Clinical Study Protocol

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

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[redacted].

AMENDMENT HISTORY

Amendment 5

The protocol was amended in response to recent nonclinical findings in the rabbit. The table below summarizes the changes and the affected sections:

Change	Sections Changed
In an embryofetal development toxicology study in rabbits, incomplete ossification of the 15th vertebra was observed in some fetuses resulting from the mating of male rabbits exposed to evinacumab with female rabbits not exposed to evinacumab. In male rabbits, there were measurable levels of evinacumab in seminal fluid and, as a safety measure, the current clinical study is amended to require consistent use of a condom for all sexually active males.	Section 6.2.3 Exclusion Criteria #28 Table 1 Screening Schedule of Events – Patients Requiring Medication Change or Daily Statin Stabilization at Study Entry Table 2 Screening Schedule of Events – Patients on Stable Statin, PCSK9 Inhibitor Antobody and Lipid Modifying Therapy Regimen at Study Entry Table 3 Schedule of Events for SC Treatment Group A Table 4 Schedule of Events for IV Treatment Group B Table 5 Schedule of Events for IV Treatment Group B (Continued for Open-Label) Table 6 Follow-up Schedule of Events for SC Treatment Group A Table 7 Follow-up Schedule of Events for IV Treatment Group B
Updated Scientific/Medical Monitor	Title page

Amendment 4

The primary purpose of this amendment is to update the study population and entry criteria to:

- Allow patients with heterozygous familial hypercholesterolemia (HeFH) who are not taking a background statin due to intolerability to at least 2 statins. This change is being made to include a patient population with high unmet medical need that requires further low-density lipoprotein cholesterol (LDL-C) lowering.
- Change the inclusion LDL-C threshold for all patients with a history of clinical atherosclerotic cardiovascular disease (ASCVD) from 100 mg/dL (2.59 mmol/L) to 70 mg/dL (1.81 mmol/L). This change aligns with clinical practice and dyslipidemia treatment guidelines. The study population enrolled in this study consists of high-risk patients, who are recommended to achieve an LDL-C <70 mg/dL (1.81 mmol/L).

Additional major changes include increasing the duration of the open-label treatment period for Group B from 24 weeks to 48 weeks. This change has been made to increase the amount of long-term safety information obtained on the evinacumab 15 mg/kg Q4W dose regimen, ensuring at least 52 weeks of continuous exposure with this regimen for all patients randomized to the intravenous (IV) treatment groups.

Additionally, the protocol is revised to state that patients may have the opportunity to enroll in an open-label extension or safety study.

Change	Sections Changed
Allow patients with HeFH who are taking no statin(s) to enter the study. This change is being made to include a patient population with high unmet medical need that requires furthers LDL-C lowering.	Section 1 Introduction Section 3.2.1 Rationale for Study Design Section 3.2.3 Benefit / Risk Assessment Section 5.1 Study Description and Duration Section 6.2.2 Inclusion Criteria Section 7.3 Background Treatment
Change the inclusion LDL-C threshold for all patients from 100 mg/dL (2.59 mmol/L) to 70 mg/dL (1.81 mmol/L). This change aligns with clinical practice and dyslipidemia treatment guidelines. The study population enrolled in this study consists of high-risk patients, who are recommended to achieve an LDL-C <70 mg/dL (1.81 mmol/L). Includes clarification of definition of persistent hypercholesterolemia, ACVSD, and of intolerance to satins.	Section 1 Introduction Section 2.1 Primary Objective Section 3.2.1 Rationale for Study Design Section 3.2.3 Benefit / Risk Assessment Section 5.1 Study Description and Duration Section 6.2 Study Population Section 6.2.1 Rescreening of Patients Section 6.2.2 Inclusion Criteria Section 10.4.3.4 Subgroup Analysis
The open-label treatment period for Group B has been increased from 24 weeks to 48 weeks. This change has been made to increase the amount of long-term safety information obtained on the evinacumab 15 mg/kg Q4W dose regimen, ensuring at least 52 weeks of continuous exposure with this regimen for all patients randomized to the IV treatment groups.	Clinical Study Protocol Synopsis (Study Design) Section 5.1 Study Description and Duration (including Figure 1) Section 5.1.2 Follow-up Table 4, Table 5, and Table 7 Section 10.4.1 Patient Disposition Section 10.4.9.3 Third Step: Final Safety Analysis
Note that patients may have the opportunity to enroll in an open-label extension or safety study.	Section 3.2.1 Rationale for Study Design Section 3.2.3 Benefit / Risk Assessment Section 5.1 Study Description and Duration Section 5.1.2 Follow-up
Provide lipid results (but not treatment assignment) to patients during the open-label treatment period. The rationale for this change is that since patients in Group B/IV treatment groups will be in the study for over a year, patients' lipid values will be disclosed when at steady state on evinacumab 15	Section 5.1 Study Description and Duration Section 7.6.1 Blinding Section 8.2.2 Efficacy Procedures Section 8.2.2.2 Specialty Lipid Panel

Change	Sections Changed
mg/kg IV Q4W to allow patients and investigators to be aware of the patients' lipid levels.	
Added a goal attainment threshold of 50 mg/dL as a secondary endpoint, as current lipid treatment guidelines are expected to change	Clinical Study Protocol Synopsis (Secondary Endpoints) Section 4.2.2 Secondary Efficacy Endpoints
For clarity, included the numbers of patients enrolled into each treatment group.	Section 6.1 Number of Patients Planned
Revised the target population to allow patients up to 80 years of age (because they should respond similarly in terms of both efficacy and safety). Clarified the target population to state that the study will aim to enroll, at a minimum, 25% of patients with LDL-C ≥130 mg/dL (3.37 mmol/L) to understand efficacy and safety in patients with higher baseline LDL-C levels.	Clinical Study Protocol Synopsis (Target Population) Section 6.2 Study Population Section 6.2.2 Inclusion Criteria
To be consistent with the recommendations from the Clinical Trial Facilitation Group (CTFG) on contraception and pregnancy testing in clinical trials, clarified sexual abstinence as "True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception." Also included prohibiting oocyte donation.	Section 6.2.3 Exclusion Criteria
Removed exclusion criterion prohibiting insulin usage, because uncontrolled diabetes, defined as HbA1c > 9%, is already an exclusion criterion and is sufficient to exclude patients with diabetes that might confound the safety results.	Section 6.2.3 Exclusion Criteria
Clarified that the IV dose should be prepared using the patient's most recent weight	Section 7.1 Investigational Treatments and Reference Treatments

Change	**Sections Changed**
Clarified fasting procedures	Section 8.2.2 Efficacy Procedures
Minor editorial/formatting changes	Section 1 Introduction Section 3.1 Hypothesis Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 3.2.3 Benefit / Risk Assessment Section 4.2.2 Secondary Efficacy Endpoints Section 5.1 Study Description and Duration Section 5.1.1 Description of Study Treatment Groups Section 6.2 Study Population Section 6.2.2 Inclusion Criteria Section 7.1 Investigational Treatments and Reference Treatments Section 7.3 Background Treatment Section 7.5.1.2 Termination of the Infusion Section 7.6 Method of Treatment Assignment Table 1 Screening Schedule of Events Table 4 Schedule of Events for IV Treatment Groups Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor

Amendment 3

The table below summarizes the changes to the protocol and the affected sections:

Change	Sections Changed
Added a 24-week open-label treatment period after the 24-week double-blind treatment period for the IV groups. The purpose of this change was to obtain long-term safety information with continuous exposure of evinacumab IV for up to 48 weeks. As a result, the mandatory 24-week follow-up period for the IV treatment groups was removed to allow patients to go directly into a separate OL study after completing the double-blind treatment period and open-label treatment period. Patients who do not participate in the OL study would enter a 24-week follow up period.	Synopsis: Study Design, Study Duration, Treatments Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 3.2.3 Benefit/Risk Assessment Section 5.1 Study Description and Duration Figure 1 Study Flow Diagram Section 5.1.1 Description of Study Treatment Groups Section 5.1.2 Follow-up Table 3 Schedule of Events for SC Treatment Group A Table 4 Schedule of Events for IV Treatment Group B Table 7 Follow-up Schedule of Events for IV Treatment Group B Section 10.3.1.2 Modified Intent-to-Treat Section 10.3.2.1 Double-Blind Safety Analysis Set Section 10.3.2.2 Open-Label Safety Analysis Set Section 10.4.1 Patient Disposition Section 10.4.2 Demography and Baseline Characteristics Section 10.4.3.1 Primary Efficacy Analysis Section 10.4.3.2 Secondary Efficacy Endpoint Analysis Section 10.4.3.3 Dose-Response Analysis Section 10.4.3.4 Subgroup Analysis Section 10.4.3.5 Multiplicity Considerations Section 10.4.4 Safety Analysis Section 10.4.4.1 Adverse Events Section 10.4.4.2 Other Safety Section 10.4.4.3 Treatment Exposure Section 10.4.4.4 Treatment Compliance Section 10.4.9.1 First Step: Group B Main Efficacy and Safety Analysis Section 10.4.9.2 Second Step: Group A Main Efficacy and Safety Analysis Section 10.4.9.3 Third Step: Final Safety Analysis
Removed PK sample at week 12 and week 20 for IV treatment Group B	Table 4 Schedule of Events for IV Treatment Group B

Change	Sections Changed
For Group A, the ADA at week 12 was removed because ADA is tested at week 4 and week 16 and, therefore, an additional evaluation at week 12 was not considered necessary.	Table 3 Schedule of Events for SC Treatment Group A
Edits/Clarifications	Synopsis: Endpoint(s) Section 3.2.1 Rationale for Study Design Section 4.2.1 Primary Efficacy Endpoint Section 5.1 Study Description and Duration Section 10 Statistical Plan Section 10.3.1.1 Intent-to-Treat

Amendment 2

The table below summarizes the changes to the protocol and the affected sections:

Change	Sections Changed
Specified that enrollment of intravenous (IV) cohorts will precede enrollment of subcutaneous (SC) cohorts. Modified run-in period	Synopsis: Treatments, Study Duration, Statistical Plan Section 5.1 Study Description and Duration Section 6.1 Number of Patients Planned Section 7.2 Run-in Treatment(s) Section 7.6 Method of Treatment Assignment Section 10.1 Statistical Hypothesis Section 10.2 Justification of Sample Size Section 10.4.3.1 Primary Efficacy Analysis Section 10.4.3.1 Secondary Efficacy Endpoint Analysis Section 10.4.3.3 Dose Response Analysis Section 10.4.3.4 Subgroup Analysis Section 10.4.3.5 Multiplicity Considerations Section 10.4.4 Safety Analysis Section 10.4.9.1 First Step: Group B Main Efficacy and Safety Analysis Section 10.4.9.2 Second Step: Group A Main Efficacy and Safety Analysis Section 10.4.9.3 Third Step: Final Safety Analysis (section added)

Change	Sections Changed
Removed query for compliance to proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor from the Schedule of Events tables	Table 1 Screening Schedule of Events - Patients Requiring Medication Change or Daily Statin Stabilization at Study Entry Table 2 Screening Schedule of Events - Patients on Stable Statin, PCSK9 Inhibitor and Lipid Modifying Therapy Regimen at Study Entry Table 3 Schedule of Events for SC Treatment Group A Table 4 Schedule of Events for IV Treatment Group B Table 6 Follow-up Schedule of Events for SC Treatment Group A Table 7 Follow-up Schedule of Events for IV Treatment Group B
Updated anti-drug antibody (ADA) variables and added a sentence for follow-up of patients whose last sample was positive in the ADA assay Added collection of a sample for ADA at week 4 (visit 6) and 12 (visit 14) for SC group A and week 4 (visit 4) and 24 (visit 10) for IV group B	Section 4.4 Anti-Drug Antibody Variables Section 8.2.4.2 Anti-Drug Antibody Measurements and Samples Table 3 Schedule of Events for SC Treatment Group A Table 4 Schedule of Events for IV Treatment Group B Section 10.3.3 Pharmacokinetic and Anti-Drug Antibody Analysis Sets Section 10.4.6 Analysis of Anti-Drug Antibody Data
Added a section Benefit Risk	Section 3.2.3 Benefit / Risk Assessment
Added assessment for HbA1c during prescreening Added PK sample at week 4	Table 1 Screening Schedule of Events – Patients Requiring Medication Change or Daily Statin Stabilization at Study Entry Table 3 Schedule of Events for SC Treatment Group A
Expanded list of adverse events of special interest (AESIs) for evinacumab	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Removed exclusion for doxycycline	Section 6.2.3 Exclusion Criteria (old Exclusion Criterion #23)
Added instruction for maximally tolerated regimen of lipid-modifying therapy (LMT)	Section 5.1 Study Description and Duration Section 7.3 Background Treatment(s)
Updated blinding text	Section 7.6.1 Blinding
Edited PCSK9 inhibitor to PCSK9 inhibitor antibody	Throughout

Amendment 1

The protocol is amended primarily to update post-dose monitoring to standardize across the evinacumab program.

