Clinical and Regulatory Development

Biostatistics and Data Management

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN

VERSION: FINAL

Title: **A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Praluent® on Neurocognitive Function in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk**

Protocol: **R727-CL-1532**

Investigational Product: **Praluent® (REGN727/SAR236553)**

Sponsor: **Regeneron Pharmaceuticals, Inc.**

Statistician: [redacted]

Clinical Trial Manager: [redacted]

Clinical Study Director: [redacted]

Version/Date: **V1.0 / May 5, 2020**

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

Regeneron Study Biostatistician ([redacted])

Regeneron Study Bioanalytical Sciences ([redacted])

Regeneron Study Medical Director ([redacted])

Regeneron Project Biostatistician [redacted])

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See appended electronic signature page

Head of BDM or designee ([redacted]

Regeneron Pharmaceuticals, Inc. Protocol: R727-CL-1532 (Praluent)
Statistical Analysis Plan May 5, 2020

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Statistical Analysis Plan
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ACB	Anticholinergic burden
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
Apo	Apolipoprotein
AST	Aspartate aminotransferase
CANTAB	Cambridge Neuropsychological Test Automated Battery
CHD	Coronary heart disease
CI	Confidence interval
CPK	Creatine phosphokinase
CRF	Case report form (paper or electronic)
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
CRO	Contract research organization
CVD	Cardiovascular disease
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated Glomerular Filtration Rate
FH	Familial hypercholesterolemia
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
heFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive voice response system

IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LMT	Lipid-modifying therapy
LOCF	Last observation carried forward
Lp(a)	Lipoprotein a
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed-effect model with repeated measures
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NCEP ATP	National Cholesterol Education Program-Adult Treatment Panel
Non-HDL-C	Non-high-density lipoprotein cholesterol
PAL	Paired Associates Learning
PCSA	Potentially clinically significant abnormal value
PCSK9	Proprotein convertase subtilisin/kexin type 9
PT	Preferred term
Q2W	Every 2 weeks
RBC	Red blood cell
RTI	Reaction Time
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SOC	System organ class
SWM	Spatial Working Memory
TEAE	Treatment-emergent adverse event
TG	Triglyceride
Total-C	Total cholesterol
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to unblinding of treatment assignments and database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data collected in the R727-CL-1532 study.

This plan may be revised during the study to accommodate protocol amendments and adapt to unexpected issues in study execution that may affect planned analyses. These revisions will be based on blinded data review of the study data, and a final plan will be issued prior to the database lock (i.e. before treatment assignments become known).

1.1. Background/Rationale

The primary goal of this study is to evaluate neurocognitive function in heFH patients and non-FH patients at high or very high cardiovascular risk receiving Praluent compared with placebo after 96 weeks of treatment. The 96-week treatment duration is considered sufficient to evaluate the effect of Praluent on neurocognitive function.

Praluent is also referred to as alirocumab, REGN727 or SAR236553. In the context of the R727-CL-1532 SAP, it will be referred to as Praluent.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is to evaluate neurocognitive function with use of Praluent after 96 weeks of treatment versus placebo.

1.2.2. Secondary and Exploratory Objectives

The secondary objectives are:

- To evaluate the effect of Praluent in comparison with placebo on lipoproteins
- To evaluate the safety and tolerability of Praluent

1.2.3. Modifications from the Statistical Section of Protocol Amendment 5

N/A.

1.2.4. Modifications from the Approved Statistical Analysis Plan

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

2. INVESTIGATING PLAN

2.1. Study Design and Randomization

This is a randomized, double-blind, placebo-controlled trial to evaluate neurocognitive function in patients with Heterozygous familial hypercholesterolemia (heFH), or in non-familial hypercholesterolemia (non-FH) patients, at high or very high cardiovascular risk.

Patients will be randomized in a 1:1 ratio to receive either placebo or 75 mg Praluent Q2W. Randomization will be stratified by age (<65 or ≥65) and by statin use (no statin, low lipophilicity of the concomitant statin, or high lipophilicity of the concomitant statin).

2.2. Sample Size and Power Considerations

To demonstrate the noninferiority of the Praluent 75 mg Q2W/up-titrate 150mg Q2W dose regimen relative to placebo for the primary endpoint of mean change in Spatial Working Memory (SWM) strategy z-score from baseline to week 96, the sample size for this study is calculated to be 1085 patients per treatment group. This sample size is based on the noninferiority margin of 0.2 for the primary outcome measure. Specifically, a worsening in the SWM strategy z-score of 0 to 0.2 at the group level (small effect size) would not be considered clinically meaningful. Whereas a worsening of 0.3 to 0.5 (or greater), a small-to-medium effect size, might be considered clinically relevant, indicating increased cognitive impairment (Roiser 2015). Therefore, a noninferiority margin of 0.2 on the SWM strategy z-score change from baseline is a conservative estimate of the largest clinically meaningless mean difference between Praluent and placebo treatment groups. Additionally, the assumed mean difference between the treatment groups is 0 and the standard deviation is 1.0 (the standard deviation is obtained from the Cambridge Cognition internal normative data). To achieve 95% power using a 2-sided 95% confidence interval (CI) approach (2-sided alpha=0.05), the sample size is calculated to require 651 patients per treatment group. Assuming dropout rate of 20% in the first year and 25% in the second year, the sample size is increased to 1085 patients per treatment group.

2.3. Study Plan

The study consists of the following 2 periods, which are shown schematically in Figure 1.

- A screening period of up to 3 weeks.

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

- A double-blind treatment period of 96 weeks.

  On day 1 (baseline), after completion of study assessments and after collection of blood samples, and as soon as possible after the patient is randomized into the study, the first dose of study drug will be administered. The patient will be

monitored at the clinical site for 30 minutes after the first dose. Subsequent doses of study drug must be administered Q2W. The last dose of study drug will be administered at week 94.

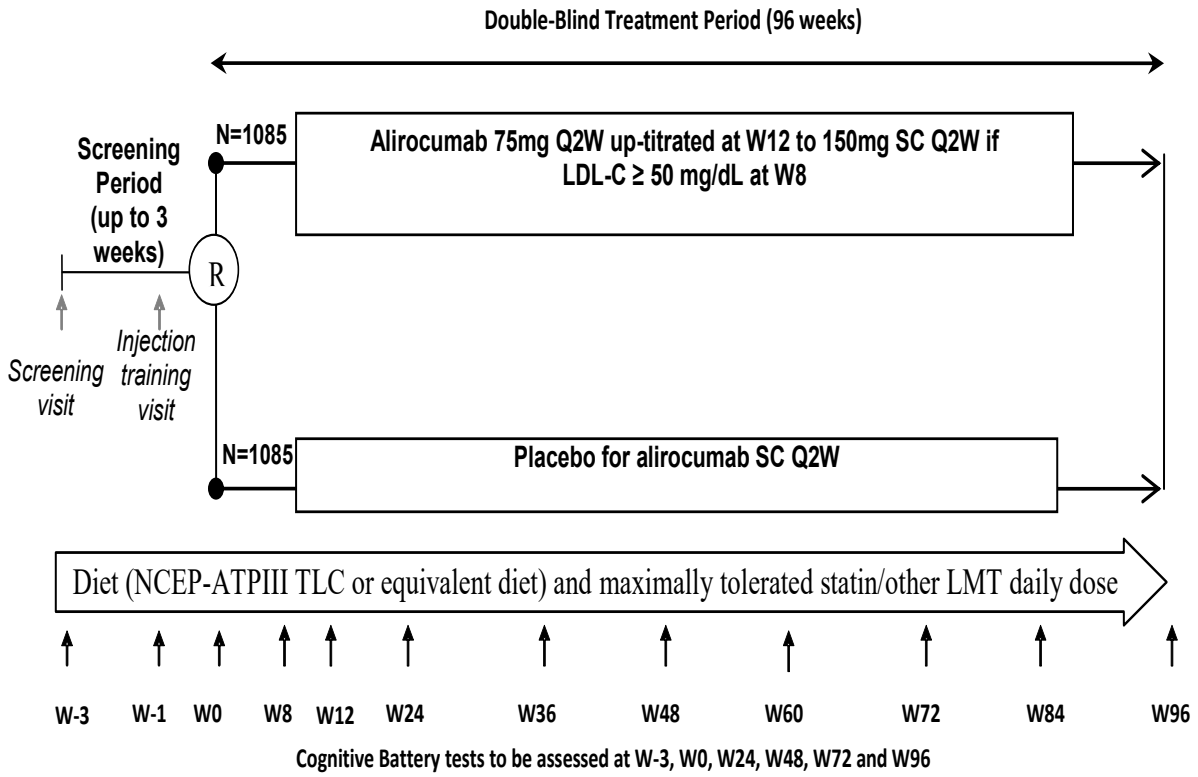
Patients' neurocognitive function will be assessed every 6 months.

The dose of study drug will be increased (using a blinded process) at the week 12 visit in patients whose LDL-C levels are ≥50 mg/dL (1.3 mmol/L) at week 8. Those patients who are randomized to Praluent will receive Praluent 150 mg Q2W at week 12 and until end of study. All patients randomized to placebo will continue to receive placebo.

Lipid results will be blinded for specimens obtained after randomization. No attempts should be made by the investigator or patient to have the patient's lipid values evaluated independently from the time of randomization until the last study visit.

Patients should be on a stable regimen of lipid-modifying therapy (LMT) (including a maximally-tolerated dose of statin, unless statin-intolerant) for 28 days prior to screening, as well as on a stable diet. Patients will be asked to maintain both their statin dose and diet from screening to the end of the study.

Figure 1: Study Flow Diagram



3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), below are the patient populations defined for statistical analysis. The Primary Safety Analysis Set will be the main analysis set for primary endpoint analyses.

For the purposes of the definitions below, a patient is considered randomized to study treatment when they have been screened and received a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not.

As with all trials, odd cases (usually rare) occur for patient eligibility in the analysis populations. The following are three common cases with the planned resolution of each type of case should they occur.

- Patients administered study treatment without randomization or before randomization will not be considered as "randomized" and therefore will not be included in any analysis population. The safety experience from these patients will be reported separately.

- For patients found to be randomized more than once in this trial, safety data from the first randomization will be included in the safety population, with safety data associated with the later randomization reported separately. Inclusion of efficacy data from the patient randomized more than once in the two efficacy populations will be decided on a case-by-case basis prior to the unblinding of treatment assignments and documented in the study report.

