Clinical Study Protocol

Long Term Safety Study of PRALUENT in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk and Previously Enrolled in the Neurocognitive Function Trial

Compound:	PRALUENT
Study Name:	Open-Label Extension after the Neurocognitive Function Study
Clinical Phase:	4 (Phase 3 in South Africa)
Protocol Number:	R727-CL-1609
Protocol Version:	R727-CL-1609 Amendment 2
Amendment 2 Date of Issue:	*See appended electronic signature page.*
Amendment 1 Date of Issue:	23 Jul 2018
Original Date of Issue:	06 May 2016
Scientific/Medical Monitor:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Amendment 2

The protocol is being amended to add back text that was inadvertently removed in protocol amendment 1, and to clarify language for blinding, study discontinuation, treatment compliance, adverse event (AE) reporting period, and procedures for reporting serious adverse events (SAEs).

The table below outlines changes made in this amendment.

Change	**Sections Changed**
Revised study hypothesis for clarity	Section 3.1 Hypothesis
Deleted reference to Company Core Data Sheet, as not applicable	Clinical Study Protocol Synopsis – Study Design Section 5.1 Study Description and Duration
Added new section for language concerning a Neurocognitive Events Review Committee, to match that in the neurocognitive function study (R727-CL-1532), and reintroduced wording that was inadvertently removed. Also clarified language regarding maintaining the blind in R727-CL-1532.	Clinical Study Protocol Synopsis – Study Design Section 5.1 Study Description and Duration Section 5.3 Study Committees (new) Section 5.3.1 Neurocognitive Events Review Committee (new)
Deleted language regarding investigational product dispensing, as not applicable	Section 7.1 Investigational and Reference Treatments
Deleted requirement to maintain patients in the trial after treatment discontinuation, as the objective of this open-label trial is to assess the long-term safety based on actual exposure to alirocumab	Section 7.3.2 Study Drug Discontinuation
Clarified follow-up on pregnancies, to be consistent within the protocol	Section 7.3.2.1 Reasons for Permanent Discontinuation of Study Drug
Revised language to reflect kit assembly; previous language was copied from the neurocognitive function study (R727-CL-1532)	Section 7.5.4 Treatment Compliance
Clarified schedule of events and applicable footnotes for assessments not collected at visit 1; clarified footnotes for assessment of	Table 1 Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Table

gonadal hormones and gonadotropins, and for study kit dispensation	
Clarified details on procedures for reporting serious adverse events	Section 9.4.2 Serious Adverse Events
Added back sub-bullet under "All neurocognitive events" from original protocol, concerning regular review by an independent panel of experts	Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor
Clarified that adverse events of special interest (AESI) will be followed until they are considered chronic and/or stable	Section 9.4.6 Follow-up
Deleted statement on patient disposition, as not applicable	Section 10.4.1 Patient Disposition
Replaced the ITT and/or mITT populations with the Safety Analysis Set	Section 10.4.3 Efficacy Analyses
Clarified the definition of the treatment-emergent adverse event (TEAE) period to align with the last dose and the last study visit	Section 10.4.4.1 Adverse Events
Made minor editorial and/or formatting changes	Clinical Study Protocol Synopsis – Objectives, Study Design, Treatments (Background Treatment), Endpoints (Primary) Section 2.1 Primary Objective Section 4.2.1 Primary Endpoint Section 5.1 Study Description and Duration Section 7.2 Background Treatments Section 7.4 Method of Treatment Assignment Section 7.6.1 Prohibited Medications Section 8.2.4.1 Review of Diet Section 11.1 Data Management Appendix 1 Factors to Consider in Assessing the Relationship of Adverse Events to Study Drug and Study Conduct

Amendment 1

The protocol is being amended to align with feedback received from the European Medicines Agency (EMA), and updated for clarity and consistency with the current R727-CL-1532 neurocognitive function protocol Amendment 5.

The table below outlines changes made in this amendment.

Change	**Sections Changed**
Corrected the EudraCT number and updated the study name to better describe the study	Title Page
Added evaluation of the effect of Praluent on gonadal steroid hormones as a secondary objective	Synopsis (Objectives) Section 2.2 Secondary Objectives Section 4.2.2 Secondary Endpoints
Clarified that eligible patients for this study must have completed treatment and the end of study (EOS) visit in the neurocognitive study	Synopsis (Study Design) Section 3.2.1 Rationale for Study Design Section 5.1 Study Description and Duration Section 6.2.1 Inclusion Criteria
Removed the requirement that at least 14 days are required between the last dose of study drug in the neurocognitive function study and the first dose of study drug in the open-label extension (OLE) study	Synopsis (Study Design) Section 5.1 Study Description and Duration Section 8.1.1 Footnotes for the Schedule of Events Table: Footnote #1
Added the statement that study drug should be administered every 2 weeks throughout the study	Section 8.1.1 Footnotes for the Schedule of Events Table: Footnote #1
Amended required measurement of low-density lipoprotein cholesterol (LDL-C) levels from within 4 to 8 weeks after initiating study treatment or dose modification, to 8 weeks after initiating study treatment or at least 4 weeks after dose modification.	Synopsis (Study Design) Section 5.1 Study Description and Duration
Updated section to reflect dose selection for the open label extension study	Section 3.2.2 Rationale for Dose Selection
Added new sections from updated protocol template	Section 5.1.1 End of Study Definition Section 18 Data Quality Assurance