The table below summarizes the changes to the protocol and the affected sections:

Change	**Sections Changed**
Updated post-dose and vital signs monitoring	Section 8.1.1 Footnotes for Schedule of Events Tables, footnote #7, footnote #11 Section 8.2.3.1 Vital Signs
Clarified measurement of LDL-C	Section 8.2.2 Efficacy Procedures
Added definition of new onset of diabetes	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Updated ADA variables and sampling times	Section 4.4 Anti-Drug Antibody Variables Section 8.1 Schedule of Events Table 3 and Table 4 Section 10.4.6 Analysis of Anti-Drug Antibody Data
Specified that lipid results after the randomization visit will be blinded	Section 5.1 Study Description and Duration Section 7.6.1 Blinding Section 8.2.2.1 Core Lipid Panel Section 8.2.2.2 Specialty Lipid Panel
Added an exclusion criterion	Section 6.2.3 Exclusion Criteria
Minor clarifications/corrections	Section 5.1.3 End of Study Definition Section 6.2.2 Inclusion Criteria #3 Section 8.1 Schedule of Events Section 10.1 Statistical Hypothesis

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Varying Doses and Dose Regimens of Evinacumab in Patients with Persistent Hypercholesterolemia Despite Maximally Tolerated Lipid Modifying Therapy
Site Location(s)	Multi-national (US and globally)
Principal Investigator	Multi-center
Objective(s)	The primary objective of the study is to evaluate the reduction of low-density lipoprotein cholesterol (LDL-C) by evinacumab in comparison to placebo after 16 weeks in patients with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [HeFH], or non-HeFH with a history of clinical atherosclerotic cardiovascular disease [clinical ASCVD]) with persistent hypercholesterolemia despite receiving maximally-tolerated lipid-modifying treatment (LMT). Persistent hypercholesterolemia is defined as LDL-C ≥70 mg/dL (1.81 mmol/L) for those patients with clinical ASCVD and LDL-C ≥100 mg/dL (2.59 mmol/L) for those patients without clinical ASCVD. Secondary objectives of the study are: • To evaluate the dose-response effect of evinacumab on other lipid parameters (ie, apolipoprotein [Apo] B, non-high-density lipoprotein cholesterol [non-HDL-C], total cholesterol [TC], Lp(a), HDL-C, triglycerides [TGs], ApoA1, apolipoprotein CIII [ApoCIII], and total Angiopoietin-like 3 [ANGPTL3]) in patients with primary hypercholesterolemia • To evaluate the safety and tolerability of subcutaneous (SC) and intravenous (IV) doses of evinacumab in patients with primary hypercholesterolemia • To assess systemic serum concentrations of evinacumab in patients with primary hypercholesterolemia • To evaluate the potential development of anti-evinacumab antibodies
Study Design	This is a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to assess varying doses of SC and IV regimens of evinacumab in patients diagnosed with primary hypercholesterolemia (HeFH, or non-HeFH with a history of clinical ASCVD) with persistent hypercholesterolemia despite receiving maximally-tolerated LMT. Persistent hypercholesterolemia is defined as LDL-C ≥70 mg/dL (1.81 mmol/L) for those patients with clinical ASCVD and LDL-C ≥100 mg/dL (2.59 mmol/L) for those patients without clinical ASCVD.

	The study consists of 4 (for Group A [SC treatment groups]) or 5 (for Group B [IV treatment groups) periods: run-in period (for patients whose background LMT has not been stable prior to screening, who are not already receiving a proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor antibody, or whose background LMT has not been optimized), a 2-week screening period, a 16-week double-blind treatment period for the SC dose groups or a 24-week double-blind treatment period for the IV dose groups, an approximately 48-week open-label treatment period for the IV dose groups, and a follow-up period that lasts 24 weeks after the last dose of study drug.
Study Duration	The duration of the study for a patient is approximately 41 or 90 weeks, for the SC and IV groups, respectively. This includes the screening, double-blind treatment, open-label treatment (for IV group), and follow-up periods. All patients who successfully complete this study (or successfully complete the double-blind treatment period and open-label treatment period for patients in the IV treatment groups) may have the opportunity to enroll in an open-label extension or safety study. All patients who enroll in the open-label extension or safety study will continue to receive evinacumab.
Population	
Sample Size:	Expected total number of patients is 252 (Group A 144; Group B 108).
Target Population:	Adult men and women, ages 18 to 80, with primary hypercholesterolemia (HeFH*, or non-HeFH with a history of clinical ASCVD) with LDL-C ≥70** mg/dL (1.81 mmol/L), despite receiving maximally-tolerated LMT. Background LMT would include a stable maximally-tolerated statin and stable PCSK9 inhibitor antibody for patients who are HeFH or non-HeFH with a history of clinical ASCVD. Patients with HeFH not on a statin are allowed to participate if there is documentation of inability to tolerate at least 2 statins. *HeFH may be diagnosed by at least 1 of the following: 1. Genotyping 2. World Health Organization/Dutch Lipid Network or Simon Broome criteria. ** Efforts will be made to enroll, at a minimum, 25% of patients with LDL-C ≥ 130 mg/dL (3.37 mmol/L). Approximately 25% of the population is targeted to have a baseline LDL-C ≥100 mg/dL (2.59 mmol/L). Please note: To ensure an adequate number of patients with HeFH, randomization will be stratified 2:1 (HeFH:non-HeFH; 24:12) within each treatment group.
Treatment(s)	

Dose/Route/Schedule:	Patients will be randomized to either Group A or Group B. Completing enrollment and randomizing patients into Group B will occur prior to commencing enrollment into Group A. The evinacumab dose regimens for Group A and Group B are as follows: Group A • Evinacumab 300 mg SC once every week (QW), for 16 weeks, or • Evinacumab 300 mg SC once every 2 weeks (Q2W), for 16 weeks (alternating with placebo on opposite weeks), or • Evinacumab 450 mg SC QW, for 16 weeks Group B • Evinacumab 5 mg/kg IV once every 4 weeks (Q4W), for 24 weeks, or • Evinacumab 15 mg/kg IV Q4W, for 24 weeks In the open-label treatment period, patients in Group B will receive 15 mg/kg IV of evinacumab Q4W for 48 weeks
Placebo Route/Schedule:	• Group A: Placebo SC QW, for 16 weeks • Group B: Placebo IV Q4W, for 24 weeks
Background Treatment	Statin (HMG CoA reductase inhibitor) PCSK9 inhibitor antibody

Endpoint(s)

Primary:	The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to week 16 in the intent-to-treat (ITT) population, using all LDL-C values regardless of adherence to treatment and subsequent therapies.
Secondary:	The secondary efficacy endpoints are: • Percent change in ApoB from baseline to week 16 • Percent change in non-HDL-C from baseline to week 16 • Percent change in TC from baseline to week 16 • Proportion of patients with ≥ 30% reduction in calculated LDL-C at week 16 • Proportion of patients with ≥ 50% reduction in calculated LDL-C at week 16 • Percent change in TGs from baseline to week 16 • Percent change in Lp(a) from baseline to week 16 • Proportion of patients with calculated LDL-C < 100 mg/dL (2.59 mmol/L) at week 16

	• Proportion of patients with calculated LDL-C < 70 mg/dL (1.81 mmol/L) at week 16 • Proportion of patients with calculated LDL-C < 50 mg/dL (1.30 mmol/L) at week 16 • Percent change in calculated LDL-C, ApoB, non-HDL-C, TC, TG, and Lp(a) from baseline to week 24 (only applicable to those patients receiving IV route of study treatment administration)
Procedures and Assessments	The efficacy of evinacumab will be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study. Lipid parameters include: TC, calculated LDL-C, HDL-C, TG, non-HDL-C, Lp(a), ApoA1, ApoB, and ApoCIII. Safety and tolerability will be assessed by clinical evaluation of treatment-emergent adverse events (TEAEs), physical examination, vital signs, electrocardiogram (ECG), and clinical laboratory tests. Patients will be monitored for all TEAEs experienced from the time of informed consent until their end of study visit. Pharmacokinetics will be assessed by analysis of evinacumab drug concentrations. Immunogenicity will be assessed by analysis for anti-drug antibodies to evinacumab. Additional pharmacodynamic effects will be assessed by analysis of total ANGPTL3.
Statistical Plan	**Justification of the sample size** Four pairwise comparisons of evinacumab to a placebo control arm corresponding to the route of administration (Group A or Group B) are hypothesized for the primary efficacy analysis of this study. A total of 216 patients are planned for assessing the primary measure at week 16. Specifically, a sample size of 36 patients per treatment arm will have 90% power to detect a treatment group difference in mean percent change LDL-C of 20% in any 1 pairwise comparison (ie, evinacumab mean = 27% and control mean = 7%), assuming that the common standard deviation (SD) is 25 using an independent group t-test. This sample size has been adjusted for a 5% dropout rate. The alpha level for each of the 4 pairwise comparisons is 0.05 (2-sided), and assumes control of the overall type-1 error rate using a pre-specified hierarchical inferential approach. Further, the evinacumab 5 mg/kg IV Q4W regimen has been added to Group B, allowing for an assessment of dose-response in the IV route of administration. The additional 36 patients for this second IV dose regimen culminate in a total of 252 patients planned for the study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
ApoA-1	Apolipoprotein A-1
ApoB	Apolipoprotein B
ApoCIII	Apolipoprotein CIII
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CVD	Cardiovascular disease
CV	Cardiovascular
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
FAS	Full analysis set
FSH	Follicle-stimulating hormone
EL	Endothelial lipase
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia

hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDL-R	Low-density lipoprotein receptor
LOF	Loss-of-function
LMT	Lipid modifying therapy
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed-effect model with repeated measures
mITT	Modified intent-to-treat
Non-HDL-C	Non High-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCI	Percutaneous coronary intervention
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
POC	Proof-of-concept
PT	Preferred term
QW	Every week
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System

SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
TIA	Transient ischemic attack
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TSH	Thyroid stimulating hormone
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION

Current medications for lowering low-density lipoprotein cholesterol (LDL-C) include statins, cholesterol absorption inhibitors, fibrates, niacin, bile acid sequestrants, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor antibodies. Statins are the most commonly prescribed medications because they are inexpensive and have demonstrated the ability to reduce coronary heart disease (CHD) events. However, even with statin therapy, many patients still have residual cardiovascular (CV) risk (Ridker 2009). Twenty-two percent (22%) of patients with a history of prior cardiovascular disease (CVD) and 10% of patients without a history of prior CVD experience a CV event in statin trials (Baigent 2005, Baigent 2010).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to lower LDL-C by approximately 60% in patients with heterozygous familial hypercholesterolemia (HeFH) on maximally tolerated statin therapy (Kastelein 2015), and have recently been approved as adjunct to statins in patients with HeFH who require additional LDL-C lowering (Praluent® and Repatha® Product Information). In the recent Odyssey familial hypercholesterolemia (FH) 1 and FH 2 studies comparing alirocumab on top of maximally tolerated statin therapy (with or without ezetimibe) in patients with HeFH and LDL-C ≥ 70 mg/dL with a history of myocardial infarction (MI)/stroke or LDL-C ≥ 100 mg/dL without a history of MI/stroke, treatment with alirocumab reduced LDL-C by up to a mean of 48.8% after 24 weeks (Kastelein 2015). Although the majority of patients achieved their target LDL-C goal, up to 19% and 28% in the FH 1 and FH 2 studies, respectively, did not meet their LDL-C target after 24 weeks of treatment.

One group of patients recognized to remain far from their LDL-C goal are those patients with severe HeFH, often defined as having an on-treatment LDL-C > 200 mg/dL. However, only approximately 2% of patients with severe elevations in LDL-C, despite statin therapy, have an identified FH-causing mutation (low-density lipoprotein receptor [LDL-R], apolipoprotein B [ApoB], PCSK9) (Khera 2016, Abul-Husn 2016). Further, those patients with severely elevated LDL-C, but without evidence of an FH-causing mutation have a 6-fold increased risk of coronary artery disease (CAD), compared with those non-FH patients with an LDL-C <130 mg/dL (Khera 2016). Thus, patients who require additional LDL-C lowering, despite maximally tolerated statin and PCSK9 inhibitor antibody therapy, include not only those patients with HeFH, but also those with polygenic etiologies.

Data generated with both alirocumab and evolocumab in patients not able to tolerate a statin due to muscle-related symptoms highlight another group of patients not able to achieve their LDL-C goal who require additional LDL-C lowering despite available treatment options. The Odyssey Alternative study evaluated the effect of alirocumab in patients at moderate to high CV risk who were unable to tolerate a statin due to muscle symptoms. At week 24, 41.9% of patients on alirocumab achieved their treatment goal (LDL-C <70 mg/dL [1.81 mmol/L] in very-high-cardiovascular-risk patients, or <100 mg/dL [<2.59 mmol/L] in moderate-to-high-risk patients) (Moriarty 2015). Similarly, evolocumab was also evaluated in patients unable to tolerate a statin due to muscle-related symptoms. In GAUSS-3, approximately 32% of the study population was able to achieve an LDL-C of <70 mg/dL (1.81 mmol/L) at week 24 (Nissen 2016). Over 50% of the study populations in these trials were not able to achieve their target LDL-C goal. Despite treatment with potent agents like PCSK9 inhibitor antibodies, a sizeable proportion of the

patients not able to tolerate a statin will not achieve their LDL-C goal and will require additional lipid-lowering therapies.

Angiopoietin-like 3 (ANGPTL3) has recently emerged as an attractive target for the treatment of elevated levels of LDL-C and triglycerides (TGs), both factors for the development of CVD. Subjects who are homozygous for loss-of-function (LOF) mutations in ANGPTL3 have significantly lower levels of TGs as compared to non-carrier controls. Those with ANGPTL3 LOF mutations also exhibit lower LDL-C levels (mean difference of 48% versus non-carriers for the mutations). The mechanism by which ANGPTL3 LOF mutations result in lower LDL-C levels is not fully understood, but appears to be independent of the effects on TGs, and occurs through a pathway independent of the LDL-R. It is noteworthy that patients with 1 or 2 ANGPTL3 LOF alleles also have reported reductions in serum high-density lipoprotein cholesterol (HDL-C) levels. The mechanism for this appears to be related to the inhibitory effect of ANGPTL3 on endothelial lipase (EL), which is involved in the hydrolysis of HDL phospholipids. No health deficits have been reported in the (relatively small number of) patients who are homozygous for ANGPTL3 LOF mutations. Importantly, population genetic studies indicate that patients heterozygous for ANGPTL3 LOF mutations have reduced CV risk. These data suggest that inhibiting ANGPTL3 may be a meaningful strategy for lowering serum lipids in patients whose elevated LDL-C levels place them at significant residual CV risk, despite otherwise optimized lipid-lowering therapy.

