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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF EVINACUMAB IN PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Compound:	Evinacumab (REGN1500)
Clinical Phase:	3
Protocol Number:	R1500-CL-1629
Protocol Version:	R1500-CL-1629 Amendment 4A
Amendment 4A Date of Issue	*See appended electronic signature page*
Amendment 3A Date of Issue:	25 Jun 2018
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Amendment 1 Date of Issue:	21 Sep 2017
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AMENDMENT HISTORY

Amendment 4A

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 6.2.2 Exclusion Criteria #23 Table 3 Schedule of Events, Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period Table 4 Schedule of Events – Follow-up Period
Updated Scientific/Medical Monitor	Title Page
Added abbreviation for WOCBP	List of Abbreviations

Amendment 3A

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

Rationale for Change	Sections Changed
Expanded Risk/Benefit section to include risk/benefit assessment of the combination of evinacumab and PCSK9 inhibitors, including alirocumab for the treatment of patients with homozygous familial hypercholesterolemia (HoFH).	Section 3.2.3 Risk/Benefit Assessment Section 21 References
Clarified the eligibility requirements by requiring that patients entering this study from R727-CL-1628 meet all of the eligibility criteria for this study. Clarified that patients enrolling from R727-CL1628 will continue to receive alirocumab 150 mg every 2 weeks (Q2W).	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Treatment(s) Section 5.1 Study Description and Duration Section 7.3 Background Treatment
To be consistent with the recommendations from the Clinical Trial Facilitation Group (CTFG) on contraception and pregnancy testing in clinical trials, added “True abstinence: When this is in line with the preferred	Section 6.2.2 Exclusion Criterion #22

Rationale for Change	Sections Changed
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."	
Added exclusion criteria for patients housed in an institution on the basis of an administrative or judicial order and patients who are dependent on the sponsor, investigator, or the study site.	Section 6.2.2 Exclusion Criterion #24, #25
Editorial or administrative edits	Section 5.1 Study Description and Duration Section 5.3.1 Independent Data Monitoring Committee Section 5.3.2 Clinical Events Committee Section 6.2.1 Inclusion Criteria #3 Section 7.6.1 Blinding Section 7.8.1 Prohibited Medications and Procedures Table 3 Schedule of Events – Baseline, Double-Blind Treatment Period Table 4 Schedule of Events – Follow-up Period Section 8.2.2 Efficacy Procedures Section 14.1 Good Clinical Practice Statement Section 14.2 Informed Consent

Amendment 2A

This version of the protocol replaces the previous US-specific amendment 1.

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

Rationale for Change	Sections Changed
The US-specific version is no longer a country-specific version of the protocol, and is now designated amendment 2A	Cover page and header.
Added a Risk/Benefit section for consistency with the sister protocol (2B)	Section 3.2.3 Risk/Benefit Assessment
Clarified confirmation of patient's HoFH status and added text for genotyping, as well as a DNA sample for genotyping in the schedule of events	Section 5.1 Study Description and Duration Table 3 Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period
Clarified text for patients who transition from study R727-CL-1628 to this study	Clinical Study Protocol Synopsis: Study Design

Rationale for Change	Sections Changed
and added a footnote to Table 3. Added consent and pharmacogenomics consent to schedule of events table.	Section 5.1 Study Description and Duration Table 3 Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period Section 8.1.3 Footnotes for Schedule of Events Table 3: #1
Clarified language for apheresis requirements and collection of clinical laboratory samples relative to the timing of apheresis procedures, administration of PCSK9 inhibitor or mipomersen	Section 5.1 Study Description and Duration Section 8.1.3 Footnotes for Schedule of Events Table 3: #2
Clarified that patients should be on a maximally tolerated regimen of lipid modifying therapy	Clinical Study Protocol Synopsis: Population Section 6.2 Study Population Section 7.3 Background Treatment
Added a footnote for timing of collection of vital signs on dosing days	Section 8.1.3 Footnotes for Schedule of Events Table 3: #5
Added Lipid Panel and Specialty Lipid Panel assessment and assessments of hematology, blood chemistry, and creatinine phosphokinase for the follow-up period	Table 4 Schedule of Events – Follow-up Period
Added "Query LMT compliance" to SoE tables	Table 1 Schedule of Events – Run-in and Screening Table 2 Schedule of Events – Screening for Patients with No Run-in Table 3 Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period Table 4 Schedule of Events – Follow-up Period
Edits/Clarifications	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Procedures and Assessments Section 6.2.2 Exclusion Criteria Section 7.8.1 Prohibited Medications and Procedures Section 8.1.1 Footnotes for Schedule of Events Table 1 Section 8.2.7.2 DNA Sample for HoFH Genotyping Section 10.4.3.2 Secondary Efficacy Analysis

US Amendment 1

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

Rationale for Change	Sections Changed
Added EQ-5D and HADS QOL questionnaires and an EQ-5D and HADS objective and exploratory endpoint to allow assessment of quality of life in this population	Section 2.3 Other Objective Section 4.2.4 Other Endpoints Table 3: Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period

Rationale for Change	Sections Changed
	Section 8.1.3 Footnotes for Schedule of Events Table 3: footnote #12 Section 8.2.3 Quality of Life Procedures
Clarified language for apheresis requirements and collection of clinical laboratory samples relative to the timing of apheresis procedures	Section 5.1 Study Description and Duration Section 6.2.1 Inclusion Criteria #3 Section 8.1.3 Footnotes for Schedule of Events Table 3 #1
Added a criterion excluding patients with LDL-C level <70 mg/dL as this is the goal for FH patients. Consequently, patients already at goal will be excluded. Update efficacy procedure for lipids Added criterion excluding members of the clinical site study team and/or his/her immediate family	Section 6.2.2 Exclusion Criteria #1 and #20 Section 8.2.2 Efficacy Procedures - (added LDL-C values below 25 mg/dL)
Clarified LDL apheresis therapy during the run-in period	Section 6.2.2 Exclusion Criteria #3 Section 7.2 Run-in Treatment(s)
Updated anti-drug antibody (ADA) variables and added a statement for follow-up of patients positive in the ADA assay	Section 4.4 Anti-Drug Antibody Variables Section 8.2.5.2 Anti-Drug Antibody Measurements and Samples
Added a section on pregnancy testing	Section 8.2.4.5 Pregnancy Testing
Clarified collection of data regarding lipid modifying therapy	Clinical Study Protocol Synopsis Section 6.2 Study Population Section 7.3 Background Treatment(s)
Added week 4 for ADA sampling Removed body weight measurement Day 15 Removed height measurement at Day 337	Table 3: Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period
Provided a definition for “new onset diabetes” as this is an adverse event of special interest (AESI) and expanded the list of AESIs for evinacumab	Section 9.4.3 Other Events that Require Accelerated Reporting
Clarified intent to treat population and updated methods of analysis to account for missing data	Section 10.3.1.1 Intent-to-Treat Section 10.4.3.1 Primary Efficacy Analysis
Edits/Clarifications	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Duration Clinical Study Protocol Synopsis: Population Section 1 Introduction Section 3.2.1 Rationale for Study Design

Rationale for Change	Sections Changed
	Section 5.1 Study Description and Duration and Synopsis, Study Duration Figure 1: Study Flow Diagram Section 6.2 Study Population Section 7.3 Background Treatment(s) Section 7.4.2 Study Drug Discontinuation Section 7.6 Method of Treatment Assignment Section 7.7.1 Packaging, Labeling, and Storage Section 7.8.2 Permitted Medications and Procedures Table 1: Schedule of Events – Run-in and Screening Table 2: Schedule of Events – Screening for Patients with no Run-in Table 3:Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period Table 4: Follow-up Period Section 8.1.1 Footnotes for Schedule of Events Table 1: #2 Section 8.1.2 Footnotes for Schedule of Events Table 2: #2 Section 8.1.3 Footnotes for Schedule of Events Table 3: #2 and #3 Section 8.2.2 Efficacy Procedures - lipid panel Section 8.1.5 Early Termination Visit Section 8.2.2 Efficacy Procedures Section 8.2.4.1 Vital Signs Section 8.2.7.2 DNA Sample and HoFH Genotyping Section 10.4.4.1 Adverse Events

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia
Site Location(s)	Approximately 30 sites multinationally
Principal Investigator	Multi-center
Objective(s)	The **primary objective** of the study is: • To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by evinacumab 15 mg/kg intravenously (IV) in comparison to placebo after 24 weeks in patients with homozygous familial hypercholesterolemia (HoFH). The **secondary objectives** of the study are: • To evaluate the effect of evinacumab 15 mg/kg IV on other lipid parameters (ie, apolipoprotein B [Apo B], non-high-density lipoprotein cholesterol [HDL-C], total-cholesterol [TC]) in patients with HoFH • To evaluate the effect of evinacumab on LDL-C goal attainment • To assess the effect of evinacumab on eligibility for apheresis (using German and US apheresis criteria) • To evaluate the safety and tolerability of evinacumab 15 mg/kg in patients with HoFH • To assess the pharmacokinetics (PK) of evinacumab in patients with HoFH • To evaluate the potential development of anti-evinacumab antibodies
Study Design	The study consists of the following periods: up to 8-week run-in period (for patients who may require HoFH genotyping, for patients whose background medical lipid modifying therapy [LMT] has not been stable prior to screening or whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a 2-week screening period, a 24-week double-blind treatment period (DBTP), and a 24-week open-label treatment period (OLTP), and a 24-week follow-up period after the last dose of study drug for those patients who choose not to enter the optional open-label study. Patients who are not undergoing apheresis therapy, patients who have been on a stable apheresis schedule for at least 8 weeks before the screening visit, and patients on stable background medical LMT (as applicable) for at least

	4 weeks (6 weeks for fibrates, 8 weeks for proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor antibodies, 12 weeks for lomitapide, 24 weeks for mipomersen) before the screening visit, will enter a 2-week screening period. Patients who participated in the R727-CL-1628 study may enter the run-in or screening period or enroll directly into this study. Patients who completed the R727-CL-1628 study and fulfill all of the eligibility criteria can be enrolled directly into this study. Data collected during the R727-CL-1628 study (ie, lab test results) can be used to assess eligibility criteria for these patients. If these patients meet all the eligibility criteria and if approved by the sponsor, the patients may not have to undergo the screening visit in this study. In this case, overlapping assessments completed at the end-of-open-label treatment visit in R727-CL-1628 do not need to be repeated during the R1500-CL-1629 baseline visit. The baseline/day 1 visit can occur immediately after the end of the open-label treatment visit in the R727-CL-1628 study. To ensure continuity of treatment with alirocumab, all patients from R727-CL-1628 entering this study will be provided alirocumab. Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized 2:1 to receive evinacumab 15 mg/kg IV every 4 weeks (Q4W) or matching placebo IV Q4W for the double-blind portion of the study (24 weeks). Randomization will be stratified by apheresis treatment (Yes, No) and by region (Japan, Rest of World). After completion of the DBTP, all patients will enter a 24-week OLTP and receive open-label evinacumab 15 mg/kg IV Q4W. After completion of the 24-week OLTP, all patients who have successfully completed this study might have the opportunity to participate in a separate open-label (OL) study. All patients that enroll in the separate OL study will continue to receive open-label evinacumab at a dose of 15 mg/kg IV Q4W. Those patients who do not participate in the separate OL study will undergo a 24-week follow-up after the last dose of study drug.
Study Duration	The duration of the study including run-in (8 weeks), screening (2 weeks), DBTP and OLTP (48 weeks), and follow-up (20 weeks) may be up to 78 weeks.
Population	
Sample Size:	Approximately 57 patients will be randomized at approximately 30 multinational sites
Target Population:	The study population will consist of males and females ≥18 years of age diagnosed with homozygous FH (HoFH), receiving stable lipid modifying therapy (LMT), as applicable. Patients should be on a maximally tolerated daily statin, ezetimibe, and a PCSK9 inhibitor antibody unless the patient has a documented history of tolerability issues, little or no response to

	therapy or other documented reason. Lipid modifying therapies may also include other lipid lowering therapies, including low-density lipoprotein (LDL)-apheresis.
Treatment(s)	
Study Drug Dose/Route/Schedule:	In the double-blind treatment period, eligible patients will be enrolled to receive evinacumab 15 mg/kg IV Q4W In the open-label portion of the study, all patients will receive evinacumab 15 mg/kg IV Q4W starting at week 24
Placebo Route/Schedule:	In the double-blind treatment period, placebo matching IV evinacumab Q4W
Background Treatment Dose/Route/Schedule:	Patients who are on LMT or who are undergoing apheresis should maintain stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study, from screening to the end of double-blind treatment period visit (week 24), and continuing through week 48 of the open-label treatment period. Patients who enter this study after completing study R727-CL-1628 will continue to receive alirocumab 150 mg subcutaneous (SC) every 2 weeks (Q2W) for the duration of the study.
Endpoint(s)	
Primary:	The primary endpoint is the percent change in calculated LDL-C from baseline to week 24.
Secondary:	• The percent change in Apo B from baseline to week 24 • The percent change in non-HDL-C from baseline to week 24 • The percent change in TC from baseline to week 24 • The proportion of patients with ≥30% reduction in LDL-C at week 24 • The proportion of patients with ≥50% reduction in LDL-C at week 24 • The proportion of patients with LDL-C <100 mg/dL (2.59 mmol/L) at week 24 • The change in calculated LDL-C from baseline to week 24 • The proportion of patients who meet EU apheresis eligibility criteria (see German Apheresis Working Group) from baseline to week 24 • The proportion of patients who meet US apheresis eligibility criteria (see US [National Lipid Association] Lipid Apheresis Criteria) from baseline to week 24
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.

	Overall safety will be assessed by monitoring/evaluation of treatment-emergent adverse events (TEAEs), physical examinations, vital signs, electrocardiogram (ECG), and clinical safety laboratory tests at pre-specified time points. The potential emergence of anti-evinacumab antibodies will also be evaluated.
Statistical Plan	**Sample Size Determination** For the primary efficacy hypothesis during the double-blind treatment period, a total sample size of 57 patients (38 on evinacumab and 19 on placebo) will have 90% power to detect a treatment group difference in mean percent change LDL-C of 38% with a 0.05 two-sided significance level and assuming a common standard deviation of 35%. This sample size has been adjusted for a 5% non-evaluable patient rate for the primary efficacy endpoint, and a 15% dropout rate. **Primary Efficacy Analysis** The double-blind primary efficacy analysis will compare the evinacumab 15 mg/kg IV treatment group to placebo at week 24. The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to week 24. The percent change from baseline in calculated LDL-C will be analyzed in the ITT (intent-to-treat) population (defined as all randomized patients who had an evaluable primary endpoint, regardless of adherence to study treatment) using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 2 to week 24 analysis windows will be used and missing data are accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group (placebo versus evinacumab), randomization strata, time point, 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. The statistical testing of the comparison for the primary measure will be evaluated at a 2-sided significance level of 0.05. **Subgroup Analyses for the Primary Efficacy Endpoint**. Analyses are planned on the primary efficacy endpoint to access the homogeneity of evinacumab treatment effect across various patient subgroups in the ITT population, including the 2 stratification factors LDL-C apheresis and region, and patients with or without receptor-negative mutations in both low-density lipoprotein receptor (LDLR) alleles. Statistical analysis methods will be provided in the statistical analysis plan (SAP) Statistical analyses will be conducted in 2 steps. The first analysis will be conducted as soon as all patients have been randomized and all data through week 24 (double-blind period) have been collected and validated. This first analysis will consist of the final analysis of the primary and secondary efficacy endpoints. The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. Since data collection for the double-blind primary efficacy measure and key secondary efficacy

	measures will have been concluded at the time of this first analysis, the significance level for the study remains at 0.05. The second analysis will be conducted at the end of the open-label treatment period (end of study) and will consist of the final analysis for safety and open-label treatment period exploratory efficacy measures.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
Apo A-1	Apolipoprotein A-1
Apo B	Apolipoprotein B
ApoCIII	Apolipoprotein CIII
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CEC	Clinical Events Committee
CI	Confidence interval
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CV	Cardiovascular
CVD	Cardiovascular disease
DBTP	Double-blind treatment period
EC	Ethics Committee
ECG	Electrocardiogram
EOT	End of treatment
EDC	Electronic data capture
FH	Familial hypercholesterolemia
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolemia
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board

ITT	Intent-to-treat
IV	Intravenously
IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LDLRAP1	Low-density lipoprotein receptor adaptor protein 1
LMT	Lipid modifying therapy
LOF	Loss-of-function
Lp(a)	Lipoprotein a
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed-effect model with repeated measures
MTD	Maximum tolerated dose
OL	Open-label
OLTP	Open-label treatment period
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PMM	Pattern Mixture Model
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation

SE	Standard error
SMT	Safety monitoring team
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of child bearing potential

1. INTRODUCTION

Homozygous familial hypercholesterolemia (HoFH) is a rare and serious genetic condition resulting in severely elevated low-density lipoprotein cholesterol (LDL-C) and accelerated cardiovascular disease (CVD). Familial hypercholesterolemia results from mutations in the low-density lipoprotein receptor (LDLR), or in 3 associated genes: proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (Apo B), and LDLR adaptor protein 1 (LDLRAP1). Regardless of the underlying mutations, patients with familial hypercholesterolemia (FH) are phenotypically similar, but vary with respect to severity of the condition. Mutations in LDLR, PCSK9, and Apo B have a dominant mode of transmission, while mutations in LDLRAP1 have a recessive mode of transmission (http://omim.org/entry/143890; http://omim.org/entry/603813). The vast majority of mutations that lead to FH derive from mutations in the LDLR (between 60-80%) (Youngblom 1993).

Homozygous FH is frequently caused by mutations in both alleles of the LDLR gene and results in the decreased clearance of LDL particles from plasma. Patients with HoFH have severe hypercholesterolemia, often 3 to 6 times normal (500 to 1000 mg/dL), which can lead to an exceedingly high risk of developing premature atherosclerosis, as well as valvular and supravalvular stenosis. In children as young as 7 years of age, mild coronary atherosclerosis can be evident even without any clinically apparent coronary artery disease. This accelerated atherosclerosis results in premature CVD and an increased risk of a cardiovascular (CV) event. A recent observational study of HoFH patients demonstrated that the mean age for first major CV event was 20 years (Goldstein 2001, Kolansky 2008, Macchiaiolo 2012, Rader 2003).

Patients with HoFH tend to be treated with multiple lipid-lowering medications in order to try and attain LDL-C levels that are closer to optimal for adults. Consensus statements recommend starting drug treatment as soon as possible and targeting LDL-C goals of <70 mg/dL or <100 mg/dL depending on risk (Cuchel 2014, France 2016). Many of the therapies for hypercholesterolemia are dependent on their stimulating an increase in activity of the LDLR. Part of the basis for the refractory nature of treatments is linked to the mutations in the LDLR that are the driver of HoFH.

Low-density lipoprotein cholesterol-lowering therapies in patients with HeFH and a single mutation in the LDLR can rely on the normally functioning LDLR allele to provide similar efficacy as in non-FH patients. However, the presence of mutations in both LDLR alleles can result in far less efficacy for therapies that rely on the LDLR as part of their mechanism of action. Examples of such therapies include statins and PCSK9 inhibitor antibodies. Mutations in the LDLR can range from being defective (where the LDLR retains some LDL-binding functionality) to null or negative mutations where no functioning LDLR is expressed. Residual LDLR activity ranges from <2% for patients who are receptor negative to 2-25% for patients who are LDLR defective (Cuchel 2014). In the most extreme cases are patients with two null/negative LDLR mutations. These patients tend to have higher LDL-C levels and worse clinical outcome than patients who are LDLR defective (Kolansky 2008, Moorjani 1993). Patients who are LDLR negative develop xanthomas sooner than patients who are LDLR defective, and untreated patients who are LDLR negative rarely live past the second decade (Kolansky 2008, Moorjani 1993). These patients tend to have untreated LDL-C levels at the highest end of the range and in many cases see no efficacy from drugs such as statins or PCSK9 inhibitor antibodies because of their near total lack of functional LDLRs (Marais 2008, Raal 2000, Raal 1997).

While statins can reduce LDL-C by more than 50% in patients with HeFH or with polygenic forms of hypercholesterolemia, in HoFH patients, statins may provide a decrease of <15 to 30% (Crestor 2003, Lipitor 1996, Zocor 1991). When ezetimibe is added to a statin, LDL-C may be reduced by 21 to 27% (Zetia 2002), but many patients with HoFH treated with a high-dose statin and ezetimibe remain far from their LDL-C goal. In patients with little or no LDLR activity, including patients with null/null mutations, statins provide minimal efficacy. Some patients who are receptor-negative (LDLR activity <2%) may respond to statin therapy (Raal 2000), but the degree of response tends to be less than those patients with residual LDLR function (Rader 2003).

Although anti-PCSK9 therapy provides an effective treatment in patients with HeFH and polygenic causes of hypercholesterolemia, it appears to be minimally effective in the HoFH patient. In the recent TESLA study in patients with HoFH, evolocumab therapy resulted in a mean percent reduction in LDL-C of 23.1% (Raal 2015). In the subset of patients known to have two LDLR negative alleles, no response was observed with evolocumab (Repatha 2015).

