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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 ALIROCUMAB IN PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Compound:	Alirocumab (Praluent®)
Study Name	ODYSSEY HoFH
Clinical Phase:	3b
Protocol Number:	R727-CL-1628
Protocol Version:	R727-CL-1628 Amendment 3
Amendment 3 Date of Issue:	*See appended electronic signature page*
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Scientific/Medical Monitor:

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AMENDMENT HISTORY

Amendment 3

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

Rationale for Change	Sections Changed
To increase the number of patients from 54 to approximately 74, the protocol includes a provision to re-estimate the sample size after approximately 75% of the patients reach the week 12 visit in the double-blind treatment period to ensure adequate power in case of a larger-than-expected variability in the data. The sample size adjustment process was implemented and due to the variability observed, a decision was made to increase the sample size.	Clinical Study Protocol Synopsis: Study design Clinical Study Protocol Synopsis: Population Clinical Study Protocol Synopsis: Statistical Plan Section 5.1 Study Description and Duration Section 6.1 Number of Patients Planned Section 10.2 Justification of Sample Size
The ITT population definition is revised to remove the requirement of a post-baseline measurement (ie, "availability of at least 1 measurement value for LDL-C within 1 of the analysis windows in the double-blind period up to week 12"), per regulatory agency feedback.	Section 10.3.1 Efficacy Analysis Sets
Added a reference to footnote 6 for the PK sample.	Table 1 Schedule of Events

Amendment 2

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

Rationale for Change	Sections Changed
Added EQ-5D QOL questionnaire and an EQ-5D 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 1 Schedule of Events Section 8.2.3.1 EuroQol-5 Questionnaire
Exclude adolescents as a separate pediatric study is planned	Clinical Study Protocol Synopsis: Study Design, Population, and Procedures & Assessments Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 4.2.3 Safety Endpoints Section 6.2 Study Population Section 6.2.1 Inclusion Criteria Section 6.2.2 Exclusion Criteria Table 1 Schedule of Events Section 8.1.1 Footnotes for Schedule of Events Table Section 8.2.4.2 Physical Examination Section 10.4.1 Patients Disposition

Rationale for Change	Sections Changed
	Section 13 Audits and Inspections Section 14.2 Informed Consent Section 14.3 Patient Confidentiality and Data Protection Section 14.4 Institutional Review Board/Ethics Committee Section 15 Protocol Amendments Section 17.2 Retention of Records
Modified ADA variables to align with other studies	Section 4.4 Anti-Drug Antibody Variables Section 10.3.4 Other Analysis Sets
Extended the treatment-emergent adverse event (TEAE) period from +21 days to +70 days to obtain additional safety information since alirocumab has not been studied previously in patients with HoFH	Section 8.1.2 Early Termination Visit Section 10.4.4.1 Adverse Events
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 #4 Section 7.3 Run-in (optional) and Background Treatment(s) Section 8.1.1 Footnotes for Schedule of Events Table
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. Added criterion excluding members of the clinical site study team and/or his/her immediate family	Section 6.2.2 Exclusion Criteria
Added an instruction for a follow-up call at week 32 to capture AEs and concomitant medications because the TEAE period was extended from +21 days to +70 days (10 weeks) and added 8-week follow-up period for patients not continuing in another lipid lowering study	Clinical Study Protocol Synopsis Section 5.1 Study Description and Duration Figure 1 Study Flow Diagram Table 1 Schedule of Events Section 8.1.1 Footnotes for Schedule of Events Table
Added provision for a retention manual to be provided to the sites to improve adherence with assessments as planned in the protocol and minimize missing data for patients who discontinue the study treatment early	Section 6.3 Premature Withdrawal from the Study Section 7.4.2 Study Drug Discontinuation Section 8.1.2 Early Termination Visit
Added assessment for hepatitis C to end of double-blind treatment period and end of open-label treatment period to assess for seroconversion	Section 8.1 Schedule of Events Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.4.4 Laboratory Testing
Provided a definition for “new onset diabetes” as this is an adverse event of special interest (AESI)	Section 9.3.3 Adverse Events of Special Interest
Clarified text concerning availability of additional studies after completion of the open-label treatment period into which patients may	Section 5.1 Study Description and Duration

Rationale for Change	Sections Changed
choose to enroll and continue to receive alirocumab	
Updated description of the method to account for missing data	Section 10.4.3.1 Primary Efficacy Analysis
Edits/Clarifications	Section 1 Introduction Section 3.2.1 Rationale for Study Design Section 5.1.1 End of Study Definition Section 6.2.1 Inclusion Criteria Section 6.2.2 Exclusion Criteria Section 9.3.3 Adverse Events of Special Interest Section 10.4.4.1 Adverse Events

Amendment 1

The purpose of this amendment is to update the following areas: add a blinded sample size adjustment to the statistical methods, refine the diagnostic criteria for HoFH, update the safety monitoring of adolescents by adding additional assessments, require mutation status for those on LDL apheresis to be known prior to screening, correct inconsistencies, and make additional editorial changes throughout the protocol.

The statistical methods section on justification of sample size is being updated to allow for a blinded sample size adjustment. During the study, the actual blinded pooled standard deviation for LDL-C will be determined by an independent, unblinded statistician and, if a larger-than-expected standard deviation is observed, a sample size re-estimation analysis will be performed. This analysis will not be binding and any potential changes to the sample size will be implemented through a protocol amendment.

The inclusion/exclusion criteria are being updated to allow the inclusion of patients considered to be double heterozygotes, defined as having different mutations on 2 different alleles affecting LDLR function. These patients, along with true homozygotes and compound heterozygotes, are considered to be part of the patient population defining HoFH. Additionally, the use of skin fibroblast LDL receptor activity as part of the clinical criteria to diagnosis HoFH is being removed based on feedback that the assessment is rarely done in clinical practice.

The safety monitoring of adolescents is being updated to add an additional height assessment at the end of the study and assess Tanner stages throughout the double-blind and open-label treatment periods.

The genotyping requirement is being updated such that for all patients on LDL apheresis whose HoFH genotype status is unknown prior to enrollment, it should be determined prior to entering the screening period. This change is being made to mitigate the risk of inadvertently enrolling a patient with null/null mutations in both LDLR alleles.

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients with Homozygous Familial Hypercholesterolemia
Site Location(s)	Multinational Multicenter
Objective(s)	**Primary Objective** The primary objective of the study is to demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) with alirocumab 150 mg subcutaneous (SC) every 2 weeks (Q2W) in comparison to placebo after 12 weeks of treatment. **Secondary Objective(s)** The secondary objectives of the study are: • To evaluate the effect of alirocumab 150 mg Q2W on other lipid parameters (ie, apolipoprotein [Apo] A-1 and B, non-high-density lipoprotein cholesterol [non-HDL-C], total-cholesterol [TC], proportion of patients with 15%, 30%, and 50% LDL-C reductions, Lp(a), HDL-C, triglycerides [TG]) in patients with HoFH • To evaluate the safety and tolerability of alirocumab 150 mg SC Q2W in patients with HoFH • To assess the pharmacokinetics of alirocumab 150 mg SC Q2W in patients with HoFH • To assess the potential development of anti-drug (alirocumab) antibodies
Study Design	This is a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of alirocumab in patients with HoFH. Approximately 74 patients will be randomized in a 2:1 ratio to receive either alirocumab 150 mg SC Q2W or matching placebo. Randomization will be stratified by apheresis treatment status. The study will consist of up to 4 periods: a 4-week optional run-in, a 2-week screening period, a 12-week double-blind treatment period, and a mandatory 12-week open-label treatment period. Patients not continuing on to another lipid-lowering study will also undergo an 8-week follow-up period. The optional run-in will last up to 4 weeks and will be available for those patients whose background therapy or apheresis schedule and/or apheresis settings have not been stable prior to screening. Additionally, all patients on LDL apheresis must be diagnosed based on genotype and, if genotype information has not been determined previously, they can enter the run-in to allow time, if needed, to determine their mutation status.

	The 2-week screening period will be used to determine eligibility and provide training on appropriate SC injection techniques. All patients who meet the inclusion criteria and none of the exclusion criteria will enter the 12-week double-blind treatment period. The first injection of double-blind study drug will occur on day 1 (baseline), and the last injection of double-blind study drug will occur on day 71 (week 10). Following the completion of the 12-week double-blind treatment period, all patients will enter a 12-week open-label treatment period. The first injection of open-label alirocumab will occur on day 85 (week 12) and the last injection of open-label alirocumab will occur on day 155/week 22. After completion of the 12-week open-label treatment period, all patients who have successfully completed this study may have the opportunity to participate in an additional lipid-lowering clinical trial.
Study Duration	This is a 24-week study, excluding the optional 4-week run-in period and the 2-week screening period.
Population	The study population will consist of male and female patients, ≥18 years of age diagnosed with HoFH.
Sample Size:	Approximately 74 patients
Target Population:	Males and females ≥18 years of age diagnosed with HoFH, except patients known to have null/null mutations in both LDLR alleles.
Treatment(s)	
Study Drug Dose/Route/Schedule:	Alirocumab 150 mg SC every 2 weeks from day 1 through week 12 (end of double-blind treatment period, last double-blind injection at week 10). Regardless of treatment assignment in the double-blind treatment period, all patients will receive open-label alirocumab 150 mg SC Q2W starting at week 12 and continuing through week 24 (last injection in the open-label period at week 22).
Reference Drug Dose/Route/Schedule:	Placebo SC Q2W
Background Treatment Dose/Route/Schedule:	Not Applicable
Endpoint(s)	
Primary:	The primary endpoint is the percent change in LDL-C from baseline to Week 12.
Secondary:	• The percent change in Apo B from baseline to week 12 (intent-to-treat [ITT] estimand). • The percent change in non-HDL-C from baseline to week 12 (ITT estimand).