REGN1500, also known as evinacumab, is a fully human monoclonal antibody that specifically binds to and inhibits ANGPTL3. Preclinical and early clinical studies have demonstrated that the administration of evinacumab results in a reduction of serum LDL-C and serum TGs.

Non-clinical experiments performed in animals demonstrate the in vivo effects of ANGPTL3, and ANGPTL3 blockade with evinacumab. Angiopoietin-like 3 knockout mice, including those fed a western or high-fat diet, have lower levels of LDL-C and TGs than those of wild-type mice. In several mouse models, administration of evinacumab induced reductions in both LDL-C (up to 46% in ApoE-/- mice) and TGs (up to 72% in ApoE-/- mice). Reductions in HDL-C of approximately 35% were also observed in ApoE-/- mice. In hyperlipidemic LDL-R-deficient (LDL-R-/-) mice, a single dose of 10 mg/kg of evinacumab reduced LDL-C levels by up to 23%, supporting the hypothesis that the reductions in LDL-C likely occurs through a pathway independent of the LDL-R.

In a phase 1, first-in-human, placebo-controlled, double-blind, single ascending dose study (R1500-HV-1214) of the safety, tolerability, and bioeffect of varying dose levels of evinacumab administered subcutaneously (SC) or intravenously (IV) to patients with TGs 150-450 mg/dL and/or LDL-C $\geq$ 100 mg/dL, administration of evinacumab was associated with dose-dependent reductions in LDL-C. The maximal mean percent LDL-C decrease from baseline of 27.8% was observed on day 15 in the 20 mg/kg IV group (n=11) compared to a decrease of 4.5% in the placebo IV group (n= 12). The duration of LDL-C reduction was dose-dependent and appeared to extend at least 64 days after administration of evinacumab 20 mg/kg IV. Evinacumab was well-tolerated at all dose levels up to 20 mg/kg IV.

In a randomized, double-blind, placebo-controlled, multiple ascending dose study (study R1500-CL-1321) of the safety, tolerability, pharmacokinetic (PK), immunogenicity, and pharmacodynamic (PD) effects of evinacumab in otherwise healthy patients with mixed dyslipidemia (TGs 150-500 mg/dL and LDL-C $\geq$ 100 mg/dL), repeated administration of evinacumab over the 8-week double-blind treatment period was associated with continuous,

dose-dependent reductions in LDL-C up to approximately 40%. The duration of LDL-C reduction with evinacumab administration was dose-dependent. It took approximately 6 weeks for the LDL-C level to return to baseline for all SC doses and 9 weeks for the IV dose group. Evinacumab was well-tolerated at all dose levels up to 20 mg/kg IV.

In an ongoing open-label, single-arm, proof-of-concept (POC) study in 9 patients with homozygous familial hypercholesterolemia (HoFH) (Study R1500-CL-1331), evinacumab demonstrated a mean percent change from baseline in LDL-C at week 4 of 49%, with a duration of effect approximately 10 weeks after a single 15 mg/kg IV dose. In this study, evinacumab, at doses up to 15 mg/kg IV, has exhibited an acceptable safety profile.

The primary objective of the current study is to assess the PD effect of varying doses/dose regimens of SC and IV administered evinacumab on serum LDL-C in patients with primary hypercholesterolemia (HeFH [heterozygous familial hypercholesterolemia], or non-HeFH with a history of clinical atherosclerotic cardiovascular disease [ASCVD]) with persistent hypercholesterolemia despite receiving maximally-tolerated lipid-modifying treatment (LMT). Persistent hypercholesterolemia is defined as LDL-C ≥70 mg/dL (1.81 mmol/L) for those patients with clinical ASCVD and LDL-C ≥100 mg/dL (2.59 mmol/L) for those patients without clinical ASCVD.

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the reduction of LDL-C by evinacumab in comparison to placebo after 16 weeks in patients with primary hypercholesterolemia (HeFH, or non-HeFH with a history of clinical ASCVD) with persistent hypercholesterolemia despite receiving maximally-tolerated LMT. Persistent hypercholesterolemia is defined as LDL-C ≥70 mg/dL (1.81 mmol/L) for those patients with clinical ASCVD and LDL-C ≥100 mg/dL (2.59 mmol/L) for those patients without clinical ASCVD.

2.2. Secondary Objective(s)

The secondary objectives of the study are:

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

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

It is hypothesized that evinacumab will reduce LDL-C in patients who need further LDL-C lowering, despite standard of care treatment, including maximally-tolerated statin and PCSK9 inhibitor antibody therapy.

3.2. Rationale

3.2.1. Rationale for Study Design

No randomized placebo-controlled clinical CV outcome trials of statin treatment have been conducted in patients with HeFH due to ethical concerns of withholding recommended therapy in this population. Clinical management of HeFH is largely based on extrapolation from the results of clinical outcomes trials conducted in patients with polygenic hypercholesterolemia, from studies in FH patients that used carotid intima-media thickness as a surrogate outcome, and from a small number of prospective observational studies in patients with FH. In 4 observational studies, statin therapy was shown to reduce the risk of CHD by 50% to 80% in patients with FH (Harada-Shiba 2010, Huijgen 2010, Vermissen 2008). Unfortunately, even after treatment, the risk in HeFH can still be almost 2-fold higher than the general population (Neil 2008).

Proprotein convertase subtilisin/kexin type 9 inhibitor antibodies have been recently approved as adjunct to statins in patients with HeFH who require additional LDL-C-lowering (Praluent® and Repatha® Product Information). The PCSK9 inhibitors have been shown to lower LDL-C by approximately 60% in patients with HeFH on maximally tolerated statin therapy (Kastelein 2015). In the recent Odyssey FH 1 and FH 2 studies comparing alirocumab (Praluent®) on top of maximally tolerated statins (with or without ezetimibe) in patients with HeFH and LDL-C ≥70 mg/dL with a history of MI/stroke or LDL-C ≥ 100 mg/dL without a history of MI/stroke, treatment with alirocumab reduced LDL-C by up to a mean of 48.8% after 24 weeks (Kastelein 2015). Moreover, these significant reductions in LDL-C by PCSK9 inhibitors also result in risk reductions in CV events. Topline results from the FOURIER study with Repatha® (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) demonstrated a 15% risk reduction in a composite endpoint of CV events (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization) in patients with clinical ASCVD treated with evolocumab (Sabatine 2017). Similarly, topline results from the Odyssey Outcomes study with alirocumab demonstrated a 15% risk reduction in the composite endpoint of major cardiac events (CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization) (Schwartz 2018). Both studies highlight the CV outcome benefits associated with lowering LDL-C to target levels or even lower.

Although the majority of patients in the Odyssey FH1 and FH2 studies achieved their target LDL-C goal, up to 19% and 28%, respectively, did not meet their LDL-C target after 24 weeks of treatment. One group of patients recognized to remain far from their LDL-C goal are those patients with severe HeFH, often defined as having a treated (statin) LDL-C >200 mg/dL. Approximately 2% of patients with severe elevations in LDL-C have an identified FH-causing mutation (Khera 2016). Those patients with severely elevated LDL-C, but without evidence of an FH-causing mutation, have a 6-fold increased risk of CAD compared with non-FH patients with

an LDL-C < 130 mg/dL (Khera 2016). Thus, patients with significant residual CV risk who require additional LDL-C lowering, despite maximally tolerated statin and PCSK9 inhibitor therapy, include not only those patients with HeFH, but also those with polygenic etiologies. It is important for all of these patients to achieve their target LDL-C goal, because the body of evidence from the statin literature shows that the relationship between LDL-C reduction and CV event reduction is approximately linear and for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C, there is a corresponding 22% risk reduction in CV events (Cholesterol Treatment Trialists' Collaboration 2010).

Another population not able to achieve their LDL-C goal with the available treatment options and require additional LDL-C lowering is those patients with FH not able to tolerate any statin regimen. Even in studies conducted with potent lipid-lowering agents such as PCSK9 inhibitor antibodies, >50% of the study population was not able to achieve their target LDL-C (Moriarty 2015) (Nissen 2016), highlighting the high unmet medical need in these patients and the need for additional lipid-lowering therapies.

This present study is a phase 2, double-blind, randomized, placebo-controlled, dose-ranging study to assess varying doses of subcutaneous (SC) and intravenous (IV) regimens of evinacumab in patients who need further LDL-C reductions, defined as those patients diagnosed with hypercholesterolemia (HeFH, or non-HeFH with clinical ASCVD) who have an LDL-C ≥70 mg/dL (1.81 mmol/L), despite receiving a stable maximally-tolerated lipid-lowering regimen. This regimen is defined as including a maximally-tolerated dose of a statin and a PCSK9 inhibitor antibody at the top recommended doses for all patients. Patients with HeFH on no statin will be allowed as long as they were treated previously with statins and have the associated documentation demonstrating inability to tolerate at least 2 statin regimens.

The primary endpoint in this study is the percent change in LDL-C from baseline to week 16. As described above, LDL-C is an accepted surrogate endpoint for CV risk, and has repeatedly been used as the primary endpoint for other lipid lowering treatments. The primary endpoint will be assessed at week 16 because that treatment duration will allow all patients in both Group A (SC treatment groups) and Group B (IV treatment groups) to achieve steady state and maximum LDL-C lowering. As such, 16 weeks is an adequate treatment duration to obtain sufficient PK and PD information to guide dose selection.

In addition to providing key information to understand the effect of evinacumab in patients with refractory hypercholesterolemia and to help with dose selection for future studies, long-term safety of IV administrations of evinacumab will be evaluated in Group B patients. For this reason, the double-blind treatment period for Group B is 8 weeks longer than for Group A (24 weeks vs 16 weeks) and a 48-week open-label treatment period will occur for patients in Group B. This additional exposure to evinacumab will help to define further the safety profile for evinacumab.

Long-term safety of SC administration will not be obtained in this study, but patients in Group A may have the opportunity to enroll in an open-label extension or safety study. The SC treatment period in this study is shorter due to the high burden of up to 3 weekly injections, which are administered by study staff at each clinic visit. Therefore, beyond the primary endpoint at week 16, patients will not be required to continue receiving evinacumab injections.

The study design includes a run-in period of variable duration. This run-in period will ensure patients have enough time to become stabilized on their background medications (if they need

stabilization). Since this can vary from patient to patient, depending on the potential changes needed to their background lipid modifying therapy (LMT), the upper limit of the run-in period is variable. Additionally, for all patients not on a PCSK9 inhibitor antibody that will require alirocumab to be provided to them, this change will allow patients to enroll into the study in advance of randomization and start to receive a beneficial lipid lowering therapy.

All patients receiving study treatment will enter a 24-week follow-up period, beginning at the time of the last study treatment administration (double-blind or open-label study treatment).

3.2.2. Rationale for Dose Selection

The doses proposed for this current study are 300 mg SC every week (QW), 300 mg SC every 2 weeks (Q2W) (alternating with placebo on opposite weeks), 450 mg SC QW, 5 mg/kg IV every 4 weeks (Q4W), and 15 mg/kg IV Q4W. These doses have been evaluated in the study R1500-CL-1321, in patients with modestly elevated LDL-C and were shown to have an acceptable safety profile. Effects in lowering LDL-C have been observed with all of the proposed SC doses. The 15 mg/kg IV dose has been studied in the HoFH POC study. The maximal LDL-C reduction from baseline ranged from approximately 15-35% during the 8-week treatment period in the R1500-CL-1321 study, whereas mean percent change in LDL-C in the HoFH POC study was approximately -49% at 2 weeks following a single 15 mg/kg IV dose.

Available data show evinacumab PK is nonlinear and dose-dependent, consistent with target-mediated elimination. Steady-state concentrations of evinacumab are predicted to be achieved after approximately 16 weeks of weekly SC administration. Target saturation with limited duration was observed at evinacumab concentrations of 100 mg/L and above. In study R1500-CL-1321, the PK profiles of 300 mg SC QW, 300 mg SC Q2W and 450 mg SC QW were clearly separated in a dose-dependent manner. Total ANGPTL3 concentrations increased with increasing doses, indicating dose-dependent target engagement. Evidence of target saturation with limited duration was observed following 8 weeks of treatment at doses of 20 mg/kg IV Q4W and 450 mg SC QW. Target saturation for the duration of the dosing interval is expected with the 15 mg/kg IV dose. Based on available data, the dosing regimens to be evaluated in the current study are expected to provide therapeutic benefit to patients with primary hypercholesterolemia, and will enable comprehensive characterization of evinacumab exposure at dose levels ranging from low to high in this patient population. Varying PD responses at each dose level, including change in total ANGPTL3 and LDL-C, can also be obtained to further inform evinacumab exposure-response relationship in this particular patient population. Data collected from this study are expected to have a wide dynamic range and support dose selection for phase 3 studies in patients with hypercholesterolemia, including, but not limited to, HeFH and non-HeFH.