Other therapies for HoFH, mipomersen and lomitapide, can provide an additional ~25% and 40% reduction in LDL-C, respectively. However, these therapies are associated with high rates of gastrointestinal side effects (lomitapide), hepatic abnormalities including hepatic steatosis and increases in liver function tests (lomitapide and mipomersen) and frequent injection site reactions (mipomersen) (Cuchel 2013, Raal 2010).

High-dose statins, ezetimibe, anti-PCSK9 monoclonal antibodies (mAb), mipomersen, and lomitapide may be effective in some patients with HoFH, but many patients still require lipid apheresis (Goldberg 2011). Lipid apheresis can be effective, but entails treatments lasting several hours multiple times a month, is both costly and associated with a risk of infections (Vella 2001, Kajinami 1999), and is not routinely available in all geographical areas (Thompson 2010).

Despite treatment with lipid modifying therapies (LMTs), such as pharmacological agents, as well as mechanical removal by lipid apheresis, many patients with HoFH remain far from their LDL-C treatment goal. Therefore, the need for more intensive treatment in HoFH, especially those patients with double null mutations remains.

Angiopoietin-like 3 (ANGPTL3) has recently emerged as a potential target for the treatment of elevated levels of triglycerides (TGs) and for the treatment of elevated levels of LDL-C, both risk factors for the development of CVD. ANGPTL3 acts as a natural inhibitor of lipoprotein lipase, an endothelial-bound enzyme involved in the hydrolysis of the TG content of very-low-density lipoproteins and chylomicron lipoproteins. Patients who are homozygous for loss-of-function (LOF) mutations in ANGPTL3 have lower levels of LDL-C (mean difference of 48% versus control family members). The mechanism by which ANGPTL3 LOF mutations result in lowered LDL-C levels is not fully understood, but appears to be independent of the effects on TGs and independent of the LDLR. It is noteworthy that patients with one or two ANGPTL3 LOF alleles also have reported reductions in serum high-density lipoprotein (HDL) cholesterol (HDL-C) levels. The mechanism for this may be related to the inhibitory effect of ANGPTL3 on endothelial lipase, which is involved in the hydrolysis of HDL phospholipids. Importantly, no health deficits have been reported in the relatively small number of patients who are homozygous for ANGPTL3 LOF mutations. These data suggest that inhibiting ANGPTL3 may be a meaningful and well-tolerated strategy for lowering serum LDL-C and TGs.

Evinacumab (REGN1500) is a fully human mAb, created with Regeneron's VelocImmune technology platform, which specifically binds to ANGPTL3. Experiments performed in animals demonstrate that the administration of evinacumab results in a reduction of serum LDL-C and serum TGs. In hyperlipemic mice models (ApoE -/-, Ldlr -/-, db/db), single administrations of evinacumab led to reductions in LDL-C, TGs, and HDL-C up to 49%, 72%, and 39%, respectively. Specifically in mice that have absent LDLR function (Ldlr -/- mice), administration of evinacumab resulted in a 23% reduction in LDL-C. Therefore, it appears that ANGPTL3 inhibition lowers LDL-C through an LDLR-independent mechanism.

In a phase 1, first-in-human, placebo-controlled, double-blind, ascending single-dose study (R1500-HV-1214) of the safety, tolerability, and bioeffect of evinacumab administered subcutaneously (SC) or intravenously (IV) in healthy volunteers with modest elevations in TGs and/or LDL-C at baseline, 99 subjects received placebo or evinacumab at 1 of the following dose levels: 75 mg SC, 150 mg SC, 250 mg SC, 5 mg/kg IV, 10 mg/kg IV, or 20 mg/kg IV. Among these subjects with elevations of TG levels 150 to 450 mg/dL (1.69 mmol/L to 5.09 mmol/L) and/or LDL-C ≥100 mg/dL (2.59 mmol/L), 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). A maximal mean percent HDL-C decrease from baseline of 27.3% was observed on day 15 in the 10 mg/kg IV group (n=9) compared to a 1.8% decrease in the placebo IV group (n=12). For all subjects in the 20 mg/kg IV group (n=11), the median percent decrease in TG from baseline on day 4 was 75.0% vs an increase of 9% in the placebo IV group (n=12). Evinacumab was well tolerated at all dose levels.

In a randomized, double-blind, placebo-controlled, multiple ascending dose study (R1500-CL-1321) of the safety, tolerability, pharmacokinetics (PK), immunogenicity, and pharmacodynamic (PD) effects of evinacumab in subjects with mixed dyslipidemia (TGs 150-500 mg/dL [1.69 mmol/L to 5.09 mmol/L] and LDL-C ≥100 mg/dL [2.59 mmol/L]), subjects who received evinacumab 20 mg/kg IV every 4 weeks (Q4W) achieved a mean percent reduction from baseline in LDL-C of 34.7% at day 57. Those patients who received evinacumab 300 mg SC every 2 weeks (Q2W) achieved a mean percent reduction in LDL-C of 33.4% from baseline. Evinacumab was well tolerated in doses up to 20 mg/kg IV Q4W.

In an open-label, single-arm, proof-of-concept study in patients with HoFH, (Study R1500-CL-1331), evinacumab demonstrated a mean percent reduction from baseline of 49.2% (n=9) at week 4, with a duration of effect of at least 10 weeks after a 15 mg/kg IV dose (n=7). A peak mean reduction of 52.1% was observed at week 6. Three patients enrolled in Study R1500-CL-1331 are homozygous for null mutations in the LDLR. Evinacumab provided meaningful reductions in LDL-C in these 3 null/null HoFH patients (26-44% percent change in LDL-C by week 4). Evinacumab has been well tolerated in this proof-of-concept study.

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 demonstrate the reduction of LDL-C by evinacumab 15 mg/kg IV in comparison to placebo after 24 weeks in patients with HoFH.

2.2. Secondary Objective(s)

The secondary objectives of the study are:

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

2.3. Other Objective

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

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Blockade of ANGPTL3 with evinacumab will reduce LDL-C in patients with HoFH.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is intended to demonstrate efficacy and safety of evinacumab in the treatment of HoFH. Diagnosis of HoFH will be based on either genotyping or clinical criteria. The genetic definition will include all individuals considered to be FH homozygotes, which is defined by the presence of the same mutation(s) in both LDLRs, Apo B, PCSK9 or LDLRAP1 alleles, or individuals considered to be compound heterozygotes, defined by the presence of different mutations in the same allele, or double heterozygotes, defined as mutations in different genes.

The percent change in LDL-C from baseline to week 24 will be the primary endpoint. LDL-C is an accepted surrogate endpoint for CV risk, and has repeatedly been used as the primary endpoint for approval of multiple other HoFH treatments. This study is designed as a placebo-controlled trial with the addition of evinacumab on top of patients' existing treatment regimens of maximally tolerated LMT, including lipid apheresis. This study will utilize a run-in period for those patients whose LMT regimen is not stable. This "add-on" design is appropriate because removal of any therapies from patients' existing treatment regimen will lead to an increase in LDL-C and possibly contribute to the serious CV sequelae seen in this severe disease with high CV risk.

The study consists of 4 periods: run-in (for patients whose background medical LMT has not been stable for at least 4 weeks prior to screening or whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), screening, double-blind treatment, and open-label treatment. In the 24-week double-blind treatment period (DBTP), patients will receive evinacumab 15 mg/kg IV Q4W or matching placebo IV Q4W.

In order to provide additional safety, PK, and long term efficacy information on evinacumab in this rare patient population, after completion of the DBTP, all patients will enter a 24-week open-label treatment period (OLTP). During the OLTP portion of the study, all patients, regardless of treatment assignment in the DBTP, will receive evinacumab 15 mg/kg IV every month.

3.2.2. Rationale for Dose Selection

The 15 mg/kg IV dose is selected based on safety and the substantial LDL-C reduction observed in HoFH patients in study R1500-CL-1331. The higher dose regimen of 20 mg/kg IV Q4W demonstrated favorable tolerability when given as an 8-week treatment in otherwise healthy subjects (R1500-CL-1321) and so the 15 mg/kg IV Q4W regimen is expected to also demonstrate favorable tolerability, because the evinacumab exposure within each dosing interval is expected to be lower and the accumulation of serum concentration with a monthly dosing frequency is predicted to be minimal. From an efficacy perspective, the 15 mg/kg IV dose has previously demonstrated evinacumab concentrations above 100 mg/L for approximately 4 weeks; an exposure threshold associated with target saturation and maximal effect on TG reduction (R1500-CL-1321 and R1500-HV-1214). Based on these PK/PD data, combined with the efficacy data from the proof-of-concept study in HoFH (R1500-CL-1331), 15 mg/kg IV is expected to maintain target saturation and thereby to provide maximal benefit during the monthly dosing interval.

3.2.3. Risk/Benefit Assessment

Patients with HoFH have extremely high LDL-C levels, are far from their target level and will require significant reductions to get to their goal. Despite the approval of newer treatments including evolocumab, lomitapide and mipomersen, the need for more intensive therapies remains. Evinacumab could be a new addition to the armamentarium of LMT that could contribute to lowering the LDL-C of patients with HoFH. In study R1500-CL-1331, evinacumab demonstrated a mean percent reduction from baseline of 49.2% (n=9) at week 4, with a duration of effect of at least 10 weeks after a 15 mg/kg IV dose (n=7). A peak mean reduction of 52.1% was observed at week 6. Three patients in the study are homozygous for null mutations in the LDLR. Treatment with evinacumab in these difficult-to-treat patients reduced LDL-C by an average of 37.3% at week 4 with peak reductions up to 59.5%. Based on these data, it is expected that the addition of evinacumab to existing treatments will lead to significant LDL-C reductions in the HoFH

population. 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 (Cholestrol Treatment Trialists' Collaboration 2010). Moreover, the results from the recent outcomes trials with ezetimibe (IMPROVE-IT [Cannon 2015]), alirocumab (ODYSSEY OUTCOMES [Steg 2018]) and evolocumab (FOURIER [Sabatine 2017]) reinforce this concept, providing additional evidence for the relationship between LDL-C lowering and reductions in CV events and the importance for patients to achieve their target LDL-C. Within the context of this study in the HoFH patient population, additional reduction in LDL-C may get patients closer their LDL-C target, which could translate into significant benefits.

It is also 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.

Patients entering this study should be on a background statin, ezetimibe, and a PCSK9 inhibitor, unless they have a documented history of tolerability issues, lack of efficacy, or other reason. Patients should be on these lipid lowering drugs because of the above mentioned proven CV risk reduction demonstrated in recent CV outcomes trials (ODYSSEY OUTCOMES, FOURIER, IMPROVE-IT). There are 2 PCSK9 inhibitors on the market; evolocumab is approved for use in patients with HoFH in most countries, and alirocumab is currently being evaluated in a double-blind placebo-controlled study in patients with HoFH (study R727-CL-1628, ODYSSEY HoFH). Patients entering this study may be taking either evolocumab or alirocumab. Patients who complete study R727-CL-1628 (ODYSSEY HoFH) with alirocumab are permitted to participate in this study and will continue to receive alirocumab as part of their background LMT. The concurrent use of evinacumab with alirocumab is considered to have an acceptable benefit/risk profile because it could be beneficial and is not considered to pose any safety concerns.

Evinacumab and alirocumab have different mechanisms of action and concomitant administration of both agents is not expected to perturb the action of the other. Rather, their distinct mechanisms of action are anticipated to complement each other to lower LDL-C since they work at different sites of action.

The safety profile of each agent is considered acceptable and the concurrent use of the 2 agents together is not expected to augment or exacerbate potential adverse events (AEs). Concomitant use of evinacumab and evolocumab was found to have an acceptable safety profile in 4 patients in the R1500-CL-1331 study, a study evaluating evinacumab in 9 patients with HoFH (details of the study are provided in the evinacumab Investigator's Brochure and the Introduction [Section 1]). No safety signals or adverse effects related to the concomitant use of both agents have been observed. The safety of the use of evinacumab along with alirocumab will be carefully monitored in this study. Safety monitoring will include ongoing reviews by an unblinded Independent Data Monitoring Committee (IDMC), by the sponsor's blinded safety monitoring team (SMT), and by the blinded clinical study team. If significant safety trends or findings are identified by either the

IDMC or the sponsor's blinded study team or SMT, they will be escalated and appropriately evaluated to understand the best course of action.

From the perspective of PK drug-drug interactions, co-administration of evinacumab, alirocumab, and the other possible background LMT (statin, ezetimibe, etc) is not expected to result in drug-drug interactions with each other or other drugs. Evinacumab and alirocumab are both eliminated via a combination of non-saturable, linear, proteolytic degradation and saturable, non-linear target-mediated clearance. The 2 molecules bind to different targets and the target-mediated pathways are entirely independent. Neither evinacumab nor alirocumab are a cytokine or cytokine modulator; therefore, it is not anticipated to interact directly or indirectly with cytochrome P450 enzymes, other drug metabolizing enzymes or drug transporters, which are known to influence the disposition of statins. Conversely, the PK of evinacumab is not expected to be impacted by statins, due to its elimination pathways.

Indeed, the concomitant administration of 2 fully human monoclonal antibodies may be a new treatment paradigm in CV medicine, but not uncommon in other therapeutic areas such as autoimmune disease or oncology. Experience in those areas has demonstrated the use of multiple biologic agents to be acceptable from a safety and tolerability perspective.

For the reasons stated above, the benefit/risk profile for the concurrent use of evinacumab and PCSK9 inhibitor antibodies or the use of evinacumab in the absence of a PCSK9 inhibitor antibody as part of the background LMT is considered favorable.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), lipid levels, medical history (including allergic history), mutation status, medication history, and apheresis schedule (if applicable) for each patient. Patients' history on other medications for treatment of HoFH will be documented on a specific page of the case report form (CRF).

4.2. Primary and Secondary Endpoints

4.2.1. Primary Efficacy Endpoint

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

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

All calculated LDL-C values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the primary efficacy endpoint, if appropriate, according to the above definition. The analysis window used to allocate a time point to a measurement will be defined in the statistical analysis plan (SAP).

4.2.2. Key Secondary Efficacy Endpoints

The key secondary endpoints are:

- The percent change in Apo B from baseline to week 24 (ITT estimand)
- The percent change in non-HDL-C from baseline to week 24 (ITT estimand)
- The percent change in TC from baseline to week 24 (ITT estimand)
- The proportion of patients with ≥30% reduction in calculated LDL-C at week 24 (ITT estimand)
- The proportion of patients with ≥50% reduction in calculated LDL-C at week 24 (ITT estimand)
- The proportion of patients with LDL-C <100 mg/dL [2.59 mmol/L] at week 24 (ITT estimand)
- The change in calculated LDL-C from baseline to week 24 (ITT estimand)
- The proportion of patients who meet EU apheresis eligibility criteria (see German Apheresis Working Group) at week 24 (ITT estimand)
- The proportion of patients who meet US apheresis eligibility criteria (see US [National Lipid Association] Lipid Apheresis Criteria) at week 24 (ITT estimand)

4.2.3. Other Secondary Efficacy Endpoints

- The percent change in TG from baseline to week 24 (ITT estimand)
- The change in Apo B from baseline to week 24 (ITT estimand)
- The change in non-HDL-C from baseline to week 24 (ITT estimand)
- The change in TC from baseline to week 24 (ITT estimand)
- The percent change in lipoprotein a [Lp(a)] from baseline to week 24 (ITT estimand)
- The proportion of patients with LDL-C <70 mg/dL [1.81 mmol/L] at week 24 (ITT estimand)
- The percent change in apolipoprotein CIII (Apo CIII) from baseline to week 24 (ITT estimand)

National Lipid Association (US) [Goldberg 2011]	**German Apheresis Working Group (EU) [Schettler 2012]**
• Patients have inadequate response to diet and LMTs after 6 months of treatment • Functional HoFH or HeFH (with 0-1 risk factor) with LDL-C ≥300 mg/dL (7.77 mmol/L)[1]	• Patients have inadequate response to diet and LMTs after 3 months of treatment • *Primary prevention* – FH with LDL-C >160 mg/dL (4.2 mmol/L) and CV events in close relatives • *Secondary prevention* – Patients with progressive CV events with LDL-C >120 to 130 mg/dL (3.1-3.4 mmol/L)

[1] Risk factors include age, elevated TC and LDL-C, low HDL-C, male sex, smoking, metabolic syndrome, diabetes, hypertension, and family history of CVD

4.2.4. Other Endpoints

- The change in hemoglobin A1c (HbA1c [%]) from baseline to week 24
- Response of each EQ-5D item, index score, and change of index score from baseline through week 24
- Response on Hospital Anxiety and Depression Scale (HADS) from baseline through week 48.

4.3. Pharmacokinetic Variables

The PK variable is total evinacumab concentration in serum.

4.4. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) status will be assessed.

- Treatment emergent response - defined as a positive response post-first dose in the ADA assay when baseline ADA 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 baseline ADA results are positive.

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

Samples positive in the ADA assay will be assessed for titer:

- 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 phase 3 study consists of the following periods: an up to 8-week run-in period (for patients who may require genotyping, for patients whose background medical LMT has not been stable prior to screening or whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a 2-week screening period, a 24-week DBTP, a 24-week OLTP, and a follow-up period for 24 weeks, after the last dose of study drug, for those patients who decide not to enter an optional open-label study (Figure 1). The total duration of the run-in, screening, DBTP and OLTP may be up to may be up 78 weeks.

Run-In:

Apheresis therapy - Patients who are undergoing apheresis therapy must be on a stable weekly (every 7±1 days) or every other week (every 14±2 days) schedule. Patients whose schedule and/or apheresis settings, which have not been stable for at least 8 weeks before the screening visit, will enter an 8-week run-in period before the screening period. After the 8-week run-in period, patients whose lipid apheresis schedule remains stable will be eligible to enter the 2-week screening period.

Lipid modifying therapy - Patients who are on background LMT (excluding lomitapide and mipomersen) that has not been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibody) before the screening visit will enter a 4-week (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibody) run-in period to stabilize their LMT before entering the screening period. For patients taking mipomersen or lomitapide, patients who have not been on a stable dose of mipomersen for 24 weeks prior to screening or on a maximum tolerated dose (MTD) of lomitapide for 12 weeks prior to screening are excluded.

Genotyping – Confirmation of patient's HoFH status can be made by either genetic or clinical criteria. If HoFH diagnosis cannot be confirmed by the clinical criteria listed or from previous genotyping results, patients can enter the run-in period to determine their mutation status in advance of screening, if deemed appropriate by the investigator.

Screening:

Patients who are not undergoing apheresis therapy, patients who have been on a stable apheresis schedule for at least 8 weeks before the screening visit, and patients on stable background medical LMT (as applicable) for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies, 12 weeks for lomitapide, 24 weeks for mipomersen) before the screening visit, will enter a 2-week screening period.

Patients who participated in the R727-CL-1628 study may enter the run-in or screening period or enroll directly into this study. Patients who completed the R727-CL-1628 study and fulfill all of the eligibility criteria can be enrolled directly into this study. Data collected during the R727-CL-1628 study (ie, lab test results) can be used to assess eligibility criteria for these patients. If these patients meet all the eligibility criteria and if approved by the sponsor, the patients may not have to undergo the screening visit in this study. In this case, overlapping assessments completed at the end of the open-label treatment visit in R727-CL-1628 do not need to be repeated during the R1500-CL-1629 baseline visit. The baseline/day 1 visit can occur immediately after the end of

the open-label treatment visit in the R727-CL-1628 study. To ensure continuity of treatment with alirocumab, all patients from R727-CL-1628 entering this study will be provided alirocumab.

Double-Blind Treatment:

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized 2:1 to receive:

- evinacumab 15 mg/kg IV Q4W

OR

- matching placebo IV Q4W

Randomization will be stratified by apheresis treatment (Yes, No) and by geographical region (Japan, Rest of World).

Study drug administration during the DBTP will take place at the site, starting on the day of randomization (day 1), and will be administered immediately after completion of the LDL-apheresis procedure (if applicable). For those patients not undergoing LDL-apheresis, study drug must be administered after all samples for clinical laboratory evaluation have been obtained. The last dose of double-blind study drug will be administered at week 20.

Patients who are on LMT or who are undergoing LDL-apheresis should maintain stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study, from screening to the end of DBTP visit (week 24), and continuing through the end of the OLTP. All patients who enter this study from R727-CL-1628 will continue to receive alirocumab 150 mg SC Q2W for the duration of this study. Alirocumab should continue to be administered after LDL-apheresis (if applicable). On days with concomitant alirocumab and evinacumab administration, the recommendation is to administer alirocumab after the end of the evinacumab post-infusion observation period.

Open-Label Treatment:

After completion of the DBTP, all patients will enter an OLTP. Starting at week 24, all patients, regardless of treatment assignment in the DBTP, will receive open-label evinacumab 15 mg/kg IV Q4W for the 24-week OLTP. The last dose of open-label study drug will be at week 44.

Patients who are on LMT or apheresis must continue their stable dose and regimen through the end of the OLTP (through week 48). All patients who enter this study from R727-CL-1628 will continue to receive alirocumab.