Updated the expected total number of patients	Synopsis (Sample Size) Section 3.2.1 Rationale for Study Design Section 6.1 Number of Patients Planned
Broadened monitoring of circulating gonadal steroid hormones and gonadotropins by removing requirement that these assessments be performed only in men with baseline luteinizing hormone (LH) <15 IU/L, and premenopausal women with baseline follicle stimulating hormone (FSH) <25 IU/L	Table 1 Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Table: Footnote #7 Section 8.2.2.3 Laboratory Testing
Added monitoring of HbA1c, Apo-B, Apo A-1, and Lp(a)	Table 1 Schedule of Events Section 8.2.2.3 Laboratory Testing
Deleted the requirement that blood sampling for lipid parameters must be collected in the morning following a 10- to 12-hour overnight fast while refraining from smoking	Section 8.2.3.1 Lipid Panel Section 8.1.1 Footnotes for the Schedule of Events Table: Footnote #6
Deleted the section referring to anti-drug antibody measurements as these will not be collected in this study	Section 8.2.4.1 Anti-Drug Antibody Measurements and Samples
Deleted the statement that events that are not a known response to the study drug should be considered not related when evaluating causality	Section 9.5.2 Evaluation of Causality
Added laboratory evaluations (gonadal hormones and gonadotropins, liver panel, hematology, blood chemistry, urinalysis, and Total-C, calculated LDL-C, HDL-C, TG, and non-HDL-C) at weeks 24, 72, 120, and 168; deleted assessment of vital signs and physical examination at weeks 24, 72, 120, and 168, and added collection of research samples on day 1, and weeks 144 and 192	Table 1 Schedule of Events
Removed review of neurocognitive adverse events (AEs) by an independent panel of experts	Section 9.4.3 Other Adverse Events that Require Accelerated Reporting to Sponsor
Updated statistical analysis methods to: add that the anticipated number of patients is	Section 10.2 Justification of Sample Size Section 10.4.3 Efficacy Analyses

based on the observed drop-out rate in the ODYSSEY program, combined the primary and secondary efficacy analysis sections and updated text, clarified the definition of the TEAE period and the definition of AEs, and clarified how unscheduled assessments will be handled.	Section 10.4.4.1 Adverse Events Section 10.5 Additional Statistical Data Handling Conventions
Made changes for consistency with R727-CL-1532 neurocognitive function protocol	Synopsis (Population) Section 6.2.2 Exclusion Criteria #6 Section 8.2.2.3 Laboratory Testing Section 12.1 Monitoring of Study Sites Section 12.3 Case Report Form Requirements
Made corrections, minor changes, and edits for clarity	Synopsis (Objectives, Study Design, Study Duration, Population, Procedures and Assessments) List of Abbreviations and Definitions of Terms Section 2.1 Secondary Objectives Section 3.1 Hypothesis Section 3.2.1 Rationale for Study Design Section 4.1 Demographic and Baseline Characteristics Section 5.1 Study Description and Duration Figure 1 Study Flow Diagram Section 6.2.1 Inclusion Criteria Section 6.2.2 Exclusion Criteria (#2 and #3) Section 7.2 Background Treatments Section 7.3.1 Dose Modification Section 7.4 Method of Treatment Assignment Section 7.6 Concomitant Medications Section 7.6.2 Permitted Medications Table 1 Schedule of Events Section 8.1.1 Footnotes for the Schedule of Events Table (#1 and #4)

	Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.3.1 Lipid Panel Section 8.2.7 Future Biomedical Research Section 9.4.1 Adverse Events Section 9.5.1 Evaluation of Severity Section 10.4.3 Efficacy Analyses Section 10.4.4.2 Other Safety Section 11.2 Electronic Systems Section 12.3 Case Report Form Requirements

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	Long Term Safety Study of PRALUENT in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk and Previously Enrolled in the Neurocognitive Function Trial
Site Locations	Site numbers and countries from enrolling sites in the neurocognitive function study (R727-CL-1532).
Principal Investigator	To be determined
Objectives	The primary objective of the study is to evaluate the long-term safety of PRALUENT in patients with heterozygous familial hypercholesterolemia (heFH) or non-familial hypercholesterolemia (FH) patients at high or very high cardiovascular risk who completed the neurocognitive function study (R727-CL-1532). The secondary objectives of the study are: • To evaluate the effect of PRALUENT on low-density lipoprotein cholesterol (LDL-C) • To evaluate the effect of PRALUENT on other lipid parameters • To evaluate the effect of PRALUENT on gonadal steroid hormones
Study Design	This is a phase 4, open-label extension (OLE), uncontrolled, multicenter, long-term safety study to be performed in patients who have completed the neurocognitive function study (R727-CL-1532). The observation period for PRALUENT treatment in the OLE study is planned to be approximately 192 weeks. Patients who completed treatment and the end of study (EOS) visit in the neurocognitive function study (R727-CL-1532) may enroll in the OLE study. The end of study (EOS) visit of the double-blind neurocognitive function study (R727-CL-1532) corresponds to visit 1 (day 1) of the OLE study. The first subcutaneous (SC) injection of PRALUENT will be administered in the clinic (day 1, visit 1). After visit 1, patients have the option to either self-administer study drug, or have another designated person (such as a spouse or caregiver) administer study drug for them. The starting dose of PRALUENT will be 75 mg administered SC every 2 weeks (Q2W, regardless of treatment assigned in the neurocognitive function study R727-CL-1532), that may be modified to 150 mg administered SC Q2W, and can be maintained or modified from 150 mg Q2W to 75 mg Q2W. Low-density lipoprotein cholesterol (LDL-C) levels

	must be measured at 8 weeks after initiating study treatment, or least 4 weeks after dose modification, to assess response and to adjust the dose, if needed. The investigator will be blinded to the treatment received in the neurocognitive function study (R727-CL-1532) until that study is completed and the database is locked. Lipid profile values from samples obtained after inclusion will be blinded until week 8 in order to prevent any potential unblinding of the neurocognitive function study (R727-CL-1532). From week 8 in the OLE study, lipid measurements will be collected and will be known by the investigator in real time. The investigator will manage the PRALUENT dose at his/her discretion based on LDL-C levels, starting at week 12, by either modifying the dose from 75 mg Q2W to 150 mg Q2W, maintaining the dose, modifying the dose from 150 mg Q2W to 75 mg Q2W, or discontinuing treatment with PRALUENT at any time during the treatment period. If a dose is missed, the patient should administer the injection as soon as possible and thereafter resume treatment from the day of the missed dose (ie, resume on the next originally planned date). The statin dose should not be modified to adjust the degree of LDL-C lowering. Background lipid modifying therapy (LMT) will be prescribed as per clinical practice and should remain the same as in the neurocognitive function study (R727-CL-1532). Lipid modifying therapy, including statins, should not be changed during the course of the study. However, if clinically necessary, background LMT may be adjusted at the investigator's discretion. Any adjustment will be documented in the case report form (CRF). Patients not treated with a statin (eg, statin intolerant patients, or patients in whom statin treatment was stopped during the neurocognitive function study [R727-CL-1532] for a safety reason) may still participate in the OLE study. The investigator should refer to the label for information on PRALUENT and other LMTs. Patients should continue on a National Cholesterol Education Program-Adult Treatment Panel III Therapeutic Lifestyle Changes (NCEP-ATPIII TLC) diet or equivalent throughout the entire study duration. Visits are planned at weeks 0, 8, 12, 24, 48, 72, 96, 120, 144, 168, and 192. At each visit, except at the EOS visit at week 192, study drug will be dispensed to the patient. If at any time during the study after the week 8 visit, the investigator, based on lipid results or safety issues, decides to modify the dose of PRALUENT, an unscheduled kit dispensation visit will be performed.
Study Duration	The duration of the OLE study for a patient is planned to be approximately 192 weeks.