Five (5) mg/kg IV Q4W is selected as the alternative lower dose as it is expected to differentiate from 15 mg/kg in evinacumab exposure, ANGPTL3 binding, TG reduction and possibly, LDL-C reduction in patients with HeFH. In otherwise healthy subjects with elevated TGs and LDL-C in study R1500-HV-1214, single-dose administrations of evinacumab 75, 150, and 250 mg SC and 5, 10, and 20 mg/kg IV led to dose-dependent target engagement and reductions in LDL-C and TGs. The total exposure (AUC) of evinacumab after 5 mg/kg IV is 4- to 5-fold lower than the predicted area under curve for 15 mg/kg IV, due to non-linearity in PK. In addition, the serum concentration of evinacumab in the single-dose study (R1500-HV-1214) after 5 mg/kg IV was above 100 mg/L for 2-3 days. Inclusion of this dose will inform whether ANGPTL3 saturation is

needed for maximal LDL-C reduction in patients with HeFH. On the other hand, 5 mg/kg IV Q4W is expected to provide some benefit in decreasing LDL-C in patients with HeFH, as evinacumab concentration after 5 mg/kg IV was much greater than that after the 250 mg SC dose, which has shown to reduce LDL-C to a varying degree in patients with HoFH (study R1500-CL-1331). Low-density lipoprotein response, although observed to lag behind drug exposure, is expected to be stabilized following 8 weeks of treatment with a Q4W dosing interval.

For the open-label phase, 15 mg/kg IV Q4W will be administered. Target saturation is expected during the 4-week dosing interval and patients are most likely to have a sustained, maximal LDL-C reduction compared to lower doses. In addition, safety information can be collected at the highest dose of evinacumab and provide the most relevant information to characterize the benefit-risk profile of evinacumab over long-term use.

3.2.3 Benefit / Risk Assessment

Of the current medications for lowering LDL-C, statins are the most commonly prescribed because they are inexpensive and have demonstrated the ability to reduce CHD events. Proprotein convertase subtilisin/kexin type 9 inhibitor antibodies are a newer class of agents that significantly lower LDL-C and recently demonstrated a reduction in the risk of CV events (Sabatine 2017). Despite all of the available treatment options, particularly statins and PCSK9 inhibitor antibodies, some patients still do not reach their LDL-C goal, and continue to have residual CV risk. In the Odyssey FH 1 and FH 2 studies, up to 19% and 28% in FH1 and FH2, respectively, did not meet their LDL-C target despite 24 weeks of treatment with alirocumab. Additionally, some patients are not able to tolerate a statin, despite trials with multiple agents and regimens. In previous studies of PCSK9 inhibitor antibodies in patients who are not able to tolerate statin therapy, over 50% of patients do not achieve their LDL-C goal.

Patient populations that continue to need additional LDL-C lowering include those with severe HeFH, as well as patients without a mutation identified as causing FH, with polygenic etiologies of their disease. It is important for all patients to achieve their LDL-C target because the body of evidence from the statin literature shows that the relationship between LDL-C reduction and CHD event reduction is approximately linear and for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C, there is a corresponding 22% risk reduction in CHD events (CTT study). Moreover, the results from recent outcomes trials with ezetimibe (IMPROVE-IT), evolocumab (FOURIER), and alirocumab (Odyssey Outcomes) reinforce this concept, providing additional evidence for the relationship between LDL-C lowering and reduction in risks for CV events, thereby emphasizing the importance for patients to achieve their target LDL-C.

Evinacumab is a new treatment option that could get patients to their target LDL-C when added to a stable lipid-lowering regimen, including statins and a PCSK9 inhibitor antibody. In the early clinical studies in healthy subjects, monotherapy treatment with evinacumab resulted in up to 40% reduction in LDL-C and up to 80% reduction in TG. In the R1500-CL-1331 study in patients with HoFH, treatment with evinacumab on top of a stable lipid lowering regimen resulted in peak mean LDL-C reductions of approximately 58%.

It is expected that treatment with evinacumab will be well tolerated and have an acceptable safety profile. The accumulated safety information from the completed and ongoing clinical studies is marked by the absence of any important identified risks. There are potential risks that include systemic hypersensitivity reactions, immunogenicity, and embryofetal toxicity. These risks will be

managed through careful patient selection and monitoring. For the potential embryofetal toxicity risk, there is a strict risk mitigation plan, including requirements for consistent use of contraception for sexually active male study participants and sexually active female study participants of child bearing potential.

Taken together, these data show the positive benefit/risk assessment of treatment with evinacumab in patients with HeFH, or non-HeFH with clinical ASCVD with persistent hypercholesterolemia despite receiving maximally-tolerated LMT. Persistent hypercholesterolemia is defined as LDL-C ≥70 mg/dL (1.81 mmol/L) for those patients with clinical ASCVD and LDL-C ≥100 mg/dL (2.59 mmol/L) for those patients without clinical ASCVD.

To obtain long-term safety data with evinacumab, all patients in Group B will receive IV study drug for 48 weeks. Due to the injection burden of weekly SC administration, Group A patients will not be required to receive study drug for 48 weeks. After the 16-week double-blind treatment period, Group A patients who wish to receive treatment with evinacumab may have the opportunity to enroll in an open-label extension or safety study. Therefore, this study design took into consideration the objective of obtaining long-term safety data and providing potential benefit to patients with continued treatment with evinacumab while balancing the burden of frequent study visits and SC injections.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, and height), medical history, and medication history for each patient.

4.2. Primary and Secondary Efficacy Endpoints

4.2.1. Primary Efficacy Endpoint

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

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

All calculated LDL-C values (scheduled or unscheduled) may be used to provide a value for the primary efficacy endpoint, if appropriate, according to the above definition. The analysis window used to allocate a time point to a measurement will be defined in the statistical analysis plan (SAP).

4.2.2. Secondary Efficacy Endpoints

The secondary endpoints are:

- Percent change in ApoB from baseline to week 16

- Percent change in non-HDL-C from baseline to week 16
- Percent change in TC from baseline to week 16
- Proportion of patients with ≥ 30% reduction in calculated LDL-C at week 16
- Proportion of patients with ≥ 50% reduction in calculated LDL-C at week 16
- Percent change in TGs from baseline to week 16
- Percent change in Lp(a) from baseline to week 16
- Proportion of patients with calculated LDL-C < 100 mg/dL (2.59 mmol/L) at week 16
- Proportion of patients with calculated LDL-C < 70 mg/dL (1.81 mmol/L) at week 16
- Proportion of patients with calculated LDL-C < 50 mg/dL (1.30 mmol/L) at week 16
- Percent change in calculated LDL-C, Apo B, non-HDL-C, TC, TG, and Lp(a) from baseline to week 24 (only applicable to those patients receiving IV route of study treatment administration)

4.3. Pharmacokinetic Variable

The PK variable is evinacumab concentrations at sampling times specified in the visit schedule (Table 3 and Table 4).

4.4. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) variables include ADA status and titer as follows:

- Treatment-emergent response - defined as a positive response post first dose in the ADA assay when baseline results are negative or missing
- Treatment-boosted response - defined as a positive response post first dose in the ADA assay that is at least 9-fold over baseline titer levels, when baselines results are positive

The definition of persistent and transient ADA will be defined a priori in the SAP.

- Titer category
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤10,000)
  - High (titer >10,000)

Samples positive in the ADA assay will be assessed for neutralizing activity.

5. STUDY DESIGN

5.1. Study Description and Duration

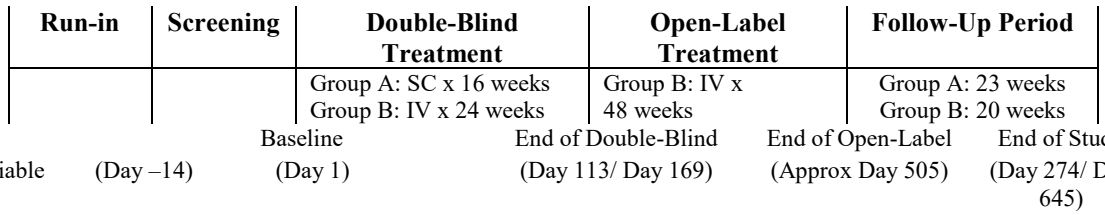
This is a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to assess varying doses of SC and IV regimens of evinacumab in patients diagnosed with primary hypercholesterolemia (HeFH, or non-HeFH with a history of clinical ASCVD) who have an

LDL-C ≥70 mg/dL (1.81 mmol/L), despite receiving a stable maximally-tolerated LMT. The LMT would include a stable, maximally-tolerated statin and stable PCSK9 inhibitor antibody for patients who are HeFH or non-HeFH with a history of clinical ASCVD. Patients with HeFH not on a statin are eligible if there is documentation of inability to tolerate at least 2 statins (see Section 7.3 Background Treatments for further information).

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

All patients in Group B who have successfully completed the double-blind treatment period and the open-label treatment period, and all patients in Group A who have successfully completed the double-blind treatment period and follow-up period in this study may have the opportunity to enroll in an open-label extension or safety study. All patients who enroll in the separate open-label extension study will continue to receive evinacumab.

Figure 1: Study Flow Diagram



Run-in:

There will be a run-in period for:

- Patients who are not receiving the maximal dose of a PCSK9 inhibitor antibody or whose dose has not been stable for at least 8 weeks before the screening visit
- Patients whose maximally tolerated statin has not been stable for at least 4 weeks before the screening visit
- Patients whose background LMT (other than statin or PCSK9 inhibitor antibody) has not been stable for at least 4 weeks (6 weeks for fibrates) before the screening visit

During this run-in period, patients will be stabilized on their statin, PCSK9 inhibitor antibody, and other background LMT (as applicable), and patients receiving alirocumab 75 mg SC Q2W will have their dose up-titrated to the maximum dose of either 150 mg SC Q2W or 300 mg SC Q4W. The duration of the run-in period will depend on the time needed for the patient to stabilize on their background LMT.

Whether or not a patient is considered to be on a maximum tolerated regimen of LMT (statin, PCSK9 inhibitor, ezetimibe, etc) and reasons why the patient is not taking the various treatments (eg, due to intolerance, lack of efficacy, etc) will need to be documented in the case report form (CRF).

Screening:

Patients who have been receiving a stable maximally tolerated statin regimen for at least 4 weeks and a stable PCSK9 inhibitor antibody regimen (alirocumab 150 mg SC Q2W, or 300 mg SC Q4W, or evolocumab 140 mg SC Q2W or 420 mg SC Q4W) for at least 8 weeks before screening, and whose additional LMT (as applicable) has been stable for at least 4 weeks (6 weeks for fibrates) before screening, will enter a 2-week screening period.

Double-blind Treatment:

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

Group A

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

Group B

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

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

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

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

Investigational medicinal product (IMP) administration during the double-blind treatment period will take place at the site and possibly, by visiting home nurses (only for the SC group). The IMP will be administered at the site on the day of randomization, after all samples for clinical laboratory evaluation have been obtained. In order to ease burden for those patients randomized to receive SC IMP, visiting home nurses may be utilized to administer SC IMP on odd visit dates, eg. Week 1, week 3, and week 5.

Open-Label Treatment Period (Group B only)

Patients in Group B (the IV treatment groups) will enter a 48-week open-label treatment period and all patients will receive evinacumab 15 mg/kg IV Q4W.

Follow-Up Period (Groups A and B)

All patients will be followed for 24 weeks after the last dose of study drug.

Patients should maintain their stable background LMT regimen from screening through the end of study (EOS) visit.

Patients will be reminded to adhere to a heart-healthy diet at screening, and continuing through the EOS visit. Patients should maintain a stable exercise level for the duration of the study, and avoid rigorous exercise 24 hours before each study visit. All lipid results will be blinded from after randomization until the week 36 visit for the IV cohorts, and until database lock for the SC cohorts.

5.1.1. Description of Study Treatment Groups

Group A double-blind treatment period (16 weeks):

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

Group B double-blind treatment period (24 weeks):

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

Group B open-label treatment period (48 weeks):

- Evinacumab 15 mg/kg IV Q4W

5.1.2. Follow-up

All patients will be followed for 24 weeks after the last dose of study drug. Thus, for IV cohorts in which the dosing interval is Q4W, patients will be followed for an additional 20 weeks after end of treatment (EOT). For SC cohorts, in which the shortest dosing interval is QW, patients will be followed for an additional 23 weeks after the EOT visit.Patients in Group B may have the option of joining an open-label extension or safety study after successfully completing the treatment period (48 weeks). Patients in Group A may have the option of joining an open-label extension or safety study after successfully completing the treatment period (16 weeks) and follow-up period (24 weeks). Those patients that do not enroll in the separate open-label study will enter a follow-up period, which lasts 20 weeks for IV groups after the last dose of study drug. It takes approximately 24 weeks for evinacumab concentration to be below lower limit of quantitation.

Sexually active patients should be reminded at the EOT visit to maintain highly effective contraceptive measures for 24 weeks after the last dose of study drug. At this visit, women of childbearing potential (WOCBP) may be provided urine pregnancy tests to perform at home with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. The patient should also be notified of Q4W follow-up phone calls to confirm contraception use, provide a reminder of pregnancy reporting, and to obtain the results of the pregnancy test.

5.1.3. End of Study Definition

The EOS for this study is defined as the last visit of the last patient.

5.2. Planned Interim Analysis

No interim analysis is planned.

5.3. Study Committees

5.3.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC), composed of members who are independent from the sponsor and the study investigators, will monitor patient safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the IDMC are described in the IDMC charter.

5.3.2. Clinical Events Committee

The Clinical Events Committee is composed of experts in the field of cardiovascular disease, independent from the sponsor and the investigators. This committee will be responsible for defining, validating, and classifying (in a blinded fashion) pre-specified cardiovascular events, and all deaths.