Throughout the Study:

For all patients undergoing LDL-apheresis, all samples for clinical laboratory evaluation must be obtained immediately prior to the LDL-apheresis procedure and prior to administration of study drug. Given the impact of LDL apheresis, PCSK9 inhibitors, and mipomersen on lipid parameters, it is important to match the time of the baseline activities with the timing of the week 24 activities. This would mean that the timing between the baseline sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen should match the timing of the week 24 sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen. For all patients

who are not undergoing apheresis, all samples for clinical laboratory evaluation must be obtained prior to administration of study drug.

The efficacy of evinacumab in this population will be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study. Overall safety will be assessed by monitoring/evaluation of treatment-emergent adverse events (TEAEs), physical examinations, electrocardiogram (ECG), and clinical safety laboratory tests at pre-specified time points. The potential emergence of anti-evinacumab antibodies will also be evaluated. Patients who experience an ongoing serious adverse event (SAE) at the pre-specified study end-date should be followed until resolution, stabilization, or collection of outcome and related data.

For all patients undergoing LDL-apheresis, the apheresis schedule and apheresis settings should remain stable throughout the duration of the DBTP and through the end of the OLTP (week 48).

The use of all medications and nutritional supplements known to alter serum lipids, including (but not limited to) statins, ezetimibe, PCSK9 inhibitor antibody, mipomersen, lomitapide, fibrates, niacin, and bile acid resins is permitted as long as that therapy has been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies, 12 weeks for the MDT of lomitapide, 24 weeks for mipomersen) prior to the screening visit. Patients should continue taking their LMT throughout the duration of the DBTP, starting at screening, and through the end of the OLTP (week 48).

Patients should be on a stable low fat or heart-healthy diet.

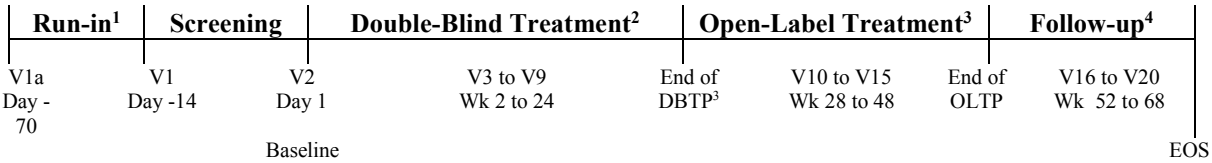
Patients' exercise regimen should remain stable throughout the duration of the study, from screening through the OLTP.

After completion of the 24-week OLTP, all patients who have successfully completed this study may have the opportunity to participate in a separate open-label (OL) study, R1500-CL-1719. All patients who enroll in the separate OL study will continue to receive open-label evinacumab at a dose of 15 mg/kg IV Q4W.

Follow-up Period (if applicable):

Patients not consenting to participate in the optional OL study (R1500-CL-1719) will enter a follow-up period for 24 weeks after completion of the OLTP. A follow-up period of 24 weeks after the last dose of study drug will be required for patients who prematurely discontinue study treatment.

Figure 1: Study Flow Diagram



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

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

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

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

5.1.1. End of Study Definition

The end of study is defined as 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 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 (eg, lipid efficacy data).

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 (CEC) is composed of experts in the field of CVD, independent of the sponsor and the investigators. This committee will be responsible for defining, validating, and classifying (in a blinded fashion) pre-specified CV events and all deaths.

Patients with suspected or confirmed CV events that occur in the time period from randomization until the end of the study will have a corresponding adjudication package prepared and submitted

to the CEC. The events should also be reported as SAEs, as appropriate. Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories include:

- Coronary heart disease death
- Nonfatal myocardial infarction (MI)
- Fatal and nonfatal ischemic stroke
- Unstable angina requiring hospitalization
- Congestive heart failure requiring hospitalization

In addition, other deaths (besides coronary heart disease deaths) will be classified by the CEC. All coronary revascularizations (percutaneous coronary intervention, coronary artery bypass graft surgery) 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 57 patients will be randomized at approximately 30 multinational sites.

6.2. Study Population

The study population will consist of males and females ≥18 years of age diagnosed with HoFH, receiving stable LMT, as applicable.

Patients should be on a maximally tolerated daily statin, ezetimibe and PCSK9 inhibitor antibody unless the patient has a documented history of tolerability issues, little or no response to therapy or other documented reason. Lipid modifying therapy may also include other lipid lowering therapies, including LDL-apheresis. Whether or not a patient is considered to be on a maximum tolerated regimen of lipid modifying treatments (statin, PCSK9 inhibitor antibody, ezetimibe, lomitapide, mipomersen, probucol, etc), reasons why or why not (eg, due to intolerance, lack of efficacy, etc) the patient is taking/not taking the various treatments will need to be documented in the CRF.

HoFH is defined by having at least one of the following (either genetic or clinical criteria):

Genetic criteria:

1. Documented functional mutation or mutations in both LDLR alleles
   - Note: patients who have null receptor mutations on both LDLR alleles, ie, double null, are eligible

OR

2. Documented homozygous or compound heterozygous mutations in Apo B or PCSK9

- Note: patients who are double heterozygous, ie, mutations on different genes (eg, LDLR/PCSK9) and patients with homozygous LDLRAP1 mutations are eligible

Clinical Criteria:

Untreated TC >500 mg/dL (12.93 mmol/L) and TGs <300 mg/dL (3.39 mmol/L)

AND

both parents with documented TC >250 mg/dL (6.47 mmol/L) OR cutaneous or tendinous xanthoma before the age of 10 years

6.2.1. Inclusion Criteria

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

1. Male or female ≥18 years of age at the time of the screening visit
2. Diagnosis of functional HoFH by at least 1 of the following:
   a. Documented functional mutation or mutations in both LDLR alleles
      Note: patients who have null receptor mutations on both LDLR alleles, ie, double null, are eligible
   b. Presence of homozygous or compound heterozygous mutations in Apo B or PCSK9
      Note: patients who are double heterozygous, ie, mutations on different genes (eg, LDLR/PCSK9) and patients with homozygous LDLRAP1 mutations are eligible
   c. Untreated TC >500 mg/dL (12.93 mmol/L) and TG <300 mg/dL (3.39 mmol/L)
      AND
      both parents with documented TC >250 mg/dL (6.47 mmol)
      OR cutaneous or tendinous xanthoma before the age of 10 years
3. If undergoing LDL apheresis, must have initiated LDL apheresis at least 3 months prior to screening and must have been on a stable weekly (every 7±1 days) or every other week (every 14±2 days) schedule and stable settings for at least 8 weeks
4. Willing and able to comply with clinic visits and study-related procedures
5. Willing to consistently maintain his/her usual low fat or heart-healthy diet for the duration of the study
6. Provide signed informed consent or assent

6.2.2. Exclusion Criteria

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

1. LDL-C level <70 mg/dL (1.81 mmol/L) at the screening visit.
2. Background medical LMT (if applicable) that has not been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies, 12 weeks for MTD of lomitapide, 24 weeks for mipomersen) before the screening visit
3. Lipid-apheresis schedule (every 7 or 14 days)/apheresis settings (if applicable) that have not been stable for at least 8 weeks before the screening visit or an apheresis schedule that is not anticipated to be stable over the next 48 weeks. Plasma exchange is excluded.

4. Use of nutraceuticals or over-the-counter therapies known to affect lipids, at a dose/amount that has not been stable for at least 4 weeks prior to the screening visit or between the screening and randomization visits
5. 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 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.
6. Newly diagnosed (within 3 months prior to randomization visit [week 0/day 1]) diabetes mellitus or poorly controlled (HbA1c >9%) diabetes
7. Unstable weight (variation >5 kg) within 2 months prior to the screening visit (week -2)
8. Initiation of a new diet or major change to a previous diet within 4 weeks prior to screening
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 screening
   Note: topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed
10. Use of estrogen or testosterone therapy unless the regimen has been stable 6 weeks prior to the screening visit and no plans to change the regimen during the study
11. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the screening visit or time of randomization (week 0/day 1)
12. History of a MI, unstable angina leading to hospitalization, coronary artery bypass graft surgery, percutaneous coronary intervention, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, valve replacement surgery, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit
13. History of New York Heart Association (NYHA) Class IV heart failure within 12 months before screening.
14. Age <18 years at the screening visit
15. 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
16. Use of any active investigational drugs (except alirocumab) within 1 month or 5 half-lives prior to the screening visit, whichever is longer
17. 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
   - 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, which the investigator feels would restrict or limit the patient's participation for the duration of the study

18. Laboratory findings during the screening period (not including randomization labs):
    - Positive test for hepatitis B surface antigen and/or hepatitis C antibody (associated with a positive HCV RNA polymerase chain reaction)
    - Positive serum beta-human chorionic gonadotropin or urine pregnancy test in women of childbearing potential (WOCBP)
    - eGFR <30 mL/min/1.73 m^2 (calculated by central lab)
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) (1 repeat lab is allowed)
    - CPK >3 x ULN (1 repeat lab is allowed)
    - TSH >1.5 x ULN of the central laboratory (1 repeat lab is allowed) for patients not on thyroid replacement therapy
19. Known hypersensitivity to mAb therapeutics
20. Member of the clinical site study team and/or his/her immediate family
21. Pregnant or breastfeeding women
22. Sexually active WOCBP*, 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 dose of study drug. Highly effective contraceptive 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 trial 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.

23. 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 dose of study drug regardless of vasectomy status. Sperm donation is prohibited during the study and for up to 24 weeks after the last injection of study drug.
24. Housed in an institution on the basis of an administrative or judicial order.
25. Dependent on the sponsor, investigator, or the study site.

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 8.1.5.

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

Early Termination from the Study

If for any reason the patient withdraws from the study prematurely, the patient should undergo an unscheduled visit with assessments normally planned at the end of the double-blind treatment visit if the patient is in the DBTP, or the end of the open-label treatment visit, if the patient is in the OLTP. The visit should take place within 5 days of treatment discontinuation. The assessments completed should include pregnancy testing for WOCBP. 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 end of study visit should take place with assessments as specified in the end of study visit (ie, follow up visit) at 24 weeks after the premature discontinuation of study drug.

Sexually active WOCBP 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, the patient will be provided 5 urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. The patient will also be notified of Q4W follow-up phone calls to confirm continued contraception use and pregnancy reporting and to obtain the results of the urine pregnancy test.

The investigator 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. 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 prematurely discontinued from the study drug will not be replaced.

6.5. Rescreening of Patients

Patients who do not meet eligibility criteria during the initial screening may re-screen only once. Patients who are re-screened 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 for the assessments that did not meet eligibility criteria.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Evinacumab or placebo IV infusion.

In the DBTP, eligible patients will be enrolled to receive an IV dose of evinacumab 15 mg/kg Q4W or matching placebo, starting on day 1. The last dose of double-blind study drug will be at week 20.

In the open-label portion of the study, patients will receive

- Evinacumab at 15 mg/kg IV Q4W starting at week 24 (day 169) with the last dose at week 44 (day 309)

Dosing should fall within a window of ±7 days; if >14 days has passed, skip the dose and return to the original schedule.

Instructions on dose preparation and administration are provided in the pharmacy manual.

Instructions on management of infusion reactions are provided in Section 7.5.1.

Sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL in a prefilled pen for patients from study R727-CL-1628 who enroll in this study.

7.2. Run-in Treatment(s)

Patients who are undergoing apheresis therapy must have initiated LDL apheresis at least 3 months prior to screening and must be on a stable weekly (every 7 days) or every other week (every 14 days) schedule and/or stable settings for at least 8 weeks prior to screening. Patients with a schedule and/or apheresis settings that have not been stable for at least 8 weeks before the screening visit will enter an 8-week run-in period before the screening period.

Patients who are on background LMT that has not been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies) before the screening visit will enter a 4-week (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies) run-in period to stabilize their LMT before entering the screening period.

7.3. Background Treatment(s)

Patients who are receiving background LMT or who are undergoing apheresis should maintain stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study, from screening to the end of DBTP visit (week 24), and continuing through the end of the OLTP. For all patients who enter this study from R727-CL-1628, alirocumab will be provided and patients will administer alirocumab 150 mg SC Q2W for the duration of the study.

Patients should be on a maximally tolerated LMT regimen. Whether or not a patient is considered to be on a maximum tolerated regimen of LMT (statin, PCSK9 inhibitor antibody, ezetimibe, lomitapide, mipomersen, probucol, etc), reasons why or why not (eg, due to intolerance, lack of efficacy) 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

During the DBTP, study drug 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 DBTP as long as possible.

Patients who permanently discontinue study drug during the DBTP should remain in the study and undergo all double-blind 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 end of the double-blind treatment visit (this should take place within 5 days of discontinuation of study drug, if possible) and then resume the original study schedule until end of the DBTP. In case of early discontinuation before week 24, all efforts should be made to perform the week 24 assessments at week 24.

Patients who permanently discontinue study drug during the OLTP should have, as soon as possible, an unscheduled visit with assessments normally planned at the end of the OLTP (this should take place within 5 days of discontinuation of study drug, if possible) and then have end-of-study assessments at least 24 weeks after their last dose of study drug.

Patients who permanently discontinue study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.5.

Sexually active WOCBP 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, the patient will be provided 5 urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. The patient will also be notified of Q4W follow-up phone calls to confirm continued contraception use and pregnancy reporting and to obtain the results of the urine pregnancy test.

7.4.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Evidence of pregnancy
- Acute systemic 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 DBTP. 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 study drug dosing 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 or 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*
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension
- other neurological symptoms (confusion, loss of consciousness, parathesia, 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 the 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 blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

7.6. Method of Treatment Assignment

Approximately 57 patients will be randomized in a 2:1 ratio to receive either 15 mg/kg IV evinacumab or matching placebo according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified by apheresis treatment (Yes/No) and by geographical region (Japan, Rest of World).

In the OLTP of the study, all patients will receive evinacumab as described in Section 7.1.

7.6.1. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the DBTP (up to week 24). 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.

Lipid results from blood samples collected after the randomization visit will not be communicated to the sites, and the sponsor's operational team will not have access to these laboratory results until after completion of the DBTP and the first-step analysis.

Although there is a slight color difference between the drug product and placebo product for IV infusion bag preparation, the color difference is not detectable when the investigational product is added to the IV infusion bag.

Further details are provided in the pharmacy manual.

After the end of the DBTP visit at week 24, the study becomes an open-label study.

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 [redacted]; storage instructions will be provided in the pharmacy manual.

7.7.2. Supply and Disposition of Treatments

Study drug will be shipped [redacted] 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 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, including apheresis, from the time of informed consent to the end of the treatment period/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

The following concomitant medications and procedures are prohibited through the end of the DBTP (week 24) and continuing through the end of the OLTP (week 48):

- Background medical LMT (if applicable) that has not been stable for at least 4 weeks (6 weeks for fibrates) before the screening visit (week -2) (unless participating in the run-in period to stabilize)
- Background mipomersen treatment that has not been stable for 24 weeks before the screening visit (week -2)
- Background lomitapide at a MTD that has not been stable for 12 weeks before the screening visit (week -2)
- Recent discontinuation of lomitapide that has not been washed out for at least 8 weeks before the screening visit (week -2).
- Background PCSK9 inhibitor antibody that has not been stable for at least 8 weeks prior to the screening visit (week -2)
- Lipid apheresis schedule that is not an every 7 day (±1 day) or an every 14 day (±2 days) regimen or has not been stable for at least 8 weeks prior to screening (week -2)
- Plasma exchange
- Nutraceuticals or over-the-counter therapies known to affect lipids, at a dose/amount that has not been stable for at least 4 weeks prior to the screening visit (week -2)
- Systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to the screening visit (week-2)
- Thyroid replacement therapy, unless the dosage of replacement therapy has been stable for at least 12 weeks prior to the screening visit (week -2).

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, lomitapide, mipomersen, and PCSK9 inhibitor antibodies is permitted as long as that therapy has been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies, 12 weeks for lomitapide, 24 weeks for mipomersen) prior to the screening visit (week-2). Patients should continue taking their background medical LMT for the duration of the study starting at screening and through the end of the OLTP (week 48). Similarly, patients should maintain their apheresis regimen (if applicable) starting at screening and through the end of the OLTP (week 48).

Patients on thyroid replacement therapy can be included if the dosage has been stable for at least 12 weeks prior to the screening visit (week -2).

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

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, and Table 4.

Table 1: Schedule of Events – Run-in and Screening

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

Table 2: Schedule of Events – Screening for Patients with No Run-in

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

Table 3: Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period

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

Study Procedure	**Double-Blind Treatment Period**								**Open-Label Treatment Period**					
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 End DBTP** [1,3]	**10**	**11**	**12**	**13**	**14**	**15 End of OLTP**
Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (Day)	**±1**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±1**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Blood Chemistry	X		X	X	X	X		X		X		X		X
Creatine Phosphokinase	X		X	X	X	X		X		X		X		X
Serum Pregnancy Test[8]														X
Urine Pregnancy Test[8]	X		X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X		X	X	X	X		X		X		X		X
hs-CRP	X							X						X
HbA1C	X[1]				X			X			X			X
LDLR function	X[1]													
Research Samples	X[1]		X	X		X		X	X					
PK and PD Samples														
ADA Sample9	X[1]		X		X			X						X
PK (evinacumab, alirocumab), ANGPTL3, PCSK9 samples[10,11]	X[1]	X	X	X	X	X	X	X			X			X
PK of statin[10]	X[1]					X								
DNA sample for HoFH genotyping	X[1]													
[redacted]	X[1]													
Other:														
EQ-5D	X							X						
HADS	X[1]							X				X[14]		X[14]
Review of diet	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4: Schedule of Events – Follow-up Period

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

8.1.1. Footnotes for Schedule of Events Table 1

1. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure; study drug will be administered after the apheresis procedure.
2. Fasting sample will be collected for the lipid panel: TC, calculated LDL-C, HDL-C, TG, non-HDL-C
3. ECG should be performed before blood samples are collected at visits requiring blood draws.
4. All laboratory samples should be collected before administration of study drug.
5. WOCBP only, confirm required contraception use and reminder pregnancy reporting
6. For patients who require HoFH genotyping, stabilization of their lipid-apheresis schedule or stabilization of their background medical LMT, ie, stable lipid-apheresis for at least 8 weeks before screening and stable background medical LMT for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies)

8.1.2. Footnotes for Schedule of Events Table 2

1. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure; study drug will be administered after the apheresis procedure.
2. Fasting sample will be collected for the lipid panel: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C
3. ECG should be performed before blood samples are collected at visits requiring blood draws.
4. All laboratory samples should be collected before administration of study drug.
5. WOCBP only, confirm required contraception use and reminder pregnancy reporting

8.1.3. Footnotes for Schedule of Events Table 3

1. For those patients enrolling directly from the R727-CL-1628 study and do not complete the R1500-CL-1629 run-in or screening period, the informed consent forms should be signed at the baseline visit. Overlapping assessments completed at the R727-CL-1628 open-label EOT visit do not need to be repeated during the R1500-CL-1629 baseline visit; only assessments footnoted will need to be performed.
2. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure; study drug will be administered after the apheresis procedure. The timing between the baseline sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen should match the timing of the week 24 sample collection relative to the most recently completed

LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen. Depending on the duration between the LDL apheresis procedure and sample collection, the visit window may not apply.

3. Fasting sample will be collected for the lipid panel: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C
4. Fasting sample will be collected for specialty lipid panel: Apo B, Apo A-1, and Lp(a)
5. On dosing days, vital signs should be recorded prior to IV infusion, and 30 minutes and 60 minutes post-IV infusion
6. ECG should be performed before blood samples are collected at visits requiring blood draws.
7. All laboratory samples should be collected before administration of study drug
8. WOCBP only, confirm required contraception use and reminder pregnancy reporting
9. The ADA sample should be drawn before study drug administration
10. For patients who are not undergoing apheresis, the PK sample should be drawn before the dose of study drug and at the end of the infusion. For patients undergoing apheresis, a PK sample should be collected immediately before the apheresis procedure and a PK sample should be collected immediately after the apheresis procedure, prior to administration of study drug, and, again at the end of the infusion of study drug.
11. Including assay of total ANGPTL3

[redacted]

13. All end of treatment (EOT) assessments are to be performed and blood samples are to be collected before the dose of open-label study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure; open-label study drug will be administered after the apheresis procedure.
14. In the OLTP, the HADS should be administered after the patients have been informed of their lipid results

8.1.4. Footnotes for Schedule of Events Table 4

1. ECG should be performed before blood samples are collected at visits requiring blood draws
2. WOCBP only, confirm required contraception use and reminder pregnancy reporting.
3. Including assay of total ANGPTL3
4. For patients who discontinue prematurely or who opt out of the OL study
5. Phone visits (PV) at weeks 56 and 64 to confirm required contraception use and obtain results of the home urine pregnancy test. Adverse events and concomitant medications will be collected

8.1.5. Early Termination Visit

In the case a patient prematurely discontinues study treatment, an unscheduled visit should occur with assessments normally planned at the (EOT) visit (it should take place within 5 days of treatment discontinuation, if possible). Patients who permanently discontinue study drug during the DBTP should then resume the original study schedule (except for study treatment administration) until end of the DBTP, and all efforts should be made to perform the week 24 assessments at week 24 (regardless of study treatment administration). All patients who prematurely discontinue study treatment (either in the double-blind period or the open-label period) should be followed for at least 24 weeks from the last dose of study drug, and a final end of study visit can take place with assessments as specified in the end of study visit (ie, follow up visit).