Population	
Sample Size:	Anticipated enrollment will depend on the number of patients who complete treatment in the neurocognitive function study (R727-CL-1532) and the number of patients who agree to participate (approximately 1600 patients).
Target Population:	The study population consists of patients with heFH, or non-FH patients at high or very high cardiovascular risk, who completed treatment in the neurocognitive function study (R727-CL-1532).
Treatments	
Study Drug Dose/Route/Schedule:	Sterile PRALUENT drug product will be supplied at a concentration of 75 mg/mL and 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose, both as 1 mL volume in an auto-injector. Subcutaneous injections in the abdomen, thigh or outer area of upper arm. 75 mg Q2W or 150 mg Q2W (dose may be modified from 75 mg Q2W to 150 mg Q2W, or from 150 mg Q2W to 75 mg Q2W).
Background Treatment Dose/Route/Schedule:	Maximally-tolerated registered daily dose of statin received during the neurocognitive function study (R727-CL-1532), with or without other LMT. The statin dose should not be modified to adjust the degree of LDL-C lowering. Background LMT, including statins, should not be changed during the course of the study. However, if clinically necessary, background LMT may be adjusted at the investigator's discretion. Any adjustment will be documented in the CRF.
Endpoints	
Primary:	The primary endpoint in the study is the incidence of adverse events (AEs) after first administration of study drug through the last dose of study drug plus 2 weeks. The following adverse events will be described: • AEs/serious adverse events (SAEs) • AEs leading to treatment discontinuation • Adverse events of special interest (AESI)
Secondary:	Secondary Endpoints: • Calculated LDL-C values and percent changes from baseline over time • Values and percent changes from baseline in other lipids and other lipoproteins, including total cholesterol (Total-C),

	non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, and triglycerides (TGs) over time • Values and percent changes from baseline in gonadal hormones and gonadotropins over time
Procedures and Assessments	Safety Procedures: Vital signs, including sitting blood pressure and pulse will be collected. A general physical examination including body weight will be performed. Hematology, chemistry, including the liver panel and HbA1c, gonadal hormones and gonadotropins, urinalysis, and pregnancy testing samples will be analyzed. Efficacy Procedures: Blood samples for the determination of lipid parameters will be analyzed.
Statistical Plan	There is no formal size calculation for this study. Patients' eligibility is based on the neurocognitive function study (R727-CL-1532). Study data will be summarized descriptively for all patients in the safety population, as well as by randomized treatment group in the neurocognitive function study (R727-CL-1532).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CHD	Coronary heart disease
CPK	Creatine phosphokinase
CRF	Case Report Form (electronic or paper)
CRO	Contract research organization
EC	Ethics Committee
EDC	Electronic data capture
EOS	End of study
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
heFH	Heterozygous familial hypercholesterolemia
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LMT	Lipid modifying therapy
Lp(a)	Lipoprotein a
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition of Term
NCEP-ATPIII TLC	National Cholesterol Education Program-Adult Treatment Panel III Therapeutic Lifestyle Changes
Non-HDL-C	Non-high-density lipoprotein cholesterol
OLE	Open-label extension
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSV	Potentially clinically significant value
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
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TG	Triglyceride
Total-C	Total cholesterol
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
γGT	γ Glutamyl transferase

1. INTRODUCTION

PRALUENT® is a human monoclonal antibody that binds proprotein convertase subtilisin/kexin type 9 (PCSK9) to inhibit its function. All relevant information concerning the compound is available in the latest version of the Investigator's Brochure. PRALUENT was approved for the treatment of hypercholesterolemia in the United States on July 24, 2015 and in the European Union on September 23, 2015. Approval has also been granted in other countries around the world. Detailed information on the approved indication is available in the respective local product information.

PRALUENT is also referred to as alirocumab, REGN727, or SAR236553. In the context of the R727-CL-1609 clinical study protocol, it will be referred to as PRALUENT.

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety of PRALUENT in patients with heterozygous familial hypercholesterolemia (heFH) or non-familial hypercholesterolemia (FH) patients at high or very high cardiovascular risk who completed the neurocognitive function study (R727-CL-1532).

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the effect of PRALUENT on low-density lipoprotein cholesterol (LDL-C)
- To evaluate the effect of PRALUENT on other lipid parameters
- To evaluate the effect of PRALUENT on gonadal steroid hormones

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

PRALUENT will have an acceptable safety profile with long-term use.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is an open-label extension (OLE) to the neurocognitive function study (R727-CL-1532) in which all patients will be treated, in a single arm, with PRALUENT. The study will be conducted on patients who completed treatment and the end of study (EOS) visit in the

neurocognitive function study (R727-CL-1532), with no premature discontinuation of study drug or placebo. This will allow for patient exposure to PRALUENT of approximately 6 years.

At the time of inclusion into the OLE study, knowledge of the treatment arm in the neurocognitive function study (R727-CL-1532) will not be available to the investigator or the sponsor. Patients eligible to participate in the OLE study will initiate treatment with PRALUENT at the starting dose of 75 mg once every 2 weeks (Q2W), regardless of the treatment group to which they were randomized in the neurocognitive function study (R727-CL-1532).

No formal sample size was calculated for this study. The anticipated number of patients is based on the previously observed drop-out rate in the ODYSSEY program.

The study duration of approximately 192 weeks, in addition to the 96-week exposure in the neurocognitive function study (R727-CL-1532), will enable the assessment of long-term exposure to PRALUENT.

3.2.2. Rationale for Dose Selection

The doses selected for this study was based on the approved doses for PRALUENT that were used in the neurocognitive function study (R727-CL-1532).