- Patients successfully randomized and administered study treatment, but later found to violate inclusion/exclusion criteria, will be included in all analyses with appropriate documentation for the protocol deviation.

3.1. Safety Analysis Sets

3.1.1. Safety Population

The safety population (SAF) will be defined as all patients randomized and exposed to at least 1 dose of study drug, regardless of the amount of treatment administered. Patients will be analyzed according to the treatment received (placebo or Praluent 75 mg Q2W/up-titrate 150 mg Q2W).

3.1.2. Primary Safety Analysis Set

The primary safety population (PSAF) used to analyze the neurocognitive endpoints will be defined as patients from the safety population who had an assessment of the SWM strategy score at baseline, and at least 1 score measured during the TEAE period. The TEAE period is defined as the first double-blind treatment dose to last dose of double-blind treatment + 70 days (10 weeks). Patients will be analyzed according to the treatment actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized.
- For patients receiving study drug from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be Praluent.

3.2. The Efficacy Analysis Sets

3.2.1. Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized patients who had an evaluable secondary efficacy endpoint. The endpoint is evaluable when the following 2 conditions are met:

- Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (ie, baseline)
- Availability of at least 1 measurement value for calculated LDL-C within 1 of the analysis windows during the main efficacy period; the main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window

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

3.2.2. Modified Intent-to-Treat Population

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

- Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (ie, baseline)
- Availability of at least 1 calculated LDL-C value during the efficacy treatment period and within 1 of the analysis windows up to week 96; the efficacy treatment

period is defined as the time from the first double-blind study drug injection up to 21 days after the last double-blind study drug injection

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

3.3. The Anti-Drug Antibody Analysis Set

The anti-drug (Praluent) antibody (ADA) analysis will be performed on all treated patients (safety population) with a blood sample at week 0 (baseline) and at least 1 evaluable blood sample for anti-alirocumab antibodies after the first dose of study drug (ADA population).

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristic Variables

For each patient, demographic and baseline characteristics are obtained from the last available value up to the date and time of the first study treatment administration (i.e. baseline definition). For patients randomized and not treated, the baseline value is defined as the last available value obtained up to the date and time of randomization.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the summary statistics in the safety and efficacy sections.

The following variables will be summarized:

Demographic Characteristics

- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Age in years (quantitative and qualitative variable: <45, ≥45 to <65, ≥65 to <75, and ≥75 years; and <65, and ≥65 years)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)

Baseline Characteristics

- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) in kg/m² (quantitative and qualitative variable defined as <30, ≥30)
- Randomization Strata as Reported in IVRS
- Randomization Strata as Reported from eCRF
- Tobacco Use (current, past, never)
- Alcohol Use (current, past, never)
- LMT at Randomization
- Female Menopausal Status

Baseline Disease Characteristics

- Lipid parameters - quantitative variables for all efficacy parameters
- LDL-C: <70, ≥ 70 to <100, ≥100 to <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL (<1.81, ≥1.81, <2.59, ≥2.59 to <3.37, ≥3.37 to <4.14, ≥4.14 to <4.91, ≥4.91 mmol/L)
- HDL-C: <40, ≥40 mg/dL (<1.04, ≥1.04 mmol/L)
- Fasting TG: <150, ≥150 to <200, ≥200 mg/dL, and category ≥150 mg/dL for mixed dyslipidaemia (<1.7, ≥1.7 to <2.3, ≥2.3 mmol/L, and category ≥ 1.7 mmol/L),
- Lp(a): <30, ≥30 to <50, ≥50 mg/dL, and category ≥30 mg/dL (<0.3, ≥0.3 to <0.5, ≥0.5 g/L, and category >=0.3 g/L)
- HbA1c both quantitative variable and qualitative variable defined as: <5.7%, ≥5.7% to <6.5%, ≥6.5%
- hs-CRP
- Hepatitis B surface antigen
- Hepatitis C antibody

4.2. Medical History and Disease Characteristics

As applicable, patient medical history, pre-listed or not in the e-CRF, will be dictionary coded by primary system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), specifically the MedDRA version in effect at the time of database lock for the analysis. Medical history of interest will be assessed through cardiovascular history and risk factors (dedicated and pre-listed e-CRF variables of acute myocardial infarction, silent myocardial infarction, etc., with outcome of occurred/not occurred), subject medical allergic history (dedicated and pre-listed e-CRF variables of allergic rhinitis, chronic sinusitis, etc., with outcome of occurred/not occurred), and family medical allergic history (dedicated and pre-listed e-CRF variables of allergic rhinitis, chronic sinusitis, etc., with outcome of occurred/not occurred). Additional other medical history (i.e., not already collected in the pre-printed e-CRFs) and surgical history will also be coded and reported.

Medical history of specific interest includes:

- Coronary heart disease (CHD)
- CHD risk equivalents

- Cardiovascular (CV) risk factors other than hypercholesterolemia (hypertension, type 2 diabetes, type 1 diabetes, family history of premature CHD). Smoking status will be summarized separately.
- Family history of type 2 diabetes
- Patient's allergies (described using all pre-printed terms collected in the medical allergic history e-CRF page).

Further for medical history variables, CHD, CHD risk equivalents, and CV risk factors are defined below, and will be based on items or combinations of items pre-listed in the dedicated medical history e-CRF page (unless otherwise specified). Patient status for primary and secondary CVD prevention is also defined below.

CHD (regardless if it is ongoing or not) is defined as at least one of the following events:

- Acute myocardial infarction
- Silent myocardial infarction
- Unstable angina
- Coronary revascularization procedure
- Other clinically significant CHD diagnosed by invasive or non-invasive testing

CHD risk equivalent (regardless if it is ongoing or not) is defined as at least one of the following events:

- Peripheral arterial disease: See definition below.
- Ischemic stroke
- Chronic kidney disease
- Known history of diabetes mellitus (type 1 or 2) AND 2 or more additional risk factors among:
  - History of ankle-brachial index ≤ 0.90
  - History of hypertension
  - History of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening (week-2) with >2+ protein
  - History of pre–proliferative or proliferative diabetic retinopathy or laser treatment for diabetic retinopathy

- Known family history of premature CHD

As listed above, "Peripheral arterial disease" history is defined as follows, using combinations of the corresponding pre-listed medical history items of the e-CRF page "Cardiovascular history and cardiovascular risk factors":

- Intermittent claudication (linked to PAD) TOGETHER WITH ankle-brachial index ≤ 0.90;

Or

- Intermittent claudication (linked to PAD) TOGETHER WITH peripheral revascularization procedure (angioplasty, stenting) for PAD or peripheral revascularization surgery (arterial bypass) for PAD;

Or

- Critical limb ischemia TOGETHER WITH peripheral revascularization procedure (angioplasty, stenting) for PAD or thrombolysis for PAD or peripheral revascularization surgery (arterial bypass) for PAD.

Secondary CVD prevention is defined as patients with any of the following history of CVD (other patients will be classified as primary CVD prevention):

- History of CHD (as defined above)
- History of ischemic stroke
- History of PAD with severity criteria defined as one of the following events:
  - Intermittent claudication and ankle brachial index ≤ 0.90
  - Peripheral revascularization procedure (angioplasty, stenting) for PAD
  - Thrombolysis for PAD
  - Peripheral revascularization surgery (arterial bypass) for PAD
  - Critical limb ischemia

CV Risk Factors are defined for this study as high risk and very high risk below.

- Very high CV risk patients are defined as patients with CHD or CHD risk equivalents (ASCVD).
- High CV risk patients are defined as all other patients.

Hyperlipoproteinemia disease history will be assessed through diagnosis of HeFH, time from diagnosis to study randomization (years), confirmation of diagnosis (genotyping [Yes/No], clinical diagnosis [Yes/No], lipid modifying therapies history and received at randomization as detailed below.

- Lipid modifying therapy history, as reported in the "History of Hypercholesterolemia/Statin Use" e-CRF page
  - Type of lipid-modifying therapy taken at screening (statin, fibrates, bile acid sequestrant, cholesterol absorption inhibitor, nicotinic acid and derivates, omega 3 fatty acids ≥1000 mg/day, other).
  - Number of patients at screening on a maximal tolerated dose of statin. For those not on not statin or not taking the maximum tolerated dose, reason for not statin or not taking a maximum tolerated dose.
  - Number of patients with a history of down-titration of statin dose due to tolerability issues
  - Number of patients with a history of changing to a different statin due to tolerability issues

Lipid modifying therapies received at randomization will be derived from the prior and concomitant medication e-CRF pages by selecting medications with the type of lipid lowering medication tick box checked ("Statin" or "Other lipid modifying therapy").

- Background lipid modifying therapy at randomization as reported in the dedicated prior and concomitant medication e-CRF pages
  - Number of patients taking atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg daily
  - Atorvastatin daily dose in mg (10, 20, 40, 80, Other)
  - Rosuvastatin daily dose in mg (5, 10, 20, 40, Other)
  - Simvastatin daily dose in mg (10, 20, 40, 80, Other)
  - Other statins
  - Any LMT other than statins
  - Any LMT other than nutraceuticals (by chemical class and drug name)
  - Nutraceuticals (Omega 3 fatty acids (<1000mg/day), Phytosterols, Psyllium/plantago, Policosanol, Other nutraceuticals)

Details (i.e. statin names, doses) for patients who had received at least 2 statins the day of randomization will be listed.

Statin use (no statin, low lipophilicity of the concomitant statin, or high lipophilicity of the concomitant statin) as per IVRS and as per eCRF will be summarized together with other baseline characteristics (Section 4.1).

4.3. Prior and Concomitant Medications

All medications (including statin, non-statin LMT, CV, and Other) taken from the time of informed consent to the end of the study, including medications that were started before the study and are ongoing during the study, will be reported in Concomitant Medications CRF.

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

Definitions for deriving prior medications, concomitant and post-treatment medications are described below, with the understanding that a given medication can be simultaneously classified both as a prior and concomitant medication.

- Prior medications are any medications the patient used within the time period between 3 months prior to the screening visit up to the day before first study treatment administration. Prior medications can be discontinued before first treatment administration or can be ongoing during the treatment phase.