	• The percent change in TC from baseline to week 12 (ITT estimand). • Proportion of patients with ≥15% reduction in LDL-C at week 12 (ITT estimand). • Proportion of patients with ≥30% reduction in LDL-C at week 12 (ITT estimand). • The percent change in Lp(a) from baseline to week 12 (ITT estimand). • Proportion of patients with ≥50% reduction in LDL-C at week 12 (ITT estimand). • The percent change in HDL-C from baseline to week 12 (ITT estimand). • The percent change in fasting TG from baseline to week 12 (ITT estimand). • The percent change in Apo A-1 from baseline to week 12 (ITT estimand).
Procedures and Assessments	The efficacy of alirocumab will be assessed by clinical laboratory evaluation of lipid levels. Overall safety will be assessed by monitoring/evaluation of treatment-emergent adverse events, physical examinations, vital signs, electrocardiograms, and clinical safety laboratory tests at specified time points. Blood samples will be collected for determination of alirocumab concentration and anti-alirocumab antibody levels at predetermined time points. Research samples will be collected.
Statistical Plan	Patients will be randomized in the double-blind treatment period to alirocumab or placebo in a ratio of 2:1 respectively, with the primary efficacy hypothesis comparing the alirocumab-treated group to the placebo group at week 12. For the primary efficacy hypothesis during the double-blind treatment period, an initial total sample size of 51 patients (34 patients in the alirocumab-treated group and 17 patients in the placebo group) will have 90% power to detect a difference in mean percent change in LDL-C of 20%, with a two-sided significance level and assuming a standard deviation of 20%. Taking into account a 5% non-evaluable patient rate for the primary efficacy endpoint, the initial study sample size is increased to 54 patients (36 patients in the alirocumab-treated group and 18 patients in the placebo group). Following the Blinded Sample Size Adjustment process, the total study sample size will increase to approximately 74 patients, adding approximately 20 patients to the initial study sample size.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
Apo	Apolipoprotein
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
BW	Body weight
CPK	Creatine phosphokinase
CRF	Case report form (electronic)
CRO	Contract research organization
CV	Cardiovascular
CVD	Cardiovascular disease
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of the study
FH	Familial hypercholesterolemia
GCP	Good Clinical Practice
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS/IWRS	Interactive voice response system/ Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LDLRAP1	LDL receptor adaptor protein 1
LMT	Lipid Modifying Therapy
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction

mITT	Modified intent-to-treat
MMRM	Mixed-effect model with repeated measures
NOD	New onset of diabetes
OTC	Over-the-counter
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
PT	Preferred term
Q2W	Every 2 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism that predisposes a person to premature severe cardiovascular disease (CVD) (Kolansky 2008). It can be either an autosomal dominant or an autosomal recessive disease that results from mutations in the low-density lipoprotein receptor (LDLR), or in 3 associated genes: proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein B (Apo B), and LDL receptor adaptor protein 1 (LDLRAP1), with a similar phenotype and varying severity. 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).

Homozygous familial hypercholesterolemia (HoFH) is a rare, serious condition genetically defined to include individuals with the same mutation(s) in both LDLR, ApoB, or PCSK9 alleles (true homozygotes), different mutations in each allele of the same gene (compound heterozygotes), or different mutations on different genes (double heterozygotes). Phenotypically, the severity of HoFH depends on the amount of residual LDLR activity, historically categorized as either receptor-negative (<2% of normal LDLR activity) or receptor-defective (2% to 25% of normal LDLR activity) based on the amount of activity in skin fibroblasts. The genetic definition used in the current study will include all individuals considered to be true homozygotes, compound heterozygotes, or double heterozygotes. However, those individuals with null LDLR mutations in both alleles will be excluded because it is expected that alirocumab will not be efficacious in those patients, as has already been shown with another PCSK9 inhibitor, evolocumab (Raal 2015).

Patients with HoFH have severe hypercholesterolemia (500-1000 mg/dL, 12.95-25.9 mmol/L), resulting in lifelong exposure to high levels of plasma LDL-C and increased risk of developing atherosclerosis at a highly accelerated rate, often manifesting within the first 2 decades of life. Persistently high levels of LDL-C can also lead to cutaneous and tendon xanthomas, valvular and supravalvular stenosis (Kolansky 2008). This accelerated atherosclerosis results in premature cardiovascular disease (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 (Kolansky 2008).

The initial goal of drug therapy in adult patients with FH is to achieve LDL-C reduction ≥50% (Goldberg 2011). If this is achieved, therapy is escalated with an aim to achieve an LDL-C of <100 mg/dL (2.59 mmol/L) in the absence of coronary artery disease or other major risk factors or <70 mg/dL (<1.81 mmol/L) in the presence of coronary artery disease or other major risk factors (Watts 2014). However, management of elevated LDL-C in patients with HoFH is challenging with the current existing treatment options. Patients with HoFH generally have a poor response to conventional drug therapies, resulting in extremely elevated LDL-C levels that are often refractory to pharmacologic management thus requiring the need to initiate LDL apheresis.

Statins inhibit cholesterol synthesis by inhibiting 3-hydroxy-3-methyl-glutaryl coenzyme reductase and are used as first-line therapy in HoFH patients because they have been proven to reduce CV mortality in non-FH patients. High-dose statins have demonstrated a mean reduction in LDL-C of 18-22% in patients with HoFH (Lipitor Product insert, Crestor Product insert, Zocor Product insert). Compare this with the 50-60% reductions seen in the non-FH population; it is clear that patients with mutations resulting in little or no LDL receptor function may not have as robust a response to statins. Patients with HoFH tend to be refractory to statins because the

mechanism of action generally lowers LDL-C levels through up-regulation of the hepatic LDL receptor. Nonetheless, despite the near total loss of functional LDL receptors in HoFH patients, statins are still used as first line therapy in order to maximize residual receptor activity (Raal 2000, Marais 2008, Raal 1997).

Ezetimibe, a cholesterol absorption inhibitor has been shown to provide an additional 14-21% LDL-C reduction when added to high dose statins (Gagné 2002), but many patients treated with the combination of high dose statin and ezetimibe remain far from their target LDL-C. Newer therapies, i.e., mipomersen and lomitapide, have been approved for use in patients with HoFH, and can provide an additional ~25% and 40% reduction in LDL-C, respectively, when used along with other LMTs). However, these new therapies are not commercially available in all countries and are associated with increases in hepatic fat content, elevated markers of liver injury, frequent injection site reactions that can be of severe intensity (mipomersen) or poorly tolerated gastrointestinal adverse effects (lomitapide) (Raal 2010, Cuchel 2013).

Mechanical removal of LDL-C using LDL apheresis is an option, but may lower the quality of life in patients and present other challenges (Schiel 1995). Low-density lipoprotein apheresis is a costly procedure that is invasive and burdensome for patients. Many patients must travel a significant distance for this procedure, which is administered over 3 hours and must be given every week to every 4 weeks, depending on the patient's LDL-C level and CV risk. In addition, this procedure may require placement of a shunt for frequent vascular access, although peripheral veins are used for vascular access in approximately 85% of cases. Low-density lipoprotein apheresis is generally well tolerated, but may result in hypotension, hypocalcemia, allergic reactions, and an acute decrease in serum protein levels. The quality of life in patients undergoing apheresis in addition to lipid-lowering drugs was lower compared with patients treated only with lipid-lowering drugs (Schiel 1995). Patients on a LMT regimen who require apheresis to lower LDL-C, may benefit from the addition of alirocumab to their current LDL-C lowering therapies by reducing or eliminating the need for apheresis.

Recently, 2 PCSK9 inhibitors (alirocumab and evolocumab) have been approved to lower LDL-C in patients with heterozygous familial hypercholesterolemia (HeFH) and one PCSK9 inhibitor (evolocumab) has been approved to lower LDL-C in patients with HoFH (Praluent Product insert, Repatha Product insert). In the non-FH and HeFH patient populations, the addition of alirocumab on top of background LMT resulted in LDL-C reductions of 45-60%. For example, in the Odyssey FH 1 and FH 2 studies comparing alirocumab on top of maximally tolerated statins (with or without other LMTs, including ezetimibe) in patients with HeFH and LDL-C ≥70 mg/dL with a history of myocardial infarction (MI)/stroke or LDL-C ≥100 mg/dL without a history of MI/stroke, treatment with alirocumab reduced LDL-C by up to a mean of 48.8% after 24 weeks (Kastelein 2015). Efficacy with another PCSK9 inhibitor, evolocumab, has also been seen in the difficult-to-treat HoFH population, although the response has not been as robust. The TESLA-B study compared evolocumab on top of statins (with or without other LMTs, including ezetimibe) in patients with HoFH and showed a mean percent reduction in LDL-C at week 12 of 23.1%. (Raal 2015). Additionally, because PCSK9 inhibitors reduce LDL-C by increasing the number of hepatic LDL receptors, evolocumab therapy did not reduce LDL-C in patients with LDL receptor-negative mutations in both alleles (Raal 2015, Repatha Product Insert).

The primary purpose of this study is to evaluate the efficacy, safety and tolerability of alirocumab in patients with HoFH (excluding those patients with null/null mutations in both LDLR alleles).

Additional background information on the investigational study drug and development program is provided in the Investigator's Brochure. For countries where alirocumab is approved, additional information can be found in the local country's prescribing information.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to demonstrate the reduction of LDL-C with alirocumab 150 mg subcutaneous (SC) every 2 weeks (Q2W) in comparison to placebo after 12 weeks of treatment.

2.2. Secondary Objective(s)

The secondary objectives of the study are:

- To evaluate the effect of alirocumab 150 mg Q2W on other lipid parameters (i.e., apolipoprotein [Apo] A-1 and B, non-high-density lipoprotein cholesterol [non-HDL-C], total cholesterol [TC], proportion of patients with 15%, 30%, and 50% LDL-C reductions, Lp(a), HDL-C, triglycerides [TG]) in patients with HoFH
- To evaluate the safety and tolerability of alirocumab 150 mg SC Q2W in patients with HoFH
- To assess the pharmacokinetics (PK) of alirocumab 150 mg SC Q2W in patients with HoFH
- To assess the potential development of anti-drug (alirocumab) antibodies

2.3. Other Objectives

- Genotype information will be collected for all patients to characterize HoFH mutation status in order to explore potential differences in efficacy and safety
- To assess the effect of alirocumab on eligibility for apheresis (using German and US apheresis criteria)
- To assess the effect of alirocumab on quality of life using the EQ-5D QOL questionnaire

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Treatment with alirocumab for 12 weeks will result in a greater percent reduction in LDL-C from baseline than placebo treatment in patients with HoFH who are not already receiving PCSK9 targeted therapy.