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, gender, race, age [years], and ethnicity), and medical history.

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary endpoint in the study is the incidence of AEs after first administration of study drug through the last dose of study drug plus 2 weeks.

The following AEs will be described:

- AEs/serious adverse events (SAEs)
- AEs leading to treatment discontinuation
- Adverse events of special interest (AESI)

4.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- Calculated LDL-C values and percent changes from baseline over time
- Values and percent changes from baseline in other lipids and other lipoproteins, including total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, and triglycerides (TGs) over time

- Values and percent changes from baseline in gonadal hormones and gonadotropins over time

4.2.3. Other Endpoints

The other endpoints of the study will include:

- Values and changes from baseline in liver tests over time

5. STUDY DESIGN

5.1. Study Description and Duration

This is a phase 4, OLE, uncontrolled, multi-center, long-term, safety study to be performed in patients who have completed the neurocognitive function study (R727-CL-1532). The observation period for PRALUENT treatment in the OLE study is planned to be approximately 192 weeks.

Patients who completed treatment and the EOS visit in the neurocognitive function study (R727-CL-1532) may enroll in the OLE study. The EOS visit of the double-blind neurocognitive function study (R727-CL-1532) corresponds to visit 1 (day 1) of the OLE study. The first SC injection of PRALUENT will be administered in the clinic (day 1, visit 1).

After visit 1, patients have the option to either self-administer study drug, or have another designated person (such as a spouse or caregiver) administer study drug for them.

The starting dose of PRALUENT will be 75 mg administered SC Q2W (regardless of treatment assigned in the neurocognitive function study R727-CL-1532), that may be modified to 150 mg administered SC Q2W, and can be maintained or modified from 150 mg Q2W to 75 mg Q2W. Low-density lipoprotein cholesterol levels must be measured at 8 weeks after initiating study treatment, or at least 4 weeks after dose modification, to assess response and to adjust the dose, if needed.

The investigator will be blinded to the treatment received in the neurocognitive function study (R727-CL-1532) until that study is complete and the database is locked. Lipid profile values from samples obtained after inclusion will be blinded until week 8, in order to prevent any potential unblinding of the neurocognitive function study (R727-CL-1532).

From week 8 in the OLE study, lipid measurements will be collected and will be known by the investigator in real time. The investigator will manage the PRALUENT dose at his/her discretion based on LDL-C levels, starting at week 12, by either modifying the dose from 75 mg Q2W to 150 mg Q2W, maintaining the dose, modifying the dose from 150 mg Q2W to 75 mg Q2W, or discontinuing treatment with PRALUENT at any time during the treatment period. If a dose is missed, the patient should administer the injection as soon as possible and thereafter resume treatment from the day of the missed dose (ie, resume on the next originally planned date). The statin dose should not be modified to adjust the degree of LDL-C lowering.

Background LMT will be prescribed as per clinical practice and should remain the same as in the neurocognitive function study (R727-CL-1532). Lipid modifying therapy, including statins, should not be changed during the course of the study. However, if clinically necessary, background LMT may be adjusted at the investigator's discretion. Any adjustment will be

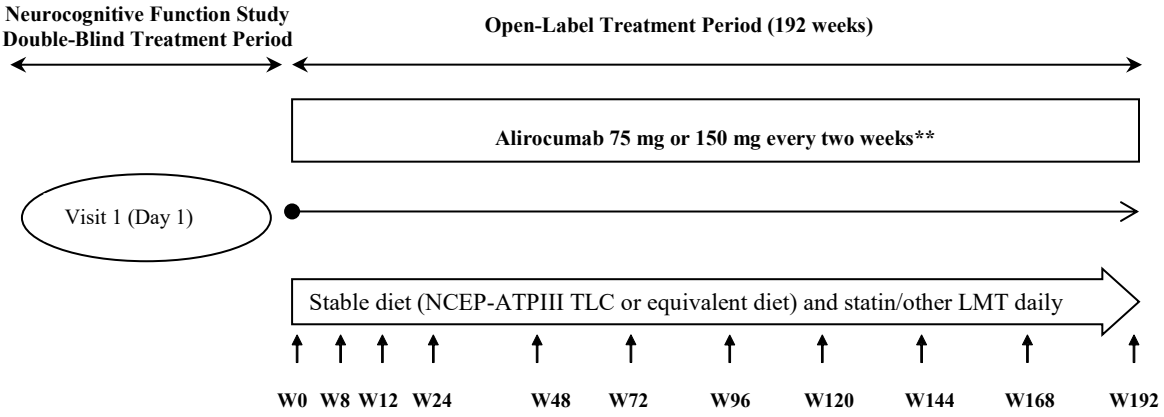
documented in the electronic case report form (CRF). Patients not treated with a statin (eg, statin intolerant patients, or patients in whom statin treatment was stopped during the neurocognitive function study [R727-CL-1532] for a safety reason) may still participate in the OLE study.

The investigator should refer to the label for information on PRALUENT and other LMTs.

Patients should continue a National Cholesterol Education Program-Adult Treatment Panel III Therapeutic Lifestyle Changes (NCEP-ATPIII TLC) diet or equivalent throughout the entire study duration.

Visits are planned at weeks 0, 8, 12, 24, 48, 72, 96, 120, 144, 168, and 192 (Figure 1). At each visit, except at the EOS visit at week 192, study drug will be dispensed to the patient. If at any time during the study after the week 8 visit, the investigator, based on lipid results or safety issues, decides to modify the dose of PRALUENT, an unscheduled kit dispensation visit will be performed.

Figure 1: Study Flow Diagram



*The end of study visit in the neurocognitive function study (R727-CL-1532) will correspond to visit 1 (day 1) of this study.
**Starting dose is 75 mg Q2W. The first LDL-C assessment is at week 8. At any time after week 8, the investigator will be responsible to manage the PRALUENT dose by either modifying from 75 mg Q2W to 150 mg Q2W, maintain the dose, modifying from 150 mg Q2W to 75 mg Q2W or discontinuing the treatment with PRALUENT at any time during the treatment period.

5.1.1. End of Study Definition

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

5.2. Planned Interim Analysis

No interim analysis is planned.