Patients with suspected or confirmed CV events, which occur during the time period from randomization until the follow-up visit, will have a corresponding adjudication package prepared and submitted to the CEC. The events should also be reported as serious adverse events (SAEs), as appropriate. Adjudicated CV events include all CV adverse events (AEs) positively adjudicated. The adjudication categories include:

- CHD death
- Non-fatal MI
- Fatal and non-fatal ischemic stroke
- Unstable angina requiring hospitalization
- Congestive heart failure requiring hospitalization

In addition, deaths will be classified by the CEC. All coronary revascularizations (percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG]) will be submitted to the CEC, and analyzed.

A charter and an adjudication operational manual will specify additional details regarding the procedures, criteria, and classification used for adjudication of these events.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Approximately 252 patients, at approximately 80 sites in the US and globally, will be randomized within either Group A (evinacumab 300 mg SC QW: evinacumab 300 mg SC Q2W: evinacumab 450 mg SC QW: placebo SC) or Group B (evinacumab 5 mg/kg IV Q4W: evinacumab 15 mg/kg IV Q4W: placebo IV). There will be 144 patients randomized to Group A (36 patients per treatment group), with 108 patients exposed to SC evinacumab and 36 exposed to SC placebo. There will be 108 patients randomized to Group B (36 patients per treatment group), with 72 patients exposed to IV evinacumab and 36 exposed to IV placebo.

6.2. Study Population

Adult men and women, ages 18 to 80, with primary hypercholesterolemia (HeFH, or non-HeFH with clinical ASCVD), with persistent hypercholesterolemia despite receiving maximally-tolerated LMT. Persistent hypercholesterolemia is defined as LDL-C ≥70 mg/dL (1.81 mmol/L) for those patients with clinical ASCVD and LDL-C ≥100 mg/dL (2.59 mmol/L) for those patients without clinical ASCVD. Background LMT would include a stable maximally-tolerated statin and stable PCSK9 inhibitor antibody for patients who are HeFH or non-HeFH with a history of clinical ASCVD. Patients with HeFH not on a statin are allowed to participate if there is documentation of inability to tolerate at least 2 statins due to muscle symptoms. Inability to tolerate a statin should be due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued.

Randomization will be stratified 2:1 (HeFH:non-HeFH; 24:12) within each treatment group to ensure an adequate number of patients with HeFH are appropriately represented at each dose. This will ensure that there is a proportionate distribution of patients with HeFH in each cohort to adequately assess the safety and efficacy of evinacumab in patients with HeFH.

Approximately 25% of the population is targeted to have a baseline LDL-C ≥100 mg/dL (2.59 mmol/L) and approximately 25% of the population should have a baseline LDL-C ≥130 mg/dL (3.37 mmol/L). The baseline value is defined as the last available value before the first dose of study drug.

6.2.1. Rescreening of Patients

Patients who do not meet eligibility criteria during the initial screening may rescreen only once. Patients who are rescreened after the screening window ends must re-consent for study participation and repeat all screening procedures.

Patients who do not meet all eligibility criteria during the initial screening, and are still within the screening window, may retest once the assessments that did not meet eligibility criteria.

Patients with a history of ASCVD who previously failed screening due to the LDL-C threshold of 100 mg/dL (2.59 mmol/L) will be eligible to rescreen once based on the eligibility criterion being amended to 70 mg/dL (1.81 mmol/L).

6.2.2. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Men and women, ages 18 through 80 at the screening visit
2. Body mass index ≥ 18.0 and ≤ 40.0 kg/m^2
3. Diagnosis of primary hypercholesterolemia, either HeFH* or non-HeFH with clinical ASCVD

   *Diagnosis of heFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the Simon Broome criteria for definite FH (Appendix 2) or the World Health Organization/Dutch Lipid Network criteria with a score of >8 points (Appendix 3).
4. A history of clinical ASCVD, for those patients who are non-HeFH. Clinical ASCVD is defined as: acute coronary syndrome, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral arterial disease presumed to be of atherosclerotic origin (Stone 2014)
5. Receiving a stable maximally tolerated* statin (± ezetimibe) for at least 4 weeks at screening

   *Patients not able to be on a high-intensity statin/statin dose should be treated with a regimen considered appropriate for the patient, according to the investigator's judgment. Some examples of acceptable reasons for a patient taking a lower statin dose or no statin include, but are not limited to: adverse effects, advanced age, low body mass index, regional practices, local prescribing information, concomitant medications, co-morbid conditions such as impaired glucose tolerance/impaired fasting glucose. The reason(s) for not receiving a high-intensity statin will be documented in the CRF.

   "High-intensity statin" is defined as (any of the following are acceptable):

   - Rosuvastatin 20 mg or 40 mg daily
   - Atorvastatin 40 mg or 80 mg daily
   - Simvastatin 80 mg daily (if already on this dose for > 1 year)
6. For those patients with HeFH who are not receiving a statin at screening, documentation of inability to tolerate at least 2 statins. Inability to tolerate a statin should be due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued.
7. Receiving alirocumab 150 mg SC Q2W or 300 mg SC Q4W, OR evolocumab 140 mg SC Q2W or 420 mg SC Q4W for at least 8 weeks prior to the screening visit
8. For those patients with a history of clinical ASCVD, serum LDL-C ≥70 mg/dL (1.81 mmol/L) at screening (1 repeat lab is allowed). ASCVD is defined as: acute coronary syndrome, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin (Stone 2014). Patients with a history of ASCVD who previously

failed screening due to the LDL-C threshold of 100 mg/dL (2.59 mmol/L) will be eligible to rescreen once based on the change to 70 mg/dL (1.81 mmol/L).

9. For those patients without a history of clinical ASCVD, serum LDL-C ≥100 mg/dL (2.59 mmol/L) at screening (1 repeat lab is allowed). Clinical ASCVD is defined as: acute coronary syndrome, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin (Stone 2014)
10. Stable heart-healthy diet, starting at screening and willing to continue through the EOS visit
11. Willing and able to comply with clinic visits and study-related procedures
12. Provide signed informed consent

6.2.3. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Known history of homozygous FH (clinically, or by previous genotyping)
2. Use of any medication or nutraceutical (other than a statin or PCSK9 inhibitor antibody) known to alter serum lipids and which has not be stable for at least 4 weeks (6 weeks for fibrates) before screening.
3. Unwilling to maintain current exercise regimen and/or general physical activity level for the duration of the study
4. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins

   Note: Patients on thyroid replacement therapy can be included if the dosage of the replacement therapy has been stable for at least 12 weeks prior to screening and the thyroid stimulating hormone (TSH) level is within the normal range of the central laboratory at the screening visit.
5. Use of thyroid medications (except for replacement therapy which has been stable for at least 12 weeks before screening)
6. Newly-diagnosed (within 3 months prior to screening visit) or poorly-controlled (hemoglobin A1c [HbA1c] > 9%) diabetes
7. Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg (except for patients on simvastatin 80 mg for > 1 year)
8. Use of estrogen or testosterone therapy unless the regimen has been stable in the past 6 weeks prior to the screening visit and there are no plans to change the regimen during the study
9. Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to randomization

   Note: Topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as ‘systemic’ and are allowed.

10. Initiation of a new diet or major change to a previous diet within 4 weeks prior to screening
11. Conditions/situations such as:
    a. Any clinically significant abnormality identified at the time of screening that, in the judgment of the investigator or any sub-investigator, would preclude safe completion of the study or constrain endpoints assessment; eg, major systemic diseases, patients with short life expectancy
    b. Considered by the investigator or any sub-investigator as inappropriate for this study for any reason, eg:
        – Deemed unable to meet specific protocol requirements, such as scheduled visits
        – Deemed unable to tolerate injections, as per the patient or the investigator
        – Investigator or any sub-investigator, pharmacist, study coordinator, other study staff or relative thereof directly involved in the conduct of the protocol, etc.
        – Presence of any other conditions (eg, geographic or social), either actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study
12. Laboratory findings during screening period (not including randomization labs):
    a. Triglycerides >400 mg/dL (>4.52 mmol/L) for patients without a known history of diabetes mellitus (1 repeat lab is allowed);

       OR

       Triglycerides >300 mg/dL (>3.39 mmol/L) for patients with a known history of diabetes mellitus (1 repeat lab is allowed)
    b. Positive test for Hepatitis B surface antigen and/or Hepatitis C antibody (associated with a positive HCV ribonucleic acid [RNA] polymerase chain reaction)
    c. Positive serum beta-human chorionic gonadotropin or urine pregnancy test in women of childbearing potential
    d. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 according to 4-variable MDRD study equation (calculated by central lab)
    e. TSH >1.5 x upper limit of normal (ULN) (1 repeat lab is allowed) for patients not on thyroid replacement therapy
    f. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x ULN at screening (1 repeat lab is allowed)
    g. Creatine phosphokinase (CPK) > 3 x ULN at screening (1 repeat lab is allowed)
13. Systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at the screening visit or time of randomization (1 repeat allowed)
14. History of heart failure (New York Heart Association [NYHA] Class III-IV) within 12 months before screening

15. History of MI, unstable angina leading to hospitalization, CABG surgery, PCI, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, TIA, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior screening
16. Having received LDL apheresis within 2 months before screening
17. Evidence of clinically significant intestinal malabsorption, or a history of ileal bypass, gastric bypass, or other bariatric surgery within 12 months before screening
18. Unstable weight (variation > 5 kg) within 2 months prior to screening visit
19. Significant concomitant illness including, but not limited to: cardiac, renal, neurological, endocrinological, hepatic, metabolic, or lymphatic disease, that would adversely affect the patient's participation in the study
20. History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer
21. Known hypersensitivity to monoclonal antibody therapeutics
22. History of a hypersensitivity reaction to PCSK9 inhibitor antibodies
23. Participation in a clinical research study evaluating an investigational drug within 30 days, or at least 5 half-lives of the investigational drug, before screening, whichever is longer
24. History or evidence of drug or alcohol abuse within 12 months before screening
25. History of noncompliance to medical treatments
26. Pregnant or breast-feeding women
27. Women of childbearing potential* who are unwilling to practice a highly effective birth control method prior to the initial dose, during the study, and for 24 weeks after the last administration of study drug. Highly effective contraception measures include:
    - Stable use of combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening:
      - oral
      - intravaginal
      - transdermal
    - Stable use of progestogen-only hormonal contraception associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening:
      - oral
      - injectable
      - implantable
    - Intrauterine device
    - Intrauterine hormone-releasing system

- Bilateral tubal ligation
- Vasectomized partner. Note: Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence. Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments.

  True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception

*Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Postmenopausal status will be confirmed by measurement of follicle-stimulating hormone (FSH). Pregnancy testing and contraception are not required for women with documented hysterectomy and/or oophorectomy.

Oocyte donation is prohibited during the study and for 24 weeks after the last administration of study drug.

28. Men who are sexually active with WOCBP and are unwilling to consistently use condoms during the study drug treatment period and for 24 weeks after the last administration of study drug, regardless of vasectomy status. Sperm donation is prohibited during the study and for up to 24 weeks after the last administration of study drug.
29. Member of the clinical site study team and/or his/her immediate family.

6.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.2.

Rules for discontinuation of study drug (permanent or temporary) are discussed in Section 7.4.2.

Early Termination from the Study

If for any reason the patient refuses to continue the study, the patient should undergo an unscheduled visit with assessments normally planned at the EOT visit (it should take place within 5 days of treatment discontinuation, if possible).

For patients that discontinue the study prematurely, the patient should be followed for at least 24 weeks from the last dose of study drug or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. A final EOS visit should take place with assessments as specified in the EOS visit (ie, follow-up visit) at 24 weeks after the last dose of study drug.

Sexually active patients who discontinue the study prematurely should be reminded at the unscheduled visit following treatment discontinuation to maintain highly effective contraceptive measures for 24 weeks after the last dose of study drug. At this visit, WOCBP will be provided 5 urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. All patients should also be notified of Q4W follow-up phone calls to confirm contraception use, remind them of pregnancy reporting, and to obtain the results of the urine pregnancy test.

The investigator or study staff should make the best effort to contact any patient (eg, contacting patient's family or private physician, review available registries or health care database) who fails to return to the site, and to determine health status, including at least vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter). The site will be provided a retention manual outlining the best practices for patient retention.

6.4. Replacement of Patients

Patients who prematurely discontinue from the study will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational Treatments and Reference Treatments

Evinacumab or placebo will be supplied for SC or IV administration. Study treatment groups are defined in Section 5.1.1.

For patients who are not receiving a PCSK9 inhibitor antibody, sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL in a prefilled pen.

All SC injections will be administered in the abdomen, thigh, or outer area of the upper arm with rotating sites of injection. Instructions for management of acute injection site and infusion reactions are provided in Section 7.5.

For SC QW regimen the dose should be administered ± 3 days; if ≥4 days have passed, skip the dose and return to the original schedule. For IV Q4W regimen the dose should be administered ± 14 days; if >14 days have passed, skip the dose and return to the original schedule.

The IV dose should be prepared using the patient's most recent weight. Further instructions on dose preparation are provided in the pharmacy manual.

7.2. Run-in Treatment(s)

There will be a run-in period for:

- Patients who are not receiving the maximal dose of a PCSK9 inhibitor antibody or whose dose has not been stable for at least 8 weeks before the screening visit
- Patients whose maximally tolerated statin has not been stable for at least 4 weeks before the screening visit
- Patients whose background LMT (other than statin or PCSK9 inhibitor antibody) has not been stable for at least 4 weeks (6 weeks for fibrates) before the screening visit

During this run-in period, patients will be stabilized on their statin, PCSK9 inhibitor antibody, and other background LMT (as applicable), and patients receiving alirocumab 75 mg SC Q2W will have their dose up-titrated to 150 mg SC Q2W or 300 mg SC Q4W. The duration of the run-in period will depend on the time needed for the patient to stabilize on their background LMT.