- Concomitant medications are defined as any treatments received by the patient concomitantly with the study treatment, specifically from the first day of study treatment administration to the last day of study treatment +70 days. Concomitant medications do not include medications started during the post-treatment period.

- Post-treatment medications are those medications administered to the patient during the time period starting from 71 days after the last study treatment administration and ending when the patient terminates the study.

4.4. Patient Disposition

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

For patient study status, the following milestone categories are defined below. For all categories of patients, percentages will be calculated using the number of randomized patients as the denominator, with two exceptions. Specifically, the two exceptions are for the screened and non-randomized categories, which will not have associated percentages shown.

- Screened patients: The total patient counts will only be shown for pre-randomization information, and percentages will not be provided
- Screen failure patients and reasons for screen failure: The total patient counts will only be shown for pre-randomization information. Non-randomized but treated patients (include if applicable): The total patient counts will only be shown for pre-randomization information, and percentages will not be provided
- Randomized patients
- Randomized but not treated patients and reason for not being treated (including patient's decision for treatment period discontinuation)
- Randomized and treated patients
- Patients complete 96 weeks of double-blind treatment period (at least 94 weeks of exposure and visit W96 performed)
- Patients completed the study treatment period (i.e. as collected on the End of Double Blind Treatment eCRF)
- Patients who did not complete the study treatment period and patient's decision for treatment period discontinuation (as per the End of Double Blind Treatment eCRF)
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation (as per the End of Double Blind Treatment eCRF)
- Patients completed the study (i.e. as collected on the Study Completion eCRF)
- Patients who early terminated the study (as per the Study Completion eCRF)
- Patients who early terminated the study by main reason for early termination (as per the Study Completion eCRF)
- Patients who will participate in the Open Label Extension Study
- Status at last study contact

As defined in Section 3. of this document, the patient analysis populations are:

- Randomized population
- Safety Population (SAF)
- Primary Safety Population (PSAF)

- Intent-to-Treat Population (ITT)
- Modified Intent-to-Treat Population (mITT)
- The Anti-alirocumab Antibody Population (ADA)

4.5. Study Treatment Exposure and Compliance Variables

Study treatment exposure variables are listed below with associated definitions:

- Patient duration of study treatment exposure in weeks defined as: (last study treatment administration date +14 – first study treatment administration date)/7, regardless of intermittent discontinuations.
- The following categories will be used for treatment exposure intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks and <24 weeks, ≥24 weeks and <28 weeks, ≥28 weeks and <32 weeks, ≥32 weeks and <36 weeks, ≥36 weeks and <40 weeks, ≥40 weeks and <44 weeks, ≥44 weeks and <48 weeks, ……., ≥92 weeks and <96 weeks, ≥96 weeks.
- The total number of study treatment injections by patient.
- Patients with up-titration are defined as up-titration according to IVRS/IWRS week 12 transaction with at least 1 injection of alirocumab 150 mg following up-titration decision.

Compliance will be assessed using the following variables with associated definitions:

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

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

4.6. Primary and Secondary Endpoints

4.6.1. Primary Neurocognitive Endpoint

The primary outcome measure is the change in CANTAB cognitive domain SWM strategy score (SWMS) from baseline to week 96. Two definitions will be provided for this endpoint, specifically:

- SWM strategy z-score change from baseline is defined for each patient as: week 96 SWM strategy z-score minus the patient's baseline SWM strategy z-score. The change from baseline SWM strategy z-score is used for the primary analysis evaluation of noninferiority. A lower score denotes better SWM function (ie, less impairment).

  – A patient's SWM strategy z-score at week 96 is defined as: (week 96 SWM strategy raw score minus the SWM strategy mean baseline score) divided by the SWM strategy baseline standard deviation. The SWM strategy mean baseline score and the SWM strategy baseline standard deviation are calculated using patients in both treatment groups (ie, Praluent and placebo).

  – The SWM strategy z-score at baseline is defined for each patient in the same manner as the calculation for the SWM strategy z-score at week 96, replacing the patient's week 96 raw score with the patient's baseline raw score.

- SWM strategy raw score change from baseline is defined for each patient as: week 96 SWM strategy raw score minus the patient's SWM strategy baseline score. The SWM strategy raw score change from baseline is provided descriptively for clinical interpretation of function at week 96. Lower change from baseline raw scores reflect better SWM performance (ie, less impairment).

The baseline SWM strategy score is the last score obtained before the first dose of study treatment. The SWM Strategy score at week 96 is the score obtained within the week 96 analysis window and during the treatment-emergent adverse event (TEAE) period. The TEAE period is defined as the time from the first double-blind study treatment injection up to 70 days after the last double-blind study treatment injection. The analysis window used to allocate a time point to a measurement is defined in Appendix 10.2 of this SAP.

4.6.2. Exploratory Neurocognitive Endpoint

Exploratory neurocognitive outcome measures to further assess neurocognitive function in the CANTAB domains are provided below for each patient:

- Paired Associates Learning (PAL) at week 96 defined as both a PAL z-score change from baseline and PAL raw score change from baseline, following the definitions and rules provided for the primary neurocognitive endpoint

- Reaction Time (RTI) at week 96 defined as both a RTI z-score change from baseline and RTI raw score change from baseline, following the definitions and rules provided for the primary neurocognitive endpoint

- SWM between-errors score (SWMBE) at week 96 defined as both an SWM between-errors z-score change from baseline and SWM between-errors raw score change from baseline, following the definitions and rules provided for the primary neurocognitive endpoint

- Global Composite score at week 96 change from baseline is defined as (the average of the following 4 measures at week 96: SWM strategy z-score, PAL z-score, RTI z-score, and the SWM between-errors z-score) minus the average of the same 4 z-score measures at baseline

4.6.3. Secondary Efficacy Variable

The secondary efficacy endpoints are provided below. For those efficacy endpoints described as percent change from baseline at a given visit, the definition is: 100 multiplied (post-baseline visit measurement – baseline measurement) divided by the baseline measurement.

The baseline measurements are the last values obtained before the first dose of study treatment.

The secondary efficacy endpoint at a given visit is the measurement obtained within the analysis window of the visit and during the main efficacy period. The main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window.

All secondary efficacy endpoints (scheduled or unscheduled) may be used to provide a value for the efficacy endpoint, if appropriate, according to above definition.

- The percent change in calculated LDL-C, apolipoprotein (Apo) B, non-high-density lipoprotein cholesterol (non-HDL-C), and Total-C from baseline to weeks 12, 24, 48, 72, and 96

- The percent change in lipoprotein a [Lp(a)], HDL-C, triglyceride (TG), and Apo A-1 from baseline to weeks 12, 24, 48, 72, and 96

- The proportion of patients reaching LDL-C <70 mg/dL (1.81 mmol/L) at weeks 12, 24, 48, 72 and 96

- The proportion of patients reaching LDL-C <50 mg/dL (1.29 mmol/L) at weeks 12, 24, 48, 72, and 96

4.7. Safety Variables

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

4.7.1. Adverse Events Variables

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

- The PRE-TREATMENT period: defined as the time from the signed informed consent up to the first study treatment injection.

- The treatment-emergent adverse event (TEAE) period: defined as the time from the first study treatment injection up to the day of the last study treatment injection + 70 days (10 weeks), as residual effect of Praluent is expected until 10 weeks after last dose of study treatment.

  The TEAE period will include:

  – The TREATMENT period is defined as the time from the first study treatment injection up to the day of last study treatment injection + 21 days, as serum concentration of alirocumab >10 µg/mL is expected for approximately 21 days following administration of 150 mg. Further, in previous studies, alirocumab concentrations declining below this concentration also showed a decrease in effect on LDL-C.

  – The RESIDUAL TREATMENT period is defined as the time from the day of last study treatment injection + 22 days up to the day of last study treatment injection + 70 days (10 weeks).

- The POST-TREATMENT period: defined as starting the day after the end of the TEAE periods (i.e., 71 days after the last study treatment injection) up to the patient's end of study.

4.7.1.1. Adverse Events and Serious Adverse Events

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

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

Adverse Event Observation Period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.

- Treatment-emergent adverse events (TEAEs) are AEs that developed or worsened or became serious during the TEAE period.

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

4.7.1.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol.

In this study, AESI are the following (their complete descriptions are provided in the protocol):

- Local injection site reactions, selected using an e-CRF specific tick box on the AE page;
- Allergic events:
- General allergic events will be tabulated. Events will be selected using standardized MedDRA query (SMQ) "hypersensitivity" (broad and narrow) excluding the preferred terms linked to local injection site reactions (i.e. preferred terms containing "injection site" or "infusion site")
- ALT ≥3 ULN in the case baseline ALT < ULN or ALT ≥2 times the baseline value in the case baseline ALT ≥ ULN, selected using laboratory data;
- Neurologic events selected using SMQs "demyelination" (broad and narrow), "peripheral neuropathy" (broad and narrow), and "Guillain-Barre syndrome" (broad and narrow) excluding the following preferred terms: "acute respiratory distress syndrome", "asthenia", "respiratory arrest" and "respiratory failure" and including selected PTs from SMQ "optic nerve disorders" (see Appendix 10.5, Table 3 for the list of terms)
- Symptomatic overdose with investigational medicine product, selected using HLT "Overdose" and the tick box "Symptomatic Overdose" in the e-CRF AE page.
- Pregnancy of female patient/subject (including male subject's partner), selected using appropriate MedDRA codes.
- Neurocognitive events:
  - Selected using a company MedDRA query (CMQ), based on the following 5 HLGTs: "deliria (including confusion)", "cognitive and attention disorders and disturbances", "dementia and amnestic conditions", "disturbances in thinking and perception", and "mental impairment disorders".
  - A second grouping of terms for neurocognitive events was defined based on Regulatory Agency request (FDA CMQ) (see Appendix 10.5, Table 4 for the list of terms)
- Cataract using HLT "Cataract conditions"
- New onset of diabetes (NOD) will be assessed in patients without diabètes at baseline: The definition of new onset of diabetes (NOD) will be the following:
  - Type 1 or type 2 diabetes TEAE (grouping of Medical Dictionary for Regulatory Activities [MedDRA®] terms in Appendix 10.4, Table 7)

  and/or

- At least 2 values of HbA1c ≥6.5% during the TEAE period

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

  For patients with several HbA1c measurements but only with the last one ≥6.5%, this single value ≥6.5% will be considered and qualify the patient as NOD by default

and/or

- At least 2 values of fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

  NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD

  For patients with several FPG measurements but only with the last one ≥126 mg/dL (7.0 mmol/L), this single value ≥ 126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD

Analyses of NOD events will also be provided using the tick box on the e-CRF AE page as an exploratory approach in patients without Diabètes at baseline.