5.3. Study Committees

5.3.1. Neurocognitive Events Review Committee

The neurocognitive events review committee is composed of recognized clinical experts in the field of cognition, independent from the sponsor and the investigators. This committee will be responsible for defining and validating, and classifying AEs of special interest possibly related to cognition impairment.

A charter and an operational manual will specify the procedures and criteria used for review of these events.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

No formal sample size was calculated for this study. The anticipated number of patients is based on the previously observed drop-out rate in the ODYSSEY program. The expected total number of patients is approximately 1600.

6.2. Study Population

The study population consists of patients with heFH or non-FH patients at high or very high cardiovascular risk. Patients must have had a history of coronary heart disease (CHD) without adequate control of their hypercholesterolemia with LDL-C ≥70 mg/dL, or with LDL-C ≥100 mg/dL with no history of CHD, and be on a maximally-tolerated dose of statin (unless they are statin-intolerant).

6.2.1. Inclusion Criteria

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

1. Patients having been randomized into the neurocognitive function study (R727-CL-1532) who completed treatment and the EOS visit with no premature or permanent discontinuation of study drug.
2. Willing and able to comply with clinic visits and study-related procedures
3. 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. Significant protocol deviation in the parent study (neurocognitive function study, R727-CL-1532) based on the investigator's or sponsor's judgment, such as noncompliance by the patient
2. Any patient who experienced an AE leading to permanent discontinuation from the neurocognitive function study, (R727-CL-1532).
3. Any new condition or worsening of an existing condition which, in the opinion of the investigator or per the PRALUENT local label, would make the patient unsuitable for enrollment or could interfere with the patient participating in or completing the OLE study
4. Known hypersensitivity to monoclonal antibody or any component of the drug product
5. Pregnant or breastfeeding women
6. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for

at least 6 months after the last dose. 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 tubal ligation.

**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. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

†Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

6.3. Premature Withdrawal from the Study

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

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

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

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.3.2.

6.4. Replacement of Patients

Patients prematurely discontinued from the OLE study/study drug will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Sterile PRALUENT drug product will be supplied at a concentration of 75 mg/mL and 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose, both as 1 mL volume in an auto-injector.

7.2. Background Treatments

Throughout the treatment period, patients should remain on stable, maximally-tolerated registered daily dose of statin received during the neurocognitive function study (R727-CL-1532), with or without other LMT. The statin dose should not be modified to adjust the degree of LDL-C lowering.

Background LMT should not be changed during the course of the study. However, if clinically necessary, background LMT may be adjusted at the investigator's discretion. Any adjustment will be documented in the CRF. For adjustments based on LDL-C values, simultaneous adjustments in PRALUENT dose and any LMT should be avoided.

For background LMT, including statins, sites must follow the national product label for the safety monitoring and management of patients.

No lipid profile will be performed until week 8, to avoid any unblinding of the neurocognitive function study.

As background treatment, the following classes of drugs are identified as non-investigational medicinal products:

- Concomitant LMT, including statins
- Cholesterol absorption inhibitors (ezetimibe)
- Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam)
- Nicotinic acid (niacin)
- Fenofibrate, fenofibric acid
- Omega-3 fatty acids

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Dose Modification

Dose modification/reduction is allowed for an individual patient according to the following specifications:

- The starting dose of PRALUENT will be 75 mg administered SC Q2W. The dose may be modified to 150 mg administered SC Q2W, and can be maintained or modified from 150 mg Q2W to 75 mg Q2W.

7.3.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug will be asked to complete early termination study assessments, per Section 8.1.2.

7.3.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Pregnancy, intention for pregnancy, or no longer using effective contraceptive method of birth control (females only). All pregnancies will be followed to their outcome.
- Acute injection reaction of clinical concern
- SAE (or non-serious but severe in intensity) of hypersensitivity reaction considered related to study drug
- At patient request, ie, withdrawal of the consent for treatment
- If, in the investigator's opinion, continued administration of study drug would be detrimental to the patient's safety or well-being. Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of permanent discontinuation of study drug
- At the specific request of the sponsor

7.3.2.2. Reasons for Temporary Discontinuation of Study Drug

Temporary treatment discontinuation may be considered by the investigator because of suspected AEs. Reinitiating of treatment with the study drug will be done under close and appropriate clinical/and or laboratory monitoring once the investigator will have considered (according to his/her best medical judgement) that the responsibility of the study drug in the occurrence of the concerned event was unlikely, and if the selection criteria for the study are still met (see Sections 6.2.1 and 6.2.2).

For all temporary treatment discontinuations, duration should be recorded by the investigator in the appropriate screens of the CRF.

Treatment interruption is defined as 1 or more scheduled injections that are not administered to the patient as decided by the investigator.

7.4. Method of Treatment Assignment

This is an open-label study and every patient will receive PRALUENT. Treatment kit numbers will be allocated via interactive voice response system (IVRS)/interactive web response system (IWRS). Patients will keep the same identification number that they were allocated in the neurocognitive function study (R727-CL-1532) or a correspondence table will be set up between the neurocognitive function study (R727-CL-1532) and this study numbering.

From week 8, the investigator will manage the PRALUENT dose at his/her discretion based on LDL-C values obtained from the sample at the previous scheduled visit, by either modifying the dose from 75 mg Q2W to 150 mg Q2W, maintaining the PRALUENT dose, or discontinuing treatment with PRALUENT at any time during the treatment period. The statin dose should not be modified to adjust the degree of LDL-C lowering.

An unscheduled kit dispensation visit may be scheduled at any time during the study after the week 12 visit if the investigator, based on lipid results or safety issues, decides to modify the dose of PRALUENT (see Section 8.1). In this instance, IVRS/IWRS will allocate a new treatment kit number and the new study drug kit will be dispensed to the patient. In specific cases, the new kit may be sent directly to the patient's home.

7.4.1. Blinding

This is an open-label, uncontrolled study; therefore, no blinding procedures will be implemented.

7.5. Treatment Logistics and Accountability

7.5.1. Packaging, Labeling, and Storage

Open-label study drug will display the product lot number on the label.

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

7.5.2. 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 study drug will be returned to the sponsor or designee.

7.5.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

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

7.5.4. Treatment Compliance

Patients will complete a dosing log to document compliance with study drug administration. Measures taken to ensure and document 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 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 the unused auto-injector.

- 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 kit(s).