Sexually active WOCBP 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, the patient will be provided 5 urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. The patient will also be notified of Q4W follow-up phone calls to confirm continued contraception use and pregnancy reporting and to obtain the results of the urine pregnancy test.

If a WOCBP is lost to follow-up, sites should attempt a minimum of 2 telephone calls. If the patient cannot be reached on the second attempt, a formal letter will be issued from the site to the patient that reminds the patient of the importance of continued use of highly effective contraception use for at least 6 months after the last dose of study drug.

8.1.6. 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:

- Hepatitis B Surface Antigen
- Hepatitis C Antibody
- 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.

Total-C, HDL-C, TG, Apo B, Apo A-1, Lp(a), and Apo CIII 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) or if calculated LDL-C values are below 25 mg/dL (0.65 mmol/L), LDL-C will be measured via the beta quantification method (rather than via the Friedewald formula). Non-HDL-C will be calculated by subtracting HDL-C from the total-C. Ratio Apo B/Apo A-1 will be calculated. All lipid results will be blinded from after the randomization visit until the week 36 visit. Every effort should be made to continue to keep the sponsor blinded to all lipid parameters for the duration of the study. No attempts should be made by the investigator or patient to have the patient's lipid values independently evaluated after randomization until after the end of study visit.

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

8.2.2.1. Lipid Panel

Fasting (at least 8 hours) blood samples will be collected at specified time points shown in Section 8.1 for assessment of the lipid profile, comprising calculated LDL-C, HDL-C, non-HDL-C, total-C, and TGs. These samples will also be used for specialty lipid panel assessment when it is scheduled at the same time as the lipid panel assessment.

8.2.2.2. Specialty Lipid Panel

Fasting (at least 8 hours) blood samples will be collected at specified time points shown in Section 8.1 for assessment of the specialty lipid profile, comprising Apo B, Apo A-1, ratio of Apo B/Apo A-1, and Lp(a) as well as for Apo CIII. The specialty lipid panels will be assessed in the same sample that is collected for the lipid panel.

8.2.3. Quality of Life Procedures

8.2.3.1. EuroQol-5 Questionnaire

The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D as a measure of health related quality of life, defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each dimension has 3 ordinal levels of severity: "no problem" (1), "some problems" (2), "severe problems" (3). Overall health state is defined as a 5-digit number. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death" and 1 represents "perfect health."

8.2.3.2. Patient Assessed Hospital Anxiety and Depression Scale

The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state (Zigmond 1983, Herrmann 1997). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off

scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression.

8.2.4. Safety Procedures

8.2.4.1. Vital Signs

Vital signs, including temperature, sitting blood pressure and pulse and respiration rate, will be collected predose at time points according to Table 1, Table 2, Table 3, and Table 4. On dosing days, vital signs consisting of blood pressure and pulse rate will also be collected pre-dose and 30 minutes and 60 minutes after completion of the IV infusion.

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.

8.2.4.2. Physical Examination

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

8.2.4.3. Electrocardiogram

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

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 (see Section 9.4.5). Each ECG tracing will be analyzed in comparison with the screening recorded trace. All ECG tracings will be kept as source data.

8.2.4.4. Laboratory Testing

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

Samples for laboratory testing will be collected at visits according to Table 1, Table 2, Table 3, and Table 4 and analyzed by a central laboratory. 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	
Chloride	Blood urea nitrogen (BUN)	
Carbon dioxide	AST	Uric acid
Calcium	ALT	CPK
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

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

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, and Table 4 and are as follows: FSH, TSH, high sensitivity C-reactive protein (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.

8.2.4.5. 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.

8.2.5. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.5.1. Drug Concentration Measurements and Samples

Samples for assessment of evinacumab and alirocumab concentration will be collected at time points listed in Table 3 and Table 4. They will be collected predose and at the end of the IV infusion on days when study drug is administered.

[redacted].

8.2.5.2. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 3 and Table 4. They will be collected predose on days when study drug is administered.

Patients who exhibit a treatment-emergent or treatment-boosted positive ADA assay response with a titer greater than 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 within two dilution steps from their baseline titer levels.

[redacted]

8.2.5.3. Statin Concentrations

Samples for statin concentration will be collected at time points shown in Table 3.

8.2.6. Pharmacodynamic Procedures

Total ANGPTL3 and total PCSK9 concentrations in serum will be measured using the PK samples collected at the time points listed in Table 3 and Table 4.

8.2.7. Other Assessments

8.2.7.1. Review of Diet

Patients will be following a low fat or heart-healthy diet at the screening visit and will be asked to continue the low fat or heart-healthy diet until the last study visit. Patients will be queried on compliance with their diet during the DBTP and OLTP, at time points according to Section 8.1.

Details are provided in Appendix 2.

8.2.7.2. DNA Sample for HoFH Genotyping

A required blood sample for DNA extraction will be collected from all patients to identify or confirm a known mutation in PCSK9, LDLR, Apo B gene, and/or LDLRAP1 gene.

8.2.7.3. LDLR Function

A blood sample for LDLR function testing will be collected from all patients at time points according to Section 8.1, in order to characterize LDLR function and explore potential differences in patient efficacy and safety.

[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 all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, ECs/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/washout 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 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 ECs/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 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 trial 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 end of study. 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 end of study or within 168 days (24 weeks) of last study drug administration if the patient prematurely discontinued from the study - 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 end of study/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 nonserious, 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 (serious or non-serious) for evinacumab include the following:

- Anaphylactic reactions
- Allergic reactions and/or local injection site reactions that require consultation with another physician for further evaluation or requiring medical treatment
- Increase in ALT or AST: ≥3 x ULN (if baseline <ULN), or ≥2 times the baseline value (if baseline ≥ ULN)
- Pregnancy
- Symptomatic overdose with investigational medicinal product
- Neurocognitive events
- New onset of diabetes (see definition below)
- 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 times the 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 investigational medicinal product
- 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 (NOD) will be the following:
  - Type 1 or type 2 diabetes TEAE (grouping of Medical Dictionary for Regulatory Activities [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 NOD by default. For patients with several HbA1c measurements but only with the last one ≥6.5%, this single value ≥6.5% will be considered and qualify the patient as NOD by default.

  and/or

  - At least 2 values of fasting glucose ≥126 mg/dL (7.0 mmol/L). NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD. For patients with several fasting glucose measurements but only with the last one ≥126 mg/dL (7.0 mmol/L), this single value ≥126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD.

Refer to the study manual for the procedures to be followed.

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.

Refer to the study manual for the procedures to be followed.

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's 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, nonsteroidal anti-inflammatory drugs, 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.

9.5.2. Evaluation of Causality

Relationship of AEs to Blinded IV Study Drug:

The relationship of AEs to study drug will be assessed by the 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 AEs to SC PCSK9 Inhibitor Antibody (if applicable):

The relationship of AEs to a PCSK9 inhibitor antibody (if applicable) will be assessed by the 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 PCSK9 inhibitor antibody?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the PCSK9 inhibitor antibody

Related: There is a reasonable possibility that the event may have been caused by the PCSK9 inhibitor antibody

A list of factors to consider when assessing the relationship of AEs to a 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 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.

9.6. Safety Monitoring

The investigator will monitor the safety of study patients 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 (evinacumab), of any SAE that 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 double-blind period completion (ie, first-step analysis).

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

Let μ0 and μ1 be the population means of the percent change from baseline in calculated LDL-C at week 24 under placebo and evinacumab, respectively. The following null hypothesis and alternative will be tested:

$$H0 : \mu 0 = \mu 1$$
$$versus$$
$$H1 : \mu 0 \neq \mu 1$$

LDL-apheresis treatment (Yes/No), and geographical region (Japan, Rest of World) will be the 2 stratification factors for patient randomization, and will be accounted for in the statistical modeling for efficacy.

10.2. Justification of Sample Size

For the primary efficacy hypothesis during the DBTP, a total sample size of 57 patients (38 on evinacumab and 19 on placebo) will have 90% power to detect a treatment group difference in mean percent change LDL-C of 38% with a 0.05 two-sided significance level and assuming a common standard deviation (SD) of 35%. This sample size has been adjusted for a 5% non-evaluable patient rate for the primary efficacy endpoint, and a 15% dropout rate.

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

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

10.3.1.1. Intent-to-Treat

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

10.3.1.2. Modified Intent-to-Treat

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

- Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (ie, baseline).
- Availability of at least 1 calculated LDL-C value during the efficacy treatment period and within one of the analysis windows in the DBTP up to week 24. The efficacy

treatment period is defined as the time from the first double-blind study drug administration up to 35 days after the last double-blind study drug administration, or up to the first dose of the open-label study drug, whichever is earlier.

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

10.3.2. Safety Analysis Sets

10.3.2.1. Double-Blind Safety Analysis Set

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

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

10.3.2.2. Open-Label Safety Analysis Set

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

10.3.3. Other Analysis Sets

The PK and the ADA analyses will be performed on all randomized patients who received any study drug, and further:

- The PK analysis set will also require for each patient at least 1 non-missing post-baseline measurement of evinacumab concentration. Treatment assignments are based on the treatment received (placebo or evinacumab).
- The ADA analysis set will also require for each patient at least 1 evaluable ADA result collected after the first dose of study treatment. Treatment assignments are based on the treatment received (placebo or evinacumab).

10.4. Statistical Methods

10.4.1. Patient Disposition

The following data will be summarized:

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

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 DBTP, defined as at least 20 weeks of study treatment exposure and visit week 24 performed.
- The total number of patients who completed the OLTP, defined as at least 44 weeks of study treatment exposure and visit week 48 performed.
- The total number of patients who prematurely discontinued study treatment during the double-blind period, and the reasons for discontinuation.
- The total number of patients who prematurely discontinued study treatment during the open-label 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 infusion. 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 DBTP, demographic and baseline characteristics will be summarized descriptively by treatment group for patients in the ITT population. For the open-label 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. Continuous variables will be descriptively summarized with mean, median, SD, minimum, and maximum. Categorical variables will be descriptively summarized with frequency and percentage.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

The double-blind primary efficacy analysis will compare the evinacumab treatment group to placebo at week 24. The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to week 24 (ITT estimand). The percent change from baseline in calculated LDL-C will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 2 to week 24 analysis windows will be used

and missing data are accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group (placebo versus evinacumab), randomization strata (apheresis [Yes/No] and region [Japan, Rest of World]), time point (weeks 2, 4, 8, 12, 16, 20, 24), strata-by-time point interaction, and treatment by time point interaction, as well as, the continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction. The statistical testing of the comparison for the primary measure will be evaluated at a 2-sided significance level of 0.05. Model assumptions for distribution normality and equal variances between treatment groups will be explored prior to the analysis testing.

This model will be run using Statistical Analysis System (SAS) Mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least squares means estimates at week 24 for both treatment groups with their corresponding standard errors (SEs).

Robustness of the primary analysis statistical methods will be assessed through sensitivity analyses detailed in the SAP, including an on-treatment analysis of the percent change in calculated LDL-C from baseline to week 24 (ie, mITT patient population using calculated LDL-C values collected during the efficacy treatment period [on-treatment estimand]), and a different methodology for missing data. Specifically, a pattern mixture model (PMM) will be employed to assess the potential violation of the missing at random assumption. For the PMM, the imputation model will account for the differing missing value patterns based on calculated LDL-C collected in the presence or absence of study treatment administration for those patients randomized into the study.

10.4.3.2. Secondary Efficacy Analysis

For the key secondary efficacy endpoints (defined in Section 4.2.2) and other secondary efficacy endpoints (described in Section 4.2.3) collected in the DBTP, descriptive summaries and analyses will be performed in the ITT population, using values obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand).

For descriptive summaries, percent change, and when appropriate change from baseline, in calculated LDL-C, total-C, TG, non-HDL-C, Apo B, Lp(a), and Apo CIII 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 SEs.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (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 4.2.2 and Section 4.2.3 anticipated to have a normal distribution (ie, lipids other than TG and Lp[a]) will be analyzed 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 4.2.2 and Section 4.2.3 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 a 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 SE estimates. The combined mean difference between the treatment groups will be provided with the SE, 95% confidence interval (CI) and p-value.

III. Binary endpoints

Binary secondary efficacy endpoints defined in Section 4.2.2 and Section 4.2.3 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 a 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% CI 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 last observation carried forward (LOCF) 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 24 time window to impute the missing week 24 value.

10.4.3.3. Multiplicity Considerations

In order to address multiple key secondary efficacy endpoints (ie, other lipid parameters) collected in the double-blind period (Section 4.2.2 and Section 4.2.3) , the overall type-I error will be controlled by the use of a hierarchical inferential approach. Statistical significance of the primary parameter is required before drawing inferential conclusions about the first key secondary parameter at the 0.05 alpha level. Inferential conclusions about successive key secondary parameters require statistical significance of the prior parameter within the hierarchy. The hierarchy testing sequence will be provided in the SAP, prior to treatment unblinding. This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.05 level.

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

No adjustment will be made for the first step (Section 10.4.9.1) and second step (Section 10.4.9.2) statistical analyses, since the primary and key secondary efficacy endpoints will have been concluded at the time of the first step analysis.

10.4.3.4. Other Efficacy Endpoints

During the OLTP, efficacy variables will be explored through descriptive statistics at each scheduled visit for the total patients administered open-label study treatment (total), as well as by the patient subgroups of study treatment received in the DBTP (ie, evinacumab, placebo). Formal statistical testing is not planned. Descriptive statistics will include the same parameters as described for each variable in the DBTP.

For patients receiving evinacumab in the DBTP, a combined summary including both the double-blind and OLTP assessments may be considered, referencing the double-blind baseline for variable calculations. Prolonged time between last dose of double-blind treatment and first dose of open-label treatment will need to be taken into consideration when combining longitudinal efficacy data. Formal statistical testing is not planned.

10.4.3.5. Subgroup Analyses for the Primary Efficacy Endpoint

Analyses are planned on the primary efficacy endpoint to access the homogeneity of evinacumab treatment effect across various patient subgroups in the ITT population, including the 2 stratification factors LDL-C apheresis and region, and patients with or without receptor-negative mutations in both LDLR alleles. Statistical analysis methods will be provided in the SAP.

With respect to the subgroup analysis for region, the primary efficacy analysis MMRM model will be used to evaluate treatment effect in Japanese patients (as recorded in the electronic data capture [EDC] system) by adding the variables of treatment-by-region strata and treatment-by time point-by region strata interaction terms to the model. With this subgroup specific MMRM model, the primary efficacy endpoint LS mean at week 24 for the evinacumab treatment group will be provided for the Japanese patients, along with the corresponding SE and 95% CI. Due to the few Japanese patients (3) expected to be randomized to the placebo group, the evinacumab group LS mean point estimate will be used to access consistency of evinacumab effect between the Japanese patients and all evinacumab treated patients in this global study (provided by the primary efficacy analysis described in Section 10.4.3.1). The evinacumab primary efficacy endpoint LS mean point estimate for the Japanese patients is considered to show consistent efficacy results with the global study point estimate when the Japanese patient's LS mean point estimate is greater by a pre-specified amount (to be provided in the SAP) than the corresponding global study point estimate (ie, ratio of point estimate for Japanese patients divided by point estimate for the global study).

10.4.3.6. On-Treatment Efficacy Analyses

For key secondary efficacy endpoints (defined in Section 4.2.2) collected in the DBTP, descriptive summaries and analyses comparing treatment groups will be performed in the mITT population, using values obtained during the efficacy treatment period (on-treatment estimand). Statistical methods described above will be used to analyze each key secondary efficacy endpoint. P-values will be provided for descriptive purposes only.

10.4.4. Safety Analysis

For the double-blind period, summaries of safety results will be presented by treatment group for patients in the double-blind SAF. 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 DBTP (ie, evinacumab, placebo). No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed using the following common rule:

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

10.4.4.1. Adverse Events

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). The verbatim text, the preferred term (PT), and the system organ class (SOC) will be provided in patient listings.

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined from the day the ICF is signed to the day before the first dose of double-blind study treatment.
- The double-blind TEAE observation period is defined 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) (residual effect of treatment for IV dose regimen is expected until 24 weeks after the last dose of study drug) for those patients not proceeding into the OLTP, or up to the day before the first dose of open-label study treatment administration for those patients proceeding into the OLTP.
- The 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.
- The post-treatment observation 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

Adverse event incidence tables will present data by SOC sorted alphabetically and PT sorted by decreasing frequency, and summarize the number (n) and percentage (%) of patients experiencing an AE. 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 special interest for alirocumab treatment (ie, increase in ALT, etc)
- All TEAEs of special interest for evinacumab treatment (anaphylactic reaction, etc)
- 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 and 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 and 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 the quantitative analysis of laboratory and vital signs data in the double-blind period is defined from the day after the first dose of double blind study treatment to the day of the last dose of double-blind study treatment + 28 days for those patients not proceeding into the OLTP, or up to the day of the first dose of open-label study treatment administration for those patients proceeding into the OLTP.
- Open-label treatment period: The treatment period used for quantitative analysis of laboratory and vital signs data in the open-label study period is defined from the day after the first dose of open-label study treatment to the day of the last dose of open-label study treatment + 28 days.

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 SE may 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 PCSV criterion or criteria

For laboratory parameters for which a PCSV criterion is not defined, similar table(s) using the normal range will be provided, regardless of baseline level.

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

10.4.4.3. Treatment Exposure

The duration of study treatment exposure for the double-blind period will be calculated as:

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

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

- Patient 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 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, will be summarized by at least; mean, median, SD, and minimum/maximum. The categorical data for number of study treatment infusions (double-blind, open-label, and cumulative across the study) will be summarized by patient counts and percentages.

10.4.4.4. Treatment Compliance

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

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

Infusion frequency for the double-blind period will be summarized by at least; mean, median, SD, and minimum/maximum.

10.4.5. Analysis of Drug Concentration and Target Concentration Data

Descriptive statistics of evinacumab concentrations and total ANGPTL3 concentration and alirocumab and PCSK9 concentration at each sampling time will be provided by treatment group. Plots of mean concentrations (linear and log scales) versus time will be presented.

10.4.6. Analysis of Anti-Drug Antibody Data

Listings of ADA positivity and titers presented by patient, time point, and study treatment received 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 received.

The influence of ADA on drug concentrations will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

10.4.7. Analysis of Statin Concentration

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

[redacted]

10.4.9. Timing of Statistical Analyses

The analyses will be conducted in 2 steps:

10.4.9.1. First Step: Main Efficacy and Safety Analysis

The first analysis will be conducted as soon as all patients have been randomized and all data through week 24 (double-blind period) has been collected and validated. This first analysis will consist of the final analysis of the primary and secondary efficacy endpoints. The safety analysis will be performed on all safety data collected and validated at the time of the first analysis.

The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. Since data collection for the double-blind primary efficacy measure and key secondary efficacy measures will have been concluded at the time of this first analysis, the significance level

for the study remains at 0.05. This first analysis maybe used for the submission dossier 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: Final Safety Analysis

The second analysis will be conducted at the end of the OLTP (end of study) and will consist of the final analysis for safety and the OLTP exploratory efficacy measures.

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 planned 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 EDC tool, iMedidata 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
- 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 (refer to current version), 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.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness. The patient will give oral consent and the impartial witness 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.

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 their 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 approvals will also be sought where applicable under local 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 must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRFs 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, parallel-group study to evaluate the efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia", 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 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 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 study procedure or background treatment, etc.
- do not reappear or worsen when dosing with study drug or study procedure or background treatment, etc is resumed
- are not a suspected response to the study drug or 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 study procedure or background treatment, etc.
- resolve or improve after discontinuation of study drug or study procedure or background treatment, etc.
- reappear or worsen when dosing with study drug or study procedure or background treatment, etc is resumed
- are known or suspected to be a response to the study drug or study procedure or background treatment, etc, based upon preclinical data or prior clinical data

NOTE: This list is not exhaustive.

APPENDIX 2. SUMMARY OF TLC DIET FOR HIGH CHOLESTEROL

Total Fat	25% - 35% total calories*
Saturated fat*	<7% total calories
Polyunsaturated fat	up to 10% total calories
Monounsaturated fat	up to 20% total calories
Carbohydrates†	50% - 60% total calories*
Protein	~15% total calories
Cholesterol	<200 mg/dL (5.172 mmol/l)
Plant Sterols	2g
Soluble Fiber such as psyllium	10g - 25g

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat. Trans-fatty acids are another LDL-raising fat that should be kept at a low intake.

† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

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, parallel-group study to evaluate the efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia

Protocol Number: R1500-CL-1629

Protocol Version: R1500-CL-1629 Amendment 4A

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00089245 v1.0

ESig Approval	[redacted]nt 10-Oct-2019 22:25:00 GMT+0000
ESig Approval	[redacted] 11-Oct-2019 01:49:52 GMT+0000
ESig Approval	[redacted] 11-Oct-2019 10:28:39 GMT+0000
ESig Approval	[redacted]2019 19:04:57 GMT+0000

Signature Page for VV-RIM-00089245 v1.0 Approved

Clinical Study Protocol

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF EVINACUMAB IN PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Compound:	Evinacumab (REGN1500)
Clinical Phase:	3
Protocol Number:	R1500-CL-1629
Protocol Version:	R1500-CL-1629 Amendment 4B
Amendment 4B Date of Issue	*See appended electronic signature page*
Amendment 3B Date of Issue:	22 Jun 2018
Amendment 2B Date of Issue:	08 Dec 2017
Original Date of Issue:	07 May 2017

Scientific/Medical Monitor: [redacted]
Director, Clinical Sciences
Cardiovascular and Metabolism
Clinical Development and Regulatory Affairs
Regeneron Pharmaceuticals, Inc.
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[redacted]

AMENDMENT HISTORY

Amendment 4B

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 3.2.3 Risk/Benefit Assessment Section 6.2.2 Exclusion Criteria #24 Table 3 Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period. Table 4 Schedule of Events – Follow-up Period
Updated Scientific/Medical monitorr	Title page
Added abbreviation for women of child bearing potential	List of abbreviations

Amendment 3B

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

Rationale for Change	Sections Changed
Expanded Risk/Benefit section to include risk/benefit assessment of the combination of evinacumab and PCSK9 inhibitors, including alirocumab for the treatment of patients with homozygous familial hypercholesterolemia (HoFH).	Section 3.2.3 Risk/Benefit Assessment Section 21 References
Clarified the eligibility requirements by requiring that patients entering this study from R727-CL-1628 meet all of the eligibility criteria for this study. Clarified that patients enrolling from R727-CL1628 will continue to receive alirocumab 150 mg every 2 weeks (Q2W).	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Treatment(s) Section 5.1 Study Description and Duration Section 7.3 Background Treatments
To be consistent with the recommendations from the Clinical Trial Facilitation Group (CTFG) on contraception and pregnancy testing in clinical trials, added “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	Section 6.2.2 Exclusion Criteria #23

Rationale for Change	Sections Changed
only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception."	
Added exclusion criteria for patients housed in an institution on the basis of an administrative or judicial order and patients who are dependent on the sponsor, investigator or the study site.	Section 6.2.2 Exclusion Criteria #25, #26
Editorial or administrative edits	Section 5.1 Study Description and Duration Section 5.3.1 Independent Data Monitoring Committee Section 5.3.2 Clinical Events Committee Section 6.2.1 Inclusion Criteria #3 Section 7.6.1 Blinding Section 7.8.1 Prohibited Medications and Procedures Section 8.2.2 Efficacy Procedures Section 14.1 Good Clinical Practice Statement Section 14.2 Informed Consent

Amendment 2B

This replaces the Global protocol. The table below summarizes the changes to the protocol and the affected sections:

Rationale for Change	Sections Changed
Added a section on Risk/Benefit	Section 3.2.3 Risk/Benefit Assessment (new)
Added EQ-5D and HADS QOL questionnaires and an EQ-5D and HADS objective and exploratory endpoint to allow assessment of quality of life in this population	Section 2.3 Other Objectives Section 4.2.4 Other Endpoints Table 3 Schedule of Events - Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period Section 8.1.3 Footnotes for Schedule of Events Table 3 Section 8.2.3 Quality of Life Procedures (new) Section 8.2.3.1 EuroQol-5Questionnaire Section 8.2.3.2 Patient Assessed Hospital Anxiety and Depression Scale
Clarified language for apheresis requirements and collection of clinical laboratory samples relative to the timing of apheresis procedures, administration of PCSK9 inhibitor or mipomersen	Section 5.1 Study Description and Duration Section 6.2.1 Inclusion Criteria: #3 Section 8.1.3 Footnotes for Schedule of Events Table 3: #2
Clarified confirmation of patients HoFH status and added text for genotyping as well as a DNA sample for genotyping in the schedule of events	Section 5.1 Study Description and Duration Table 3 Schedule of Events - Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period
Clarified text for patients who transition from study R727-CL-1628 to this study and	Clinical Study Protocol Synopsis: Study Design Section 5.1 Study Description and Duration

Rationale for Change	Sections Changed
added a footnote to Table 3. Added consent and pharmacogenomics consent to schedule of events table	Table 3 Schedule of Events - Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period Section 8.1.3 Footnotes for Schedule of Events Table 3: #1
Clarified that patients should be on a maximally tolerated regimen of lipid modifying therapy	Clinical Study Protocol Synopsis: Population Section 6.2 Study Population Section 7.3 Background Treatment(s)
Added a footnote for timing of collection of vital signs on dosing days	Section 8.1.3 Footnotes for Schedule of Events Table 3: #5
Added Lipid Panel and Specialty Lipid Panel assessments and assessments of hematology, blood chemistry, and creatinine phosphokinase for the follow-up period	Table 4 Schedule of Events – Follow-up Period
Added a criterion excluding patients with LDL-C level <70 mg/dL as this is the goal for FH patients. Consequently, patients already at goal will be excluded. Update efficacy procedure for lipids Added criterion excluding members of the clinical site study team and/or his/her immediate family	Section 6.2.2 Exclusion Criteria: #1, #21 Section 8.2.2 Efficacy Procedures – (added LDL-C values below 25 mg/dL)
Clarified LDL apheresis therapy during the run-in period	Section 6.2.2 Exclusion Criteria: #3 Section 7.2 Run-in Treatments
Updated anti-drug antibody (ADA) variables and added a statement for follow-up of patients positive in the ADA assay Added ADA sample at week 4	Section 4.4 Anti-Drug Antibody Variables Section 8.2.5.2 Anti-Drug Antibody Measurements and Samples Table 3 Schedule of Events - Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period
Clarified collection of data regarding lipid modifying therapy	Section 6.2 Study Population Section 7.3 Background Treatment(s)
Modified text for lipid results	Section 8.2.2 Efficacy Procedures
Added a section of pregnancy testing	Section 8.2.4.6 Pregnancy Testing
Added sex hormones to assessments for adolescents	Table 1 Schedule of Events – Run-in and Screening Table 2 Schedule of Events – Screening for Patients with No Run-in Table 3 Schedule of Events - Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period Table 4 Schedule of Events – Follow-up Period Section 8.1.1 Footnotes for Schedule of Events Table 1: #4 Section 8.1.2 Footnotes for Schedule of Events Table 2: #4 Section 8.1.3 Footnotes for Schedule of Events Table 3: #6 Section 8.1.4 Footnotes for Schedule of Events Table 4: #2 Section 8.2.4.5 Laboratory Testing

Rationale for Change	Sections Changed
Modified timing of one assessments for weight and one assessment for PK	Table 3 Schedule of Events - Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period
Provided a definition for "new onset diabetes" as this is an adverse event of special interest (AESI) and expanded the list of AESIs for evinacumab	Section 9.4.3 Other Events that Require Accelerated Reporting
Clarified intent to treat population and updated methods of analysis to account for missing data	Section 10.3.1.1 Intent-to-Treat Section 10.4.3.1 Primary Efficacy Analysis
Query LMT Compliance added to the schedule of events tables	Table 1 Schedule of Events – Run-in and Screening Table 2 Schedule of Events – Screening for Patients with No Run-in Table 3 Schedule of Events - Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period Table 4 Schedule of Events – Follow-up Period
Edits/Clarifications	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Duration Clinical Study Protocol Synopsis: Population Section 1 Introduction Section 3.2.1 Rationale for Study Design Section 4.2.1 Primary Efficacy Endpoint Section 5.1 Study Description and Duration and Synopsis, Study Duration Figure 1 Study Flow Diagram Section 6.2.2 Exclusion Criteria Section 7.4.2 Study Drug Discontinuation Section 7.6 Method of Treatment Assignment Section 7.6.1 Blinding Section 7.7.1 Packaging, Labeling, and Storage Section 7.8.1 Prohibited Medications and Procedures Section 7.8.2 Permitted Medications and Procedures Section 8.1 Schedule of Events (Tables) Section 8.1.1 Footnotes for Schedule of Events Table 1: #2, #7 Section 8.1.2 Footnotes for Schedule of Events Table 2: #2 Section 8.1.3 Footnotes for Schedule of Events Table 3: #2, #3 Section 8.1.5 Early Termination Visit Section 8.2.4.1 Vital Signs Section 8.2.7.2 DNA Sample and HoFH Genotyping Section 10.4.3.2 Secondary Efficacy Analysis Section 10.4.4.1 Adverse Events

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia
Site Location(s)	Approximately 30 sites multinationally
Principal Investigator	Multi-center
Objective(s)	The **primary objective** of the study is: • To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by evinacumab 15 mg/kg intravenously (IV) in comparison to placebo after 24 weeks in patients with homozygous familial hypercholesterolemia (HoFH). The **secondary objectives** of the study are: • To evaluate the effect of evinacumab 15 mg/kg IV on other lipid parameters (ie, apolipoprotein B [Apo B], non-high-density lipoprotein cholesterol [HDL-C], total-cholesterol [TC]) in patients with HoFH • To evaluate the effect of evinacumab on LDL-C goal attainment • To assess the effect of evinacumab on eligibility for apheresis (using German and US apheresis criteria) • To evaluate the safety and tolerability of evinacumab 15 mg/kg in patients with HoFH • To assess the pharmacokinetics (PK) of evinacumab in patients with HoFH • To evaluate the potential development of anti-evinacumab antibodies
Study Design	The study consists of the following periods: up to 8-week run-in period (for patients who may require HoFH genotyping, for patients whose background medical lipid modifying therapy (LMT) has not been stable prior to screening or whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a 2-week screening period, a 24-week double-blind treatment period (DBTP), and a 24-week open-label treatment period (OLTP), and a 24-week follow-up period after the last dose of study drug for those patients who choose not to enter the open-label study. Patients who are not undergoing apheresis therapy, patients who have been

	on a stable apheresis schedule for at least 8 weeks before the screening visit, and patients on stable background medical LMT (as applicable) for at least 4 weeks (6 weeks for fibrates, 8 weeks for proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor antibodies, 12 weeks for lomitapide, 24 weeks for mipomersen) before the screening visit, will enter a 2-week screening period. Patients who participated in the R727-CL-1628 study may enter the run-in or screening period or enroll directly into this study. Patients who completed the R727-CL-1628 study and fulfill all of the eligibility criteria can be enrolled directly into this study. Data collected during the R727-CL-1628 study (ie, lab test results) can be used to assess eligibility criteria for these patients. If these patients meet all the eligibility criteria and if approved by the sponsor, the patients may not have to undergo the screening visit in this study. In this case, overlapping assessments completed at the end-of-open-label treatment visit in R727-CL-1628 do not need to be repeated during the R1500-CL-1629 baseline visit. The baseline/day 1 visit can occur immediately after the end of the open-label treatment visit in the R727-CL-1628 study. To ensure continuity of treatment with alirocumab, all patients from R727-CL-1628 entering this study will be provided alirocumab. Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized 2:1 to receive evinacumab 15 mg/kg IV every 4 weeks (Q4W) or matching placebo IV Q4W for the double-blind portion of the study (24 weeks). Randomization will be stratified by apheresis treatment (Yes, No) and by region (Japan, Rest of World). After completion of the DBTP, all patients will enter a 24-week OLTP and receive open-label evinacumab 15 mg/kg IV Q4W. After completion of the 24-week OLTP, all patients who have successfully completed this study might have the opportunity to participate in a separate open-label (OL) study. All patients that enroll in the separate OL study will continue to receive open-label evinacumab at a dose of 15 mg/kg IV Q4W. Those patients who do not participate in the separate open-label study will undergo a 24-week follow-up after the last dose of study drug.
Study Duration	The duration of the study including run-in (8 weeks), screening (2 weeks), DBTP and OLTP (48 weeks), and follow-up (20 weeks) periods may be up to 78 weeks.
Population	
Sample Size:	Approximately 57 patients will be randomized at approximately 30 multinational sites
Target Population:	The study population will consist of males and females ≥12 years of age diagnosed with homozygous FH (HoFH), receiving stable lipid modifying

therapy (LMT), as applicable. Patients should be on a maximally tolerated daily statin, ezetimibe, and a PCSK9 inhibitor antibody unless the patient has a documented history of tolerability issues, little to no response to therapy or other documented reason. Lipid modifying therapies may also include other lipid lowering therapies, including low-density lipoprotein (LDL)-apheresis.

Treatment(s)

Study Drug Dose/Route/Schedule:

In the double-blind treatment period, eligible patients will be enrolled to receive evinacumab 15 mg/kg IV Q4W

In the open-label portion of the study, all patients will receive evinacumab 15 mg/kg IV Q4W starting at week 24

Placebo Route/Schedule:

In the double-blind treatment period, placebo matching IV evinacumab Q4W

Background Treatment Dose/Route/Schedule:

Patients who are on LMT or who are undergoing apheresis should maintain stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study, from screening to the end of double-blind treatment period visit (week 24), and continuing through week 48 of the open-label treatment period.

Patients who enter this study after completing study R727-CL-1628 will continue to receive alirocumab 150 mg subcutaneous (SC) every 2 weeks (Q2W) for the duration of the study.

Endpoint(s)

Primary:

The primary endpoint is the percent change in calculated LDL-C from baseline to week 24.

Secondary:

- The percent change in Apo B from baseline to week 24
- The percent change in non-HDL-C from baseline to week 24
- The percent change in TC from baseline to week 24
- The proportion of patients with ≥30% reduction in LDL-C at week 24
- The proportion of patients with ≥50% reduction in LDL-C at week 24
- The proportion of patients with LDL-C <100 mg/dL (2.59 mmol/L) at week 24
- The change in calculated LDL-C from baseline to week 24
- The proportion of patients who meet EU apheresis eligibility criteria (see German Apheresis Working Group) from baseline to week 24
- The proportion of patients who meet US apheresis eligibility criteria (see US [National Lipid Association] Lipid Apheresis

	Criteria) from baseline to week 24
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. Overall safety will be assessed by monitoring/evaluation of treatment-emergent adverse events (TEAEs), physical examinations, vital signs, electrocardiogram (ECG), Tanner stage (for adolescents only), and clinical safety laboratory tests at pre-specified time points. The potential emergence of anti-evinacumab antibodies will also be evaluated.
Statistical Plan	**Sample Size Determination** For the primary efficacy hypothesis during the double-blind treatment period, a total sample size of 57 patients (38 on evinacumab and 19 on placebo) will have 90% power to detect a treatment group difference in mean percent change LDL-C of 38% with a 0.05 two-sided significance level and assuming a common standard deviation of 35%. This sample size has been adjusted for a 5% non-evaluable patient rate for the primary efficacy endpoint, and a 15% dropout rate. **Primary Efficacy Analysis** The double-blind primary efficacy analysis will compare the evinacumab 15 mg/kg IV treatment group to placebo at week 24. The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to week 24. The percent change from baseline in calculated LDL-C will be analyzed in the ITT (intent-to-treat) population (defined as all randomized patients who had an evaluable primary endpoint, regardless of adherence to study treatment) using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 2 to week 24 analysis windows will be used and missing data are accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group (placebo versus evinacumab), randomization strata, time point, 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. The statistical testing of the comparison for the primary measure will be evaluated at a 2-sided significance level of 0.05. **Subgroup Analyses for the Primary Efficacy Endpoint**. Analyses are planned on the primary efficacy endpoint to access the homogeneity of evinacumab treatment effect across various patient subgroups in the ITT population, including the 2 stratification factors LDL-C apheresis and region, and patients with or without receptor-negative mutations in both low-density lipoprotein receptor (LDLR) alleles. Statistical analysis methods will be provided in the statistical analysis plan (SAP) Statistical analyses will be conducted in 2 steps. The first analysis will be conducted as soon as all patients have been randomized and all data through week 24 (double-blind period) have been collected and validated. This first analysis will consist of the final analysis of the primary and secondary efficacy endpoints. The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. Since data collection for the

	double-blind primary efficacy measure and key secondary efficacy measures will have been concluded at the time of this first analysis, the significance level for the study remains at 0.05. The second analysis will be conducted at the end of the open-label treatment period (end of study) and will consist of the final analysis for safety and open-label treatment period exploratory efficacy measures.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANGPTL3	Angiopoietin-like 3
Apo A-1	Apolipoprotein A-1
Apo B	Apolipoprotein B
ApoCIII	Apolipoprotein CIII
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CEC	Clinical Events Committee
CI	Confidence interval
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CV	Cardiovascular
CVD	Cardiovascular disease
DBTP	Double-blind treatment period
EC	Ethics Committee
ECG	Electrocardiogram
EOT	End of treatment
EDC	Electronic data capture
FH	Familial hypercholesterolemia
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolemia
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenously

IVRS	Interactive voice response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LDLRAP1	Low-density lipoprotein receptor adaptor protein 1
LMT	Lipid modifying therapy
LOF	Loss-of-function
Lp(a)	Lipoprotein a
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed-effect model with repeated measures
MTD	Maximum tolerated dose
OL	Open-label
OLTP	Open-label treatment period
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PMM	Pattern Mixture Model
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMT	Safety Monitoring Team
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TC	Total cholesterol

TEAE	Treatment-emergent adverse event
TG	Triglyceride
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of child bearing potential

1. INTRODUCTION

Homozygous familial hypercholesterolemia (HoFH) is a rare and serious genetic condition resulting in severely elevated low-density lipoprotein cholesterol (LDL-C) and accelerated cardiovascular disease (CVD). Familial hypercholesterolemia results from mutations in the low-density lipoprotein receptor (LDLR), or in 3 associated genes: proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (Apo B), and LDLR adaptor protein 1 (LDLRAP1). Regardless of the underlying mutations, patients with familial hypercholesterolemia (FH) are phenotypically similar, but vary with respect to severity of the condition. Mutations in LDLR, PCSK9, and Apo B have a dominant mode of transmission, while mutations in LDLRAP1 have a recessive mode of transmission (http://omim.org/entry/143890, http://omim.org/entry/603813). The vast majority of mutations that lead to FH derive from mutations in the LDLR (between 60-80%) (Youngblom 1993).

Homozygous FH is frequently caused by mutations in both alleles of the LDLR gene and results in the decreased clearance of LDL particles from plasma. Patients with HoFH have severe hypercholesterolemia, often 3 to 6 times normal (500 to 1000 mg/dL), which can lead to an exceedingly high risk of developing premature atherosclerosis, as well as valvular and supravalvular stenosis. In children as young as 7 years of age, mild coronary atherosclerosis can be evident even without any clinically apparent coronary artery disease. This accelerated atherosclerosis results in premature CVD and an increased risk of a cardiovascular (CV) event. A recent observational study of HoFH patients demonstrated that the mean age for first major CV event was 20 years (Goldstein 2001, Kolansky 2008, Macchiaiolo 2012, Rader 2003).

Patients with HoFH tend to be treated with multiple lipid-lowering medications in order to try and attain LDL-C levels that are closer to optimal for adults. Consensus statements recommend starting drug treatment as soon as possible and targeting LDL-C goals of <70 mg/dL or <100 mg/dL depending on risk (Cuchel 2014, France 2016). Many of the therapies for hypercholesterolemia are dependent on their stimulating an increase in activity of the LDLR. Part of the basis for the refractory nature of treatments is linked to the mutations in the LDLR that are the driver of HoFH.

Low-density lipoprotein cholesterol-lowering therapies in patients with HeFH and a single mutation in the LDLR can rely on the normally functioning LDLR allele to provide similar efficacy as in non-FH patients. However, the presence of mutations in both LDLR alleles can result in far less efficacy for therapies that rely on the LDLR as part of their mechanism of action. Examples of such therapies include statins and PCSK9 inhibitor antibodies. Mutations in the LDLR can range from being defective (where the LDLR retains some LDL-binding functionality) to null or negative mutations where no functioning LDLR is expressed. Residual LDLR activity ranges from <2% for patients who are receptor negative to 2-25% for patients who are LDLR defective (Cuchel 2014). In the most extreme cases are patients with two null/negative LDLR mutations. These patients tend to have higher LDL-C levels and worse clinical outcome than patients who are LDLR defective (Kolansky 2008, Moorjani 1993). Patients who are LDLR negative develop xanthomas sooner than patients who are LDLR defective, and untreated patients who are LDLR negative rarely live past the second decade (Kolansky 2008, Moorjani 1993). These patients tend to have untreated LDL-C levels at the highest end of the range and in many cases see no efficacy from drugs such as statins or PCSK9

inhibitor antibodies because of their near total lack of functional LDLRs (Marais 2008, Raal 2000, Raal 1997).

While statins can reduce LDL-C by more than 50% in patients with HeFH or with polygenic forms of hypercholesterolemia, in HoFH patients, statins may provide a decrease of <15 to 30% (Crestor 2003, Lipitor 1996, Zocor 1991). When ezetimibe is added to a statin, LDL-C may be reduced by 21 to 27% (Zetia 2002), but many patients with HoFH treated with a high-dose statin and ezetimibe remain far from their LDL-C goal. In patients with little or no LDLR activity, including patients with null/null mutations, statins provide minimal efficacy. Some patients who are receptor-negative (LDLR activity<2%) may respond to statin therapy (Raal 2000), but the degree of response tends to be less than those patients with residual LDLR function (Rader 2003).