In addition, the following grouping of events will be provided:

- Hepatic disorder events using SMQ “Hepatic disorder”
- Diabetes mellitus or diabetic complications using 1/ the HLGT “diabetes complications” (including PTs pertaining to the secondary SOC included in the HLGT),2/ the HLT “diabetes mellitus”, 3/ the HLT “carbohydrate tolerance analyses (incl diabetes)” excluding PTs “blood glucose decreased” and “Glycosylated haemoglobin decreased” and 4/ from the HLT "Hyperglyceamic conditions NEC" only the following PTs “hyperglycaemia”, “Hyperglycaemic unconsciousness” and “Hyperglycaemic seizure”

Neurocognitive Events of Special Interest

Neurocognitive events are defined in this study as AESI, specifically, neurocognitive AEs (serious or nonserious) required to be monitored, documented, and managed in a pre-specified manner as described in this protocol. The neurocognitive events will be adjudicated by the neurocognitive events review committee which is composed of experts in the field of cognition, independent from the sponsor and the investigators. This committee will be responsible for defining, validating, and classifying (in a blinded fashion) AEs of interest possibly related to cognition impairment. A charter and an operational manual will specify the procedures and criteria used for review of these events.

The committee will adjudicate whether a neurocognitive event identified by investigator or the CMQs is indeed a neurocognitive event (Yes/No).

The committee will also adjudicate whether possible etiology of the neurocognitive event is identified.

- Yes: means that there is a clear alternative explanation for the neurocognitive event.
- No: means that there is no clear alternative explanation for the neurocognitive event, and it might be study related.

4.7.1.3. Events Causing Death

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

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

4.7.2. Clinical Laboratory Safety Variables

Clinical laboratory tests will consist of blood analyses (including hematology and clinical chemistry) and urinalysis. Clinical laboratory values will be converted and analyzed in international units, including associated normal ranges provided by the central laboratory. International units will be used in all listings and tables. Clinical laboratory values in conventional (US) units will also be available in the database, with associated normal ranges (analyses can be provided upon request). Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries. Potentially clinically significant abnormalities (PCSA) ranges will be applied to the laboratory test values as applicable (see Appendix 10.3 for PCSA definitions).

Unless otherwise specified below, blood samples for clinical laboratories will be collected at the protocol scheduled visits, and visits will be assigned to the Analysis Windows (See Appendix 10.2). The laboratory parameters (excluding those considered as efficacy parameters) will be classified as follows:

- Hematology:
  - Red blood cells and platelets: hemoglobin, hematocrit, erythrocytes count, platelets count, reticulocyte count, ery. mean corpuscular Hemoglobin (MCH), ery. mean corpuscular HGB concentration (MCHC), ery. mean corpuscular volume (MCV)
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase

- Electrolytes: sodium, potassium, chloride, calcium, phosphorus, bicarbonate
- Renal function: creatinine, creatinine clearance, blood urea nitrogen (BUN), uric acid
- Liver function: alanine Aminotransferase (ALT), aspartate aminotransferases (AST), alkaline phosphatase (ALP), GGT, bilirubin, LDH

- Hepatitis screen: anti-hepatitis-C antibody and hepatitis B surface antigen collected at week -3 and week 96.

4.7.3. Vital Sign Variables

Vital signs parameters will include height (cm), weight (kg), heart rate (bpm), systolic and diastolic blood pressure (mmHg) after resting at least five minutes. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be provided for protocol specified visits and visits will be assigned to the Analysis Windows (See Appendix 10.2). Potentially clinically significant Abnormalities (PCSA) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.3 for PCSA definitions).

4.8. Other Variables

Other assessment endpoints are listed and defined below. Protocol schedule visits will be assigned to the Analysis Windows (See Appendix 10.2).

- The percent change in hs-CRP from baseline to protocol specified visits. Hs-CRP values greater or equal to 10 mg/L will be excluded from analyses in a second approach, since these are suggestive of concurrent infection(1). PCSA (potentially clinically significant abnormalities) criteria for hs-CRP are listed in Appendix 10.3.

- The absolute change in HbA1c (%) from baseline to protocol specified visits. PCSA criteria for HbA1c are listed in Appendix 10.3.

- The proportion of patients with two consecutives results, separated by at least 21 days, of calculated LDL-C <25 mg/dL (<0.65 mmol/L) (and again for calculated LDL-C <15 mg/dL [< 0.39 mmol/L]) during the treatment period.

- The proportion of patients with at least one result of calculated LDL-C <25 mg/dL (<0.65 mmol/L) (and again for calculated LDL-C <15 mg/dL [< 0.39 mmol/L]) during the treatment period.

- For the patients with two consecutive results as described above, the time to the first calculated LDL-C <25 mg/dL (<0.65 mmol/L) (and again for calculated LDL-C <15 mg/dL [< 0.39 mmol/L]) during the treatment period.

- Gonadal hormone levels (for female patients - estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH); for male patients - testosterone, FSH and LH)

4.9. Anti-Drug Antibody Variables

Anti-drug (Praluent) antibody (ADA) are assessed at baseline (before the first study treatment injection), at weeks 48 and 96. ADA measurements will be assigned to the analysis windows as defined in Appendix 10.2. As appropriate, patient frequencies and percentages will be depicted, and the percentages will be calculated based on the ADA population.

The following variables will be described:

- ADA response (Positive or Negative). For ADA positive:
  - Titer levels
  - Neutralizing status (Positive or Negative)
- Pre-existing positive ADA defined as patients with positive ADA response at baseline with less than 4-fold increase in titer in the post-baseline period
- Treatment-emergent positive ADA response defined as 1) Patients with no ADA positive response at baseline but with any positive response in the post-baseline period or 2) Patients with a positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period. For treatment-emergent positive ADA, the following categories for ADA duration will be applied:
  - A persistent positive response is a treatment-emergent ADA positive response detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period
  - An indeterminate duration positive response is defined as ADA present only at the last sampling time point
  - A transient positive response is defined as any treatment-emergent positive ADA response that is neither considered persistent nor indeterminate

[redacted]

5. STATISTICAL METHODS

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the safety population. Parameters described in Section 4.1 will be summarized for the safety population, the primary safety population in the case of a 10% difference (in any treatment group) from the number of safety population, and again for the ITT population in the case of a 10% difference (in any treatment group) from the number of safety population.

Continuous data will be summarized using the number of patients with data, mean, SD, median, minimum and maximum for each treatment group. First quartile (Q1) and third quartile (Q3) will be also provided for baseline lipid parameters, HbA1c and hs-CRP. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Treatment group comparisons for demographic characteristics and disease characteristics will be provided for descriptive purposes (i.e., confirmation of the randomization process to equally distribute relevant patient background profiles among the two treatment groups) using the Chi-squaretest for categorical data and the asymptotic one-way ANOVA test for Wilcoxon scores (Kruskal-Wallis test) for continuous data. As applicable, other safety baseline data is presented collectively in the descriptive statistics summary tables containing respective post-baseline data.

5.2. Medical History and Disease Characteristics

Medical history and disease characteristics will be descriptively summarized by treatment group and overall for the study in safety population.

All reported patient's medical history and surgical history will be presented by primary SOC and HLT. The tables will be sorted by SOC internationally agreed order and decreasing patient frequency of HLT based on the overall incidence in the study. In addition, all medical history of specific interest, as described in Section 4.2, will be summarized by patient incidence and percentage.

For the patients with primary CVD prevention status (see definition in Section 4.2), the number (and percentage) of patients with the following comorbidities/risk factors will be tabulated:

- Diabetes mellitus with target organ damage (renal damage (microalbuminuria, or macroalbuminuria, moderate CKD) and/or retinopathy (pre-proliferative or proliferative diabetic retinopathy and/or laser treatment for diabetic retinopathy)),
- Diabetes mellitus with 2 or more risk factors (see Section 4.2),

- Family History of premature CHD
- Hypertension,
- Moderate CKD
- Current smoker
- At least 2 of the above comorbidities/risk factors

In addition, smoking status will be summarized in patients with primary CVD prevention status.

For the patients with a secondary prevention status, the CVD history will be described using the number (%) of patients with:

- History of CHD (see Section 4.2)
- History of ischemic stroke
- History of PAD with severity criteria
  - Intermittent claudication and ankle brachial index ≤ 0.90
  - Peripheral revascularization procedure (angioplasty, stenting) for PAD
  - Thrombolysis for PAD
  - Peripheral revascularization surgery (arterial bypass) for PAD
  - Critical limb ischemia

Additionally:

- The number (%) of patients with a secondary prevention status with 1 or more associated comorbidity among hypertension, diabetes mellitus, and/or moderate CKD will be summarized.
- The number (%) of patients with history of CHD and 1 or more associated comorbidity among hypertension, diabetes mellitus, moderate CKD and/or other CVD (ischemic stroke, PAD) will be summarized.

For patient disease characteristics, as described in Section 4.2, continuous data will be summarized using the number of patients with data, mean, SD, median, minimum and maximum for the study and for each of the strata. Categorical and ordinal data will be summarized using the number and percentage of patients in the study and for each stratum.

5.3. Prior and Concomitant Medications

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

All concomitant medications during the treatment period, dictionary coded by WHO-DD, will be descriptively summarized by treatment group, for patients in the safety population. Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications (including statin, non-statin LMT, CV), by decreasing frequency of the Praluent group incidence of ATC followed by therapeutic class. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication. Additionally, concomitant medications pre-specified as statin, non-statin LMT, and CV will be summarized by patient counts (and percentages) by therapeutic class or e-CRF pre-specified categories as appropriate and standardized medication name.

Post-treatment medications will be summarized as described above for all medications.

LMT (statins and other LMTs) use after randomization will be summarized over time graphically by treatment group and LMTs intensity at randomization using the following categories:

- atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily or;
- atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily or simvastatin at any daily dose, or other statins,
- LMT other than statin only,
- no LMT.

The LMTs intensity at randomization is defined as:

- patients treated at randomization with atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily (high intensity statin),
- patients treated at randomization with atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily or simvastatin at any daily dose (low intensity statin), or other statins,

- non-statin LMT only,
- no LMT.