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

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

7.6. Concomitant Medications

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

Concomitant medications should be kept to a minimum during the study. However, if considered necessary for the patient's welfare and unlikely to interfere with study drug, a stable dose, when possible, may be given at the discretion of the investigator.

Concomitant medications allowed during the study include:

Lipid Modifying Therapy

Throughout the treatment period, patients should stay on a stable maximally-tolerated registered daily dose of statin, with or without other LMT, received during the neurocognitive function study (R727-CL-1532).

Lipid modifying therapy, including statins, should not be changed during the course of the study. However, if clinically necessary, background LMT may be adjusted at the investigator's discretion. Any adjustment will be documented in the CRF.

Contraception

Women of childbearing potential must use an effective contraceptive method throughout the study treatment, and for at least 6 months after the last study drug injection.

7.6.1. Prohibited Medications

PCSK9 inhibitors, other than PRALUENT, taken from the time of informed consent until the last study visit, are prohibited during the study.

7.6.2. Permitted Medications

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the study drug, they may be given at the discretion of the investigator at a stable dose (when possible). Besides the specific information related to concomitant medications provided in this section, any other

concomitant medication(s) will be allowed and are required to be recorded in the CRF and source data.

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

	Treatment Period										End of Treatment/Early Termination/ End of Study[1]
Study Procedure	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
Day	1										
Week	0	8	12	24	48	72	96	120	144	168	192
Visit Window (days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Screening/Baseline:											
Inclusion/Exclusion	X										
Informed Consent	X										
Demographics	X										
Prior Medication History	X										
IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	
Treatment:											
Review of Diet	X	X	X	X	X	X	X	X	X	X	X
Administer Study Drug	X[2]										
Study Drug Kit Dispensation[3, 4]	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication[5]	X	X	X	X	X	X	X	X	X	X	X
Patient Drug Log Dispensation/Collection	X	X	X	X	X	X	X	X	X	X	X
Safety:											
Vital Signs	X				X		X		X		X
Physical Examination and Body Weight	X				X		X		X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Efficacy:											
Total-C, LDL-C, HDL-C, TG, non-HDL-C[6]	X[7]	X		X	X	X	X	X	X	X	X
Apo B, Apo A-1, Lp(a)	X[7]				X		X		X		X
Laboratory Testing:											
Hematology	X[7]			X	X	X	X	X	X	X	X

	Treatment Period										End of Treatment/Early Termination/ End of Study[1]
Study Procedure	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
Day	1										
Week	0	8	12	24	48	72	96	120	144	168	192
Visit Window (days)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Blood Chemistry	X[7]			X	X	X	X	X	X	X	X
Urinalysis	X[7]			X	X	X	X	X	X	X	X
hs-CRP	X[7]			X	X	X	X	X	X	X	X
Gonadal Hormones & Gonadotropins[8]	X[7]			X	X	X	X	X	X	X	X
Urine Pregnancy Test (for women of childbearing potential)	X[7]	X	X	X	X	X	X	X	X	X	X
Research Testing											
Research Samples (serum/plasma)	X[7]				X		X		X		X

8.1.1. Footnotes for the Schedule of Events Table

1. Patients who prematurely discontinue study treatment: any study treatment discontinuation should be initially considered temporary, and the investigator should make every effort to resume study drug treatment as early as possible, pending no safety concerns, and to perform all study visits and assessments as usual. When a treatment discontinuation is considered 'permanent', an extra visit (early termination visit) should be performed within 5 days of the decision to permanently discontinue study drug. This visit will be the last visit for the patient.
2. The end of study (EOS) visit of the double-blind neurocognitive function study (R727-CL-1532) corresponds to visit 1 (day 1) of the OLE study. Patients may enroll in the OLE study after completing treatment and the EOS visit in the neurocognitive function study (R727-CL-1532). The first SC injection of PRALUENT will be administered in the clinic (day 1, visit 1). After visit 1, patients have the option to either self-administer study drug, or have another designated person (such as a spouse or caregiver) administer study drug for them. Study drug should be administered Q2 weeks throughout the study.
3. The kit will include study drug and the study drug compliance log.
4. If at any time during the study after the week 8 visit, the investigator, based on lipid results or safety issue, decides to modify the dose of study drug, an unscheduled kit dispensation visit will be performed. During this visit, a call to the IVRS/IWRS will be performed.
5. Concomitant medication: received concomitantly to the study drug, from the time of informed consent to the final study visit.
6. Alcohol consumption within 48 hours and intense physical exercise within 24 hours prior to blood sampling for lipid parameters are discouraged.
7. Assessments completed at EOS in the neurocognitive function study (R727-CL-1532).
8. For male patients (luteinizing hormone [LH], follicle-stimulating hormone [FSH], and testosterone) and for female patients (LH, FSH, and estradiol). Menstrual cycle data will be collected for women of childbearing potential who are not on hormonal contraceptives.

8.1.2. Early Termination Visit

This visit is only to be done for patients who discontinue the treatment prematurely, whatever the reason, and will take place as soon as practically possible (within 1 month after the last injection of PRALUENT). For patients who prematurely permanently discontinue study drug, see Section 7.3.2.

8.1.3. Unscheduled Visits

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

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility: inclusion/exclusion criteria.

8.2.2. Safety Procedures

8.2.2.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, and pulse will be collected at time points indicated in Table 1.

8.2.2.2. Physical Examination and Body Weight

A general physical examination including body weight will be performed at time points indicated in Table 1.

If a new clinically significant abnormality or worsening from baseline is detected after informed consent, the patient should be considered for further clinical investigation and/or specialist consultation at the investigator's discretion.

Body weight will be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study.

Calibrated balance scales should be used to guarantee accuracy of patients' weight. Self-reported weights are not acceptable, and patients must not read the scales themselves.

8.2.2.3. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. A liver panel will be forwarded to the central laboratory. In case of total bilirubin values above the normal range, differentiation into conjugated and nonconjugated bilirubin will occur automatically.

Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits at time points according to Table 1. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Uric acid
Chloride	Blood urea nitrogen (BUN)	Creatine phosphokinase (CPK)
Carbon dioxide	AST	γGT
Calcium	ALT	HbA1c
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 (urine) will be performed for women of childbearing potential at time points according to Table 1.