Although anti-PCSK9 therapy provides an effective treatment in patients with HeFH and polygenic causes of hypercholesterolemia, it appears to be minimally effective in the HoFH patient. In the recent TESLA study in patients with HoFH, evolocumab therapy resulted in a mean percent reduction in LDL-C of 23.1% (Raal 2015). In the subset of patients known to have two LDLR negative alleles, no response was observed with evolocumab (Repatha 2015).

Other therapies for HoFH, mipomersen and lomitapide, can provide an additional ~25% and 40% reduction in LDL-C, respectively. However, these therapies are associated with high rates of gastrointestinal side effects (lomitapide), hepatic abnormalities including hepatic steatosis and increases in liver function tests (lomitapide and mipomersen) and frequent injection site reactions (mipomersen) (Cuchel 2013, Raal 2010).

High-dose statins, ezetimibe, anti-PCSK9 monoclonal antibodies (mAb), mipomersen, and lomitapide may be effective in some patients with HoFH, but many patients still require lipid apheresis (Goldberg 2011). Lipid apheresis can be effective, but entails treatments lasting several hours multiple times a month, is both costly and associated with a risk of infections (Vella 2001, Kajinami 1999), and is not routinely available in all geographical areas (Thompson 2010).

Despite treatment with lipid modifying therapies (LMTs), such as pharmacological agents, as well as mechanical removal by lipid apheresis, many patients with HoFH remain far from their LDL-C treatment goal. Therefore, the need for more intensive treatment in HoFH, especially those patients with double null mutations remains.

Angiopoietin-like 3 (ANGPTL3) has recently emerged as a potential target for the treatment of elevated levels of triglycerides (TGs) and for the treatment of elevated levels of LDL-C, both risk factors for the development of CVD. ANGPTL3 acts as a natural inhibitor of lipoprotein lipase, an endothelial-bound enzyme involved in the hydrolysis of the TG content of very-low-density lipoproteins and chylomicron lipoproteins. Patients who are homozygous for loss-of-function (LOF) mutations in ANGPTL3 have lower levels of LDL-C (mean difference of 48% versus control family members). The mechanism by which ANGPTL3 LOF mutations result in lowered LDL-C levels is not fully understood, but appears to be independent of the effects on TGs and independent of the LDLR. It is noteworthy that patients with one or two ANGPTL3 LOF alleles also have reported reductions in serum high-density lipoprotein (HDL) cholesterol (HDL-C) levels. The mechanism for this may be related to the inhibitory effect of ANGPTL3 on endothelial lipase, which is involved in the hydrolysis of HDL phospholipids. Importantly, no health deficits have been reported in the relatively small number of patients who

are homozygous for ANGPTL3 LOF mutations. These data suggest that inhibiting ANGPTL3 may be a meaningful and well-tolerated strategy for lowering serum LDL-C and TGs.

Evinacumab (REGN1500) is a fully human mAb, created with Regeneron's VelocImmune technology platform, which specifically binds to ANGPTL3. Experiments performed in animals demonstrate that the administration of evinacumab results in a reduction of serum LDL-C and serum TGs. In hyperlipemic mice models (ApoE -/-, Ldlr -/-, db/db), single administrations of evinacumab led to reductions in LDL-C, TGs, and HDL-C up to 49%, 72%, and 39%, respectively. Specifically in mice that have absent LDLR function (Ldlr -/- mice), administration of evinacumab resulted in a 23% reduction in LDL-C. Therefore, it appears that ANGPTL3 inhibition lowers LDL-C through an LDLR-independent mechanism.

In a phase 1, first-in-human, placebo-controlled, double-blind, ascending single-dose study (R1500-HV-1214) of the safety, tolerability, and bioeffect of evinacumab administered subcutaneously (SC) or intravenously (IV) in healthy volunteers with modest elevations in TGs and/or LDL-C at baseline, 99 subjects received placebo or evinacumab at 1 of the following dose levels: 75 mg SC, 150 mg SC, 250 mg SC, 5 mg/kg IV, 10 mg/kg IV, or 20 mg/kg IV. Among these subjects with elevations of TG levels 150 to 450 mg/dL (1.69 mmol/L to 5.09 mmol/L) and/or LDL-C $\geq$ 100 mg/dL (2.59 mmol/L), 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). A maximal mean percent HDL-C decrease from baseline of 27.3% was observed on day 15 in the 10 mg/kg IV group (n=9) compared to a 1.8% decrease in the placebo IV group (n=12). For all subjects in the 20 mg/kg IV group (n=11), the median percent decrease in TG from baseline on day 4 was 75.0% vs an increase of 9% in the placebo IV group (n=12). Evinacumab was well tolerated at all dose levels.

In a randomized, double-blind, placebo-controlled, multiple ascending dose study (R1500-CL-1321) of the safety, tolerability, pharmacokinetics (PK), immunogenicity, and pharmacodynamic (PD) effects of evinacumab in subjects with mixed dyslipidemia (TGs 150-500 mg/dL [1.69 mmol/L to 5.09 mmol/L] and LDL-C $\geq$ 100 mg/dL [2.59 mmol/L]), subjects who received evinacumab 20 mg/kg IV every 4 weeks (Q4W) achieved a mean percent reduction from baseline in LDL-C of 34.7% at day 57. Those patients who received evinacumab 300 mg SC every 2 weeks (Q2W) achieved a mean percent reduction in LDL-C of 33.4% from baseline. Evinacumab was well tolerated in doses up to 20 mg/kg IV Q4W.

In an open-label, single-arm, proof-of-concept study in patients with HoFH, (Study R1500-CL-1331), evinacumab demonstrated a mean percent reduction from baseline of 49.2% (n=9) at week 4, with a duration of effect of at least 10 weeks after a 15 mg/kg IV dose (n=7). A peak mean reduction of 52.1% was observed at week 6. Three patients enrolled in Study R1500-CL-1331 are homozygous for null mutations in the LDLR. Evinacumab provided meaningful reductions in LDL-C in these 3 null/null HoFH patients (26-44% percent change in LDL-C by week 4). Evinacumab has been well tolerated in this proof-of-concept study.

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 demonstrate the reduction of LDL-C by evinacumab 15 mg/kg IV in comparison to placebo after 24 weeks in patients with HoFH.

2.2. Secondary Objectives

The secondary objectives of the study are:

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

2.3. Other Objective

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

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Blockade of ANGPTL3 with evinacumab will reduce LDL-C in patients with HoFH.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is intended to demonstrate efficacy and safety of evinacumab in the treatment of HoFH. The study population will include individuals ≥12 years of age. Because this disease is characterized by severe hypercholesterolemia from birth and, subsequently, the onset of premature CVD during childhood, the HoFH population includes children and adolescents. Allowing individuals ≥12 years of age to enroll in this study will ensure the study population is reflective of the patient population manifesting disease in adolescence and adulthood. Diagnosis

of HoFH will be based on either genotyping or clinical criteria. The genetic definition will include all individuals considered to be FH homozygotes, which is defined by the presence of the same mutation(s) in both LDLRs, Apo B, PCSK9, or LDLRAP1 alleles, or individuals considered to be compound heterozygotes, defined by the presence of different mutations in the same allele, or double heterozygotes, defined as mutations in different genes.

The percent change in LDL-C from baseline to week 24 will be the primary endpoint. LDL-C is an accepted surrogate endpoint for CV risk, and has repeatedly been used as the primary endpoint for approval of multiple other HoFH treatments. This study is designed as a placebo-controlled trial with the addition of evinacumab on top of patients' existing treatment regimens of maximally tolerated LMT, including lipid apheresis. This study will utilize a run-in period for those patients whose LMT regimen is not stable. This "add-on" design is appropriate because removal of any therapies from patients' existing treatment regimen will lead to an increase in LDL-C and possibly contribute to the serious CV sequelae seen in this severe disease with high CV risk.

The study consists of 4 periods: screening, run-in (for patients whose background medical LMT has not been stable for at least 4 weeks prior to screening or whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), double-blind treatment, and open-label treatment. In the 24-week double-blind treatment period (DBTP), patients will receive evinacumab 15 mg/kg IV Q4W or matching placebo IV Q4W.

In order to provide additional safety, PK, and long term efficacy information on evinacumab in this rare patient population, after completion of the DBTP, all patients will enter a 24-week open-label treatment period (OLTP). During the OLTP portion of the study, all patients, regardless of treatment assignment in the DBTP, will receive evinacumab 15 mg/kg IV every month.

3.2.2. Rationale for Dose Selection

The 15 mg/kg IV dose is selected based on safety and the substantial LDL-C reduction observed in HoFH patients in study R1500-CL-1331. The higher dose regimen of 20 mg/kg IV Q4W demonstrated favorable tolerability when given as an 8-week treatment in otherwise healthy subjects (R1500-CL-1321) and so the 15 mg/kg IV Q4W regimen is expected to also demonstrate favorable tolerability, because the evinacumab exposure within each dosing interval is expected to be lower and the accumulation of serum concentration with a monthly dosing frequency is predicted to be minimal. From an efficacy perspective, the 15 mg/kg IV dose has previously demonstrated evinacumab concentrations above 100 mg/L for approximately 4 weeks; an exposure threshold associated with target saturation and maximal effect on TG reduction (R1500-CL-1321 and R1500-HV-1214). Based on these PK/PD data, combined with the efficacy data from the proof-of-concept study in HoFH (R1500-CL-1331), 15 mg/kg IV is expected to maintain target saturation and thereby to provide maximal benefit during the monthly dosing interval.

Evinacumab has not previously been administered to patients aged 12 to 17 years. In adults, its PK profile indicates that systemic elimination is the result of a combination of concentration-independent (linear) clearance and concentration-dependent (nonlinear) target-mediated clearance. Typically, linear clearance for immunoglobulin G antibodies is similar between adults and adolescents, after adjusting for body weight. The comparison of

nonlinear clearance between adolescents and adults is less well understood. However, at the proposed dose of 15 mg/kg IV, it is expected that the target will be essentially saturated, hence linear clearance will be the main determinant of evinacumab exposure. Therefore, the 15 mg/kg dose is expected to yield exposure in the adolescent patients that is similar to what has been shown to be associated with efficacy and tolerability in adults.

3.2.3. Risk / Benefit Assessment

Patients with HoFH have extremely high LDL-C levels, are far from their target level and will require significant reductions to get to their goal. Despite the approval of newer treatments including evolocumab, lomitapide and mipomersen, the need for more intensive therapies remains. Evinacumab could be a new addition to the armamentarium of LMT that could contribute to lowering the LDL-C of patients with HoFH. As mentioned above, in study R1500-CL-1331, evinacumab demonstrated a mean percent reduction from baseline of 49.2% (n=9) at week 4, with a duration of effect of at least 10 weeks after a 15 mg/kg IV dose (n=7). A peak mean reduction of 52.1% was observed at week 6. Three patients in the study are homozygous for null mutations in the LDLR. Treatment with evinacumab in these difficult-to-treat patients reduced LDL-C by an average of 37.3% at week 4 with peak reductions up to 59.5%. Based on these data, it is expected that the addition of evinacumab to existing treatments will lead to significant LDL-C reductions in the HoFH population. 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). Moreover, the results from the recent outcomes trials with ezetimibe (IMPROVE-IT [Cannon 2015]), alirocumab (ODYSSEY OUTCOMES [Steg 2018]) and evolocumab (FOURIER [Sabatine 2017]) reinforce this concept, providing additional evidence for the relationship between LDL-C lowering and reductions in CV events and the importance for patients to achieve their target LDL-C. Within the context of this study in the HoFH patient population, additional reduction in LDL-C may get patients closer their LDL-C target, which could translate into significant benefits.

It is also 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.

Patients entering this study should be on a background statin, ezetimibe, and a PCSK9 inhibitor, unless they have a documented history of tolerability issues, lack of efficacy, or other reason. Patients should be on these lipid lowering drugs because of the above mentioned proven CV risk reduction demonstrated in recent CV outcomes trials (ODYSSEY OUTCOMES, FOURIER, IMPROVE-IT). There are 2 PCSK9 inhibitors on the market; evolocumab is approved for use in patients with HoFH in most countries, and alirocumab is currently being evaluated in a double-blind placebo-controlled study in patients with HoFH (study R727-CL-1628, ODYSSEY HoFH). Patients entering this study may be taking either evolocumab or alirocumab. Patients

who complete study R727-CL-1628 (ODYSSEY HoFH) with alirocumab are permitted to participate in this study and will continue to receive alirocumab as part of their background LMT. The concurrent use of evinacumab with alirocumab is considered to have an acceptable benefit/risk profile because it could be beneficial and is not considered to pose any safety concerns.

Evinacumab and alirocumab have different mechanisms of action and concomitant administration of both agents is not expected to perturb the action of the other. Rather, their distinct mechanisms of action are anticipated to complement each other to lower LDL-C since they work at different sites of action.

The safety profile of each agent is considered acceptable and the concurrent use of the 2 agents together is not expected to augment or exacerbate potential adverse events (AEs). Concomitant use of evinacumab and evolocumab was found to have an acceptable safety profile in 4 patients in the R1500-CL-1331 study, a study evaluating evinacumab in 9 patients with HoFH (details of the study are provided in the evinacumab Investigator's Brochure and the Introduction [Section 1]). No safety signals or adverse effects related to the concomitant use of both agents have been observed. The safety of the use of evinacumab along with alirocumab will be carefully monitored in this study. Safety monitoring will include ongoing reviews by an unblinded Independent Data Monitoring Committee (IDMC), by the sponsor's blinded safety monitoring team (SMT), and by the blinded clinical study team. If significant safety trends or findings are identified by either the IDMC or the sponsor's blinded study team or SMT, they will be escalated and appropriately evaluated to understand the best course of action.

From the perspective of PK drug-drug interactions, co-administration of evinacumab, alirocumab, and the other possible background LMT (statin, ezetimibe, etc) is not expected to result in drug-drug interactions with each other or other drugs. Evinacumab and alirocumab are both eliminated via a combination of non-saturable, linear, proteolytic degradation and saturable, non-linear target-mediated clearance. The 2 molecules bind to different targets and the target-mediated pathways are entirely independent. Neither evinacumab nor alirocumab are a cytokine or cytokine modulator; therefore, it is not anticipated to interact directly or indirectly with cytochrome P450 enzymes, other drug metabolizing enzymes or drug transporters, which are known to influence the disposition of statins. Conversely, the PK of evinacumab is not expected to be impacted by statins, due to its elimination pathways.

Indeed, the concomitant administration of 2 fully human monoclonal antibodies may be a new treatment paradigm in CV medicine, but not uncommon in other therapeutic areas such as autoimmune disease or oncology. Experience in those areas has demonstrated the use of multiple biologic agents to be acceptable from a safety and tolerability perspective.

For the reasons stated above, the benefit/risk profile for the concurrent use of evinacumab and PCSK9 inhibitor antibodies or the use of evinacumab in the absence of a PCSK9 inhibitor antibody as part of the background LMT is considered favorable.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), lipid levels, medical history (including allergic history), mutation status, medication history, and apheresis schedule (if applicable) for each patient. Patients' history on other medications for treatment of HoFH will be documented on a specific page of the case report form (CRF).

4.2. Primary and Secondary Endpoints

4.2.1. Primary Efficacy Endpoint

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

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

All calculated LDL-C values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the primary efficacy endpoint, if appropriate, according to the above definition. The analysis window used to allocate a time point to a measurement will be defined in the statistical analysis plan (SAP).

4.2.2. Key Secondary Efficacy Endpoints

The key secondary endpoints are:

- The percent change in Apo B from baseline to week 24 (ITT estimand)
- The percent change in non-HDL-C from baseline to week 24 (ITT estimand)
- The percent change in TC from baseline to week 24 (ITT estimand)
- The proportion of patients with ≥ 30% reduction in calculated LDL-C at week 24 (ITT estimand)
- The proportion of patients with ≥ 50% reduction in calculated LDL-C at week 24 (ITT estimand)
- The proportion of patients with LDL-C <100 mg/dL [2.59 mmol/L] at week 24 (ITT estimand)
- The change in calculated LDL-C from baseline to week 24 (ITT estimand)
- The proportion of patients who meet EU apheresis eligibility criteria (see German Apheresis Working Group) at week 24 (ITT estimand)
- The proportion of patients who meet US apheresis eligibility criteria (see US [National Lipid Association] Lipid Apheresis Criteria) at week 24 (ITT estimand)

4.2.3. Other Secondary Efficacy Endpoints

- The percent change in TG from baseline to week 24 (ITT estimand)
- The change in Apo B from baseline to week 24 (ITT estimand)
- The change in non-HDL-C from baseline to week 24 (ITT estimand)
- The change in TC from baseline to week 24 (ITT estimand)
- The percent change in lipoprotein a [Lp(a)] from baseline to week 24 (ITT estimand)
- The proportion of patients with LDL-C <70 mg/dL [1.81 mmol/L] at week 24 (ITT estimand)
- The percent change in apolipoprotein CIII (Apo CIII) from baseline to week 24 (ITT estimand)

National Lipid Association (US) [Goldberg 2011]	**German Apheresis Working Group (EU) [Schettler 2012]**
• Patients have inadequate response to diet and LMTs after 6 months of treatment • Functional HoFH or HeFH (with 0-1 risk factor) with LDL-C ≥300 mg/dL (7.77 mmol/L)[1]	• Patients have inadequate response to diet and LMTs after 3 months of treatment • *Primary prevention* – FH with LDL-C >160 mg/dL (4.2 mmol/L) and CV events in close relatives • *Secondary prevention* – Patients with progressive CV events with LDL-C >120 to 130 mg/dL (3.1-3.4 mmol/L)

[1] Risk factors include age, elevated TC and LDL-C, low HDL-C, male sex, smoking, metabolic syndrome, diabetes, hypertension, and family history of CVD

4.2.4. Other Endpoints

- The change in hemoglobin A1c (HbA1c [%]) from baseline to week 24
- Response of each EQ-5D item, index score, and change of index score from baseline through week 24.
- Response on Hospital Anxiety and Depression Scale (HADS) from baseline through week 48.

4.3. Pharmacokinetic Variables

The PK variable is total evinacumab concentration in serum.

4.4. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) status will be assessed.

- Treatment emergent response - defined as a positive response post-first dose in the ADA assay when baseline ADA 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 the baseline titer levels when baseline ADA results are positive.

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

Samples positive in the ADA assay will be assessed for titer:

- 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 phase 3 study consists of the following periods: an up to 8-week run-in period (for patients who may require HoFH genotyping, for patients whose background medical LMT has not been stable prior to screening or whose apheresis settings and/or schedule have not been stable for at least 8 weeks prior to screening), a 2-week screening period, a 24-week DBTP, a 24-week OLTP, and a follow-up period for 24 weeks after the last dose of study drug, for those patients who decide not to enter an optional open-label study (Figure 1). The total duration of the run-in, screening, DBTP and OLTP may be up to 78 weeks .

Run-In:

Apheresis therapy - Patients who are undergoing apheresis therapy must be on a stable weekly (every 7±1 days) or every other week (every 14±2 days) schedule. Patients whose schedule and/or apheresis settings have not been stable for at least 8 weeks before the screening visit, will enter an 8-week run-in period before the screening period. After the 8-week run-in period, patients whose lipid apheresis schedule remains stable will be eligible to enter the 2-week screening period.

Lipid modifying therapy - Patients who are on background LMT (excluding lomitapide and mipomersen) that has not been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibody) before the screening visit will enter a 4-week (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibody) run-in period to stabilize their LMT before entering the screening period. For patients taking mipomersen or lomitapide, patients who have not been on a stable dose of mipomersen for 24 weeks prior to screening or on a maximum tolerated dose (MTD) of lomitapide for 12 weeks prior to screening are excluded.

Genotyping – Confirmation of a patient's HoFH status can be made by either genetic or clinical criteria. If HoFH diagnosis cannot be confirmed by the clinical criteria listed or from previous genotyping results, patients can enter the run-in period to determine their mutation status in advance of screening, if deemed appropriate by the investigator.

Screening:

Patients who are not undergoing apheresis therapy, patients who have been on a stable apheresis schedule for at least 8 weeks before the screening visit, and patients on stable background medical LMT (as applicable) for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies, 12 weeks for lomitapide, 24 weeks for mipomersen) before the screening visit, will enter a 2-week screening period.

Patients who participated in the R727-CL-1628 study may enter the run-in or screening period or enroll directly into this study. Patients who completed the R727-CL-1628 study and fulfill all of the eligibility criteria can be enrolled directly into this study. Data collected during the R727-CL-1628 study (ie, lab test results) can be used to assess eligibility criteria for these patients. If these patients meet all the eligibility criteria and if approved by the sponsor, the patients may not have to undergo the screening visit in this study. In this case, overlapping assessments completed at the end of the open-label treatment visit in R727-CL-1628 do not need to be repeated during the R1500-CL-1629 baseline visit. The baseline/day 1 visit can occur immediately after the end of the open-label treatment visit in the R727-CL-1628 study. To ensure continuity of treatment with alirocumab, all patients from R727-CL-1628 entering this study will be provided alirocumab.