5.4. Patient Disposition

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

Patient study status will be summarized by treatment group and overall for the study (screened patients, screen failures, and non-randomized but treated patients only). Summaries will provide the frequency (and percentage as applicable) of patients that met the criteria for the variables described in Section 4.4. Exception listings will be generated for any subject treated but not randomized, randomized but not treated, and treated differently than randomized.

Patient analysis populations will be summarized by treatment group, depicting frequencies (and percentages) of patients that met the criteria for each population described in Section 3.

5.5. Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure and study compliance parameters for the treatment period described in Section 4.5 will be assessed and summarized by treatment group, for patients in the safety population.

5.5.1. Exposure to Investigational Product

Study treatment exposure for the treatment period will be descriptively summarized for the treatment duration and total number of injections as described in Section 4.5. Treatment duration will be summarized using the number of patients with data, mean, SD, median, minimum and maximum. Categorized 4-week intervals of treatment duration will be summarized descriptively by counts and percentages.

The incidence of premature study treatment discontinuation (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically by treatment group in the safety population using the Kaplan-Meier method.

Patient Up-titration

The number and percentage of patients with an up-titration in the Praluent group will be described. Patients with an up-titration are defined as up-titrated according to IVRS/IWRS Week 12 transaction with at least one injection of alirocumab 150 mg following the up-titration decision.

5.5.2. Measurement of Compliance

Study treatment compliance parameters will be descriptively summarized using the number of patients with data, mean, SD, median, minimum and maximum for the variables listed in Section 4.5. According to protocol, cases of overdose are reported in the AE e-CRF pages and will be described in the AE analysis.

Both monitored and derived protocol deviations will be summarized for important deviations (counts of deviations), patients (incurring a deviation by count and percentage), and by type of important deviation (patient count and percentage). A patient listing of all major and minor protocol deviations will be provided.

5.6. Analyses of Primary and Secondary Endpoints

5.6.1. Analyses of Primary Neurocognitive Variable

The primary neurocognitive analysis is a statistical evaluation of the noninferiority of the Praluent 75 mg Q2W/up-titrate 150 mg Q2W dose regimen to placebo for the primary endpoint of change in SWM strategy z-score from baseline to week 96 in the primary safety population. The 2-sided 95% CI for the mean treatment difference at week 96 will be determined using an appropriate contrast statement in a mixed-effect model with repeated measures (MMRM). The upper CI limit will be compared to the noninferiority margin which is defined as 0.2 and the noninferiority will be declared if the upper CI limit is below the noninferiority margin.

In the case noninferiority is achieved for the primary neurocognitive function endpoint comparison, superiority of the primary neurocognitive function endpoint will be assessed using the same upper CI limit calculated for the primary comparison. Specifically, the upper CI limit will be compared to zero and superiority will be declared if the upper CI limit is below zero. A statistical multiplicity adjustment is not needed, since this process of noninferiority achievement followed by superiority assessment using the same 95% upper CI limit on the primary endpoint corresponds to a simple closed test procedure (EMA/CPMP/EWP/482/99 – 27July 2000).

The MMRM model will include the fixed categorical effects of treatment group (placebo, Praluent), both randomization strata (as per IVRS/IWRS), time point (weeks 24, 48, 72, and 96), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous covariate of baseline SWM strategy raw score value and baseline value-by-time point interaction. Post-baseline assessments within a patient's TEAE period will be included in the analysis and missing data are accounted for by the MMRM model. Model assumptions for normality will be explored prior to the analysis testing.

This model will be run using Statistical Analysis Software (SAS) mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation.

This model will provide baseline adjusted least-squares means estimates at week 96 for both treatment groups with their corresponding standard errors.

To support the clinical interpretation of the primary neurocognitive analysis, the SWM strategy raw score change from baseline to week 96 in the primary safety population will also be provided using the MMRM analysis method described above (at least includes least squares mean and 95% CI).

Model Assumption Checks

Homogeneity of treatment effect across baseline SWM strategy z-score

In order to check the homogeneity of treatment effect versus baseline SWM strategy z-score, the following interaction terms will be added in the primary MMRM model:

- Treatment group * baseline SWM strategy z-score
- Treatment group * time-point * baseline SWM strategy z-score

Within the framework of this model with interaction terms, a graph presenting the LS means difference versus placebo at week 96 and the corresponding 95% CI will be provided by baseline SWM strategy z-score value.

Analysis of residuals:

The analysis of the residuals of the MMRM will be primarily based on studentized residuals. It will include:

- Normality of studentized residuals, presented graphically using histogram and QQ-plot.
- Plot of studentized residuals versus predicted values.
- Distribution of studentized residuals, presented graphically using boxplots, within each category of the fixed categorical effects of the MMRM:
  - treatment group (Praluent, placebo)
  - time point (weeks 24, 48, 72, and 96)
  - treatment-by-time point interaction
  - randomization strata
  - randomization strata-by-time point interaction.

5.6.1.1. Sensitivity to Stratification at Randomization

In order to assess the robustness of the primary analysis to stratification mistakes made at the time of randomization (i.e. the stratum recorded in IVRS/IWRS differs from the actual stratum recorded in the e-CRF), the MMRM model will be re-run replacing the IVRS/IWRS strata with the e-CRF actual strata.

5.6.1.2. Sensitivity to the Handling of Missing Data

Sensitivity analyses will be conducted to assess the robustness of primary analysis with regards to handling of missing data (3).

Visual examination:

- In order to explore the missing data pattern, post-baseline SWM strategy z-score observations during the TEAE period (in the primary safety population) will be described according to the following groups:
  - SWM strategy z-score available at week 96 (i.e. primary endpoint available),
  - SWM strategy z-score available at week 72 but missing at week 96,
  - SWM strategy z-score available at week 48 but missing from week 72,
  - SWM strategy z-score available at week 24 but missing from week 48,
  - SWM strategy z-score missing from week 24.

A graph of mean SWM strategy z-score (respectively change from baseline in SWM strategy z-score) ± SE at baseline, and weeks 8, 12, 24, 48, 72, and week 96 will be provided by missing data pattern, for each treatment group.

- In the primary safety population, demographic and baseline characteristics will be described within the missing data pattern number 1 versus the pooled others. P-values from Chi-square test for categorical data and from asymptotic one-way ANOVA test for Wilcoxon scores (Kruskal-Wallis test) for continuous data, will be also provided, for descriptive purposes.

Multiple Imputations:

In addition to the MMRM method, the multiple imputation method (see Appendix 10.5 for more details) will be used to address missing values, in the primary safety population, followed by the testing of treatment arms using an analysis of covariance (ANCOVA) model, with the intent to evaluate the robustness of the primary analysis using a different statistical method.

Missing data from the primary safety population will be imputed 100 times to generate 100 complete data sets, using the MI SAS procedure (using Markov Chain Monte Carlo). The

percent change from baseline at week 96 will be then derived from observed and imputed SWM strategy z-score at this time point. The 100 complete data sets will be then analyzed using an ANCOVA model with treatment group and randomization strata (as per IVRS/IWRS) as fixed effects, and the baseline SWM strategy z-score as continuous covariate, and the MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae (4).

Pattern mixture model:

The MMRM model relies on the "missing-at-random" (MAR) assumption. Because the possibility for a not-missing-at-random (NMAR) missingness mechanism can never be excluded, sensitivity analysis to explore the impact of non-ignorable missingness on the primary neurocognitive endpoint analysis will be conducted using the pattern mixture model approach as described below (see Appendix 10.6 for more details).

In the pattern-mixture model approach, different imputation strategies will be applied to the primary neurocognitive endpoint (i.e. CANTAB cognitive domain SWM strategy z-score change from baseline to Week 96) values missing during TEAE period (i.e. within the time period from the first double-blind IMP injection up to the day of the last double-blind injection +70 days) in contrast to those missing after the TEAE period. Presented below are the reasons for considering differences in the impact of alirocumab dependent on the timing of the last study treatment administration:

- Patients who discontinued study treatment due to adjudicated neurocognitive events but are still within the TEAE period would continue to show impact from treatment similar to that observed for other patients who also had adjudicated neurocognitive events.

  Note: The neurocognitive events recorded on the AE eCRF by the investigator are defined below, by any of the following programmatical procedures:

  – Sponsor neurocognitive events CMQ;
  – FDA neurocognitive events CMQ;
  – Investigator identified NC events, as entered in the eCRF.

- Patients who discontinued study treatment due to reasons other than adjudicated neurocognitive events but are still within the TEAE period would continue to show impact from treatment similar to that observed for patients without any adjudicated neurocognitive events.

- Patients who discontinued study treatment (alirocumab or placebo) but are after the TEAE period would no longer be impacted by study treatment, and thus would have SWMS values similar to patients receiving placebo.

Missing data from the primary safety population will be imputed 100 times to generate 100 complete data sets, using the approach described above. The 100 completed datasets of

observed and imputed LDL-C data will be used for primary neurocognitive endpoint analyses.

The 100 complete datasets of observed and imputed SWMS data at week 96 will be analyzed using an ANCOVA model with treatment group and randomization strata as fixed effect, and the baseline SWMS value as continuous covariate. The MIANALYZE SAS procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae (4).

5.6.1.3. Sub-group Analyses

To assess the homogeneity of the treatment effect across various subgroups, treatment-by-subgroup factor, time point-by-subgroup factor and treatment-by time point-by subgroup factor interaction terms and a subgroup factor term will be added in the primary MMRM model. LS mean difference versus placebo at week 96 will be provided, as well as the corresponding SE and 95% CI, within each subgroup. The significance level of the treatment-by-subgroup factor interaction term at week 96 will be also provided for each factor for descriptive purpose. Forest plots will be provided. In order to handle unbalances between randomization stratification factors levels, population weights will be used as for the primary analysis model.

The following subgroups of interest will be evaluated, assuming there are enough patients in each subgroup level to perform the evaluation. For the subgroup factors that are also randomization stratification factors, the IVRS strata will be used.