Patients have to be consented prior to entering the run-in period.

7.3. Background Treatment(s)

All patients should be on a stable, maximally-tolerated LMT regimen throughout the duration of the study.

All patients should be on maximal background LMT, which includes a stable maximally tolerated statin and stable PCSK9 inhibitor antibody. Patients with HeFH who are not on a statin are allowed to participate if there is documentation of inability to tolerate at least 2 statins due to muscle symptoms. Inability to tolerate a statin should be due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued.

For the background LMT, sites must follow the national product label for patient safety monitoring and management. The dose of statin and of PCSK9 inhibitor, such as alirocumab or evolocumab, as well as other LMT (if applicable), should remain stable throughout the study duration, from screening through the EOS visit. If a patient is not considered to be on a maximum tolerated LMT regimen (high-intensity statin, PCSK9 inhibitor antibody, ezetimibe, etc) at the start of the run-in or at screening, reasons why or why not (eg, due to intolerance, lack of efficacy, not marketed in the region) the patient is taking/not taking the various treatments will need to be documented in the CRF.

7.4. Dose Modification and Study Treatment Discontinuation Rules

7.4.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.4.2. Study Drug Discontinuation

Study treatment should be continued whenever possible. In the event study drug dosing is stopped, it should be determined if the stop can be made temporarily; permanent discontinuation should be a last resort. Regardless, the patient should remain in the study treatment period as long as possible.

Patients who prematurely discontinue study drug should remain in the study and undergo all study visits and procedures, with the exception of dosing with study drug. At the time of study drug

discontinuation, the patient should have, as soon as possible, an unscheduled visit with assessments normally planned at EOT visit (this should take place within 5 days of discontinuation of study drug, if possible), and then resume the original study schedule until the EOS visit. In case of early discontinuation before week 16, all efforts should be made to perform EOT assessments as soon as possible.

Patients who permanently discontinue from study drug, and who opt to withdraw from the study, will be asked to complete study assessments, per Section 6.3.

7.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in a patient in the event of the following, but not limited to:

- Evidence of pregnancy
- Acute systemic injection/infusion reactions with AEs including, but not limited to, anaphylaxis, laryngeal/pharyngeal edema, severe bronchospasm, chest pain, seizure, or severe hypotension
- Patient requires a prohibited concomitant medication during the study. The principal investigator should contact the Regeneron study monitor. Based on the discussion, study drug may be continued, or may be temporarily or permanently discontinued
- Patient withdraws consent

The investigator may permanently discontinue dosing with study drug at any time, even without consultation with the medical monitor, if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of permanent study drug discontinuation.

7.5. Management of Acute Reactions

7.5.1. Acute Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 9.4.1) and graded using the grading scales, as instructed in Section 9.5.1.

7.5.1.1. Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension

- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment of the reaction or need for discontinuation of the infusion, other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

7.5.1.2. Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- anaphylaxis*
- severe bronchospasm
- chest pain
- seizure
- severe hypotension
- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc.)
- any other symptom or sign that, in the opinion of the investigator, warrants discontinuation of the infusion

*Consider anaphylaxis if the following is observed (Sampson 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

7.5.2. Acute Injection Reactions

7.5.2.1. Systemic Injection Reactions

Acute systemic reactions following administration of study drug (IV or SC), should be treated using clinical judgment, based on standard clinical practice, in order to determine the appropriate response.

7.5.2.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to the Food and Drug Administration (FDA) September 2007 Guidance for Industry, Toxicity Grading Scale for Healthy

Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (provided in the study Regulatory Binder, also see Section 9.5.1).

7.6. Method of Treatment Assignment

Patients will be randomized within either Group A (SC treatment regimens) in a 1:1:1:1 ratio or Group B (IV treatment regimens) in a 1:1:1 ratio. Enrollment of IV cohorts will occur before enrollment of SC cohorts; accordingly, enrollment of Group A will not begin until Group B enrollment is completed. There will be 144 patients randomized to Group A (36 patients per treatment group), with 108 patients exposed to SC evinacumab and 36 exposed to SC placebo. There will be 108 patients randomized to Group B (36 patients per treatment group), with 72 patients exposed to IV evinacumab and 36 exposed to IV placebo.

Patients in Group A will receive treatment from day 1 through week 16 (last dose of study drug at week 15). Patients in Group B will receive treatment from day 1 through week 24 (last dose of study drug week 20). Patients will be randomized to a treatment group according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

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

7.6.1. Blinding

Study patients, principal investigators, and study site personnel will remain blinded to all randomized study treatment group assignments throughout the study. The Regeneron Study Director, Medical Monitor, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments. All lipid results will be blinded from after randomization until the week 36 visit for the IV cohorts, and until database lock for the SC cohorts.

Due to differences in the color of the study drug as compared to placebo, an unblinded pharmacist or qualified unblinded designee will prepare the IV infusion bags and SC injections. Further details are provided in the pharmacy manual.

7.6.2. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy).

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment
- Only the affected patient will be unblinded

- The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient
- The investigator will notify Regeneron and/or designee before unblinding the patient, whenever possible

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

7.7. Treatment Logistics and Accountability

7.7.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

7.7.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed, or returned to the sponsor or designee.

7.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.7.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

7.8. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

7.8.1. Prohibited Medications and Procedures

Any background medical LMT, which has not been stable for at least 4 weeks prior to the screening visit, is prohibited.

- Simvastatin 80 mg (unless having received for > 1 years), lomitapide, and mipomersen are prohibited.
- LDL apheresis is a prohibited procedure.

7.8.2. Permitted Medications and Procedures

The use of all medications and nutritional supplements known to alter serum lipids, including (but not limited to) statins, ezetimibe, fibrates, niacin, bile acid resins, red yeast rice, and PCSK9 inhibitor antibodies is permitted, as long as that therapy has been stable for at least 4 weeks (6 weeks for fibrates and 8 weeks for PCSK9 inhibitor antibodies) prior to the screening visit. Patients should continue taking their background medical LMT for the duration of the study, starting at screening and continuing through the EOS visit.

Thyroid replacement therapy can be used, if the dosage of thyroxine has been stable for at least 12 weeks prior to the screening visit (week -2).

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7.

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

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

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

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

Table 3: Schedule of Events for SC Treatment Group A

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

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

Table 4: Schedule of Events for IV Treatment Group B

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

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

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

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

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

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

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

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

8.1.1. Footnotes for the Schedule of Events Tables

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

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

[redacted]

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

8.1.2. Early Termination Visit

Patients who withdraw or are withdrawn from the study before EOT visit

Patients who withdraw or are withdrawn from the study before the week 16 visit, will be asked to return to the clinic for 2 visits: once for an early termination/EOT visit, consisting of the EOT assessments described in Table 3 and Table 4, and again at the EOS visit. The EOT visit should take place within 5 days of treatment discontinuation, if possible. A final EOS visit should take place with assessments as specified in the EOS visit (ie, follow-up visit) at 24 weeks after the last dose of study drug (Table 6 and Table 7).

Patients who withdraw or are withdrawn from the study after EOT Visit

Patients who are withdrawn from the study after the EOT visit (week 16 for SC group or week 24 for IV group) will be asked to return to the clinic for early termination assessments/EOS, only. The EOS visit should take place with assessments as specified in the EOS visit (ie, follow-up visit) at 24 weeks after the last dose of study drug.

Sexually active patients who discontinue the study prematurely should have an unscheduled visit to remind patients to maintain highly effective contraceptive measures for 24 weeks after the last dose of study drug. At this visit, WOCBP will be provided urine pregnancy tests with instructions to test for pregnancy Q4W until the EOS visit. All patients should also be notified of Q4W follow-up phone calls to confirm contraception use, remind them of pregnancy reporting, and to obtain the results of the urine pregnancy test.

8.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Demographics,
- Past medical/surgical history, alcohol/smoking habits
- Medication history,
- Medication adjustments
- Height, weight, vital signs, physical examination, ECG
- Hepatitis B and C serology,
- TSH,
- FSH

8.2.2. Efficacy Procedures

All laboratory samples will be collected before the dose of study drug is administered.

Blood samples for lipid panels should be collected in the morning, in fasting condition (ie, overnight, at least 8 hours fast, only water) for all clinic visits. Alcohol consumption within 48 hours, and smoking or intense physical exercise within 24 hours, preceding blood sampling are discouraged.

Note: If the patient is not in the fasting condition, the blood sample may not be collected and a new appointment can be scheduled the day after (or as close as possible to this date) with a

reminder to be fasted. Patients who are not fasted should 1) be reminded that they should fast, and 2) should be seen by study staff the next day or close as possible in fasted state.

Total-C, HDL-C, TG, ApoB, ApoA-1, Lp(a), and ApoCIII will be directly measured by the central laboratory. LDL-C will be calculated using the Friedewald formula. If TG values exceed 400 mg/dL (4.52 mmol/L), LDL-C will be measured via the beta quantification method (rather than via the Friedewald formula). If the LDL-C value is less than 25 mg/dL (0.65 mmol/L), LDL-C will be measured via the beta quantification method (rather than the Friedewald formula). Non-HDL-C will be calculated by subtracting HDL-C from TC. Ratio ApoB/ApoA-1 will be calculated. All lipid results will be blinded from after randomization until the week 36 visit for the IV cohorts, and until database lock for the SC cohorts. No attempts should be made by the investigator or patient to have the patient's lipid values independently evaluated after randomization and through the EOS visit.

Detailed procedures of sample preparation, storage, and shipment are provided in the laboratory manual.

8.2.2.1. Core Lipid Panel

Fasting blood (at least 8 hours) samples for the core lipid panel (TC, TG, HDL-C, non-HDL-C, and calculated LDL-C) will be collected at time points described in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7. These samples will also be used for specialty lipid panel assessment when it is scheduled at the same time as the lipid panel assessment. All lipid results after the randomization visit will be blinded.

8.2.2.2. Specialty Lipid Panel

Fasting (at least 8 hours) blood samples for the specialty lipid panel (ApoB, ApoA-1, ApoB/ApoA-1 ratio, and Lp[a]), as well as for ApoCIII will be collected at time points according to in Table 3, Table 4, Table 5, Table 6, and Table 7. The specialty lipid panels will be assessed in the same sample that is collected for the lipid panel. All lipid results will be blinded from after randomization until the week 36 visit for the IV cohorts, and until database lock for the SC cohorts .

8.2.3. Safety Procedures

8.2.3.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration rate, will be collected pre-dose at time points according to in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7. Post-dose vital signs consist of blood pressure and pulse rate and will be collected 30 minutes and 60 minutes after completion of the IV infusion.

Blood pressure should be measured in the same arm throughout the study, after the patient has been resting quietly for at least 5 minutes. Pulse rate will be measured at the time of the measurement of blood pressure.

8.2.3.2. Physical Examination

A thorough and complete physical examination will be performed at time points according to in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

8.2.3.3. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at time points according to in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7. Electrocardiograms should be performed before blood is drawn during visits that require blood draws.

The 12-lead ECGs should be performed in the supine position after resting for at least 10 minutes. For each ECG recording throughout the study, the electrodes should be positioned at the same place as much as possible. The ECG will be interpreted locally by the investigator. Any new and/or clinically significant changes in ECG parameters should be immediately rechecked for confirmation before making any decision for the concerned patient.

Any clinically significant abnormality should be documented as an AE/SAE, as applicable. Each ECG tracing will be analyzed in comparison with the screening recorded trace. All ECG tracings will be kept as source data (see Section 9.4.5).

8.2.3.4. Laboratory Testing

All laboratory samples will be collected before the dose of study drug is administered.

Samples for laboratory testing will be collected at time points according to in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7 and analyzed by a central laboratory during the study. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites and specific tests are listed below.

Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin*
Potassium	Creatinine	Uric acid
Chloride	Blood urea nitrogen (BUN)	Creatine phosphokinase (CPK)
Bicarbonate	Aspartate aminotransferase (AST)	
Calcium	Alanine aminotransferase (ALT)	
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Blood chemistry tests should be performed with fasting samples.
* Samples with elevated values are automatically fractionated

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Platelet count	Basophils
Reticulocyte count	Eosinophils
Red blood cell distribution width (RDW)	

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Other laboratory tests will be performed at time points shown in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7 are as follows: FSH, TSH, hs-CRP, HbA1c, and serum and urine pregnancy test.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.4.5.

8.2.3.5. Pregnancy Testing

Women of childbearing potential will undergo pregnancy testing approximately every 4 weeks throughout the study from baseline through EOS. Pregnancy testing will be via a urine pregnancy test, except for the screening visit and EOS visit, which will be via a serum pregnancy test. During some follow-up visits, and in case of early termination, pregnancy testing may occur at home via a urine pregnancy test where the results will be reported to the clinical site by the patient.

8.2.4. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.4.1. Drug Concentration Measurements and Samples

Serum samples for assessment of evinacumab and alirocumab concentration will be collected at specified time points listed in Table 3, Table 4, Table 5, Table 6, and Table 7.

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or other investigations.

8.2.4.2. Anti-Drug Antibody Measurements and Samples

Serum samples for anti-evinacumab antibody (ADA) assessment will be collected at time points listed in Table 3, Table 4, Table 5, Table 6, and Table 7. They will be collected pre-dose on days when study drug is administered.