3.2. Rationale

3.2.1. Rationale for Study Design

Patients with HoFH have persistently elevated LDL-C, which is a contributing factor to a number of health concerns, principally accelerated atherosclerosis resulting in premature CV disease. Despite treatment with LMTs such as pharmacological agents including statins, and mechanical removal of lipids by LDL apheresis, many patients with HoFH–remain far from their LDL-C treatment goal. In a cohort study, the age of first CVD event was in the third decade of life in HoFH (Raal 2011). While this is later than the early teen years as seen before implementation of medical regimens such as statins, the need for more intensive treatments remain in order to delay the onset of CVD and occurrence of events.

This study is intended to demonstrate the efficacy and safety of alirocumab in patients with HoFH. The study population will include individuals ≥18 years of age. Diagnosis of HoFH will be based on either genotyping data or clinical criteria. The genetic definition will include all individuals considered to be true homozygotes, compound heterozygotes, or double heterozygotes for mutations in the LDLR, ApoB, PCSK9, or LDLRAP1 genes. In this study, however, individuals with history null/null LDLR mutations will be excluded because PCSK9 inhibitors, including alirocumab, will not be efficacious in those patients. This was confirmed in the evolocumab HoFH study (TESLA-B, TASSIG), where patients with null/null LDLR mutation status were treated with evolocumab, but did not have any response or had a minimal response to treatment.

Percent change in LDL-C from baseline will be the primary endpoint. Low-density lipoprotein cholesterol 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 alirocumab on top of patients' existing treatment regimens of maximally tolerated LMT, including lipid apheresis. This study will utilize an optional run-in period for those patients that have not yet achieved a stable background treatment regimen that will be required to be maintained throughout the double-blind treatment period. An add-on design is appropriate because removal of any therapies from the patient's existing treatment regimen will lead to an increase in LDL-C and possibly contribute to the serious CV sequelae seen in this disease. Treatment duration of 12 weeks for the primary endpoint will allow alirocumab to achieve steady state and exert its full effect on LDL-C. An additional 12-week open-label treatment period in which all patients will be administered alirocumab will allow further assessment of safety in this population.

3.2.2. Rationale for Dose Selection

Alirocumab 75 mg and 150 mg SC Q2W are the approved doses and is currently authorized in 40 countries worldwide (including the US, European Union, Canada, Norway, Iceland, Brazil, and Japan). The 150 mg SC Q2W dose has demonstrated saturation of free PCSK9 through the dosing interval and provides maximum efficacy. The need for a higher starting dose in hard-to-treat patients as characterized by a higher baseline LDL-C was seen in the Odyssey FH1, FH2 and HIGH FH studies. The Odyssey FH1 and FH2 studies enrolled patients with HeFH not controlled on maximally tolerated statins (with or without ezetimibe) and evaluated the addition of alirocumab 75 mg SC Q2W, with a possible up-titration to 150 mg SC Q2W, on LDL-C. Approximately 40% of the patients needed their dose titrated from 75 mg SC Q2W to 150 mg SC

Q2W, and the need for titration was a reflection of the baseline LDL-C value. Patients requiring up-titration had a mean LDL-C of 160 mg/dL (4.14 mmol/L) at baseline vs. 118 mg/dL (3.05 mmol/L) in those patients not requiring titration. The Odyssey HIGH FH study included patients with HeFH receiving maximally tolerated statin therapy and baseline LDL-C levels ≥160 mg/dL (4.14 mmol/L) and used a starting dose of 150 mg SC Q2W. At this higher starting dose, alirocumab was able to reduce LDL-C by approximately 45.7% from baseline (Ginsberg 2016). Because patients with HoFH are proven to be a hard-to-treat population compared to non-FH and HeFH patients and will have a very high baseline LDL-C far from their target level, the dose of alirocumab proposed for this study is the highest approved dose, 150 mg SC Q2W.

In addition to being efficacious, alirocumab has a favorable safety profile. Overall, the most commonly occurring treatment-emergent adverse events (TEAEs), reported in a higher proportion of patients in the alirocumab group compared to placebo (ie, incidence ≥2.0% in the alirocumab group) were: injection site reaction (7.2% vs 5.1%), nasopharyngitis (11.3% vs 11.1%), influenza (5.7% vs 4.6%), myalgia (4.3% vs 3.4%), urinary tract infection (4.8% vs 4.6%), diarrhea (4.7% vs 4.4%) and bronchitis (4.3% vs 3.8%) (Praluent Product Insert). No differences in the safety profile have been observed between the two approved doses of 75 mg and 150 mg.

It is expected that treatment with alirocumab 150 mg Q2W in patients with HoFH already receiving maximally tolerated LMT or LDL apheresis will be well-tolerated and have an acceptable safety profile while providing maximal LDL-C lowering effect.

3.2.3. Benefit / Risk Assessment

Patients with HoFH have extremely high LDL-C levels, are far from their target LDL-C, and will require significant reductions in LDL-C. Despite the approval of newer treatments including lomitapide and mipomersen, the need for more intensive therapies remain. PCSK9 inhibitors are a new addition to the armamentarium of LMT that has proven to profoundly decrease LDL-C. In TESLA-B, evolocumab on top of statins (with or without ezetimibe) in patients with HoFH showed a 23.1% mean reduction in LDL-C at week 12 (Raal 2014). In the Odyssey HIGH FH study, alirocumab reduced LDL-C by approximately 45.7% in patients with HeFH receiving maximally tolerated statin therapy and baseline LDL-C levels ≥160 mg/dL (4.14 mmol/L) (Ginsberg 2016). Based on these data, it is expected that the addition of alirocumab 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). Within the context of this study in the HoFH patient population, even a modest reduction in LDL-C may translate into significant benefit for these patients.

It is also expected that treatment with alirocumab will be well tolerated and have an acceptable safety profile. The accumulated safety information show that the most commonly occurring TEAEs with alirocumab were nasopharyngitis, injection site reactions, influenza, myalgia, musculoskeletal pain, and contusion. Moreover, the rates of these adverse events (AEs) were relatively low, ranging from 11.3% to 2.1% for the alirocumab treatment group (vs 11.1% - 1.6% in the placebo group) (Praluent Product Insert).

Taken together, these data show that the benefit/risk assessment of treatment with alirocumab in the HoFH populations is favorable.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (age, race, weight, height, etc), disease characteristics including lipid levels, mutation status, medical history, medication history and apheresis schedule (if applicable) for each patient.

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary efficacy endpoint is the percent change in LDL-C from baseline to week 12 in the ITT population for alirocumab 150 mg Q2W as compared with placebo in patients with HoFH.

The percent change in LDL-C from baseline to week 12 is defined as:

$$100 \times \frac{\text{(LDL-C value at week 12 -LDL-C value at baseline)}}{\text{LDL-C value at baseline}}$$

For LDL-C analysis, both calculated and measured LDL-C values will be taken into account. In case both calculated and measured LDL-C values are available for the same sampling time point, the measured LDL-C will be considered. The baseline LDL-C value will be the last LDL-C value obtained before the first dose of double-blind-study drug. For randomized but not-treated patients, baseline will be defined as the last value before randomization. The LDL-C at week 12 will be the LDL-C value obtained within the week 12 analysis window, regardless of adherence to treatment (ITT estimand).

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

4.2.2. Secondary Efficacy Endpoints

4.2.2.1. Key Secondary Efficacy Endpoints

- The percent change in Apo B from baseline to week 12 (ITT estimand).
- The percent change in non-HDL-C from baseline to week 12 (ITT estimand).
- The percent change in total cholesterol from baseline to week 12 (ITT estimand).
- Proportion of patients with ≥15% reduction in LDL-C at week 12 (ITT estimand).
- Proportion of patients with ≥30% reduction in LDL-C at week 12 (ITT estimand).
- The percent change in Lp(a) from baseline to week 12 (ITT estimand).

- Proportion of patients with ≥50% reduction in LDL-C at week 12 (ITT estimand).
- The percent change in HDL-C from baseline to week 12 (ITT estimand).
- The percent change in fasting TG from baseline to week 12 (ITT estimand).
- The percent change in Apo A-1 from baseline to week 12 (ITT estimand).

The same definition and rules apply to these key secondary efficacy endpoints as are applied to the primary efficacy endpoint.

4.2.2.2. Other Secondary Efficacy Endpoints

- The percent change in LDL-C from baseline to week 12 in the modified (m)ITT population (Section 10.3.1), using all LDL-C values within the week 12 analysis window and during the efficacy treatment period (on-treatment estimand).
- The percent change in Apo B, non-HDL-C, TC, Lp(a), HDL-C, fasting TG and Apo A-1 from baseline to week 12 (on-treatment estimand).
- Proportion of patients with ≥15% reduction, ≥30% reduction, and ≥50% reduction in LDL-C at week 12 (on treatment estimand).
- The absolute change in the ratio of Apo B/Apo A-1 from baseline to week 12 (ITT estimand).

The efficacy treatment period is defined as the time from the first double-blind study drug injection up to 21 days after the last double-blind study drug injection, or the first open-label alirocumab injection (if applicable), whichever comes first.

4.2.3. Safety Endpoints

- Safety parameters (AEs, laboratory data, vital signs, and electrocardiogram [ECG]) assessed throughout the study.

4.2.4. Other Endpoints

- Exploratory relationships between HoFH genotype status and lipid parameters.
- The change in the proportion of patients who meet US apheresis eligibility criteria from baseline to week 12 (Goldberg 2011).
- The change in the proportion of patients who meet German apheresis eligibility criteria from baseline to week 12 (Schettler 2012).
- Response of each EQ-5D item, index score, and change of index score from baseline through week 12.

4.3. Pharmacokinetic Variables

The PK variable will be alirocumab serum concentration collected at specified sampling time.

4.4. Anti-Drug Antibody Variables

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

- Total patients negative in the ADA assay at all time points.
- Pre-existing immunoreactivity - defined as either an anti-drug antibody (ADA) positive response in the assay at baseline with all post-dose ADA results negative, OR a positive response at baseline with all post-treatment ADA responses less than 4-fold baseline titer levels.
- Treatment emergent - defined as either any post-dose positive ADA response when baseline results are negative, OR any post-dose positive ADA response that is at least 4-fold over the baseline level when baseline is positive in the ADA assay.