- The age group (<65, ≥65) per IVRS,
- The statin use strata per IVRS (no statin, low lipophilicity of the concomitant statin, high lipophilicity of the concomitant statin),
- Gender (Female, Male)

5.6.2. Analyses of Exploratory Neurocognitive Variables

To further understand the effects of Praluent on cognitive function and support the primary neurocognitive analysis, the 3 domain endpoints (specifically PAL, RTI, and SWM between error scores) and the Global Composite score will also be evaluated for noninferiority at week 96 in the primary safety population. These 4 measures will not be evaluated for superiority. The analysis method (MMRM) and noninferiority evaluation approach (evaluation of the 95% CI for the mean treatment difference at week 96) described for the primary neurocognitive analysis will also be used for the 3 domain's z-scores change from baseline and the Global Composite score change from baseline. To support the clinical interpretation of the 3 domains, the raw score change from baseline to week 96 in the primary safety population will also be provided using the MMRM analysis method.

The 4 domain endpoint scores (including the primary neurocognitive endpoint) and the Global Composite scores will be summarized by time point (weeks 24, 48, 72, and 96) for the primary safety population as described below:

- For the 4 domain's z-score: LS mean and SE for each treatment group, obtained from the same MMRM models as used for endpoints above and including planned time points (see Section 5.6.1) and with z-score values, changes from baseline in the model as appropriate.

- For the 4 domain's raw score and the Global Composite score: LS mean and SE for each treatment group, obtained from the same MMRM models as used for endpoints above and including planned time points (see Section 5.6.1) and with raw score values, changes from baseline in the model as appropriate.

The 4 domain endpoint scores (including the primary neurocognitive endpoint) and the Global Composite scores will also be summarized descriptively by time point.

Descriptive statistics by time point for the SWM Strategy z-score and raw score will be provided for patients with 2 consecutive LDL-C < 25 mg/dL results separated by at least 21 days, or with 2 consecutive LDL-C < 15 mg/dL results separated by at least 21 days, if applicable (i.e., with enough patients).

5.6.3. Analyses of Secondary Efficacy Variables

For secondary efficacy endpoints of lipids (defined in Section 4.6.3), descriptive summaries and analyses will be performed in the ITT population (for ITT analysis) and the mITT population (for on-treatment analysis). P-values for the testing of study treatment effect will be provided for descriptive purposes only (nominal p-values).

For descriptive summaries, percent change from baseline in calculated LDL-C, Total-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, and Lp(a) will be provided at each time point for each treatment group. All measurements, scheduled or unscheduled, will be assigned to analysis windows defined in the SAP in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. The time profile of each parameter will be plotted by treatment group with the corresponding standard errors. For TG and Lp(a), summary statistics will include Q1 and Q3.

Multiple types of measurements are planned to be analyzed during the trial, specifically continuous measurements expected to have a normal distribution (eg, percent change in calculated LDL-C), continuous measurements expected to have a non-normal distribution (eg, TG), and binary measurements (eg, proportion of patients reaching LDL-C <70 mg/dL).

5.6.3.1. Continuous Endpoints Anticipated to Have a Normal Distribution

Continuous secondary efficacy variables, defined in Section 4.6.3, anticipated to have a normal distribution (ie, lipids other than TG and Lp(a)) will be analyzed in the analysis populations using the same MMRM method as described for the primary neurocognitive

endpoint (Section 4.6.1). Specifically, the model will contain fixed categorical effects of treatment group, both randomization strata, planned time points up to week 96 (specific time points are weeks 8, 12, 24, 48, 72, and 96), strata-by-time point interaction and treatment-by-time point interaction, as well as, the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

5.6.3.2. Continuous Endpoints Anticipated to Have a Non-normal Distribution

Continuous secondary efficacy endpoints, defined in Section 4.6.3, anticipated to have a non-normal distribution (ie, TG and Lp(a)) will be analyzed in the analysis populations using a robust regression model (ie, ROBUSTREG SAS procedure with M-estimation option) with treatment group and randomization strata as main effect and corresponding baseline value(s) as the covariate. Missing values will be addressed using the same multiple imputation approach as described for primary neurocognitive endpoint (and using the same time points in the imputation model as described above for Section 5.6.1.2), with data log-transformed before imputation process and then back transformed to create the imputed data sets using the TRANSFORM statement of SAS MI procedure. The variables in the multiple imputation model will at least include the same variables as used in the robust regression model.

The percent change from baseline at time point of interest will be derived from observed and imputed lipid values at this time point. Multiple imputation will be followed by robust regression model to compare treatment group differences, with the endpoint of interest as the response variable using M-estimation (using SAS ROBUSTREG procedure) with treatment group, randomization strata (as per IVRS/IWRS) and corresponding baseline value(s). Combined means estimates for both treatment groups, as well as the differences of these estimates, with their corresponding SEs, 95% CIs and p-value will be provided through the SAS MIANALYZE procedure.

5.6.3.3. Binary Endpoint Variables

Binary secondary efficacy endpoints, defined in Section 4.6.3, will be analyzed in the analysis populations using stratified logistic regression (using the strata option of the SAS logistic procedure) with treatment group and randomization strata as main effect and corresponding baseline value(s) as the covariate. Missing values will be addressed using the same multiple imputation approach as described for primary neurocognitive endpoint (and using the same time points in the imputation model as described above for Section 5.6.1.2). The variables in the multiple imputation model will at least include the same variables as used in the robust regression model.

The binary endpoint at time point of interest will be derived from observed and imputed lipid values at this time point. Multiple imputation will be followed by stratified logistic regression, (with strata defined as randomized in the IVRS/IWRS) using the strata option of the SAS logistic procedure. The logistic regression procedure will be used to compare treatment group differences, with the model containing treatment group and corresponding baseline value(s) as covariate, stratified by randomization strata defined as per IVRS/IWRS. Combined estimates of odds ratio versus placebo, 95% CI, and p-value will be obtained through the SAS MIANALYZE procedure.

In the data dependent case that the logistic regression method is not applicable (eg, the response rate is zero in 1 treatment group and thus the maximum likelihood estimate may not exist), the last observation carried forward (LOCF) approach would be used for handling of missing values. Treatment effects would be compared using the stratified exact conditional logistic regression method, specifically using the strata option of the SAS logistic procedure (with strata defined as randomized in the IVRS/IWRS). The LOCF imputation method will consist of using the last value obtained up to the applicable time point window (weeks 8, 12, 24, 48, 72, and 96 as applicable) to impute the missing week value. In case the model would not converge with stratification variables, an unstratified exact logistic regression will be performed.

5.6.3.4. Summary of Results by Time Point

Central laboratory values (in conventional (US) and international units), percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units), for LDL-C, Total-C, HDL-C, fasting TG, non-HDL-C, Lp(a), Apo-B, Apo-A1 and ratio Apo-B/Apo-A1 (absolute change from baseline) at weeks 8, 12, 24, 48, 72, and 96 time points will be summarized by treatment group in both the ITT and mITT populations as described below:

- For lipids other than TG and Lp(a): LS mean and SE for each treatment group, obtained from the same MMRM models as used for endpoints above and including planned time points (see Section 5.6.3.1) and with raw values, changes from baseline, and percent change from baseline as response variable in the model as appropriate.

- For lipids other than TG and Lp(a): Observed data raw values, change from baseline (as applicable), and percent change from baseline response variables will be summarized by patient counts, mean and SD for each treatment group at all planned time points.

- For TG and Lp(a): mean and SE for each treatment group obtained from multiple imputation approach followed by the robust regression models as used for endpoints above and including planned time points (see Section 5.6.3.2) and with raw values or percent changes from baseline as response variable in the model as appropriate.

- For TG and Lp(a): Observed data raw values and percent change from baseline response variables will be summarized by patient counts, mean and SD for each treatment group at all planned time points.

5.6.4. Adjustment for Multiple Comparisons

Adjustments to the alpha level for the purposes of multiple testing are not applicable for this safety study. The exploratory neurocognitive and secondary efficacy lipid endpoints are supportive of the primary analysis and not hypothesis-testing. Any statistical testing is for descriptive purposes only (ie, any p-values provided are nominal).

5.7. Analysis of Safety Data

The summary of safety results will be presented by treatment groups (Praluent, placebo) on the safety population (Section 3.1). No formal inferential testing will be performed. Summaries will be descriptive in nature. All summaries of safety results described below will be presented for each period respectively, unless otherwise noted.

General common rules

All safety analyses will be performed, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (i.e., exposed but not randomized) will be listed separately.
- The baseline value is defined as the last available value obtained up to the date and time of the first study treatment, except otherwise specified.
- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (PCSA version dated January 2009 [Appendix 10.3]). Considering that the threshold defined in the PCSA list for monocytes and basophils can be below the ULN, the following PCSA criterion will be used for the PCSA analysis of monocytes and basophils:
  - PCSA criterion for monocytes: >0.7 Giga/L or >ULN (if ULN ≥0.7 Giga/L).
  - PCSA criterion for basophils: >0.1 Giga/L or >ULN (if ULN ≥0.1 Giga/L).
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations including nonscheduled or repeated evaluations.
- The treatment-emergent PCSA denominator by treatment group for a given parameter will be based on the number of patients assessed for that given parameter at least once during the TEAE period.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Appendix 10.2, Table 2 in order to provide an assessment for week 8 to week 96 time points.
- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize results and change from baseline values by visit, the last on-treatment value and the worst on-treatment value. The last on-treatment value is defined as the last post-baseline value collected during the respective treatment period (as defined in

Section 4.7.1). The worst on-treatment value is defined post-baseline as the nadir and/or the peak value collected during the respective treatment period, according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.

- For exploratory purposes, specific safety analyses could also be provided according to up-titration status, ie, according to whether the patients remained on the alirocumab 75 mg Q2W doses or whether they were up titrated to 150 mg Q2W. These analyses will be exploratory and descriptive (no formal comparison per dose) as it is expected that there could be inherent differences in the baseline characteristics between those patients titrating to 150 mg Q2W and those remaining on the alirocumab 75 mg Q2W doses. In order to reduce the bias of this analysis, the period before the up-titration time point (planned at Week 12) will be analyzed separately since only the alirocumab 75 mg Q2W doses are proposed for this time period and consequently the early events occurring before Week 12 can only be attributed to those doses. Therefore, the descriptive analysis per dose will include any safety events occurring from the first injection post Week 12 IVRS/IWRS transaction to the end of the TEAE period. Baseline characteristics of patients receiving each dose will be summarized.

