examination				X
Electrocardiogram[3]				X
Height				X
Weight		X		X
Adverse Events	X	X	X	X
Tanner Stage				X
Laboratory Testing[4]:				
Hematology		X		X
Blood Chemistry		X		X
Sex Hormones[5]				X
HbA1c				X
Urine Pregnancy Test[6]	X	X	X	X
Urinalysis		X		X
TSH				
Hs-CRP				
PK/Drug Concentration and ADA Samples:				
PK/Drug conc. Sample[7,8,9]				X
ADA sample[10]				X

	Follow-Up Period[15]			
Study Procedure	**Phone Visit 12**	**Visit 13**	**Phone Visit 14**	**Visit 15 EOS**
Day	225	253	281	309
Week	32	36	40	44
Visit Window (day)	±5	±5	±5	±5
Biomarkers:				
Future Biomedical Research Serum				X
Future Biomedical Research Plasma				X
Pharmacogenomics:				
Whole Blood for DNA (optional)[11]				
Other				
Review of Diet, compliance with LMT	X	X	X	X
Carotid Ultrasound Imaging				

Footnotes for Schedule of Events – Part B, 24-Week Efficacy and Safety Portion

1. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected before the apheresis procedure; every effort should be made to administer study drug within 1 day of the apheresis procedure.
2. On dosing days, vital signs consisting of blood pressure and pulse rate will also be collected pre-dose and 30 minutes and 60 minutes after completion of the IV infusion
3. ECG should be performed before blood samples are collected at visits requiring blood draws.
4. All laboratory samples should be collected before administration of study drug.
5. Sex hormones include luteinizing hormone, follicle stimulating hormone, estradiol, and total testosterone.
6. Pregnancy test with a local urine pregnancy test should be done on sexually active females of childbearing potential.
7. Including assay of total ANGPTL3. Extra samples may be used to assess the concentration of concomitant medications, e.g., statins.
8. The PK sample should be collected predose and at the end of the IV infusion on days when study drug is administered.
9. For patients who are not undergoing apheresis, the PK sample should be drawn before the administration of study drug. For patients undergoing apheresis, a PK sample should be collected immediately before the apheresis procedure if it is performed before the evinacumab infusion.

10. For patients who are not undergoing apheresis, the ADA sample should be drawn before study drug administration. For patients undergoing apheresis, the ADA sample should be drawn before the apheresis procedure if it is performed before the evinacumab infusion.
11. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent prior to collection of Future Biomedical Research samples. Patients are still eligible to enroll in the study if they do not wish to participate in the Future Biomedical Research.
12. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent to participate in the optional genomics sub-study prior to collection of whole blood DNA samples. Patients are still eligible to enroll in the study if they do not wish to participate in the genomics sub-study. One DNA sample for the genomics sub-study should be collected on day 1 (visit 2) but can be collected at any visit after that.
13. Carotid ultrasound imaging will be performed only at sites with this capability. Every effort should be made for patients to undergo 2 carotid ultrasound imaging assessments before the first dose of study drug. The assessments should be separated by at least 1 day.
14. For patients who require stabilization of their background LMT (including apheresis) or need to undergo genotyping to confirm diagnosis of HoFH.
15. Only for patients who do not enter Part C.
16. If continuing to Part C, this visit can occur on the same day as visit 1 of Part C.
17. If the patient requires a run-in, the ICF should be signed at that time; otherwise, the ICF should be signed at the screening visit.