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 is a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of alirocumab in patients with HoFH.

Approximately 74 patients will be randomized in a 2:1 ratio to receive either alirocumab 150 mg SC Q2W or matching placebo. Randomization will be stratified by apheresis treatment status (Yes/No).

The study will consist of up to 4 periods: an optional 4-week run-in period (for patients whose background medical LMT regimen or apheresis schedule and/or apheresis settings have not been stable prior to screening), a 2-week screening period, a 12-week double-blind treatment period, and a mandatory 12-week open-label treatment period (Figure 1). Patients not continuing on to another lipid lowering study will also undergo an 8-week follow-up period.

Optional Run-in:

Apheresis therapy - Patients who are undergoing apheresis therapy must be on a stable weekly or every other week schedule. Patients whose schedule or apheresis settings that have not been stable for at least 8 weeks before the screening visit will enter a 4-week run-in period before the screening period. After the 4-week run-in period, patients whose lipid-apheresis schedule/settings remain stable (and have been stable for at least 8 weeks in total) will be eligible to enter the 2-week screening period. Additionally, all patients on LDL apheresis must be diagnosed based on genotype and, if genotype information has not been determined previously, they can enter the run-in to allow time, if needed, to determine their mutation status.

Lipid-modifying therapy - Patients who are on background LMT that has not been stable for at least 4 weeks before the screening visit will enter a 4-week run-in period to stabilize their LMT before entering the screening period. Patients who have not been on a stable dose of mipomersen for 6 months prior to screening or on a maximum tolerated dose of lomitapide for 12 weeks prior to screening are excluded.

Screening:

Once on a stable background regimen as defined above, patients will enter a 2-week screening period. Initial eligibility will be determined during this screening period by standard screening procedures. A DNA sample will be collected for HoFH mutation status.

Patients should be on a stable low fat or heart-healthy diet throughout the duration of the study, starting at screening through the end of the double-blind treatment period and through the open-label treatment period.

Patients' exercise regimen should remain stable throughout the duration of the study, from screening, through the end of the double-blind treatment period and through the open-label treatment period.

The patient or caregiver will be trained to self-inject/inject using a dose of placebo during the screening period or at the first visit of the double-blind treatment period.

Double-blind Treatment:

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

alirocumab 150 mg SC Q2W

OR

matching placebo SC Q2W

Study drug administration during the double-blind treatment period will start on the day of randomization and will be administered immediately after completion of the LDL apheresis procedure (if applicable). For those patients not undergoing LDL apheresis, administration of study drug must be made after all samples for clinical laboratory evaluation have been obtained. The last injection during the double-blind treatment period will be on day 71/week 10.

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 on lipid parameters, it is important to match the time of the baseline activities with the timing of the week 12 activities. This would mean that timing between the baseline sample collection relative to the most recently completed LDL apheresis procedure should match the timing of the week 12 sample collection relative to the most recently completed LDL apheresis procedure.

For all patients who are not undergoing apheresis, all samples for clinical laboratory evaluation must be obtained prior to administration of investigational medical product. The efficacy of alirocumab will be assessed by clinical laboratory evaluation of lipid levels at pre-specified time points throughout the study.

Patients who are receiving 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 through the end of the open-label treatment period/end-of-study visit (week 24).

Patients who prematurely discontinue study drug during the double-blind treatment period should be encouraged to 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 the end of the double-blind treatment visit (this should take place within 5 days of discontinuation of study drug, if possible).

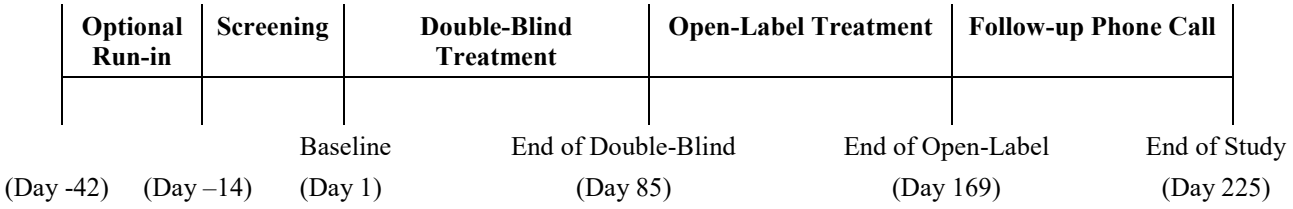
Open-label Treatment:

To provide further safety data in this rare patient population, all patients will participate in an open-label treatment period. Regardless of treatment assignment in the double-blind treatment period, patients will receive open-label study drug (alirocumab 150 mg SC Q2W) starting at week 12 (day 85) and continuing through week 24 (end of open-label treatment period, last injection of study drug on day 155/week 22). Patients who are receiving LMT or who are undergoing LDL apheresis should continue a stable dose and regimen and a stable LDL apheresis schedule and settings (as applicable) throughout the duration of the open-label treatment period.

Upon completion of the open-label treatment period, the sponsor may offer each patient the opportunity to participate in an additional lipid-lowering clinical trial. The patient and investigator may decline participation in further treatment trials.

Patients who do not participate in another lipid-lowering study will undergo an 8-week follow-up period. A follow-up phone call will be made at week 32 (corresponding to the 70 day follow-up) to collect AE and concomitant medication information.

Figure 1: Study Flow Diagram



5.1.1. End of Study Definition

The end of study definition for this study is the last visit of the last patient.

5.2. Planned Interim Analysis

No interim analysis is planned.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Approximately 74 patients with a 2:1 randomization to alirocumab and placebo are planned.

6.1.1. Rescreening of Patients

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

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

6.2. Study Population

The study population will consist of male and female patients, ≥18 years of age diagnosed with HoFH, except patients known to have null/null mutations in both LDLR alleles.

6.2.1. Inclusion Criteria

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

1. Males and females ≥18 years of age at the time of the screening visit.

2. Diagnosis of HoFH by at least 1 of the following genotype or clinical criteria (all patients on LDL apheresis must be diagnosed based on genotype):
   a. Documented homozygous or compound heterozygous mutations in both LDLR alleles

      Note: Patients with known null mutations in both LDLR alleles are excluded (see Exclusion Criteria)

   b. Presence of homozygous or compound heterozygous mutations in Apo B, PCSK9 or LDLRAP1
   c. Presence of double heterozygous mutations, ie, mutations on different genes in the LDLR, Apo B or PCSK9 alleles
   d. Untreated TC >500 mg/dL (12.93 mmol/L) and TG <300 mg/dL (3.39 mmol/L)

      AND

      Both parents with history of TC >250 mg/dL (6.46 mmol/L) **OR** cutaneous or tendinous xanthoma before age 10
3. Receiving a stable dose of a statin at the screening visit

   Note: Patients who are not able to tolerate a statin or if statins were found to be ineffective may be included in the study but the reason should be documented in the case report form (CRF).
4. 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 days) or every other week (every 14 days) schedule or stable settings for at least 8 weeks
5. Willing to maintain a stable low fat or heart-healthy diet for the duration of the study
6. Willing and able to comply with clinic visits and study related procedures
7. Provide signed informed consent

6.2.2. Exclusion Criteria

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

1. Documented evidence of a null mutation in both LDLR alleles
2. Use of a PCSK9 inhibitor within 10 weeks from screening visit
3. Background medical LMT that has not been stable for at least 4 weeks (6 weeks for fibrates, 24 weeks for mipomersen, 12 weeks for maximum tolerated dose of lomitapide) before the screening visit

   Patients will have the option to enter the optional run-in period. Once the patient is stable on his/her background medical LMT for the appropriate amount of time, the patient may enter the screening period.
4. LDL apheresis schedule/apheresis settings that have not been stable for at least 8 weeks before the screening visit or an apheresis schedule/settings that is not anticipated to be stable over the next 24 weeks

Patients will have the option to enter the optional run-in period. Once the patient is stable on his/her background lipid apheresis schedule/settings for the appropriate amount of time, the patient may enter the screening period.

5. Use of nutraceuticals or over-the-counter (OTC) 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.

   Patients will have the option to enter the optional run-in period. Once the patient is stable on his/her nutraceuticals or OTC therapies for the appropriate amount of time, the patient may enter the screening period.

6. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins. This may include newly diagnosed (within 3 months prior to randomization visit [week 0/day 1]) diabetes mellitus, or signs and symptoms of hypothyroidism.

   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 at the screening visit

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. Chronic use of systemic corticosteroids, unless on a stable regimen of 10 mg daily prednisone equivalent or less for at least 6 weeks prior to randomization

   Note: topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed

10. Use of estrogen or testosterone therapy unless the regimen has been stable in the past 6 weeks prior to the screening visit and there are no plans to change the regimen during the study
11. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the screening visit (1 repeat measurement is allowed)
12. LDL-C level <70 mg/dL (1.81 mmol/L) at the screening visit
13. 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
14. History of New York Heart Association (NYHA) class IV heart failure within 12 months before screening
15. History of cancer within the past 2 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 within 1 month or 5 half-lives prior to the screening visit, whichever is longer

17. Conditions/situations such as:
    - 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
    - Considered by the investigator or any sub-investigator as inappropriate for this study for any reason, eg:
        - Deemed unable to meet specific protocol requirements, such as scheduled visits
        - Deemed unable to tolerate injections as per the patient or the investigator
        - Investigator or any sub-investigator, pharmacist, study coordinator, other study staff or relative thereof directly involved in the conduct of the protocol, etc.
        - Presence of any other conditions (eg, geographic or social), either actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study
18. Laboratory findings during screening period (not including randomization labs):
    - Hepatitis B surface antigen and/or Hepatitis C antibody (associated with a positive HCV RNA polymerase chain reaction) at the screening visit
    - Positive serum beta-human chorionic gonadotropin (hCG) or urine pregnancy test in women of childbearing potential
    - Estimated glomerular filtration rate (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)
    - Unexplained serum creatine phosphokinase CPK >5 x ULN (1 repeat lab is allowed)
19. Known hypersensitivity to monoclonal antibody therapeutics
20. Member of the clinical site study team and/or his/her immediate family
21. Pregnant or breastfeeding women
22. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment and for the duration of the study. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence**.

*Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or oophorectomy.

**Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.

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. The site will be provided a retention manual outlining the best practices for patient retention.

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

The investigator should make the best effort to contact any patient (eg, contacting patient's family or private physician, reviewing available registries or health care database) who fails to return to the site and to determine health status, including vital status at a minimum. 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).

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

6.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

7. STUDY TREATMENTS

The investigational study drug injections will be provided in prefilled pens and will be administered SC into the abdomen, thigh, or outer area of the upper arm. The patient or caregiver will use placebo for injection training at the clinical site.

7.1. Injection Training

After study eligibility is confirmed, the patient or caregiver will be trained to self-inject/inject using placebo.

Injection training can be done during the screening period or at baseline (visit 2) using placebo. All patients and caregivers who will inject the investigational study drug must be trained by the study staff.

Investigators will have the option of providing a second placebo dose to patients who require additional injection training before randomization. The patient and/or investigator may elect to inject the additional dose of placebo at home or at the study site.

7.2. Investigational and Reference Treatments

Double-blind-Treatment:

Study drug administration during the double-blind treatment period will start on the day of randomization and will be administered immediately after completion of the LDL apheresis procedure (if applicable). For those patients not undergoing LDL apheresis, administration of the investigational study drug must be made after all samples for clinical laboratory evaluation have been obtained. The last injection of double-blind study drug will occur on day 71/week 10.

If a dose is missed, the patient will be instructed to administer the injection within 7 days from the missed dose. If the missed dose is not administered within 7 days, the patient will be instructed to skip the dose and resume the original schedule.

Patients will be randomized in a 2:1 ratio to receive:

- alirocumab 150 mg SC Q2W

  OR

- matching placebo SC Q2W

Sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL in a prefilled pen.

Placebo will also be supplied in a prefilled pen.

Open-label Treatment:

To provide further safety data in this rare patient population, all patients will receive open-label investigational study drug (alirocumab 150 mg SC Q2W), starting at week 12 and continuing through week 24 (end-of open-label treatment period/EOS visit, last injection at week 22) regardless of treatment assignment in the double-blind treatment period. Patients who are receiving LMT or who are undergoing apheresis should continue a stable dose and regimen and a stable apheresis schedule and settings (as applicable) throughout the duration of the open-label treatment period.

Sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL in a prefilled pen.

7.3. Run-in (optional) and Background Treatment(s)

Apheresis therapy - Patients who are undergoing apheresis therapy without a stable weekly or every other week schedule or stable settings for at least 8 weeks before the screening visit will enter a 4-week optional run-in period before the screening period. After the 4-week run-in period, patients whose lipid apheresis schedule/settings remain stable will be eligible to enter the 2-week screening period. Additionally, all patients on LDL apheresis must be diagnosed based on

genotype and, if genotype information has not been determined previously, they can enter the run-in to allow time, if needed, to determine their mutation status.

Lipid modifying therapy - Patients who are on background LMT that has not been stable for at least 4 weeks before the screening visit will enter a 4-week run-in period to stabilize their LMT. Patients who have not been on a stable dose of mipomersen within 6 months prior to screening or a maximum tolerated dose of lomitapide for 12 weeks prior to screening are excluded.

7.4. Dose Modification and Study Treatment Discontinuation Rules

7.4.1. Dose Modification

Dose modification for an individual patient is not allowed.

7.4.2. Study Drug Discontinuation

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

Patients who permanently discontinue study drug during the double-blind treatment period 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 double-blind treatment visit (this should take place within 5 days of discontinuation of study drug, if possible). Then, patients should resume the original study schedule until the end of the double-blind treatment period and all efforts should be made to perform the week 12 assessments at week 12. The original study schedule will continue until the end of the study visit (ie, follow-up phone call visit).

Patients who permanently discontinue study drug during the open-label period should have, as soon as possible, an unscheduled visit with assessments normally planned at the end of the open-label treatment period (this should take place within 5 days of discontinuation of the study drug, if possible). Upon completion of this visit, the original study schedule will resume until end of study (ie, follow-up phone visit).

Assessment of patients who do not consent to remain in the study after discontinuation of the investigational study drug should be managed according to Section 8.1.2.

7.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Patients should permanently discontinue study drug for the following reasons:

- For female patients, individuals that have become pregnant, are actively trying to become pregnant, or discontinue use of protocol-defined methods of effective birth control
- Acute injection reaction of clinical concern
- At patient request

- If, in the investigator's opinion, continuation of the investigational study drug dosing would be detrimental to the patient's well being
- Intercurrent condition that requires discontinuation of the investigational study drug
- At the specific request of the sponsor
- Patient receives double-blind treatment before randomization

7.4.2.2. Reasons for Temporary Discontinuation of Study Drug

Temporary discontinuation of the investigational study drug may be considered by the investigator because of suspected AEs, including allergic events related to the dose of the investigational study drug. Reinitiating the investigational study drug dosing will be done under close and appropriate clinical and/or laboratory monitoring.

Temporary discontinuation of the investigational study drug is defined as 1 or more scheduled injections that are not administered to the patient as decided by the investigator.

7.5. Management of Acute Reactions

7.5.1. Acute Injection Reactions

7.5.1.1. Systemic Injection Reactions

Acute systemic reactions following injection of the investigational study drug (subcutaneous [SC]) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

7.6. Method of Treatment Assignment

The randomized list of treatment kit numbers will be generated centrally. An interactive voice response system (IVRS) and/or interactive web response system (IWRS) will be used in this study. The investigational study drug will be packaged in accordance with this list.

Patients will be randomly assigned to receive alirocumab 150 mg or matching placebo in a 2:1 ratio, stratified by LDL apheresis treatment status (on vs off treatment).

The treatment kit numbers will be allocated using the centralized treatment allocation system at the randomization visit, at weeks specified in Table 1 as re-supply visits, and at unscheduled visits, if needed.

7.6.1. Blinding

Study patients, the investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron Study Director, Medical Monitor, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

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 the completion of the double-blind treatment period and the first-step analysis.

Blinded investigational study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Anti-drug antibody (ADA) will not be communicated to the sites, and the sponsor's operational team will not have access to results associated with patient identification until after the database lock after completion of the double-blind treatment period.

While the study is ongoing, it is anticipated that unblinded data, after the first step analysis (Section 10.5), will be submitted to health authorities. Sponsor representatives who will conduct and review such data analyses for submission to the health authorities will not be part of the study operational team from that point forward, and patient level results will not be provided to the study sites. The analysis process, the measures used to protect the blind and the integrity of the study, and a communication plan and confidentially agreement will be described in a separate document.

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 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 the investigational study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Training kits containing 1 placebo prefilled pen will be provided to the sites for patient/caregiver injection training that will be performed before randomization during the screening period or at the baseline visit. A second placebo prefilled pen can be used before randomization if the patient/caregiver requires additional injection training.

Study drug will be refrigerated at the site at a temperature of 2ºC to 8ºC. Storage temperature will be logged. Detailed storage instructions are provided in the study manual.

7.7.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2°C to 8°C 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 investigational study drug should be returned to the sponsor or designee.

The investigational study drug will be dispensed to each patient. The investigational study drug will be stored, prepared, and administered by the patient/caregiver according to instructions provided to each patient/caregiver.

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 investigational 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

Patients will complete a dosing log to document compliance with the investigational study drug administration. Measures taken to ensure and document the investigational study drug accountability and compliance are as follows:

- The investigator or designee will obtain via IVRS/IWRS the treatment kit number(s) and will dispense the treatment kit(s) to the patient
- Accountability is to be verified during the investigational study drug kit re-supply visits only. The used and unused kit(s) should be brought to these visits for accountability purposes.
- All kits, including used and unused kits, are to be returned by the patient at the designated visit. An unused kit contains all of the unused prefilled pens. A used kit is one from which the patient has removed 1 or more prefilled pens. A used prefilled pen is one that has been removed from the kit with the intention of administration, including those injections that have been partially or fully injected. The patient should discard all used prefilled pens into the sharps container and never put used prefilled pens back into the used kit.
- All sharps containers should be returned to the site by the patient
- The investigator/study coordinator will enter data in the appropriate CRF pages, according to data recorded in the treatment log form

- The monitor will check the data consistency among CRF pages, treatment log form and returned unused prefilled pens of a corresponding kit

All treatments kits will be retrieved by the sponsor. A detailed treatment log of the returned investigational study drug will be established with the investigator or designee and countersigned by the investigator and the monitoring team.

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. Patients will complete a dosing log to document compliance with the investigational study drug administration.

7.8. Concomitant Medications

Concomitant medications should be kept to a minimum during the study. If considered necessary for the patient's welfare and unlikely to interfere with the investigational study drug, concomitant medications (other than those that are prohibited during the study) may be given at the discretion of the investigator, at a stable dose when possible.

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

7.8.1. Prohibited Medications and Procedures

Use of a PCSK9 inhibitor within 10 weeks from the screening visit is prohibited.

Initiation of or changes to the LDL apheresis schedule and/or settings (if applicable) or background medical LMT from the initial screening visit until the end of study visit is prohibited.

Use of continuous estrogen or testosterone hormone replacement therapy is prohibited unless the regimen has been stable in the past 6 weeks prior to the screening visit.

Chronic use of systemic corticosteroids, unless on a stable regimen of 10 mg daily prednisone equivalent or less for at least 6 weeks prior to randomization, is prohibited. **Note**: topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed.

7.8.2. Permitted Medications and Procedures

Lipid modifying therapies, nutraceuticals, and over-the-counter therapies that may affect lipids are allowed only if they have been used at a stable dose and regimen for at least 4 weeks (6 months for mipomersen, 12 weeks for the maximum tolerated dose of lomitapide) before the screening visit. The dose and regimen must remain stable until the end of study visit.

Low-density lipoprotein apheresis is allowed only if the schedule/settings have been stable for at least 8 weeks before the screening visit and will remain stable until the end of study visit.