Patients who exhibit a treatment-emergent or treatment-boosted positive ADA assay response with a titer >240 in their last sample analyzed and who do not participate in an open-label study will be followed until the titers are <240 or have returned to within 2 dilution steps from their baseline titer levels.

8.2.5. Pharmacodynamic Procedures

Blood samples for measurement of total ANGPTL3, free and total PCSK9, and lipid profile (core lipid panel, specialty lipid panel) will be collected at specified time points listed in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7. ANGPTL3 concentration in serum will be measured from the PK samples collected at the time points listed in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7.

8.2.6. Other Assessments

8.2.7. Review of Diet

Patients will be following a heart-healthy diet at the screening visit and will be asked to continue the dietary plan until the last study visit. Patients will be queried on compliance with the dietary plan during the double-blind treatment period, at time points according to Section 8.1.

Details are provided in the study reference manual.

8.2.8. Low Density Lipid-Receptor Function

A blood sample for LDL-R function testing will be collected from a subset of patients at time points according to in Table 3, and Table 4 in order to characterize LDL-R function and explore potential differences in safety and efficacy.

8.2.9. Future Biomedical Research

Biomarker samples will be collected at time points according to Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, and Table 7. The biomarker samples unused for study-related research, as well as unused PK and ADA, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research of hyperlipidemia and other

related diseases. No additional samples will be collected for future biomedical research. After 15 years, any residual samples will be destroyed.

[redacted]

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner as per national regulatory requirements in participating countries, all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction, to the health authorities, IECs/IRBs as appropriate, and to the investigators.

Any AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered as unexpected. Any worsening of or new onset of symptoms related to hypercholesterolemia which occur during the screening period prior to study drug administration will be considered expected.

In addition, the sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the evinacumab to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and IECs/IRB as appropriate.

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug, which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

9.3.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that, had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

9.3.3. Adverse Events of Special Interest

An AE of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the

event, rapid communication by the study sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3).

9.3.4. Infusion Reactions

Infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. All infusion reactions must be reported as AEs (defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the EOS. Refer to the study reference manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the EOS/early termination visit- the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the EOS/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification,

any pregnancy occurring in a female or female partner of a male, during the study or within 24 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor

Adverse Events of Special Interest: All AESIs, serious and non-serious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2.

Adverse events of special interest for evinacumab include the following:

- Anaphylactic reactions
- Allergic reactions and/or local injection site reactions that require medical treatment or consultation with another physician for further evaluation
- Increase in ALT or AST: ≥3 x ULN (if baseline <ULN), or ≥2 x baseline value (if baseline ≥ ULN)
- Pregnancy
- Symptomatic overdose with IMP
- Neurocognitive events
- New onset of diabetes
- Pancreatitis

Adverse events of special interest for alirocumab include the following:

- Increase in ALT: ALT ≥3 x ULN (if baseline ALT < ULN), or ALT ≥2 x baseline value (if baseline ALT ≥ ULN)
- Allergic events and/or local injection site reactions that require consultation with another physician for further evaluation
- Pregnancy
- Symptomatic overdose with IMP
- Neurologic events that require additional examinations/procedures and/or referral to a specialist
- Neurocognitive events
- Cataracts
- New onset of diabetes:

  The definition of new onset of diabetes will be the following:

  – Type 1 or type 2 diabetes treatment-emergent adverse event (TEAE) (grouping of MedDRA terms will be specified in the SAP)

  and/or

– at least 2 values of HbA1c ≥6.5% during the TEAE period

NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥6.5% will be considered and qualify the patient as new onset of diabetes 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 new onset of diabetes by default

and/or

– At least 2 values of fasting plasma 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 new onset of diabetes

For patients with several fasting plasma 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 new onset of diabetes

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

9.4.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs will be graded according to the following scale:

- **Mild:** Does not interfere in a significant manner with the patient normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Infusion Reactions

The severity of infusion reactions will be graded according to the following scale (semi-colon indicates "or" within description of the grade):

- **Mild**: Mild transient reaction; infusion interruption not indicated; intervention not indicated.
- **Moderate**: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.
- **Severe**: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

- **Mild**: Pain that does not interfere with activity; mild discomfort to touch; < 5 cm of erythema or induration that does not interfere with activity
- **Moderate**: Pain that requires repeated use of non-narcotic pain reliever > 24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

- **Severe**: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; > 10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

The relationship of AEs to study drug will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

A list of factors to consider when assessing the relationship of AEs to study drug is provided in Appendix 1.

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Study Conduct:

The relationship of AEs to study conduct will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by study conduct?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by study conduct

Related: There is a reasonable possibility that the event may have been caused by study conduct

A list of factors to consider when assessing the relationship of AEs to study conduct is provided in Appendix 1.

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Injection Procedure, Study Procedure

The relationship of AEs to injection procedure, study procedure, or background treatment, etc. will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the injection procedure, study procedure, or background treatment, etc.?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the injection procedure, study procedure, or background treatment, etc.

Related: There is a reasonable possibility that the event may have been caused by the injection procedure, study procedure, or background treatment, etc.

A list of factors to consider in assessing the relationship of AEs to injection procedure, study procedure, or background treatment, etc. is provided in Appendix 1.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

9.6. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that potentially meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure or this protocol, and has a reasonable suspected causal relationship to the medicinal/study drug).

10. STATISTICAL PLAN

This section provides the basis for the SAP for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked at the time of the Group B patients' first step analysis.

10.1. Statistical Hypothesis

Let $\mu 0$ and $\mu 1$ be the population means of the percent change from baseline in calculated LDL-C at week 16 under each of the 2 placebo control arms and the 4 evinacumab treatment arms, respectively. For the primary efficacy variable, the following null hypothesis and alternative will be tested:

$$H0 : \mu 0 = \mu 1$$

versus

$$H1 : \mu 0 \neq \mu 1$$

Study treatment route of administration (Group A or B), HeFH diagnosis (Yes/No), and high-intensity statin (Yes/No) (high-intensity statin defined as rosuvastatin 20 mg to 40 mg daily, atorvastatin 40 mg to 80 mg daily, or simvastatin 80 mg daily) will be the 3 stratification factors for patient randomization. Stratification factors HeFH diagnosis and high-intensity statin will be accounted for in the statistical modeling for efficacy.

10.2. Justification of Sample Size

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

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

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

Blinded Sample Size Adjustment

Referencing the ICH E9 regulatory guidance, the study sample size may be re-estimated after approximately 75% of the patients reach the week 8 visit in the double-blind period, to ensure adequate power in the case of a larger-than-expected variability in the data. This sample size

re-estimation process may be performed twice; once for Group A and again for Group B. The sample size re estimation will be based on the actual blinded pooled SD (adjusted as described in Keiser 2003) for the primary efficacy measure. Since the patients' post-baseline LDL-C levels are masked to all study participants (patients, site personnel, and sponsor staff), the blinded pooled SD will be calculated by a designated statistician external to Regeneron who has access to the lipid data. As mentioned in Kieser 2003, the blinded sample size re-estimation does not affect type-I error materially for continuous endpoints.

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

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

10.3.1.1. Intent-to-Treat

The ITT population (also known as the full analysis set) is defined as all randomized patients who received at least 1 dose or part of a dose of double-blind study drug and have an evaluable primary endpoint. The endpoint is evaluable when the following 2 conditions are met:

- Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (ie, baseline).
- Availability of at least 1 measurement value for calculated LDL-C within 1 of the analysis windows up to week 16.

Patients in the ITT population will be analyzed according to the treatment group allocated by randomization (ie, as-randomized group).

10.3.1.2. Modified Intent-to-Treat

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

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

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

10.3.2. Safety Analysis Set

10.3.2.1. Double-Blind Safety Analysis Set

The double-blind safety analysis set (SAF) population considered for safety analyses will be the randomized patients who received at least 1 dose or part of a dose of study drug. Patients will be analyzed according to the treatment received (as-treated placebo or evinacumab).

In addition:

- Randomized patients, for whom it is unclear whether they took the study drug, will be included in the SAF as randomized.
- For patients receiving study drug from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be the one in which the patient was treated with the highest number of injections (Group A) or infusions (Group B).

Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

10.3.2.2. Open-Label Safety Analysis Set

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

10.3.3. Pharmacokinetic and Anti-drug Antibody Analysis Sets

The PK population includes all treated patients who received any study drug (safety population) and had at least 1 non-missing drug concentration result following the first dose of study drug.

The ADA population includes all treated patients who received any study drug (safety population) and had at least one non-missing ADA assay result following the first dose of study drug.

10.3.4. Pharmacodynamic Analysis Set

The PD population includes all treated patients who received any study drug (safety population) and had at least one non-missing ANGPTL3 value or other protocol defined PD marker (Section 8.2.5) following the first dose of study drug.

10.4. Statistical Methods

Unless otherwise noted, descriptive statistics for continuous variables will include the following information: the number of patients reflected in the calculation (n), mean, median, SD, minimum, and maximum. For categorical variables, frequencies and percentages will be displayed for each category.

10.4.1. Patient Disposition

The following data will be summarized:

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

  For any patient randomized more than once, safety data from the first randomization will be included in the SAF, with safety data associated with the later randomization reported separately. Since this is expected to be a rare event, inclusion of efficacy data from the patient randomized more than once in the efficacy population will be decided on a case-by-case basis prior to the unblinding of treatment assignments and will be documented in the clinical study report.
- The total number of patients randomized, but not receiving study treatment
- The total number of patients randomized and receiving study treatment
- The total number of patients who completed the double-blind treatment period, defined for Group A as at least 15 weeks of study treatment exposure and week 16 visit performed; and defined for Group B as at least 20 weeks of study treatment exposure and week 24 visit performed
- The total number of Group B patients who completed week 16 visit, defined as at least 12 weeks of study treatment exposure and week 16 visit performed
- The total number of Group B patients who completed the open-label treatment period, defined as at least 44 weeks of open-label study treatment exposure and visit week 72 performed.
- The total number of patients who prematurely discontinued study treatment during the double-blind treatment period, and the reasons for discontinuation
- The total number of patients who prematurely discontinued study treatment during the open-label treatment period, and the reasons for discontinuation
- The total number of patients who did not complete the study follow-up period, defined as the last visit performed less than 23 weeks after the last study treatment administration. Patients who died during the study are excluded
- The total number of patients in each analysis set
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

For the double-blind treatment period, demographic and baseline characteristics will be summarized descriptively by treatment group in the ITT population. For the Group B open-label treatment period, demographic and baseline characteristics will be summarized descriptively by

treatment group assigned in the double-blind period, as well as for patient total, for patients in the open-label SAF.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

For the double-blind primary efficacy analysis, the percent change from baseline in calculated LDL-C at week 16, as defined in Section 4.2, will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 2 to week 16 analysis windows will be used and missing data are accounted for by the MMRM model. Each model will include the fixed categorical effects of treatment group (placebo and evinacumab dose regimens), randomization strata, time point (weeks 4, 8, 12, 16 for the Group B treatment groups; weeks 2, 4, 6, 8, 12, 16 for the Group A treatment groups), strata-by-time point interaction, and treatment-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Contrast and estimate statements will be used to assess the treatment effects (LS means with confidence intervals) and each dose regimen pairwise comparison to placebo (mean difference and p-values).

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

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

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

The statistical testing of the 4 pairwise comparisons for the primary measure will be evaluated at a 2-sided significance level of 0.05 per pair wise comparison, adjusting for multiplicity through a hierarchical inferential approach.

Robustness of this statistical method will be assessed through sensitivity analyses detailed in the SAP, including the effects of missing data on the primary efficacy endpoint (pattern mixture modeling which will take into account the differing missing value patterns based on calculated LDL-C collected in the presence or absence of study treatment administration), and an on-treatment analysis of the primary endpoint (mITT patient population).

10.4.3.2. Secondary Efficacy Endpoint Analysis

For secondary efficacy endpoints (defined in Section 4.2) collected in the double-blind treatment period, descriptive summaries and analyses will be performed in the ITT population for each of the 5 pairwise treatment group comparisons, including the comparison of evinacumab 5 mg/kg IV Q4W patient treated group to the Placebo IV group.

For descriptive summaries, percent change, and when appropriate absolute change from baseline, in calculated LDL-C, total-C, HDL-C, TG, non-HDL-C, ApoB, ApoA-1, and Lp(a) will be provided at each time point. All measurements, scheduled or unscheduled, will be assigned to analysis windows defined in the SAP in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. For TG, measurements on non-fasting patients will be excluded. The time profile of each parameter will be plotted by treatment group with the corresponding standard errors.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (example: percent change in calculated LDL-C), continuous measurements expected to have a non-normal distribution (example: TG), and binary measurements (example: proportion of patients reaching LDL-C < 100mg/dL).

I. Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables defined in Section 4.2 anticipated to have a normal distribution (ie, lipids other than TG and Lp[a]) will be analyzed separately for Group A and Group B using the same MMRM model as for the primary endpoint. Specifically, the model will contain fixed categorical effects of treatment group, randomization strata, planned time points up to the time point of interest, strata-by-time point interaction and treatment-by-time point interaction, as well as the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

II. Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy endpoints defined in Section 4.2 anticipated to have a non-normal distribution (ie, TG and Lp(a)), will be analyzed using a robust regression model (ie, ROBUSTREG SAS procedure with M-estimation option) with treatment group and randomization stratum as main effect and corresponding baseline value(s) as covariate. Missing values will be addressed using a multiple imputation approach, which will be described in the SAP. The variables in the multiple imputation model will at least include the same variables as used in the robust regression model. The treatment group combined means will be provided with respective standard error (SE) estimates. The combined mean difference between the treatment groups will be provided with the SE, 95% confidence interval and p-value.