Samples for high-sensitivity C-reactive protein (hs-CRP), and gonadal hormones (for female patients - estradiol, follicle-stimulating hormone [FSH] and luteinizing hormone [LH]; for male patients – testosterone, FSH and LH) 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.

8.2.3. Efficacy Procedures

8.2.3.1. Blood Sampling

Blood sampling for determination of lipid parameters includes Total-C, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, and Lp(a). Alcohol consumption within 48 hours and intense physical exercise within 24 hours prior to the blood sampling are discouraged.

The blood sampling schedule is described in Table 1.

8.2.4. Other Assessments

8.2.4.1. Review of Diet

Patients will follow a diet equivalent to the NCEP-ATP III TLC diet at visit 1 (week 0) and will be asked to continue the dietary plan until the last study visit. Patients will be queried about compliance with the dietary plan during the treatment period, at time points according to Table 1.

Details are provided in Appendix 2.

8.2.5. Research Samples

8.2.6. Biomarker Procedures

Research samples for possible biomarker assessments will be collected at time points listed in Table 1. Biomarker results will be reported separately from the clinical study report.

8.2.7. Future Biomedical Research

Research samples unused for study-related research, may be utilized for future biomedical research. These samples will be stored for up to 15 years after the final database lock. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the CSR.

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 patient. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, ECs/IRBs as appropriate, and to the investigators.

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

9.3. Definitions

9.3.1. Adverse Event

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

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

9.3.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.

- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

9.3.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3).

9.4. Recording and Reporting Adverse Events

9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study.

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

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours, as follows:.

- Complete the SAE form utilizing the AE electronic CRF in the electronic data capture (EDC) system and submit within 24 hours of learning of the event

or

- Telephone the sponsor (or designee) at the contact information provided in the SAE completion guidelines, within 24 hours of learning of the event

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/early termination visit - the SAE will be reported to the sponsor. The investigator should make every effort to

obtain follow-up information on the outcome until the event is considered chronic and/or stable.

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

9.4.3. Other Events that Require Accelerated Reporting to Sponsor

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

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

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 180 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest: All AESI, serious and nonserious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2. Adverse events of special interest for this study include the following:

- ALT ≥3 upper limit of normal (ULN; if baseline ALT < ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN). Baseline to be considered is the baseline of the present OLE study.
- Allergic events and/or local injection site reactions that are allergic in nature and that require consultation with another physician for further evaluation
- Neurologic events that require additional examinations/procedures and/or referral to a specialist
- All neurocognitive events
  - Neurocognitive AEs will be reviewed on a regular basis by an independent panel of experts (neurologists/specialists of neurocognition) to ensure that all the necessary information pertinent to these AESIs is collected
- Cataracts
- New onset of diabetes

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

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

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

9.4.5. Abnormal Laboratory or Vital Signs

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

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs (excluding local injection site reactions) will be graded according to the following scale:

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

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

Local Injection Site Reactions

The severity of local injection site reactions will be graded by the investigator using a 4-point scale (mild, moderate, severe, or very severe), adapted from the toxicity grading scale table from the Food and Drug Administration Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials dated April 2005. Local injection site reactions will be reported in detail as indicated on the CRF and/or SAE form, as appropriate.

The complete severity grading scale for assessing local injection site reactions is provided in Appendix 3.

9.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

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

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

The possible answers are:

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

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

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

The investigator should justify the causality assessment of each SAE.

Causality Evaluation Factors

Factors to consider when determining the relationship of an AE to study drug are included below.

Not Related:

- Existence of a clear alternative explanation or nonplausibility (eg, the patient is struck by an automobile when there is no indication that the drug caused disorientation, or cancer diagnosed a few days after first drug administration)
- Due to external causes such as other treatment(s) being administered
- Due to the patient's disease state or clinical condition
- Does not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- Does not reappear or worsen when dosing with study drug is resumed (ie, negative re-challenge)

Related:

- Could not be explained by other treatment(s) being administered
- Could not be explained by the patient's disease state or clinical condition
- Follows a reasonable temporal sequence following the time of administration of the dose of study drug
- Resolves or improves after discontinuation of study drug
- Reappears or worsens when dosing with study drug is resumed (ie, positive re-challenge)
- Known to be a response to the study drug based upon preclinical data or prior clinical data
- Known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson Syndrome)

9.6. Safety Monitoring

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

9.7. Investigator Alert Notification

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

10. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (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.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

There will be no formal testing for safety variables. Descriptive statistics will be provided.

For the secondary efficacy endpoints, no formal statistical hypothesis will be tested.

10.2. Justification of Sample Size

No formal sample size was calculated for this study. The anticipated number of patients is based on the previously observed drop-out rate in the ODYSSEY program.

10.3. Analysis Sets

10.3.1. Safety Analysis Set

Since this is a single-arm, open-label study, treatment allocated and the actual treatment received will be the same. Therefore, a single analysis set (ie, the safety analysis set [SAF]) will be used for safety and efficacy analyses. The SAF includes all patients who received any study drug. All safety and efficacy variables will be analyzed using the SAF.

10.4. Statistical Methods

Study data will be summarized descriptively for all patients in the safety population, as well as by the randomized treatment group in the neurocognitive function study (R727-CL-1532).

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. For continuous efficacy endpoints, the first and third quartiles will also be provided.

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

10.4.1. Patient Disposition

The following will be provided:

- The total number of enrolled patients: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- The total number of patients in the safety population
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics (gender, race, age [years], ethnicity, body mass index [kg/m^2], and region [North America, Western Europe, Eastern Europe, and Rest of World) will be summarized descriptively by treatment group in the neurocognitive function study (R727-CL-1532), and by all patients combined.

The baseline value will generally be defined as the baseline value in the neurocognitive function study (R727-CL-1532) (ie, the last available value before the first dose of double-blind study treatment in that study).

10.4.3. Efficacy Analyses

All lipid and special lipid measurements obtained from the central laboratory will be used to provide a value for the efficacy variables, if appropriate. The baseline value will be defined as the last available value before the first dose of double-blind study treatment in the neurocognitive function study (R727-CL-1532).

The efficacy variables will be explored through descriptive statistics at each scheduled visit, including the assessment prior to the first dose of the open-label study administration. The descriptive summaries will be performed in the Safety Analysis Set (for on-treatment analysis). Formal statistical testing is not planned. While describing the long-term effectiveness of Praluent, simple testing can be performed as appropriate.