Double-Blind Treatment:

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized 2:1 to receive:

- evinacumab 15 mg/kg IV Q4W

OR

- matching placebo IV Q4W

Randomization will be stratified by apheresis treatment (Yes, No) and by geographical region (Japan, Rest of World).

Study drug administration during the DBTP will take place at the site, starting on the day of randomization (day 1), and will be administered immediately after completion of the LDL-apheresis procedure (if applicable). For those patients not undergoing LDL-apheresis, study drug must be administered after all samples for clinical laboratory evaluation have been obtained. The last dose of double-blind study drug will be administered at week 20.

Patients who are on LMT or who are undergoing LDL-apheresis should maintain stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study, from screening to the end of DBTP visit (week 24), and continuing through the end of the OLTP. All patients who enter this study from R727-CL-1628 will continue to receive alirocumab 150 mg SC Q2W for the duration of this study. Alirocumab should continue to be administered after LDL-apheresis (if applicable). On days with concomitant alirocumab and evinacumab administration, the recommendation is to administer alirocumab after the end of the evinacumab post-infusion observation period.

Open-Label Treatment:

After completion of the DBTP, all patients will enter an OLTP. Starting at week 24, all patients, regardless of treatment assignment in the DBTP, will receive open-label evinacumab 15 mg/kg IV Q4W for the 24-week OLTP. The last dose of open-label study drug will be at week 44.

Patients who are on LMT or apheresis must continue their stable dose and regimen through the end of the OLTP (through week 48). All patients who enter this study from R727-CL-1628 will continue to receive alirocumab.

Throughout the Study:

For all patients undergoing LDL-apheresis, all samples for clinical laboratory evaluation must be obtained immediately prior to the LDL-apheresis procedure and prior to administration of study drug. Given the impact of LDL apheresis, PCSK9 inhibitors, and mipomersen on lipid parameters, it is important to match the time of the baseline activities with the timing of the week 24 activities. This would mean that the timing between the baseline sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen should match the timing of the week 24 sample collection relative to the most recently completed LDL apheresis procedure, administration of a PCSK9 inhibitor or mipomersen. For all patients who are not undergoing apheresis, all samples for clinical laboratory evaluation must be obtained prior to administration of study drug.

The efficacy of evinacumab in this population will be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study. Overall safety will be assessed by monitoring/evaluation of treatment-emergent adverse events (TEAEs), physical examinations, electrocardiogram (ECG), and clinical safety laboratory tests at pre-specified time points. The potential emergence of anti-evinacumab antibodies will also be evaluated. Patients who experience an ongoing serious adverse event (SAE) at the pre-specified study end-date should be followed until resolution, stabilization, or collection of outcome and related data.

For all patients undergoing LDL-apheresis, the apheresis schedule and apheresis settings should remain stable throughout the duration of the DBTP and through the end of the OLTP (week 48).

The use of all medications and nutritional supplements known to alter serum lipids, including (but not limited to) statins, ezetimibe, PCSK9 inhibitor antibody, mipomersen, lomitapide, fibrates, niacin, and bile acid resins is permitted as long as that therapy has been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies, 12 weeks for the MTD of lomitapide, 24 weeks for mipomersen) prior to the screening visit. Patients should continue taking their LMT throughout the duration of the DBTP, starting at screening, and through the end of the OLTP (week 48).

Patients should be on a stable low fat or heart-healthy diet.

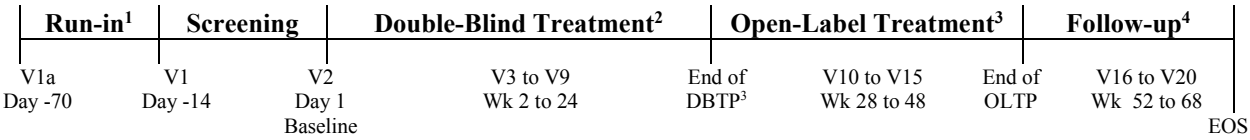
Patients' exercise regimen should remain stable throughout the duration of the study, from screening through the OLTP.

After completion of the 24-week OLTP, all patients who have successfully completed this study may have the opportunity to participate in a separate open-label (OL) study, R1500-CL-1719. All patients who enroll in the separate OL study will continue to receive open-label evinacumab at a dose of 15 mg/kg IV Q4W.

Follow-up Period (if applicable):

Patients not consenting to participate in the optional OL study (R1500-CL-1719) will enter a follow-up period for 24 weeks after completion of the OLTP. A follow-up period of 24 weeks after the last dose of study drug will be required for patients who prematurely discontinue study treatment.

Figure 1: Study Flow Diagram



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

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

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

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

5.1.1. End of Study Definition

The end of study is defined as 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 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 (eg, lipid efficacy data).

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 (CEC) is composed of experts in the field of CVD, independent of the sponsor and the investigators. This committee will be responsible for defining, validating, and classifying (in a blinded fashion) pre-specified CV events and all deaths.

Patients with suspected or confirmed CV events that occur in the time period from randomization until the end of the study will have a corresponding adjudication package prepared and submitted

to the CEC. The events should also be reported as SAEs, as appropriate. Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories include:

- Coronary heart disease death
- Nonfatal myocardial infarction (MI)
- Fatal and nonfatal ischemic stroke
- Unstable angina requiring hospitalization
- Congestive heart failure requiring hospitalization

In addition, other deaths (besides coronary heart disease deaths) will be classified by the CEC. All coronary revascularizations (percutaneous coronary intervention, coronary artery bypass graft surgery) 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 57 patients will be randomized at approximately 30 multinational sites.

6.2. Study Population

The study population will consist of males and females ≥12 years of age diagnosed with HoFH, receiving stable LMT, as applicable.

Patients should be on a maximally tolerated daily statin, ezetimibe and a PCSK9 inhibitor antibody (evolocumab or alirocumab) unless the patient has a documented history of tolerability issues, little to no response to therapy or other documented reason. Lipid modifying therapy may also include other lipid lowering therapies, including LDL-apheresis. Whether or not a patient is considered to be on a maximum tolerated regimen of lipid modifying treatments (statin, PCSK9 inhibitor antibody, ezetimibe, lomitapide, mipomersen, probucol, etc) reasons why or why not (eg, due to intolerance, lack of efficacy, etc) the patient is taking/not taking the various treatments will need to be documented in the CRF.

HoFH is defined by having at least one of the following (either genetic or clinical criteria):

Genetic criteria:

1. Documented functional mutation or mutations in both LDLR alleles
   - Note: patients who have null receptor mutations on both LDLR alleles, ie, double null, are eligible

OR

2. Documented homozygous or compound heterozygous mutations in Apo B or PCSK9

- Note: patients who are double heterozygous, ie, mutations on different genes (eg, LDLR/PCSK9) and patients with homozygous LDLRAP1 mutations are eligible

Clinical Criteria:

Untreated TC > 500 mg/dL (12.93 mmol/L) and TGs <300 mg/dL (3.39 mmol/L)

AND

Both parents with documented TC > 250 mg/dL (6.47 mmol/L) OR cutaneous or tendinous xanthoma before the age of 10 years

6.2.1. Inclusion Criteria

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

1. Male or female ≥12 years of age at the time of the screening visit
2. Diagnosis of functional HoFH by at least 1 of the following:

   a. Documented functional mutation or mutations in both LDLR alleles
   Note: patients who have null receptor mutations on both LDLR alleles, ie, double null, are eligible
   b. Presence of homozygous or compound heterozygous mutations in Apo B or PCSK9
   Note: patients who are double heterozygous, ie, mutations on different genes (eg, LDLR/PCSK9) and patients with homozygous LDLRAP1 mutations are eligible
   c. Untreated TC > 500 mg/dL (12.93 mmol/L) and TG <300 mg/dL (3.39 mmol/L)
   AND
   both parents with documented TC > 250 mg/dL (6.47 mmol)
   OR cutaneous or tendinous xanthoma before the age of 10 years
3. If undergoing LDL apheresis, must have initiated LDL apheresis at least 3 months prior to screening and must have been on a stable weekly (every 7±1 days) or every other week (every 14±2 days) schedule and stable settings for at least 8 weeks
4. Willing and able to comply with clinic visits and study-related procedures
5. Willing to consistently maintain his/her usual low fat or heart-healthy diet for the duration of the study
6. Provide signed informed consent or assent

6.2.2. Exclusion Criteria

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

1. LDL-C level <70 mg/dL (1.81 mmol/L) at the screening visit.
2. Background medical LMT (if applicable) that has not been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies, 12 weeks for MTD of lomitapide, 24 weeks for mipomersen) before the screening visit
3. Lipid-apheresis schedule (every 7 or 14 days)/apheresis settings (if applicable) that have not been stable for at least 8 weeks before the screening visit or an apheresis schedule that is not anticipated to be stable over the next 48 weeks. Plasma exchange is excluded

4. Use of nutraceuticals or over-the-counter therapies known to affect lipids, at a dose/amount that has not been stable for at least 4 weeks prior to the screening visit or between the screening and randomization visits
5. 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 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.
6. Newly diagnosed (within 3 months prior to randomization visit [week 0/day 1]) diabetes mellitus or poorly controlled (HbA1c >9%) diabetes
7. Unstable weight (variation >5 kg) within 2 months prior to the screening visit (week -2)
8. Initiation of a new diet or major change to a previous diet within 4 weeks prior to screening
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 screening
   Note: topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed
10. Use of estrogen or testosterone therapy unless the regimen has been stable 6 weeks prior to the screening visit and no plans to change the regimen during the study
11. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the screening visit or time of randomization (week 0/day 1)
12. History of a MI, unstable angina leading to hospitalization, coronary artery bypass graft surgery, percutaneous coronary intervention, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, valve replacement surgery, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit
13. History of New York Heart Association (NYHA) Class IV heart failure within 12 months before screening.
14. Age <12 years at the screening visit
15. Tanner stage <2 at the screening visit
16. 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
17. Use of any active investigational drugs (except alirocumab) within 1 month or 5 half-lives prior to the screening visit, whichever is longer
18. 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
   - 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, which the investigator feels would restrict or limit the patient's participation for the duration of the study

19. Laboratory findings during the screening period (not including randomization labs):
    - Positive test for Hepatitis B surface antigen and/or Hepatitis C antibody (associated with a positive HCV RNA polymerase chain reaction)
    - Positive serum beta-human chorionic gonadotropin or urine pregnancy test in women of childbearing potential (WOCBP)
    - eGFR <30 mL/min/1.73 m^2 (calculated by central lab)
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) (1 repeat lab is allowed)
    - CPK >3 x ULN (1 repeat lab is allowed)
    - TSH >1.5 x ULN of the central laboratory (1 repeat lab is allowed) for patients not on thyroid replacement therapy
20. Known hypersensitivity to mAb therapeutics
21. Member of the clinical site study team and/or his/her immediate family
22. Pregnant or breastfeeding women
23. Sexually active WOCBP*, 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 dose of study drug. Highly effective contraceptive 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 trial 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.

24. 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 dose of study drug regardless of vasectomy status. Sperm donation is prohibited during the study and for up to 24 weeks after the last injection of study drug.
25. Housed in an institution on the basis of an administrative or judicial order.
26. Dependent on the sponsor, investigator or the study site.

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 8.1.5.

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

Early Termination from the Study

If for any reason the patient withdraws from the study prematurely, the patient should undergo an unscheduled visit with assessments normally planned at the end of the double-blind treatment visit if the patient is in the DBTP, or the end of the open-label treatment visit, if the patient is in the OLTP. The visit should take place within 5 days of treatment discontinuation. The assessments completed should include pregnancy testing for WOCBP. 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 end of study visit should take place with assessments as specified in the end of study visit (ie, follow up visit) at 24 weeks after the premature discontinuation of study drug.

Sexually active WOCBP 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, the patient will be provided 5 urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. The patient will also be notified of Q4W follow-up phone calls to confirm continued contraception use and pregnancy reporting and to obtain the results of the urine pregnancy test.

The investigator 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. 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 prematurely discontinued from the study drug will not be replaced.

6.5. Rescreening of Patients

Patients who do not meet eligibility criteria during the initial screening may re-screen only once. Patients who are re-screened 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 for the assessments that did not meet eligibility criteria.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Evinacumab or placebo IV infusion.

In the DBTP, eligible patients will be enrolled to receive an IV dose of evinacumab 15 mg/kg Q4W or matching placebo, starting on day 1. The last dose of double-blind study drug will be at week 20.

In the open-label portion of the study, patients will receive

- Evinacumab at 15 mg/kg IV Q4W starting at week 24 (day 169) with the last dose at week 44 (day 309)

Dosing should fall within a window of ±7 days; if >14 days has passed, skip the dose and return to the original schedule.

Instructions on dose preparation and administration are provided in the pharmacy manual.

Instructions on management of infusion reactions are provided in Section 7.5.1.

Sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL in a prefilled pen for patients from study R727-CL-1628 who enroll in this study.

7.2. Run-in Treatments

Patients who are undergoing apheresis therapy must have initiated LDL apheresis at least 3 months prior to screening and must be on a stable weekly (every 7 days) or every other week (every 14 days) schedule and/or stable settings for at least 8 weeks prior to screening. Patients with a schedule and/or apheresis settings, which have not been stable for at least 8 weeks before the screening visit will enter an 8-week run-in period before the screening period.

Patients who are on background LMT that has not been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies) before the screening visit will enter a 4-week (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies) run-in period to stabilize their LMT before entering the screening period.

7.3. Background Treatments

Patients who are receiving background LMT or who are undergoing apheresis should maintain stable LMT and a stable apheresis schedule (as applicable) throughout the duration of the study, from screening to the end of DBTP visit (week 24), and continuing through the end of the OLTP. For all patients who enter this study from R727-CL-1628, alirocumab will be provided and patients will administer alirocumab 150 mg SC Q2W for the duration of the study.

Patients should be on a maximally tolerated LMT regimen. Whether or not a patient is considered to be on a maximum tolerated regimen of LMT (statin, PCSK9 inhibitor antibody, ezetimibe, lomitapide, mipomersen, probucol, etc), reasons why or why not (eg, due to intolerance, lack of efficacy, etc) 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

During the DBTP, study drug 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 DBTP as long as possible.

Patients who permanently discontinue study drug during the DBTP should remain in the study and undergo all double-blind 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 end of the double-blind treatment visit (this should take place within 5 days of discontinuation of study drug, if possible) and then resume the original study schedule until end of the DBTP. In case of early discontinuation before week 24, all efforts should be made to perform the week 24 assessments at week 24.

Patients who permanently discontinue study drug during the OLTP should have, as soon as possible, an unscheduled visit with assessments normally planned at the end of the OLTP (this should take place within 5 days of discontinuation of study drug, if possible) and then have end-of-study assessments at least 24 weeks after their last dose of study drug.

Patients who permanently discontinue study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.5.

Sexually active WOCBP 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, the patient will be provided 5 urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. The patient will also be notified of Q4W follow-up phone calls to confirm continued contraception use and pregnancy reporting and to obtain the results of the urine pregnancy test.

7.4.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Evidence of pregnancy
- Acute systemic 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 DBTP. 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 study drug dosing 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 or 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*
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension

- other neurological symptoms (confusion, loss of consciousness, parathesia, 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 the 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 blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

7.6. Method of Treatment Assignment

Approximately 57 patients will be randomized in a 2:1 ratio to receive either 15 mg/kg IV evinacumab or matching placebo according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified by apheresis treatment (Yes/No) and by geographical region (Japan, Rest of World).

In the OLTP of the study, all patients will receive evinacumab as described in Section 7.1.

7.6.1. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the DBTP (up to week 24). 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.

Lipid results from blood samples collected after the randomization visit will not be communicated to the sites, and the sponsor's operational team will not have access to these laboratory results until after completion of the DBTP and the first-step analysis.

Although there is a slight color difference between the drug product and placebo product for IV infusion bag preparation, the color difference is not detectable when the investigational product is added to the IV infusion bag.

Further details are provided in the pharmacy manual.

After the end of the DBTP visit at week 24, the study becomes an open-label study.

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 [redacted]; storage instructions will be provided in the pharmacy manual.

7.7.2. Supply and Disposition of Treatments

Study drug will be shipped [redacted] 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 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, including apheresis, from the time of informed consent to the end of the treatment period/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

The following concomitant medications and procedures are prohibited through the end of the DBTP (week 24) and continuing through the end of the OLTP (week 48):

- Background medical LMT (if applicable) that has not been stable for at least 4 weeks (6 weeks for fibrates) before the screening visit (week -2) (unless participating in the run-in period to stabilize)
- Background mipomersen treatment that has not been stable for 24 weeks before the screening visit (week -2)
- Background lomitapide at a MTD that has not been stable for 12 weeks before the screening visit (week -2)
- Recent discontinuation of lomitapide that has not been washed out for at least 8 weeks before the screening visit (week -2).
- Background PCSK9 inhibitor antibody that has not been stable for at least 8 weeks prior to the screening visit (week -2)
- Lipid apheresis schedule that is not an every 7 day (+/- 1 day) or an every 14 day (+/- 2 days) regimen or that has been stable for at least 8 weeks prior to screening (week -2)
- Plasma exchange
- Nutraceuticals or over-the-counter therapies known to affect lipids, at a dose/amount that has not been stable for at least 4 weeks prior to the screening visit (week -2)
- Systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to the screening visit (week-2)
- Thyroid replacement therapy, unless the dosage of replacement therapy has been stable for at least 12 weeks prior to the screening visit (week -2).

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, lomitapide, mipomersen, and PCSK9 inhibitor antibodies is permitted as long as that therapy has been stable for at least 4 weeks (6 weeks for fibrates, 8 weeks for PCSK9 inhibitor antibodies, 12 weeks for lomitapide, 24 weeks for mipomersen) prior to the screening visit (week-2). Patients should

continue taking their background medical LMT for the duration of the study starting at screening and through the end of the OLTP (week 48). Similarly, patients should maintain their apheresis regimen (if applicable) starting at screening and through the end of the OLTP (week 48).

Patients on thyroid replacement therapy can be included if the dosage has been stable for at least 12 weeks prior to the screening visit (week -2).

Topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed.

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, and Table 4.

Table 1: Schedule of Events – Run-in and Screening

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

Table 2: Schedule of Events – Screening for Patients with No Run-in

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

Table 3: Schedule of Events – Baseline, Double-Blind Treatment Period, and Open-Label Treatment Period

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

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

Table 4: Schedule of Events – Follow-up Period

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

8.1.1. Footnotes for Schedule of Events Table 1

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

8.1.2. Footnotes for Schedule of Events Table 2

1. Study assessments are to be performed and blood samples are to be collected before the dose of study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure; study drug will be administered after the apheresis procedure.
2. Fasting sample will be collected for the lipid panel: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C
3. ECG should be performed before blood samples are collected at visits requiring blood draws.
4. Assessment of Tanner Stage and sex hormones (includes luteinizing hormone, follicle stimulating hormone, estradiol, total testosterone) only applicable to patients <18 years old.
5. All laboratory samples should be collected before administration of study drug.
6. WOCBP only, confirm required contraception use and reminder pregnancy reporting

8.1.3. Footnotes for Schedule of Events Table 3

1. For those patients enrolling directly from the R727-CL-1628 study and do not complete the R1500-CL-1629 run-in or screening period, the informed consent forms should be signed at the baseline visit. Overlapping assessments completed at the R727-CL-1628

open-label EOT visit do not need to be duplicated during the R1500-CL-1629 baseline visit; only assessments footnoted will need to be performed.

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

[redacted]

14. All end of treatment (EOT) assessments are to be performed and blood samples are to be collected before the dose of open-label study drug in all patients. For patients undergoing apheresis: Study assessments are to be performed and blood samples are to be collected immediately before the lipid-apheresis procedure; open-label study drug will be administered after the apheresis procedure.
15. In the OLTP, the HADS should be administered after the patients have been informed of their lipid results.

8.1.4. Footnotes for Schedule of Events Table 4

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

8.1.5. Early Termination Visit

In the case a patient prematurely discontinues study treatment, an unscheduled visit should occur with assessments normally planned at the (EOT) visit (it should take place within 5 days of treatment discontinuation, if possible). Patients who permanently discontinue study drug during the DBTP should then resume the original study schedule (except for study treatment administration) until end of the DBTP, and all efforts should be made to perform the week 24 assessments at week 24 (regardless of study treatment administration). All patients who prematurely discontinue study treatment (either in the double-blind period or the open-label period) should be followed for at least 24 weeks from the last dose of study drug, and a final end of study visit can take place with assessments as specified in the end of study visit (ie, follow up visit).

Sexually active WOCBP 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, the patient will be provided 5 urine pregnancy tests with instructions to test for pregnancy 4 weeks after this visit and Q4W thereafter. The patient will also be notified of Q4W follow-up phone calls to confirm continued contraception use and pregnancy reporting and to obtain the results of the urine pregnancy test.

If a WOCBP is lost to follow-up, sites should attempt a minimum of 2 telephone calls. If the patient cannot be reached on the second attempt, a formal letter will be issued from the site to the patient that reminds the patient of the importance of continued use of highly effective contraception use for at least 6 months after the last dose of study drug.