III. Binary endpoints

Binary secondary efficacy endpoints defined in Section 4.2 will be analyzed using stratified logistic regression (using the strata option of the SAS logistic procedure) with treatment group and randomization stratum as main effect and corresponding baseline value(s) as covariate. Missing values will be addressed using a multiple imputation approach, which will be described in the SAP. The variables in the multiple imputation model will at least include the same variables as used in the logistic regression model. Treatment effects will be compared and the combined odds ratio estimate between the treatment groups, with their corresponding 95% confidence intervals and p-value will be provided.

In the data dependent case that the logistic regression method is not applicable (eg, the response rate is zero in one treatment arm and thus the maximum likelihood estimate may not exist), the LOCF (last observation carried forward) approach would be used for handling of missing values

and an exact conditional logistic regression would be performed to compare treatment effects. The LOCF imputation method will consist of using the last value obtained up to the week 16 time window to impute the missing week 16 value.

10.4.3.3. Dose-Response Analysis

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

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

10.4.3.4. Subgroup Analysis

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

In addition, evinacumab treatment effect will also be explored in patients with a baseline LDL-C ≥100 mg/dL or ≥130 mg/dL during the double-blind treatment period.

10.4.3.5. Multiplicity Considerations

To control the 5% overall type-I error for the 4 pairwise comparisons in the primary analysis, the overall study α level will be controlled by the use of a hierarchical inferential approach. Statistical significance of the first pairwise treatment comparison is required before drawing inferential conclusions about the second pairwise treatment comparison at the 0.05 alpha level. Inferential conclusions about successive pairwise treatment comparisons require statistical significance of the prior treatment comparison. The hierarchy testing sequence is the order of treatment comparisons as presented in Section 10.4.3.1. This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.05 level for each evinacumab dose regimen comparison.

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

10.4.4. Safety Analysis

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

For Group B, summaries of safety results for the open-label period will be presented for patients in the open-label SAF, by the total patients administered open-label study treatment (total), as well as by the patient subgroups of study treatment received in the double-blind treatment period (ie, evinacumab dose, placebo).

All safety analyses will use the following common rule:

- The baseline value is defined as the last available value before the first dose of study drug.

10.4.4.1. Adverse Events

Definitions

For safety variables, the following observation periods are defined:

- The pre-treatment period is defined as the day the ICF is signed to the day before the first dose of double-blind study drug.
- The double-blind TEAE period is defined for each route of administration from the day of the first dose of double-blind study treatment to the day of the last dose of double-blind study treatment + 168 days (24 weeks) (based on PK considerations, residual effect of study treatment might be observed until 24 weeks after the last dose of study drug) for those patients not proceeding into the open-label treatment period (ie, Group A patients and Group B patients who prematurely discontinue study treatment), or up to the day before the first dose of open-label study treatment administration for those patients proceeding into the open-label treatment period
- The open-label TEAE observation period is defined from the day of the first open-label study treatment administration to the day of the last open-label study treatment administration + 168 days (24 weeks).
- The post-treatment period is defined as the time from the day after the end of the respective TEAE periods to the last study visit.

Double-blind TEAEs are defined as those events that developed, worsened, or became serious during the double-blind TEAE period. Open-label TEAEs are defined as those events that developed, worsened, or became serious during the open-label TEAE period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Adverse event incidence tables will present data by system organ class (SOC) sorted alphabetically and preferred term (PT) sorted by decreasing frequency, and summarize the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables. Data conventions for missing or partial AE dates will be addressed in the SAP. The denominator for computation of percentages is the respective SAF populations (ie, double-blind SAF or open-label SAF) within each treatment group.

Summaries of TEAEs incidences will include:

- All TEAEs (and patient listing)
- All treatment-emergent SAEs, including patient deaths (and patient listing)
- All TEAEs of interest, which will be defined by a PT or a prespecified grouping of terms
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), depicting the worse TEAE severity for those patients with multiple occurrences of the same event
- All TEAEs leading to permanent treatment discontinuation (and patient listing)

An AE patient listing will be provided for all patient deaths occurring during the respective TEAE periods (ie, double-blind or open-label) and the post-treatment period.

10.4.4.2. Other Safety

Definitions

The following definitions will be applied to laboratory parameters and vital signs:

- The potentially clinically significant value (PCSV) criteria 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 criteria will be provided in the SAP.
- PCSV criteria will determine which patients had at least 1 PCSV during the respective TEAE periods (double-blind or open-label), taking into account all evaluations performed during the respective TEAE periods, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSV percentage.
- Double-blind treatment period: The treatment period used for quantitative analysis in the double-blind period is defined as the day after the first study drug administration to the day of the last double-blind study drug injection + 7 days for Group A. For Group B, the treatment period is defined from the day after the first administration of double-blind study treatment to the day of the last administration of double-blind study

treatment + 28 days for those patients not proceeding into the open-label treatment period, or up to the day of the first open-label study treatment administration for those patients proceeding into the open-label treatment period.

- Open-label treatment period: The treatment period used for quantitative analysis in the open-label study period is defined from the day after the first dose of open-label study treatment to the day of the last dose of open label study treatment + 28 days.

Analysis

Summary statistics of all laboratory variables (including lipid HDL-C) and all vital signs parameters (raw data and changes from baseline) will be calculated for each protocol scheduled visit assessed during the respective treatment periods. For selected parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in each treatment group.

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/missing
- Abnormal according to PCSA criterion or criteria

For laboratory parameters for which PCSA criterion is not defined, similar table(s) using the normal range will be provided.

Listings will be provided with flags indicating the laboratory values meeting PCSV criteria.

10.4.4.3. Treatment Exposure

The duration of treatment exposure for Group A patients will be calculated as:

- Duration of study drug exposure in weeks defined as: (last study drug dosing date +7 – first study drug dosing date + 1 day)/7, regardless of unplanned intermittent discontinuations
- The total number of injections by patient

The duration of treatment exposure in the double-blind period for Group B patients will be calculated as:

- Duration of study drug exposure in weeks defined as: (last double-blind study drug administration date + 28 – first double-blind study drug administration date + 1 day)/7, regardless of unplanned intermittent discontinuations
- The total number double-blind treatment of infusions by patient

The duration of evinacumab exposure in the open-label period for Group B patients will be calculated as:

- Duration of evinacumab exposure in weeks: (last open-label evinacumab administration date + 28 – first open-label evinacumab treatment administration date)/7, regardless of unplanned intermittent discontinuations.
- The total number of open-label evinacumab infusions by patient.

The duration of evinacumab cumulative exposure in the double-blind and open-label periods for Group B patients will be calculated as:

- Combined patient duration of evinacumab exposure in weeks: double-blind evinacumab treatment duration + open-label evinacumab treatment duration, regardless of unplanned intermittent discontinuations.
- Combined total number of evinacumab treatment infusions by patient defined as: total number of double-blind evinacumab infusions + total number of open-label evinacumab infusions.

The durations of study treatment exposure (double-blind, open-label, and cumulative across the study) measured in weeks, and the categorical data of maximum number of injections/infusions (double-blind, open-label, and cumulative across study) will be summarized for each treatment group and for the pooled evinacumab dose regimens within each group as applicable (A or B).

10.4.4.4. Treatment Compliance

Compliance during the double-blind period will be assessed by injection/infusion frequency, specifically:

- For Group A, defined for each patient as the average number of days between 2 injections, that is: (last dose date – first dose date)/(number of injections).
- For Group B, defined for each patient as the average number of days between 2 infusions, that is: (last dose date – first dose date)/(number of infusions).

This parameter will be summarized descriptively by treatment group.

10.4.5. Analysis of Drug Concentration Data and Total ANGPTL3 Data

Descriptive statistics of evinacumab concentrations and ANGPTL3 concentration at each sampling time will be provided by treatment group. Plots of mean concentrations (linear and log scales) versus time will be presented.

No formal statistical analysis will be performed.

10.4.6. Analysis of Anti-Drug Antibody Data

Listings of ADA positivity and titers presented by patient, time point, and treatment group will be provided. Prevalence of treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study treatment groups.

Plots of drug concentrations will be examined and the influence of ADAs on individual concentration-time profiles evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

10.4.7. Analysis of Quality of Life Data

Quality of life data is not collected in this study.

[redacted]

10.4.9. Timing of Statistical Analyses

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

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

The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. Since the Group B primary efficacy measure data collection will have been concluded at the time of this first analysis, the significance level for the study remains at 0.05. This first analysis may be used for submission to health authorities.

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

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

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

Results of the second analysis will not be used to change the conduct of the ongoing study in any aspect. Since the Group A primary efficacy measure data collection will have been concluded at the time of this second analysis, the significance level for the study will remain at 0.05. This second analysis may be used for submission to health authorities.

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

10.4.9.3. Third Step: Final Safety Analysis

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

10.5. Additional Statistical Data Handling Conventions

Additional analysis and data conventions will be provided in the SAP, including the definitions for the analysis windows around each visit.

10.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical) history will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) tool Medidata Rave.

11.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study.

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

13. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

14.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patient who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patient who can understand, but who can neither write nor read, will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient 's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient’s study record and a copy must be given to the patient.

The principles of informed consent are described in ICH guidelines for Good Clinical Practice.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient and his/her parent(s) or legal guardian(s) prior to the patient’s participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the patient and the parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient’s parent(s) or legal guardian(s) and the same investigator or designee who explained the ICF.

The patient may also be required to sign and date the ICF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Patients who can write but cannot read will have the ICF form read to them before writing their name on the form.
- Patients who can understand, but who can neither write nor read, will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient's parent(s) or legal guardian(s).

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients and their parent(s) or legal guardian(s) must be informed of the new information and provide their written consent if they wish the patient to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient's parent(s) or legal guardian(s).

14.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Regulatory authority approvals will also be sought where required by applicable regulations.

16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

16.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

16.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF/eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRF/eCRF that will be provided to the sponsor.

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

21. REFERENCES

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22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Varying Doses and Dose Regimens of Evinacumab in Patients with Persistent Hypercholesterolemia Despite Maximally Tolerated Lipid Modifying Therapy, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

Appendix 1: Factors to Consider in Assessing the Relationship of Adverse Events to Study Drug and Study Conduct or Injection Procedure, Study Procedure, or Background Treatment, etc.

Is there a reasonable possibility that the event may have been caused by the study drug or study conduct or injection procedure, study procedure, or background treatment, etc.?

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug or injection procedure, study procedure, or background treatment, etc.
- do not reappear or worsen when dosing with study drug or injection procedure, study procedure, or background treatment, etc. is resumed
- are not a suspected response to the study drug or injection procedure, study procedure, or background treatment, etc. based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug or injection procedure, study procedure, or background treatment, etc.
- resolve or improve after discontinuation of study drug or injection procedure, study procedure, or background treatment, etc.
- reappear or worsen when dosing with study drug or injection procedure, study procedure, or background treatment, etc. is resumed
- are known or suspected to be a response to the study drug or injection procedure, study procedure, or background treatment, etc. based upon preclinical data or prior clinical data

NOTE: This list is not exhaustive.

Appendix 2: Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia

Definite familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/l (260 mg/dL) or LDL cholesterol above 4.0 mmol/l (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/l (290 mg/dL) or LDL cholesterol above 4.9 mmol/l (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

PLUS

- Tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)

OR

- DNA-based evidence of an LDL receptor mutation or familial defective ApoB-100

Possible familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/l (260 mg/dL) or LDL cholesterol above 4.0 mmol/l (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/l (290 mg/dL) or LDL cholesterol above 4.9 mmol/l (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

And at least one of the following:

- Family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.
- Family history of raised cholesterols >7.5 mmol/l (290 mg/dL) in adult 1st or 2nd degree relative or >6.7 mmol/l (260 mg/dL) in child or sibling under 16 years of age.

Appendix 3: WHO Criteria (Dutch Lipid Network clinical criteria) for Diagnosis of Heterozygous Familial Hypercholesterolemia (HeFH)

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia				
Family history				
a	First degree relative with known premature (men <55 yrs, women <60 yrs) coronary and vascular disease.			1
b	First degree relative with known LDL-cholesterol >95th percentile for age and sex.			
and/or				
a	First degree relative with tendon xanthomata and/or arcus cornealis.			2
b	Children below 18 yrs. with LDL-cholesterol >95th percentile for age and sex.			
Clinical history				
a	Patient has premature (men <55 yrs, women <60 yrs) coronary artery disease			2
b	Patient has premature (men <55 yrs, women <60 yrs) cerebral or peripheral vascular disease.			1
Physical examination				
a	Tendon xanthomata			6
b	Arcus cornealis below the age of 45 yrs.			4
Laboratory analysis				
		mmol/L	mg/dL	
a	LDL-cholesterol	>8.5	>330	8
b	LDL-cholesterol	6.5-8.4	250-329	5
c	LDL-cholesterol	5.0-6.4	190-249	3
d	LDL-cholesterol	4.0-4.9	155-189	1

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia	
(HDL-cholesterol and triglycerides are normal)	
DNA-analysis	
a Functional mutation low-density lipoprotein receptor gene present	8
Diagnosis of HeFH is:	
Certain When	>8 points
Probable When	6-8 points
Possible When	3-5 points

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this protocol accurately describes the conduct of the study.

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

Protocol Number: R1500-CL-1643

Protocol Version: R1500-CL-1643 Amendment 5

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

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Sponsor's Responsible Clinical Study Team Lead

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Sponsor's Responsible Biostatistician

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