Schedule of Events – Part C

	Treatment Period													**24-Week Follow-up Period[14]**			
Study Procedure	**V1[15]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13 EOT**	**PV 14**	**V 15**	**PV 16**	**EOS V17**
														Weeks post last dose			
Week	0	4	8	12	16	20	24	28	32	36	40	44	48	+8	+12	+16	+24
Visit Window (day)		±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Treatment:																	
Administer Study Drug	X[16]	X	X	X	X	X	X	X	X	X	X	X					
Concomitant Meds and Treatment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:																	
Lipid Panel (fasting): total C, LDL-C, HDL-C, TG, non-HDL-C[1]			X		X		X	X	X	X	X	X	X		X		X
Specialty Lipid Panel (fasting): Apo B, Apo A-1, ApoCIII, ApoE, Lp(a)[1]			X		X		X	X	X	X	X	X	X		X		X
Safety:																	
Vital Signs[2]		X	X	X	X	X	X	X	X	X	X	X	X		X		X
Physical Examination													X				X
Electrocardiogram[3]													X				X
Tanner Stage[4]							X						X				X
Height[4]							X						X				X
Weight		X	X	X	X	X	X	X	X	X	X	X	X				X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[5]:																	
Hematology			X		X		X		X		X		X		X		X
Blood Chemistry			X		X		X		X		X		X		X		X
HbA1c				X			X			X			X		X		X
Sex Hormones[4,6]							X						X				X
Urine Pregnancy Test[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis			X		X		X		X		X		X				X
Hs-CRP				X			X										X

	Treatment Period													**24-Week Follow-up Period[14]**			
Study Procedure	**V1[15]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13 EOT**	**PV 14**	**V 15**	**PV 16**	**EOS V17**
														Weeks post last dose			
Week	0	4	8	12	16	20	24	28	32	36	40	44	48	+8	+12	+16	+24
Visit Window (day)		±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
PK/Drug Concentration and ADA Samples:																	
PK/Drug conc. Sample[8,9,10]				X			X			X			X				X
ADA sample[11]							X						X				X
Biomarkers:																	
Future Biomedical Research Serum[12]			X				X						X				X
Future Biomedical Research Plasma[12]			X				X						X				X
Other																	
Review of Diet, compliance with LMT		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Carotid Ultrasound Imaging[13]							X						X				

Footnotes for Schedule of Events – Part C

1. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected before the apheresis procedure; every effort should be made to administer study drug within 1 day of the apheresis procedure.
2. On dosing days, vital signs consisting of blood pressure and pulse rate will also be collected pre-dose and 30 minutes and 60 minutes after completion of the IV infusion
3. ECG should be performed before blood samples are collected at visits requiring blood draws.
4. Assessment of Tanner Stage, sex hormones, and post-baseline height only applicable to patients < 18 years old.
5. All laboratory samples should be collected before administration of study drug.
6. Sex hormones include luteinizing hormone, follicle stimulating hormone, estradiol, and total testosterone.
7. Pregnancy test with a local urine pregnancy test should be done on sexually active females of childbearing potential.
8. Including assay of total ANGPTL3. Extra samples may be used to assess the concentration of concomitant medications, e.g., statins.
9. The PK sample should be collected predose and at the end of the IV infusion on days when study drug is administered.
10. For patients who are not undergoing apheresis, the PK sample should be drawn before the dose of study drug. For patients undergoing apheresis, a PK sample should be collected immediately before the apheresis procedure if it is performed before the evinacumab infusion.
11. For patients who are not undergoing apheresis, the ADA sample should be drawn before study drug administration. For patients undergoing apheresis, the ADA sample should be drawn immediately before the apheresis procedure if it is performed before the evinacumab infusion.
12. Parent or legal guardian must sign a separate informed consent form (ICF) and patient must sign a separate informed assent prior to collection of Future Biomedical Research samples. Patients are still eligible to enroll in the study if they do not wish to participate in the Future Biomedical Research
13. Carotid ultrasound imaging will be performed only at sites with this capability. The assessment should be performed approximately every 6 months at every other Visit F.
14. 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.

Sexually active females of childbearing potential will report the results of their home pregnancy test.

15. Overlapping assessments completed at the EOT visit of Part A or Part B do not need to be duplicated during visit 1 of Part C. Part C visit 1 should occur on the same day as Part A visit 11 or Part B visit 11. All necessary assessments are listed in the applicable SOE (Part A or Part B) column for visit 11.
16. Patient can only receive the dose once all assessments from Part A or Part B Visit 11 are completed.

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