- Analyses performed according to diabetes status will be done considering diabetic patients as patients with either type 1 or type 2 diabetes in the medical history e-CRF page (regardless of the ongoing status).

5.7.1. Analysis of Adverse Events

In general, the primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be provided separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine pre-treatment or post-treatment status. Details on classification of AEs with missing or partial onset dates are provided in Section 6.4.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by SOC, HLGT (when applicable), HLT (when applicable), and PT. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. For tables presenting severity of events, the worst severity will be chosen for patients with multiple instances of the same event. The denominator for computation of percentages is the safety population within each treatment group.

The table of all TEAEs presented by SOC and PT will be sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs (in the Praluent group). This will define the presentation order for all other tables by SOC and PT, unless otherwise specified. The tables of AEs by SOC, HLGT, HLT and PT will be sorted by the SOC internationally

agreed order and the other levels (HLGT, HLT, PT) will be presented in alphabetical order, unless otherwise specified.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE;
  - Serious TEAE;
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC, HLT and PT (HLT incidence ≥ 5 % in any treatment group), sorted by SOC internationally agreed order and by alphabetic order for the other levels (HLT and PT);
- All TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC (in the Praluent group).
- All TEAEs by treatment group regardless of relationship in one column and, in the same table a second column with TEAEs related to alirocumab according to investigator's opinion by primary SOC, HLGT, HLT and PT;
- All TEAEs by maximal severity (i.e., mild, moderate or severe), presented by primary SOC and PT, sorted as defined above;
- The event rate per patient-year (the number of patients with an event in question divided by total patient-years) will be provided for all TEAEs by SOC and PT. For a patient with event, patient year is censored at time of first event; for patient without event, it corresponds to length of TEAE period;
- Kaplan-Meier curves will be provided, when appropriate, for time from first dose of study treatment to the first occurrence of selected TEAEs as well as incidence rates at 24, 48, 72, and 96 weeks of exposure. Patients without any event will be censored at the end of the TEAE period. Selected TEAEs could be AESIs (e;g neurocognitive events), or TEAE related to any clinically significant signal that needs further characterization;

- The frequency of selected AEs by SOC and PT over time during the treatment period (number of patients experiencing AE and percentage by patient-months) will be provided by time intervals defined as: ≤24 weeks, >24 to ≤48 weeks, >48 to ≤72 weeks, >72 to ≤96 weeks, using the PROC LIFETEST with the actuarial method. Only the first event will be counted.

Analysis of all treatment emergent serious adverse event(s)

- All serious TEAEs by primary SOC, HLGT, HLT, and PT and by SOC/PT; Patient listings of serious TEAEs will be provided for the report appendix.

- All serious TEAEs by treatment group regardless of relationship in one column and in the same table a second column with TEAEs related to alirocumab according to investigator's opinion, by primary SOC, HLGT, HLT, and PT;

- The event rate per patient-year will be provided for all serious TEAEs by SOC and PT.

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

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

Analysis of groupings of adverse events including selected adverse events of special interest

- All grouping of TEAEs including adverse events of special interest, as listed in Section 4.7.1.2, will be presented by SMQ/CMQ and PT (when selection is based on SMQs/CMQs) and by SOC and PT (when selection is based on the e-CRF tick box or HLGT/HLT). The summaries will be sorted by decreasing incidence of PT within each SOC/SMQ (in the Praluent group).

- Neurocognitive events adjudicated by the neurocognitive events review committee will also be summarized by primary SOC and PT. They will also be summarized according to the adjudication of possible etiology of the neurocognitive events (Yes/No) (Section 4.7.1.2).

- All TEAEs within diabetes grouping will be analyzed overall and according to the diabetic status at baseline (i.e., in patients With and without diabètes at baseline).

The following variables will also be tabulated for the local injection site reactions TEAEs:

- Intensity of the event (mild, moderate, severe);

- Number of events divided by the number of study treatment injections received;

- Time from first study treatment injection to first injection site reaction;
- Description of the highest intensity of each symptom recorded in the specific e-CRF page with table and bar chart.

Description of symptoms and possible etiologies for General Allergic Reaction TEAE reported by investigator (using the tick box), will be presented.

Post-treatment adverse events

- All post-treatment AEs by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs (in the Praluent group) within each SOC;
- All post-treatment SAEs by primary SOC and PT, sorted by the sorting order defined above.

Subgroup of patients with two consecutive LDL-C <25 mg/dL (<0.65 mmol/L)and LDL-C <15 mg/dL [< 0.39 mmol/L])

If applicable, similar summaries of TEAEs as those described above will be provided on the safety subgroup population of patients with two consecutive results of LDL-C <25 mg/dL (as defined in Section 4.8) in both treatment groups. Only TEAEs for which it will be confirmed or unclear that they occurred, worsened or became serious on the day or after the day the first level of LDL-C <25 mg/dL was observed will be considered in this summary.

In addition, the neurocognitive event rate in patients with 2 consecutive results separated by at least 21 days, and with only 1 such event for calculated LDL-C <25 mg/dL, and calculated LDL-C <15 mg/dL, will be assessed.

5.7.1.1. Patient Deaths

The following summaries of deaths will be generated.

- Number (%) of patients who died by study period (TEAE and post-treatment);
- Deaths in nonrandomized patients or randomized but not treated patients;
- TEAEs leading to death (death as an outcome on the AE CRF page, as reported by the Investigator) by (at least) SOC (sorted by internationally agreed order), and PT (sorted by decreasing frequency, showing the number (n) and percentage (%) of patients) for the safety population.

5.7.2. Analysis of Clinical Laboratory Variables

Clinical laboratory parameter actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit (collected up to the

day of last dose of study treatment +21 days) by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum for each treatment group. Additionally, laboratory parameter measures for last on-treatment values and worst on-treatment values will be summarized in a similar manner. Clinical laboratory parameters mean changes from baseline, with the corresponding SE, can be plotted at each visit by treatment group, in the case results warrant further investigation. These parameters will be presented by the biological functions defined in Section 4.7.2. For glucose, only fasting samples will be included in the summaries.

Individual patient laboratory parameter measurements will be additionally evaluated by PCSA criteria, specifically identifying patients with at least one post-baseline measurement that meets the PCSA criteria within the TEAE period. The following additional project specific PCSA criteria will also be evaluated during the TEAE period:

- Patients with a hemoglobin decrease from baseline ≥ 15 g/L.
- Patients meeting the ALT increase defined in Section 4.7.1.2.

Glucose (quantitative summary and PCSA) will also be analyzed, overall and according to the diabetic status at baseline.

Patients meeting the PCSA criteria at least once will be summarized by patient count (and percent) for a post-baseline PCSA measurement while accounting for the baseline PCSA status (PSCA normal/missing; PCSA abnormal), for each treatment group. For the appendix, this laboratory parameter PCSA table will be reproduced with patients meeting the PCSA criteria at least once during the TEAE period regardless of baseline PCSA status. These laboratory parameters will be presented by the biological functions defined in Section 4.7.2. Patient listings of laboratory measurements that meet PCSA criteria will be provided for the report appendix. For those laboratory parameters that don't have an associated PCSA criteria, similar summary tables can be provided based on measurements outside the central laboratory normal ranges, if applicable.

Hepatitis C antibody

The number and percentage of patients with a post-baseline seroconversion for hepatitis C test will be provided by treatment group in post-baseline (including the TEAE and post TEAE periods) as well as in the TEAE period alone. Post-baseline seroconversion is defined for patients with a negative baseline status who had either a "positive RNA" or a "confirmed positive antibody with negative RNA" post-baseline status as defined in the table below. Other situations require case by case evaluation and will be described individually if relevant.

The status as regards hepatitis C virus for a patient will be defined as follows for all evaluations (baseline and post-baseline).

Table 1: Definition of the patient status regarding hepatitis C virus

	Hepatitis C Antibody test result				
	Negative		Positive		
Reflexive test[a] – hepatitis C RNA test	Not available or HCV RNA not detected	HCV RNA detected	HCV RNA not detected[b]	HCV RNA detected	Not available
Hepatitis C status – label	Negative	Positive RNA	Negative[b]	Positive RNA	Positive Ab – no RNA available

[a] test performed at the same time or after the antibody test in pre-treatment period (for baseline evaluation), or post-baseline, respectively

[b] For post-baseline evaluation, a second antibody test with a different type of assay is to be done at the same date or after the first antibody test. The result of this test will modify the final hepatitis C status of the patient in some cases (see details in the text below the table)

The baseline evaluation will be based on tests performed during the pre-treatment period.

In case of multiple hepatitis C tests available for the post-baseline evaluation, the positive status of the patient will be defined as follows:

- "Positive RNA" status if at least 1 post-baseline positive RNA is detected, regardless of status of the patient at the end of treatment.
- Else "Positive Ab – no RNA available" status if no post-baseline reflexive RNA test is available for at least 1 post-baseline positive antibody test.

If no antibody test is available or with "indeterminate" as result pre-treatment or post-baseline respectively, the RNA test (if available) will be used alone to determine the status of the patient. If no RNA test is available then the hepatitis C status of the patient will be missing.

The post-baseline status "confirmed positive antibody with negative RNA" will replace "Negative" status as defined above in the case where no RNA was detected post-baseline and the 2 antibody tests surrounding the same visit (from 2 different types of assay) are positive.

For a conservative approach, the post-baseline status "Positive Ab – no RNA available" will not be modified by the availability of a second antibody test from a different assay.

For the description of the positive hepatitis C virus test during the TEAE period, all above rules will apply while replacing post-baseline by TEAE period.

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values or ALT increase as defined as AESI (see Section 4.7.1.2) during TEAE period by baseline status will be displayed by treatment group for each parameter.

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

Listing of possible Hy's law cases identified by treatment group (i.e., patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin >2 x ULN, concomitantly or not) with ALT, AST, ALP, total bilirubin, and if available direct and indirect bilirubin will be provided.

The incidence of liver-related TEAEs will be summarized by treatment group. The selection of PTs will be based on SMQ Hepatic disorder (see Section 4.7.1.2).

5.7.3. Analysis of Vital Sign Variables

The vital sign actual values and change from baseline values obtained while sitting will be descriptively summarized at baseline and each post-baseline visit (collected up to the day of last dose of study treatment +21 days) by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum for each treatment group. Additionally, vital sign measures for last on-treatment value and worst on-treatment value will be summarized in a similar manner. Vital sign mean changes from baseline, with the corresponding SE, can be plotted at each visit by treatment group, in the case results warrant further investigation.