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 1: Schedule of Events

	Optional Run-in	Screening Period	Double-Blind Treatment Period					Open-label Treatment Period		Follow-up[10]
Study Procedure	**Run-in Visit 1a**	**Screening Visit 1**	**Baseline Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**End of Double-Blind Treatment Visit 6**	**Visit 7**	**End of Open-Label Treatment Visit 8**	**End of Study Phone Visit 9**
Day	-42 to -14	-14 to -1	1(±1)	29(±5/±1[9])	57(±5/±1[9])	71(±5/±1[9])	85(±3/±1[9])	127(±7)	169(±3/±1[9])	225(±5)
Week	-6 to -2	-2 to -1	0	4	8	10	12	18	24	32
Screening/Baseline:										
Inclusion/Exclusion	X	X								
Informed Consent/Assent[1]	X	X								
Pharmacogenomics Consent/Assent		X								
Medical/Surgical History, Alcohol habits, Smoking habits		X								
Demographics		X								
Treatment:										
Injection training[2]		X	X							
Investigational study drug kit dispensation			X	X			X	X		
Administer SC double-blind investigational study drug[3]			X	X	X	X				
Administer open-label investigational study drug[3]							X	X		
Kit return				X	X			X	X	
Review of dosing log				X	X			X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Efficacy:										
Lipid panel[4]		X	X	X	X		X	X	X	
Specialty lipid panel[4]			X	X	X		X		X	

	Optional Run-in	Screening Period	Double-Blind Treatment Period					Open-label Treatment Period		Follow-up[10]
Study Procedure	**Run-in Visit 1a**	**Screening Visit 1**	**Baseline Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**End of Double-Blind Treatment Visit 6**	**Visit 7**	**End of Open-Label Treatment Visit 8**	**End of Study Phone Visit 9**
EQ-5D			X				X		X	
Safety										
Adverse events	X	X	X	X	X	X	X	X	X	X
Physical examination		X					X		X	
Body weight	X	X					X		X	
Vital signs	X	X	X	X	X	X	X	X	X	
Electrocardiogram[5]		X					X		X	
Laboratory Testing:										
Hematology[6]		X	X		X		X		X	
Blood chemistry[6]		X	X		X		X		X	
Creatine Phosphokinase[6]		X	X		X		X		X	
Hepatitis B surface antigen[6]		X								
Hepatitis C antibody[6]		X					X		X	
Serum pregnancy test		X								
Urine pregnancy test (done locally)	X						X		X	
Urinalysis		X	X		X		X		X	
TSH		X								
hs-CRP[6]		X	X				X		X	
Research samples[6]			X	X	X		X		X	
Mandatory DNA collection for HoFH Genetic Testing[7]	X	X								
PK/Drug Concentration and ADA Samples:										
PK Sample[6]			X	X	X	X	X		X	
ADA Sample[6]			X				X		X	

	Optional Run-in	Screening Period	Double-Blind Treatment Period					Open-label Treatment Period		Follow-up[10]
Study Procedure	**Run-in Visit 1a**	**Screening Visit 1**	**Baseline Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**End of Double-Blind Treatment Visit 6**	**Visit 7**	**End of Open-Label Treatment Visit 8**	**End of Study Phone Visit 9**
[redacted]			X							

8.1.1. Footnotes for the Schedule of Events Table

1. Informed consent/assent will be obtained either at Visit 1a (for patients who need the optional run-in time) or at Visit 1 (for the patients who do not need optional run-in).
2. Injection training will be performed with the patient and/or caregiver during the screening period or at baseline using placebo.
3. After the investigational study drug administration (double-blind and open-label), patients will need to be monitored for 30 minutes.
4. Lipid panel will consist of: total-C, LDL-C, HDL-C, TG, non-HDL-C. Specialty lipid panel will consist of: ApoB, Apo A-1, ratio Apo B/Apo A-1, and Lp(a). Lipid panels should be collected after an approximately 8 hour fast.
5. ECG should be performed before blood samples are collected.
6. On days when a clinic visit coincides with a dosing day, all blood samples (including ADA samples) will be collected immediately prior to LDL apheresis (if applicable) and before the investigational study drug administration, but after study assessments are performed. PK samples will also be used for free and total PCSK9 analysis.
7. Sample should be obtained prior to randomization and will be used to determine HoFH mutation status. Patients on apheresis may collect this during visit 1a.

[redacted]

9. Visit window is ±3 days for patients not on apheresis and +1 day for patients on apheresis. Every attempt should be made to ensure all samples are collected immediately prior to LDL apheresis. The timing between the baseline sample collection relative to the most recently completed LDL apheresis procedure should match the timing of the week 12 sample collection relative to the most recently completed LDL apheresis procedure. Depending on the duration between the LDL apheresis procedure and sample collection, the visit window may not apply.
10. This visit is only for patients who do not participate in another lipid-lowering study.

8.1.2. Early Termination Visit

If for any reason the patient refuses to continue the study, the patient should undergo an unscheduled visit as soon as possible with assessments normally planned at the end of double-blind treatment visit if the patient is in the double-blind treatment period (week 12 visit assessments); if the patient is in the open-label treatment visit, then the end of the open-label treatment assessments should be used (week 24 visit assessments). This visit should take place within 5 days of treatment discontinuation, if possible. The patient should be followed for at least 70 days 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.

8.1.3. Unscheduled Visits

All attempts should be made to keep the 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:

- medical/surgical history
- medication history
- demographics
- hepatitis B surface antigen
- serum pregnancy testing

On day 1, after completion of study assessments, collection of blood samples, LDL apheresis (if applicable), and the first dose of double-blind investigational study drug will be administered. The patient will be monitored at the clinical site for 30 minutes after the first dose. Subsequent doses of the investigational study drug must be administered subcutaneously Q2W. Doses of the investigational study drug should be administered at approximately the same time of day (based upon patient preference) throughout the study. After day 1, it is acceptable for dosing to fall within a window of ± 5 days, with the exception of the week 10 and week 22 doses, which will have a ± 3 day dosing window for patients not on apheresis and a +1 day dosing window for patients on apheresis since there are key efficacy assessments at week 12 and week 24.

In the event an injection is delayed by more than 7 days or completely missed, the patient should return to the original schedule of the investigational study drug dosing without administering additional injections. If the delay is less than or equal to 7 days from the missed date, the patient should administer the delayed injection and then resume the original dosing schedule. Site personnel will provide the patient/caregiver with detailed instructions for transport, storage, preparation, and administration of the investigational study drug.

8.2.2. Efficacy Procedures

Total cholesterol, HDL-C, TG, Apo B, Apo A-1, and Lp(a) will be directly measured by the central laboratory. Low-density lipoprotein cholesterol 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 15 mg/dL, then the central lab will reflexively measure LDL-C using the beta quantification method. Non-HDL-C will be calculated by subtracting HDL-C from the Total-C. The Apo B/Apo A-1 ratio will be calculated.

8.2.2.1. Lipid Panel

Blood samples for the lipid panel and specialty lipid panel will be collected at time points according to Table 1. See Section 8.2.4.4 Laboratory Testing for a list of what is included in the lipid panel and special 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."

8.2.4. Safety Procedures

8.2.4.1. Vital Signs

Vital signs, including blood pressure and heart rate will be collected at time points according to Table 1.

8.2.4.2. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 1. Body weight will be collected at time points according to Table 1. 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

Electrocardiogram should be performed before blood is drawn during the visits requiring blood draws. A standard 12-lead ECG will be performed with the patient in the supine position after resting quietly for 10 minutes at time points according to Table 1. Heart rate will be recorded from the ventricular rate and the PR, QRS, RR and QT intervals will be recorded. The ECG strips or reports will be retained with the source.

8.2.4.4. Laboratory Testing

All laboratory samples (including ADA samples) will be collected after assessments are performed and before a dose of the investigational study drug is administered at visits that correspond with a dosing day. Alcohol consumption within 48 hours or intense physical exercise within 24 hours preceding blood sampling is discouraged. Samples for laboratory testing will be collected at time points according to Table 1 and analyzed by a central laboratory during the study. Lipid panel samples will be collected after 8 hour fasting. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites. Tests include:

Lipid Panel and Specialty Lipid Panel

Total cholesterol	Apo B
Triglyceride	Apo A-1
Calculated LDL-C	Apo B/Apo A-1 ratio
HDL-C	Lp(a)
Non-HDL-C	

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Uric acid
Chloride	Blood urea nitrogen (BUN)	Creatine phosphokinase (CPK)
Carbon dioxide	Aspartate aminotransferase (AST)	
Calcium	Alanine aminotransferase (ALT)	
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

Pregnancy testing (serum and urine) will be performed at time points according to Table 1.

Pregnancy testing (urine) will be assessed locally at time points according to Table 1.

Samples for the liver panel (ALT, AST, alkaline phosphatase, and total bilirubin), high-sensitivity C-reactive protein (hs-CRP) will be collected at time points according to Table 1.

A sample for hepatitis B surface antigen, hepatitis C antibody, and TSH will be collected at screening. Samples for hepatitis C antibody will be collected at time points according to Table 1.***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.

8.2.5. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.5.1. Drug Concentration Measurements and Samples

Samples for drug concentration will be collected at time points listed in Table 1.

[redacted]

8.2.5.2. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 1.

At visits that take place on dosing days, all samples for ADA assessments will be collected before a dose of the investigational study drug is administered.

To maintain the blind of the study, ADA samples will be collected from all patients, including those who received only placebo.

[redacted].

8.2.6. HoFH Genetic Testing

A sample will be collected for mandatory HoFH genetic testing to characterize the mutation status of each patient as listed in Table 1.

8.2.7. Research Samples

Samples for exploratory research will be collected as allowed by local regulations to study PCSK9 levels, PCSK9 function, effects of PCSK9 inhibition with a monoclonal antibody, and mechanisms of hyperlipidemia and heart disease.

Research sampling will be collected at time points according to Table 1. Research samples will be coded to maintain patient confidentiality.

8.2.7.1. Biomarker Procedures

Biomarker samples will be collected at time points according to Table 1 as part of the Research Samples. Biomarker measurements will be performed in matrix, for example, serum samples to determine effects on biomarkers of indication or relevant physiological and pathogenic processes.