8.1.6. 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:

- Hepatitis B Surface Antigen
- Hepatitis C Antibody
- 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.

Total-C, HDL-C, TG, Apo B, Apo A-1, Lp(a), and Apo CIII 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) or if calculated LDL-C values are below 25 mg/dL (0.65 mmol/L), LDL-C will be measured via the beta quantification method (rather than via the Friedewald formula). Non-HDL-C will be calculated by subtracting HDL-C from the total-C. Ratio Apo B/Apo A-1 will be calculated. All lipid results will be blinded from after the randomization visit until the week 36 visit. Every effort should be made to continue to keep the sponsor blinded to all lipid parameters for the duration of the study. No attempts should be made by the investigator or patient to have the patient's lipid values independently evaluated after randomization until after the end of study visit.

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

8.2.2.1. Lipid Panel

Fasting (at least 8 hours) blood samples will be collected at specified time points shown in Section 8.1 for assessment of the lipid profile, comprising calculated LDL-C, HDL-C, non-HDL-C, total-C, and TGs. These samples will also be used for specialty lipid panel assessment when it is scheduled at the same time as the lipid panel assessment.

8.2.2.2. Specialty Lipid Panel

Fasting (at least 8 hours) blood samples will be collected at specified time points shown in Section 8.1 for assessment of the specialty lipid profile, comprising Apo B, Apo A-1, ratio of Apo B/Apo A-1, and Lp(a) as well as for Apo CIII. The specialty lipid panels will be assessed in the same sample that is collected for the lipid panel.

8.2.3. Quality of Life Procedures

8.2.3.1. EuroQol-5 Questionnaire

The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D as a measure of health related quality of life, defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each dimension has 3 ordinal levels of severity: "no problem" (1), "some problems" (2), "severe problems" (3). Overall health state is defined as a 5-digit number. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death" and 1 represents "perfect health."

8.2.3.2. Patient Assessed Hospital Anxiety and Depression Scale

The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state (Zigmond 1983, Herrmann 1997). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression.

8.2.4. Safety Procedures

8.2.4.1. Vital Signs

Vital signs, including temperature, sitting blood pressure and pulse and respiration rate, will be collected predose at time points according to Table 1, Table 2, Table 3, and Table 4. On dosing days, vital signs consisting of blood pressure and pulse rate will also 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.

8.2.4.2. Physical Examination

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

8.2.4.3. Tanner Stages

The Tanner stages will be assessed throughout the study for all patients <18 years old according to Table 1, Table 2, Table 3, and Table 4. If possible, for each adolescent patient, the Tanner stages assessment should be performed by the same investigator/designee trained to assess pubertal development.

8.2.4.4. Electrocardiogram

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

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 (see Section 9.4.5). Each ECG tracing will be analyzed in comparison with the screening recorded trace. All ECG tracings will be kept as source data.

8.2.4.5. Laboratory Testing

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

Samples for laboratory testing will be collected at visits according to Table 1, Table 2, Table 3, and Table 4 and analyzed by a central laboratory. 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	
Chloride	Blood urea nitrogen (BUN)	
Carbon dioxide	AST	Uric acid
Calcium	ALT	CPK
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

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

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, and Table 4 and are as follows: FSH, TSH, high sensitivity C-reactive protein (hs-CRP), HbA1c, serum and urine pregnancy test, and sex hormones (for adolescents only and includes luteinizing hormone, follicle stimulating hormone, estradiol, total testosterone).

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.

8.2.4.6. 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.

8.2.5. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.5.1. Drug Concentration Measurements and Samples

Samples for assessment of evinacumab and alirocumab concentration will be collected at time points listed in Table 3, and Table 4. They will be collected predose and at the end of the IV infusion on days when study drug is administered.

[redacted]

8.2.5.2. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 3, and Table 4. They will be collected predose on days when study drug is administered.

Patients who exhibit a treatment-emergent or treatment-boosted positive ADA assay response with a titer greater than 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 within two dilution steps from their baseline titer levels.

[redacted].

8.2.5.3. Statin Concentrations

Samples for statin concentration will be collected at time points shown in Table 3.

8.2.6. Pharmacodynamic Procedures

Total ANGPTL3 and total PCSK9 concentrations in serum will be measured using the PK samples collected at the time points listed in Table 3, and Table 4.

8.2.7. Other Assessments

8.2.7.1. Review of Diet

Patients will be following a low fat or heart-healthy diet at the screening visit and will be asked to continue the low fat or heart-healthy diet until the last study visit. Patients will be queried on compliance with their diet during the DBTP and OLTP, at time points according to Table 1, Table 2, Table 3, and Table 4.

Details are provided in Appendix 2.

8.2.7.2. DNA Sample for HoFH Genotyping

A required blood sample for DNA extraction will be collected from all patients to identify or confirm a known mutation in PCSK9, LDLR, Apo B gene, and/or LDLRAP1 gene.

8.2.7.3. LDLR Function

A blood sample for LDLR function testing will be collected from all patients at time points according to Table 3, in order to characterize LDLR function and explore potential differences in patient efficacy and safety.

[redacted]

[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 all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, ECs/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/washout 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 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 ECs/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 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 trial 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 end of study. 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 end of study or within 168 days (24 weeks) of last study drug administration if the patient prematurely discontinued from the study - 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 end of study/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 nonserious, 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 (serious or non-serious) for evinacumab include the following:

- Anaphylactic reactions
- Allergic reactions and/or local injection site reactions that require consultation with another physician for further evaluation or requiring medical treatment
- Increase in ALT or AST: ≥3 x ULN (if baseline <ULN), or ≥2 times the baseline value (if baseline ≥ ULN)
- Pregnancy
- Symptomatic overdose with investigational medicinal product
- Neurocognitive events
- New onset of diabetes (see definition below)
- 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 times the 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 investigational medicinal product
- 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 (NOD) will be the following:
  - Type 1 or type 2 diabetes TEAE (grouping of Medical Dictionary for Regulatory Activities [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 NOD by default. For patients with several HbA1c measurements but only with the last one ≥6.5%, this single value ≥6.5% will be considered and qualify the patient as NOD by default.

and/or

– At least 2 values of fasting glucose ≥126 mg/dL (7.0 mmol/L). NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD. For patients with several fasting glucose measurements but only with the last one ≥126 mg/dL (7.0 mmol/L), this single value ≥ 126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD.

Refer to the study manual for the procedures to be followed.

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.

Refer to the study manual for the procedures to be followed.

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's 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, nonsteroidal anti-inflammatory drugs, 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.

9.5.2. Evaluation of Causality

Relationship of AEs to Blinded IV Study Drug:

The relationship of AEs to study drug will be assessed by the 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 AEs to SC PCSK9 Inhibitor Antibody (if applicable):

The relationship of AEs to a PCSK9 inhibitor antibody (if applicable) will be assessed by the 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 PCSK9 inhibitor antibody?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the PCSK9 inhibitor antibody

Related: There is a reasonable possibility that the event may have been caused by the PCSK9 inhibitor antibody

A list of factors to consider when assessing the relationship of AEs to a 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 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.

9.6. Safety Monitoring

The investigator will monitor the safety of study patients 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 (evinacumab), of any SAE that 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 double-blind period completion (ie first-step analysis).

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

Let μ0 and μ1 be the population means of the percent change from baseline in calculated LDL-C at week 24 under placebo and evinacumab, respectively. The following null hypothesis and alternative will be tested:

$$H0 : \mu 0 = \mu 1$$
$$versus$$
$$H1 : \mu 0 \neq \mu 1$$

LDL-apheresis treatment [Yes/No], and geographical region [Japan, Rest of World] will be the 2 stratification factors for patient randomization, and will be accounted for in the statistical modeling for efficacy.

10.2. Justification of Sample Size

For the primary efficacy hypothesis during the DBTP, a total sample size of 57 patients (38 on evinacumab and 19 on placebo) will have 90% power to detect a treatment group difference in mean percent change LDL-C of 38% with a 0.05 two-sided significance level and assuming a common standard deviation (SD) of 35%. This sample size has been adjusted for a 5% non-evaluable patient rate for the primary efficacy endpoint, and a 15% dropout rate.

To gain experience with evinacumab in the population of Japanese patients, this study will plan to enroll up to 9 patients in Japan. Due to the rare patient population planned for evaluation, the sample size of 9 patients (15% of the planned study sample size) was chosen for practical reasons, centered on the feasibility to identify and enroll these patients into the trial. Based on the Ministry of Health, Labor, and Welfare 2007 "Basic Principles on Global Clinical Trials"

method 1, a sample size of 12 (21%) will be needed to achieve 80% probability that the effect in Japan is at least ½ of the global effect. A sample size of 9 provides approximately 77% probability.

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

10.3.1.1. Intent-to-Treat

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

10.3.1.2. Modified Intent-to-Treat

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

- Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (ie, baseline).
- Availability of at least 1 calculated LDL-C value during the efficacy treatment period and within one of the analysis windows in the DBTP up to week 24. The efficacy treatment period is defined as the time from the first double-blind study drug administration up to 35 days after the last double-blind study drug administration, or up to the first dose of the open-label study drug, whichever is earlier.

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

10.3.2. Safety Analysis Sets

10.3.2.1. Double-Blind Safety Analysis Set

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

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

10.3.2.2. Open-Label Safety Analysis Set

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

10.3.3. Other Analysis Sets

The PK and the ADA analyses will be performed on all randomized patients who received any study drug, and further:

- The PK analysis set will also require for each patient at least 1 non-missing post-baseline measurement of evinacumab concentration. Treatment assignments are based on the treatment received (placebo or evinacumab).
- The ADA analysis set will also require for each patient at least 1 evaluable ADA result collected after the first dose of study treatment. Treatment assignments are based on the treatment received (placebo or evinacumab).

10.4. Statistical Methods

10.4.1. Patient Disposition

The following data will be summarized:

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

  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 DBTP, defined as at least 20 weeks of study treatment exposure and visit week 24 performed.
- The total number of patients who completed the OLTP, defined as at least 44 weeks of study treatment exposure and visit week 48 performed.
- The total number of patients who prematurely discontinued study treatment during the double-blind period, and the reasons for discontinuation.
- The total number of patients who prematurely discontinued study treatment during the open-label 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 infusion. 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 DBTP, demographic and baseline characteristics will be summarized descriptively by treatment group for patients in the ITT population. For the open-label 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. Continuous variables will be descriptively summarized with mean, median, SD, minimum, and maximum. Categorical variables will be descriptively summarized with frequency and percentage.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

The double-blind primary efficacy analysis will compare the evinacumab treatment group to placebo at week 24. The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to week 24 (ITT estimand). The percent change from baseline in calculated LDL-C will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 2 to week 24 analysis windows will be used and missing data are accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group (placebo versus evinacumab), randomization strata (apheresis [Yes/No] and region [Japan, Rest of World]), time point (weeks 2, 4, 8, 12, 16, 20, 24), strata-by-time point interaction, and treatment by time point interaction, as well as, the continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction. The statistical testing of the comparison for the primary measure will be evaluated at a 2-sided significance level of 0.05. Model assumptions for distribution normality and equal variances between treatment groups will be explored prior to the analysis testing.

This model will be run using Statistical Analysis System (SAS) Mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least squares means estimates at week 24 for both treatment groups with their corresponding standard errors (SEs).

Robustness of the primary analysis statistical methods will be assessed through sensitivity analyses detailed in the SAP, including an on-treatment analysis of the percent change in calculated LDL-C from baseline to week 24 (ie, mITT patient population using calculated LDL-C values collected during the efficacy treatment period [on-treatment estimand]), and a different methodology for missing data. Specifically, a pattern mixture model (PMM) will be employed to assess the potential violation of the missing at random assumption. For the PMM, the imputation model will account for the differing missing value patterns based on calculated

LDL-C collected in the presence or absence of study treatment administration for those patients randomized into the study.

10.4.3.2. Secondary Efficacy Analysis

For the key secondary efficacy endpoints (defined in Section 4.2.2) and other secondary efficacy endpoints (described in Section 4.2.3) collected in the DBTP, descriptive summaries and analyses will be performed in the ITT population, using values obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand).

For descriptive summaries, percent change, and when appropriate change from baseline, in calculated LDL-C, total-C, TG, non-HDL-C, Apo B, Lp(a), and Apo CIII 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 SEs.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (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 4.2.2 and Section 4.2.3 anticipated to have a normal distribution (ie, lipids other than TG and Lp[a]) will be analyzed 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 4.2.2 and Section 4.2.3 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 a 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 SE estimates. The combined mean difference between the treatment groups will be provided with the SE, 95% confidence interval (CI) and p-value.

III. Binary endpoints

Binary secondary efficacy endpoints defined in Section 4.2.2 and Section 4.2.3 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 a 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% CI 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 last observation carried forward (LOCF) 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 24 time window to impute the missing week 24 value.

10.4.3.3. Multiplicity Considerations

In order to address multiple key secondary efficacy endpoints (ie, other lipid parameters) collected in the double-blind period (Section 4.2.2 and Section 4.2.3) , the overall type-I error will be controlled by the use of a hierarchical inferential approach. Statistical significance of the primary parameter is required before drawing inferential conclusions about the first key secondary parameter at the 0.05 alpha level. Inferential conclusions about successive key secondary parameters require statistical significance of the prior parameter within the hierarchy. The hierarchy testing sequence will be provided in the SAP, prior to treatment unblinding. This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.05 level.

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

No adjustment will be made for the first step (Section 10.4.9.1) and second step (Section 10.4.9.2) statistical analyses, since the primary and key secondary efficacy endpoints will have been concluded at the time of the first step analysis.

10.4.3.4. Other Efficacy Endpoints

During the OLTP, efficacy variables will be explored through descriptive statistics at each scheduled visit for the total patients administered open-label study treatment (total), as well as by the patient subgroups of study treatment received in the DBTP (ie, evinacumab, placebo). Formal statistical testing is not planned. Descriptive statistics will include the same parameters as described for each variable in the DBTP.

For patients receiving evinacumab in the DBTP, a combined summary including both the double-blind and OLTP assessments may be considered, referencing the double-blind baseline for variable calculations. Prolonged time between last dose of double-blind treatment and first dose of open-label treatment will need to be taken into consideration when combining longitudinal efficacy data. Formal statistical testing is not planned.

10.4.3.5. Subgroup Analyses for the Primary Efficacy Endpoint

Analyses are planned on the primary efficacy endpoint to access the homogeneity of evinacumab treatment effect across various patient subgroups in the ITT population, including the 2 stratification factors LDL-C apheresis and region, and patients with or without

receptor-negative mutations in both LDLR alleles. Statistical analysis methods will be provided in the SAP.

With respect to the subgroup analysis for region, the primary efficacy analysis MMRM model will be used to evaluate treatment effect in Japanese patients (as recorded in the electronic data capture [EDC] system) by adding the variables of treatment-by-region strata and treatment-by time point-by region strata interaction terms to the model. With this subgroup specific MMRM model, the primary efficacy endpoint LS mean at week 24 for the evinacumab treatment group will be provided for the Japanese patients, along with the corresponding SE and 95% CI. Due to the few Japanese patients (3) expected to be randomized to the placebo group, the evinacumab group LS mean point estimate will be used to access consistency of evinacumab effect between the Japanese patients and all evinacumab treated patients in this global study (provided by the primary efficacy analysis described in Section 10.4.3.1). The evinacumab primary efficacy endpoint LS mean point estimate for the Japanese patients is considered to show consistent efficacy results with the global study point estimate when the Japanese patient's LS mean point estimate is greater by a pre-specified amount (to be provided in the SAP) than the corresponding global study point estimate (ie, ratio of point estimate for Japanese patients divided by point estimate for the global study).

10.4.3.6. On-Treatment Efficacy Analyses

For key secondary efficacy endpoints (defined in Section 4.2.2) collected in the DBTP, descriptive summaries and analyses comparing treatment groups will be performed in the mITT population, using values obtained during the efficacy treatment period (on-treatment estimand). Statistical methods described above will be used to analyze each key secondary efficacy endpoint. P-values will be provided for descriptive purposes only.

10.4.4. Safety Analysis

For the double-blind period, summaries of safety results will be presented by treatment group for patients in the double-blind SAF. 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 DBTP (ie, evinacumab, placebo). No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed using the following common rule:

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

10.4.4.1. Adverse Events

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). The verbatim text, the preferred term (PT), and the system organ class (SOC) will be provided in patient listings.

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined from the day the ICF is signed to the day before the first dose of double-blind study treatment.
- The double-blind TEAE observation period is defined 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) (residual effect of treatment for IV dose regimen is expected until 24 weeks after the last dose of study drug) for those patients not proceeding into the OLTP, or up to the day before the first dose of open-label study treatment administration for those patients proceeding into the OLTP.
- The 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.
- The post-treatment observation 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

Adverse event incidence tables will present data by SOC sorted alphabetically and PT sorted by decreasing frequency, and summarize the number (n) and percentage (%) of patients experiencing an AE. 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 special interest for alirocumab treatment (ie, increase in ALT etc)
- All TEAEs of special interest for evinacumab treatment (anaphylactic reaction etc)
- 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 and 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 and 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 the quantitative analysis of laboratory and vital signs data in the double-blind period is defined from the day after the first dose of double blind study treatment to the day of the last dose of double-blind study treatment + 28 days for those patients not proceeding into the OLTP, or up to the day of the first dose of open-label study treatment administration for those patients proceeding into the OLTP.
- Open-label treatment period: The treatment period used for quantitative analysis of laboratory and vital signs data in the open-label study period is defined from the day after the first dose of open-label study treatment to the day of the last dose of open-label study treatment + 28 days.

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 SE may 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 PCSV criterion or criteria

For laboratory parameters for which a PCSV criterion is not defined, similar table(s) using the normal range will be provided, regardless of baseline level.

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

10.4.4.3. Treatment Exposure

The duration of study treatment exposure for the double-blind period will be calculated as:

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

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

- Patient 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 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, will be summarized by at least; mean, median, SD, and minimum/maximum. The categorical data for number of study treatment infusions (double-blind, open-label, and cumulative across the study) will be summarized by patient counts and percentages.

10.4.4.4. Treatment Compliance

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

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

Infusion frequency for the double-blind period will be summarized by at least; mean, median, SD, and minimum/maximum.

10.4.5. Analysis of Drug Concentration and Target Concentration Data

Descriptive statistics of evinacumab concentrations and total ANGPTL3 concentration and alirocumab and PCSK9 concentration at each sampling time will be provided by treatment group. Plots of mean concentrations (linear and log scales) versus time will be presented.

10.4.6. Analysis of Anti-Drug Antibody Data

Listings of ADA positivity and titers presented by patient, time point, and study treatment received 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 received.

The influence of ADA on drug concentrations will be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

10.4.7. Analysis of Statin Concentration

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

[redacted]

10.4.9. Timing of Statistical Analyses

The analyses will be conducted in 2 steps:

10.4.9.1. First Step: Main Efficacy and Safety Analysis

The first analysis will be conducted as soon as all patients have been randomized and all data through week 24 (double-blind period) has been collected and validated. This first analysis will consist of the final analysis of the primary and secondary efficacy endpoints. The safety analysis will be performed on all safety data collected and validated at the time of the first analysis.

The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. Since data collection for the double-blind primary efficacy measure and key secondary efficacy measures will have been concluded at the time of this first analysis, the significance level for the study remains at 0.05. This first analysis maybe used for the submission dossier 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: Final Safety Analysis

The second analysis will be conducted at the end of the OLTP (end of study) and will consist of the final analysis for safety and the OLTP exploratory efficacy measures.

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 planned 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 EDC tool, iMedidata 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
- 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 (refer to current version), 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.

Adults.:

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.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness. The patient will give oral consent and the impartial witness 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.

Pediatric Patients:

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.

Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. 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 assent 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 their 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 approvals will also be sought where applicable under local 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 must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRFs 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.

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22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: "A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia", 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 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 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 study procedure or background treatment, etc.
- do not reappear or worsen when dosing with study drug or study procedure or background treatment, etc is resumed
- are not a suspected response to the study drug or 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 study procedure or background treatment, etc.
- resolve or improve after discontinuation of study drug or study procedure or background treatment, etc.
- reappear or worsen when dosing with study drug or study procedure or background treatment, etc is resumed
- are known or suspected to be a response to the study drug or study procedure or background treatment, etc, based upon preclinical data or prior clinical data

NOTE: This list is not exhaustive.

APPENDIX 2. SUMMARY OF TLC DIET FOR HIGH CHOLESTEROL

Total Fat	25% - 35% total calories*
Saturated fat*	<7% total calories
Polyunsaturated fat	up to 10% total calories
Monounsaturated fat	up to 20% total calories
Carbohydrates†	50% - 60% total calories*
Protein	~15% total calories
Cholesterol	<200 mg/dL (5.172 mmol/l)
Plant Sterols	2g
Soluble Fiber such as psyllium	10g - 25g

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat. Trans-fatty acids are another LDL-raising fat that should be kept at a low intake.

† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

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, parallel-group study to evaluate the efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia

Protocol Number: R1500-CL-1629

Protocol Version: R1500-CL-1629 Amendment 4B

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00089244 v1.0

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