Continuous variables will be summarized using the number of patients with data, mean, SD, median, first quartile (Q1) and third quartile (Q3), minimum and maximum.

Categorical variables (including the binary outcome variables) will be described by patient frequency of occurrence. Since these descriptive analyses are exploratory in nature, alpha adjustments for multiple testing are not needed.

Descriptive statistics for calculated LDL-C will also be provided for patients with or without any study medication modification, separately.

Time windows used to allocate a time point to a measurement will be defined in the SAP.

10.4.4. Safety Analysis

The safety analyses address the primary objective of this study, and all safety analyses will be performed on the SAF population. The safety analyses will be conducted on all safety data collected during the study.

10.4.4.1. Adverse Events

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 study drug.
- The TEAE period is defined as the day from first dose of study drug to the last study visit.

Pretreatment AEs are defined as those that developed, worsened, or became serious during the pretreatment period

Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Post-treatment AEs are defined as those that developed, worsened, or became serious during the post-treatment period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping). If any signal is detected with any AESI which warrants further characterization, the time-to event approach (Kaplan-Meier methodology) will be used. Time from the first dose of 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. Incidence rates at 6, 12, 24, 36, and 48 months of exposure will be presented and Kaplan-Meier curves will be provided.
- Drug-induced liver injury (namely ALT, AST, alkaline phosphatase and total bilirubin). The proportion of patients with potentially clinically significant abnormality values at any post-baseline visit by baseline status will be displayed for each parameter. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. The ALT and total bilirubin values will be presented on a logarithmic scale. The graph will be divided into 2 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

10.4.4.2. Other Safety

Vital Signs

Vital signs (temperature, sitting blood pressure, and pulse) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value (PCSV) at any time point will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

10.4.4.3. Treatment Exposure

The duration of treatment exposure will be calculated as:

Date of the last study medication dose – date of the first study medication dose + 14

In addition, for patients previously exposed to PRALUENT, the duration of treatment will be calculated as:

(Date of the last study medication dose in the neurocognitive function study (R727-CL-1532) – date of the first study medication dose in the neurocognitive function study (R727-CL-1532) + 14) + (Date of the last study medication dose in R727-CL-1609 [current study] – date of the first study medication dose in R727-CL-1609 [current study + 14])

The treatment exposures will be summarized.

The number (n) and percentage (%) of patients with a dose modification of PRALUENT will be described.

10.4.4.4. Treatment Compliance

Study treatment compliance will be assessed by treatment group 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 minus first dose date)/(number of injections minus 1)

These parameters will be summarized descriptively (N, mean, standard deviation, median, minimum and maximum).

10.4.5. Other Endpoints

The other endpoints described in Section 4.2.3 will be summarized descriptively by the randomized treatment group in the neurocognitive function study (R727-CL-1532).

10.5. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The last available value before the first dose in the neurocognitive function study, R727-CL-1532.
- In addition to the OLE study database, some data will be recovered from the neurocognitive function study (R727-CL-1532) database

General rules for handling missing data:

- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing safety data will be made.

Visit windows:

- Assessments taken outside of the analysis windows specified in the SAP will be displayed according to the case report form (CRF) assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory safety data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will be summarized based on the analysis windows specified in the SAP. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.
- Extra assessment (laboratory safety data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will also be used in PCSA analyses if within the TEAE period.

10.6. Statistical Considerations Surrounding the Premature Termination of a Study

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

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

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

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

The CRF data for this study will be collected with an EDC tool.

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 –management of study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- AWARE, Business Objects XI – pharmacovigilance activities

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, CRO monitor) will visit each site following enrollment of the first patient, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

12.2. Source Document Requirements

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

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

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on CRFs by trained site personnel. A CRF must be completed for 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 CRF page 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 the corrections, will be available via a system-generated audit trail. 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 International Council for Harmonisation (ICH) guidelines for GCP and applicable regulatory requirements.

14.2. Informed Consent

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

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

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

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.

- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, 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 their initials and 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 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. DATA QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are summarized.

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 11.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 12.1, Section 12.2, and Section 13).

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 12.1).

All subject/patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient/subject final CRF (Section 12.3 and Section 17.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 12.3).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 17.2).

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

22. REFERENCES

None

23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: Long Term Safety Study of PRALUENT in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk and Previously Enrolled in the Neurocognitive Function Trial, 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

Is there a reasonable possibility that the event may have been caused by the study drug or study conduct?

No:

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

Yes:

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

NOTE: This list is not exhaustive.

APPENDIX 2. SUMMARY OF TLC DIET FOR HIGH CHOLESTEROL

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

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

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

APPENDIX 3. ASSESSMENT OF LOCAL INJECTION SITE REACTIONS

Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Emergency Room (ER) visit or hospitalization
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalization
Erythema / Redness *	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Itching	Does not interfere with activity	Interferes with activity or repeated use of topical or systemic treatment	Prevents daily activity or leads to other significant dermatologic conditions (such as infection, scarring, etc.)	Emergency Room (ER) visit or hospitalization
Other (Please specify)***	No modification of daily activities and/or does not require symptomatic treatment.	Hinders normal daily activities and/or requires symptomatic treatment.	Prevents daily activities and requires symptomatic treatment.	Emergency Room (ER) visit or hospitalization

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

*** Please specify the other signs or symptoms (for example, hematoma, discoloration, re-activation, etc.).

ADAPTED from the toxicity grading scale table from the FDA Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials April 2005

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: Long Term Safety Study of PRALUENT in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk and Previously Enrolled in the Neurocognitive Function Trial

Protocol Number: R727-CL-1609

Protocol Version: R727-CL-1609 Amendment 2

Sponsor's Responsible Scientific/Medical Monitor:

See appended electronic signature page

Sponsor's Responsible Regulatory Representative:

See appended electronic signature page

Sponsor's Responsible Biostatistician:

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead:

See appended electronic signature page

Signature Page for VV-RIM-00057919 v1.0

Approval	[redacted]-2018 16:54:38 GMT+0000
Approval	[redacted]18 17:05:18 GMT+0000
Approval	[redacted]-2018 18:11:36 GMT+0000
Approval	[redacted]00

Signature Page for VV-RIM-00057919 v1.0 Approved