The biomarkers studied will be ones believed to be relevant to the pathophysiology of indication target engagement, mechanism of action and possible toxicities. Biomarkers studied may include but not limited to PCSK9. [redacted].

Biomarkers results will be reported separately from the clinical study report.

[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 the patient. This includes death from any cause and all serious adverse events (SAEs) related to the use of the investigational 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 investigational study drug (suspected

unexpected serious adverse reaction), to the health authorities, IRBs/ECs as appropriate, and to the investigators.

Any AE not listed as an expected event in the prescribing information or Investigators Brochure for alirocumab or in this protocol will be considered as unexpected. Any worsening of or new onset of symptoms related to the patient's CVD, which occur during the screening/washout period prior to the investigational study drug administration will be considered expected.

In addition, the sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the investigational study drug 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 IRBs/ECs as appropriate.

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered an investigational study drug, which may or may not have a causal relationship with the investigational 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 the investigational study drug, whether or not considered related to the investigational 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 investigational 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 the investigational 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).

Criteria for reporting SAEs must be followed for these events. See Section 9.4 for more information on recording and reporting SAEs.

9.3.3. Adverse Events of Special Interest

An adverse event of special interest (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 (e.g., regulators) might also be warranted (Section 9.4.3).

Adverse events of special interest for this study 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 plasma glucose (FPG) ≥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 FPG 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

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/assent 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 the investigational 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 30 days of the last dose of the investigational study drug if the patient terminated early 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 recovered, chronic and/or stable, or fatal.

- 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 recovered, chronic and/or stable, or fatal.

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 the investigational 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 study patient, during the study or within 30 days of the last dose of the investigational 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 adverse events of special interest, serious and nonserious, must be reported with 24 hours of identification using the same reporting process as the SAE reporting, per Section 9.4.2.

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 reference 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 recovered, chronic and/or stable, or fatal.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

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

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

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

Injection Site Reactions

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

- **Mild**: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity
- **Moderate**: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity
- **Severe**: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

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

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

The possible answers are:

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

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

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

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Study Conduct:

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

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

The possible answers are:

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

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

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

The investigator should justify the causality assessment of each SAE.

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

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

The possible answers are:

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

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

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

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

9.6. Safety Monitoring

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

9.7. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the alirocumab prescribing information or Investigators Brochure or this protocol, and has a reasonable suspected causal relationship to the medicinal/investigational 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 after the double-blind period completion.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

Let $\mu 0$ and $\mu 1$ be the population means of the percent change from baseline in LDL-C at week 12 under placebo and alirocumab, respectively for the primary analysis. For the primary and main efficacy variables, the following null hypothesis and alternative will be tested:

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

10.2. Justification of Sample Size

Patients will be randomized in the double-blind treatment period to alirocumab or placebo in a ratio of 2:1 respectively, with the primary efficacy hypothesis comparing the alirocumab-treated group to the placebo group at week 12. For the primary efficacy hypothesis during the double-blind treatment period, an initial total sample size of 51 patients (34 patients in the alirocumab-treated group and 17 patients in the placebo group) will have 90% power to detect a difference in mean percent change in LDL-C of 20%, with a two-sided significance level and assuming a standard deviation (SD) of 20%. Taking into account a 5% non-evaluable patient rate for the primary efficacy endpoint, the initial study sample size is increased to 54 patients (36 patients in the alirocumab-treated group and 18 patients in the placebo group).

Following the Blinded Sample Size Adjustment process (see below for details), the total study sample size will increase to approximately 74 patients, adding approximately 20 patients to the initial study sample size.

Blinded Sample Size Adjustment

Referencing the ICH E9 regulatory guidance, the study sample size may be re-estimated after approximately 75% of the patients reach the week 12 visit in the double-blind treatment period to ensure adequate power in case of a larger-than-expected variability in the data. The sample size re-estimation will be based on the actual blinded pooled standard deviation (adjusted as described in Kieser 2003) for the primary efficacy measure. Since the patients' post-baseline LDL-C levels are masked to all study participants (patients, site personnel, and sponsor staff), the blinded pooled standard deviation will be calculated by a designated unblinded CRO statistician who will have access to the lipid data. As mentioned in Kieser and Friede (Kieser 2003), the blinded sample size re-estimation does not affect type I error materially for continuous endpoints.

This re-estimation procedure will assess the need for an increase in sample size and will maintain the initial planned enrollment if the procedure yields a smaller sample size (restricted recalculation). The result of this procedure is non-binding, since the decision to increase the sample size will also take into account other study execution factors (eg, availability of patients). In the case the re-estimated sample size is implemented, a protocol amendment will document the modification.

The blinded sample size adjustment process was implemented in October 2018 when approximately 75% of the patients reached the week 12 visit. The Kieser adjusted pooled standard deviation for LDL-C percent change from baseline was calculated at Week 12 to be 35%, which is larger than the protocol initial planned standard deviation of 20%. Applying the Kieser adjusted pooled standard deviation of 35 (while keeping all other assumptions as described in the protocol), the sample size would increase to 156 patients. With this large sample size increase, enrollment of

additional patients with HoFH, a rare disease, depends on the operational feasibility to identify eligible patients. After an assessment to identify eligible patients, a total sample size of 156 patients is not operationally feasible, but an additional 20 patients is considered realistic. Maintaining all other initial sample size assumptions, a new sample size of approximately 74 patients yields 61% power to detect a treatment group difference in mean percent change in LDL-C of 20%. Taking into account the conservative nature of the assumptions for the initial protocol sample size calculation, the new study sample size of approximately 74 patients will be implemented.

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

Intent-to-Treat Primary Efficacy Analysis Set:

The primary efficacy analysis population is the ITT population (also known as the full analysis set), defined as all randomized patients who had at least 1 measurement value for LDL-C before the first dose of double blind investigational study drug (ie, baseline).

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

Modified Intent-to-Treat Analysis Set:

The modified (m)ITT population is defined as the all randomized population who took at least 1 dose or part of a dose of double-blind investigational study drug and has 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 LDL-C before first dose of double-blind investigational study drug (ie, baseline).
- Availability of at least 1 LDL-C value during the efficacy treatment period and within one of the analysis windows in the double-blind period up to week 12. The efficacy treatment period is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

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

10.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any double-blind investigational study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

10.3.3. The Open-Label Analysis Set

For the open-label treatment period, the open-label extension population for all measurements (efficacy, safety, PK and ADA) will be defined as those patients who received at least 1 dose or part of a dose of open-label investigational study drug alirocumab.

10.3.4. Other Analysis Sets

For the double-blind treatment period, the PK and the ADA analyses will be performed on all randomized patients who received any double-blind investigational study drug, and further:

- The PK population will also require at least 1 non-missing result after the first dose of double-blind investigational study drug.
- The anti-alirocumab antibody analysis will be performed on all treated patients (safety population) with a blood sample at week 0 (baseline) and at least 1 evaluable blood sample for anti-alirocumab antibodies after the first dose of study drug.

10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, SD, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

10.4.1. Patients Disposition

Screened patients are defined as any patient who signed the ICF (informed assent form).

Randomized patients consist of all screened patients with a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not. Patients treated in the double-blind treatment period without being randomized, or treated with a double-blind treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population. The safety experience of patients treated and not randomized will be reported separately.

For any patient randomized more than once during the double-blind treatment period, safety data from the first randomization will be included in the double-blind safety population, with the 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.

Lastly, patients in the open-label treatment period consist of all double-blind treated patients who receive any amount of open-label alirocumab treatment.

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group on the randomized population for the double-blind treatment period and again on the open-label population for the open-label treatment period (which will also include the patient total). Continuous variables will be summarized with mean, median, SD, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

For the double-blind primary comparison of the alirocumab treated group to the placebo treated group, the percent change from baseline in LDL-C at week 12, as defined in Section 4.2.1 will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 4 to week 12 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 (alirocumab versus placebo), randomization strata (undergoing apheresis treatment [Yes vs. No] per IVRS/IWRS), time point (weeks 4, 8, 10, 12), and treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Model assumptions for normality will be explored prior to the analysis testing.

This model will be run using Statistical Analysis Software (SAS) mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least-squares means estimates at week 12 for both treatment groups with their corresponding standard errors.

Let $\mu 0$ and $\mu 1$ be the population means of the percent change from baseline in LDL-C at week 12 under placebo and alirocumab, respectively. The hypothesis that will be tested is "H0: $\mu 0 = \mu 1$" versus "H1: $\mu 0 \neq \mu 1$". Therefore, the alirocumab treated group will be compared to the placebo group using an appropriate contrast statement tested at the 2-sided 0.05 level, with corresponding least squares estimate of mean difference, SE and 95% confidence interval.

Robustness of this statistical method will be assessed via sensitivity analyses detailed in the SAP, including a different methodology to assess the potential violation of the missing-at-random assumption, specifically a pattern mixture model (PMM). For the PMM, the imputation model will account for the differing missing value patterns based on 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

The key secondary efficacy endpoints (defined in Section 4.2.2.1) and other secondary efficacy endpoints (described in Section 4.2.2.2 for the double-blind treatment period, descriptive summaries and analyses will be performed in the ITT population or mITT population, corresponding to the specified estimand for the endpoint.

For descriptive summaries, percent change, and when appropriate, absolute change from baseline in LDL-C, total-C, HDL-C, TG, and non-HDL-C will be provided at each time point for each treatment group. 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 not fasting patients will be excluded. The time profile of each parameter will be plotted by treatment group with the corresponding standard errors. Similar tables (with either

percent change from baseline or absolute change from baseline for the ratio) and plots will be provided for other efficacy parameters: ApoB, ApoA-1, ratio ApoB/ApoA-1, Lp(a).

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (example: percent change in LDL-C), continuous measurements expected to have a non-normal distribution (example: TG), and binary measurements (example: proportion of patients with at least 30% reduction in LDL-C).

I. Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables defined in Section 4.2.2 anticipated to have a normal distribution (ie, lipids other than TG and Lp(a)) will be analyzed in the analysis populations 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 week 12, 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, anticipated to have a non-normal distribution (ie, TG and Lp(a)), will be analyzed in the analysis populations using a robust regression model (ie, ROBUSTREG SAS procedure with M-estimation option) with treatment group and randomization strata as main effect and corresponding baseline value(s) as covariate. Missing values will be addressed using a multiple imputation approach, which will be described in the SAP. The variables in the multiple imputation model will at least include the same variables as used in the robust regression model. The treatment group combined means will be provided with respective SE estimates. The combined mean difference between the treatment groups will be provided with the SE, 95% confidence interval and p-value.

III. Binary endpoints

Binary secondary efficacy endpoints defined in Section 4.2.2 will be analyzed in the analysis populations using stratified logistic regression (using the strata option of the SAS logistic procedure) with treatment group as main effect and corresponding baseline value(s) as covariate, stratified by randomization factor (as per IVRS). 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% CIs 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 1 treatment arm and thus the maximum likelihood estimate may not exist), the last observation carried forward approach would be used for handling of missing values and an exact conditional logistic regression would be performed to compare treatment effects. The last observation carried forward imputation method will consist of using the last value obtained up to the week 12 time window to impute the missing week 12 value.

10.4.3.3. Other Efficacy Endpoints

During the open-label treatment period, 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 double-blind treatment period (ie, alirocumab, placebo). Formal statistical testing is not planned. Descriptive statistics will include the same parameters as described for each variable in the double-blind treatment period.

For patients receiving alirocumab in the double-blind treatment period, a combined summary including both the double-blind and open-label treatment period 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. Again, formal testing is not planned due to the absence of control group.

10.4.3.4. Multiplicity Considerations

In order to handle multiple key secondary endpoints during the double-blind treatment period for the comparison of the alirocumab group and the placebo group, the overall type-I error will be controlled by the use of a hierarchical inferential approach. Statistical significance of the double-blind primary parameter at the 0.05 alpha level is required before drawing inferential conclusions about first key secondary parameter. Inferential conclusions about successive key secondary parameters require statistical significance of the prior one. The hierarchy testing sequence is the order of endpoints as presented in Section 4.2.2.1.

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

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

10.4.4. Safety Analysis

No formal inferential testing is planned for safety analyses. Summaries will be descriptive in nature. All safety analyses will be performed on the safety population using the following common rule:

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

10.4.4.1. Adverse Events

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

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of double-blind investigational study drug.
- The double-blind TEAE observation period is defined as the time from first dose of double-blind investigational study drug to the last dose of double-blind investigational study drug + 70 days, or up to the day before first dose of open-label investigational study drug administration, whichever is earlier.
- The open-label TEAE observation period is defined as the time from first open-label study treatment administration to the last open-label study treatment administration + 70 days.
- The post-treatment observation period is defined as the time from the day after the end of the respective TEAE periods up to the patient's end of study.
- Pre-treatment AEs are defined as those that developed, worsened, or became serious during the pre-treatment period.
- Double-blind and open-label TEAEs are defined as those that developed, worsened, or became serious during the respective TEAE periods.
- Double-blind and open-label post-treatment AEs are defined as those that developed, worsened, or became serious during the post-treatment period.

Analysis

Treatment-emergent and post treatment AEs in both the double-blind and open-label study periods will be summarized in incidence tables by (at least) SOC (sorted by internationally agreed order), and PT (sorted by decreasing frequency, and the number (n) and percentage (%) of patients experiencing an AE). The high level group term and high level term can be added in alphabetical order, as applicable. Multiple occurrences of the same event in the same patient will be counted only once in the tables within the TEAE period. Data conventions for missing or partial AE dates will be addressed in the SAP. The denominator for computation of percentages is the safety set within each treatment group.

Adverse event incidence tables will be provided by treatment group for all types of TEAEs: all TEAEs, all TEAEs of interest (defined with a PT or a pre-specified grouping), TEAE by severity, all treatment-emergent SAEs, and all TEAEs leading to permanent treatment discontinuation.

If any clinically significant signal is detected and further characterization is needed, or for AEs of clinical interest, selected TEAEs will be analyzed using a time-to-event approach (Kaplan Meier methodology) to account for the differential exposure time in all patients. Time from the first dose of the investigational study drug to the first occurrence of the event will be calculated (only the first event will be counted). Patients without any event will be censored at the end of the TEAE period.

Death

The following death summaries will be generated:

- Number (%) of patients who died by study period (TEAE and post treatment in both the double-blind and open-label study periods)

- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the AE CRF page, as reported by the investigator) by (at least) SOC (sorted by internationally agreed order), and PT (sorted by decreasing frequency, showing the number (n) and percentage (%) of patients) for both the double-blind and open-label study periods

10.4.4.2. Laboratory Data and Vital Signs

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

- The baseline value is defined as the last available value before first dose of double-blind investigational study drug.
- The PCSA values are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests and vital signs.
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage.
- Double-blind treatment period: the treatment period used for quantitative analysis (laboratory results and vital signs) in the double-blind period is defined as the time from the first double-blind dose of the investigational study drug to the last double-blind dose of the investigational study drug + 21 days, or up to the first open-label dose of the investigational study drug, whichever comes first.
- Open-label treatment period: the treatment period used for quantitative analysis (laboratory results and vital signs) in the open-label study period is defined as the time from the first open-label dose of the investigational study drug to the last open-label dose of the investigational study drug + 21 days.

Summary statistics (including mean, median, Q1, Q3, standard error, minimum and maximum) of all laboratory variables and all vital sign parameters (raw data and changes from baseline) will be calculated for each visit, last and worst value assessed during the treatment period, and presented by treatment group. For selected parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in each treatment group.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group for the double-blind study period, and by all patients and by the as-treated treatment group for the open-label study period, whatever the baseline level and/or according to the following baseline categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

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

Hepatitis C Test

The number and percentage of patients with an observed seroconversion for the hepatitis C test will be provided by treatment group for the double-blind study period, and by all patients and also by treatment group of double-blind period for the open-label study period.

10.4.4.3. Treatment Exposure

The double-blind duration of treatment exposure will be calculated for each of the 2 treatment arms as:

- Duration of alirocumab exposure in weeks defined as: (last double-blind study treatment administration date + 14 – first double-blind study treatment administration date)/7, regardless of unplanned intermittent discontinuations.
- The total number of double-blind treatment injections by patient.

The double-blind study treatment duration of exposure, measured in weeks, will be summarized by at least mean, median, SD, and minimum/maximum. The categorical data of number of injections will be summarized by patient counts and percentages.

The OLE duration of treatment exposure will be calculated for each of the 2 treatment arms of the double-blind period as well as patient total:

- Duration of open-label alirocumab exposure in weeks defined as: (last open-label alirocumab treatment administration date + 14 – first open-label alirocumab treatment administration date)/7, regardless of unplanned intermittent discontinuations.
- The total number of open-label alirocumab treatment injections by patient.

The open-label duration of exposure measured in weeks will be summarized by at least mean, median, SD, and minimum/maximum. The categorical data of number of injections will be summarized by patient counts and percentages.

The combined duration of treatment exposure for patients who received the alirocumab treatment in the double-blind period is calculated as:

- Combined duration of alirocumab exposure in weeks defined as: double-blind treatment exposure plus open-label treatment exposure, regardless of unplanned intermittent discontinuations.
- Combined total number of alirocumab treatment injections by patient defined as: total number of double-blind injections plus total number of open-label injections for each patient.

The combined duration of exposure measured in weeks will be summarized by at least mean, median, SD, and minimum/maximum. The categorical data of number of injections will be summarized by patient counts and percentages.

10.4.4.4. Treatment Compliance

Compliance during the double-blind period will be assessed using the following parameter: The injection frequency will be defined for each patient as the average number of days between 2

injections, that is: (last dose date – first dose date)/(number of injections -1) for patients receiving at least 2 injections.

The parameter will be summarized descriptively (N, mean, SD, median, min and max).

10.4.5. Analysis of Drug Concentration Data

Descriptive statistics of concentrations of alirocumab will be provided by treatment group. Plots of the individual concentrations of alirocumab will be presented versus actual time (linear and log scales). Plots of the mean or median concentrations of alirocumab will be presented by time point (linear and log scales).

10.4.6. Analysis of Pharmacodynamics Data

Descriptive statistics of concentrations of total PCSK9 and free PCSK9 will be provided by treatment group. Plots of the individual concentrations of total and free PCSK9 will be presented versus actual time (linear and log scales). Plots of the mean or median concentrations of total and free PCSK9 will be presented by time point (linear and log scales).

10.4.7. Analysis of Anti-Drug Antibody Data

The ADA status and ADA titers will be summarized by treatment group and visit using descriptive statistics. If appropriate, correlations between ADA titers, safety and/or efficacy endpoints will be provided.

10.5. Timing of Statistical Analysis

The analyses will be conducted in 2 steps. The first analysis will be conducted as soon as all patients have been randomized and all data through week 12 (double-blind period) have been collected and validated; this will consist of the final analysis of the double-blind primary and secondary efficacy endpoints. The safety analysis will be performed on all safety data collected and validated at the time of the first analysis.

Since the double-blind primary efficacy measure data collection will have been concluded at the time of this first analysis, the significance level for the study remains at 0.05. This first analysis may be used for the submission to health authorities or other interested parties.

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

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

10.6. Additional Statistical Data Handling Conventions

Additional data handling conventions will be described in the statistical analysis plan.

10.7. 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/ophthalmic history) will be done using internationally recognized and accepted dictionaries.

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

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, investigational study drug supply
- EDC system – data capture
- Statistical Analysis Software – 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. Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

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

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

13. AUDITS AND INSPECTIONS

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

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

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

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

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

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

14.2. Informed Consent/Assent

The principles of informed consent and assent 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 the investigational 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, who will sign and date the ICF to confirm that informed consent was given.

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

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

14.3. Patient Confidentiality and Data Protection

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

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

14.4. Institutional Review Board/Ethics Committee

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

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study

- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

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

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

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

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment

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's final CRF 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 Alirocumab in Patients with Homozygous Familial Hypercholesterolemia, Amendment 2, and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

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

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

No:

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

Yes:

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

NOTE: This list is not exhaustive.

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 Alirocumab in Patients with Homozygous Familial Hypercholesterolemia

Protocol Number: R727-CL-1628

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-00067475 v1.0

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