Individual patient vital sign measurements (regardless of sitting position) will be additionally evaluated by PCSA criteria, specifically identifying patients with at least one post-baseline measurement that meets the PCSA criteria within the TEAE period. Patients meeting the PCSA criteria at least once will be summarized by patient count (and percent) and treatment group. Patient listings of vital sign measurements that meet PCSA criteria will be provided for the report appendix.

5.8. Analysis of Other Variables

The summary of other variables will be presented by treatment groups (Praluent, placebo) on the safety population. No formal inferential testing will be performed for either period. Summaries will be descriptive in nature.

All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows in order to provide an assessment for week 8 to week 96 time points.

Hs-CRP and HbA1c parameters (Section 4.8) will be summarized by treatment group for the number of patients with data, mean, SD, median, minimum, and maximum (for hs-CRP, Q1 and Q3 will be also provided) by analysis visit during the treatment period. For HbA1c, summaries will also be provided according to diabetes mellitus status at baseline. The time profile will be plotted by treatment group for HbA1c showing the means and the corresponding SEs, while medians (with Q1-Q3) will be plotted for hs-CRP. Applying the PCSA criteria to these variables at any time during the TEAE period, the number of patients (and percentages) meeting the criteria will be summarized by treatment group.

The gonadal hormone parameters (Section 4.8) will be summarized by treatment group for the number of patients with data, mean, SD, median, minimum, and maximum by analysis visit during the treatment period. For FSH and LH, the summaries will be performed for all patients, female patients, and male patients. Estradiol will be summarized for female patients only, and testosterone will be summarized for male patients only. Summary tables will also be provided for gonadal hormone parameters based on measurements outside the central laboratory normal ranges, if applicable.

In order to minimize confounding factors with menopause or exogenous estrogens, the summaries of estradiol, FSH, and LH for female patients will be repeated by excluding patients who were receiving hormone replacement therapy, were ≥50 years, or had FSH levels ≥25 IU/L at baseline.

For male patients, the summaries of testosterone, FSH, and LH will be repeated by excluding patients who were receiving testosterone supplementation or had LH levels ≥15 IU/L at baseline.

Binary endpoints defined in Section 4.8 will be described through patient counts and percentages. Kaplan-Meier curves will be provided for the variables assessing time to first occurrence of an event (i.e., calculated LDL-C related outcome). Patients not meeting the event will be censored at the end of the treatment period. For the analysis of the time to the first of the two consecutive LDL-C events, patients without post-baseline LDL-C result or with only one post-baseline LDL-C result will not be included in the analysis.

5.9. Analysis of Anti-Drug Antibody Variables

The summary of ADA variables will be presented by treatment groups (Praluent, placebo) on the ADA population. No formal inferential testing will be performed. Summaries will be descriptive in nature.

ADA variables will be summarized, taking into account all samples regardless of timing in relation to injections. ADA results will be summarized as follows:

- ADA results (negative or positive) by time point
- Neutralizing status (negative or positive) by time point for positive ADA

- ADA titers using descriptive statistics (median, minimum and maximum) for positive ADA by time point
- Number (%) of patients with pre-existing ADA and number (%) of patients with treatment-emergent ADA positive response
- Number (%) of patients with persistent/indeterminate/transient treatment-emergent ADA positive response
- Time to onset of treatment-emergent ADA positive response using descriptive statistics.
- Number (%) of patients with at least 1 neutralizing ADA.

Correlations between ADA parameters (e.g., titers, treatment-emergent ADA positive status, neutralizing status) and safety and/or efficacy endpoints will also be explored (e.g., scatter plot).

[redacted].

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Efficacy and Safety Variables

Unless otherwise specified, the baseline assessment is programmatically defined as the latest available measurement taken before first administration of study treatment. For patients randomized but not-treated, the baseline will be the last available measurement before randomization.

6.2. Data Handling Conventions for Primary and Secondary Endpoints

Data handling conventions, including addressing missing data, is addressed for the primary and secondary endpoints in Section 5.6.1, 5.6.2, and 5.6.3.

6.3. General Data Handling Conventions

In general, the following formulas will be used for computation of parameters:

Time from diagnosis

Time from diagnosis (years) = (Date of informed consent – Date of diagnosis*) / 365.25.

(*):In case the month of diagnosis would be missing, it will be put equal to JANUARY if the year of diagnosis equals the year of informed consent; it will be put equal to JUNE otherwise. In the case the day is missing, the day will be put equal to 1st if the month and year of diagnosis equals the month and year of informed consent; otherwise it will be put equal to the 15th of the month.

Date of last dose of study treatment

The date of the last injection is equal to the last date of administration reported on injection administration case report form page, or missing if the last administration date is unknown.

Renal function formulas

Estimated GFR will be derived using the Modification of the Diet in Renal Disease (MDRD) equation:

$186.3 \times (\text{creatinine in } \mu\text{mol/L} / 88.4)^{-1.154} \times (\text{age in years})^{-0.203}$ (x 0.742 if female, x 1.21 if race is "black or African American").

Lipids variables, laboratory safety variables, hs-CRP

For data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.4. General Missing Data Conventions

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of baseline definition if "time" of first study treatment administration or time of assessment at week 0 visit is missing

If the time of the first study treatment administration or the time of assessment at week 0 visit is missing, then the baseline value is defined as the last available value obtained before or on the day of the first study treatment administration.

Handling of computation of treatment duration and compliance if study treatment first or end of treatment date is missing

If the last or first injection date is missing, the exposure duration and compliance will be left as missing.

Handling of safety and efficacy analysis periods and survival analysis if end of study treatment date is missing

If the last injection date is missing, then this date is imputed to the earliest between:

- the last day of the month and year, when applicable or else the 31st of December of the year,
- the date of the end of treatment visit (week 96 visit for completer, early end of treatment visit for patients who prematurely discontinued the study treatment),
- the date of the last contact

for the purpose of safety and efficacy analysis period start and/or end.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of adverse events with missing or partial date/time of onset, worsening, seriousness

Missing or partial AE dates and times will be imputed so that if the partial AE date/time information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Handling of adverse events when date and time of first study treatment administration is missing

When the date and time of the study treatment administration is missing, all AEs that occurred on or after the day of randomization will be considered as TEAEs.

When the time of the first study treatment administration is missing, all AEs that occurred on the day of the first study treatment administration will be considered as treatment-emergent AEs.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment has to be assumed as possibly related in the frequency tables, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

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

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

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

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

6.5. Visit Windows for Time Points

Visit windows will be programmatically imposed on those efficacy and safety measures repeatedly collected over the course of the study. These visit windows are derived from the number of days in study, specifically assigning day ranges to mimic the study assessment

schedule provided in the protocol. Data analyzed by time point (including efficacy, laboratory safety data, vital signs, physical examinations, and ADA) will be summarized using the analysis windows given in Appendix 10.2. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses. If multiple valid values of a variable exist within an analysis window, the nearest from the targeted study day will be selected. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values of a variable exist within a same day, then the first value of the day will be selected when time is available, else the scheduled visit will be selected.

6.6. Unscheduled Assessments

For efficacy, safety laboratory data, vital signs, physical examinations, and ADA, unscheduled visit measurements may be used to provide a measurement for a time point, a baseline, a last or a worst value, if appropriate according to their definitions. The measurements may also be used to determine abnormal values and PCSA.

6.7. Pooling of Centers for Statistical Analyses

The randomization scheme was not stratified by center because the primary efficacy variable is centrally assessed and expected not to be influenced by the center when other factors such as diet are already controlled. Therefore, the center will not be added as factor in the primary analysis model.

6.8. Statistical Technical Issues

Not Applicable.

7. TIMING OF STATISTICAL ANALYSES

There are no interim analyses planned. Therefore, no multiplicity adjustment for multiple analyses is needed (see Section 5.6.4).

The statistical analysis will be conducted at the end of the study and will consist of the final analysis of primary and secondary endpoints and final safety analysis.

8. SOFTWARE

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

9. REFERENCES

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10. APPENDIX

10.1. Summary of Statistical Analyses

Primary Neurocognitive Endpoint Analysis:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Change from baseline to week 96 in SWM strategy z-score	Primary Safety Population	MMRM	Yes, including handling of missing data	Yes	1) Actual stratification factor 2) Multiple Imputations + ANCOVA 3) Pattern Mixture Model

10.2. Windows for Analysis Time Points

Below are the definitions for the visit windows programmatically imposed on measures repeatedly collected over the course of the study. These visit windows reflect the study schedule of assessments as described in the protocol. The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected. Day 1 is defined as the first date of double-blind study treatment administration, and is labeled as baseline for most variables. Since the protocol specifies that measurements be collected before study treatment is administered on a given day, it is appropriate that baseline include Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

Table 2: Analysis Windows Definition – All Endpoints Except Lipids or Vital Signs

Time point	Targeted study day	Analysis window in study days
Week 24	169	85 to 252
Week 48	337	253 to 420
Week 72	505	421 to 588
Week 96	673	589 to 756

Study days are calculated from the day of first IMP injection, the day of first IMP injection being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

Table 3: Analysis Windows Definition – Lipids

Time point	Targeted study day	Analysis window in study days
Week 8	57	29 to 70
Week 12	85	71 to 126
Week 24	169	127 to 252
Week 48	337	253 to 420
Week 72	505	421 to 588
Week 96	673	589 to 756

Study days are calculated from the day of first IMP injection, the day of first IMP injection being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

Table 4: Analysis Windows Definition – Vital Signs

Time point	Targeted study day	Analysis window in study days
Week 8	57	29 to 70
Week 12	85	71 to 126
Week 24	169	127 to 210
Week 36	253	211 to 294
Week 48	337	295 to 378
Week 60	421	379 to 462
Week 72	505	463 to 546
Week 84	589	547 to 630
Week 96	673	631 to 714

Study days are calculated from the day of first IMP injection, the day of first IMP injection being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

10.3. Criteria for Potential Clinical Significant Abnormalities (PCSA)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis :	Enzymes activities must be expressed in ULN, not in IU/L.
	>3 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
	>5 ULN	Internal DILI WG Oct 2008.
	>10 ULN	Categories are cumulative.
	>20 ULN	First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis :	Enzymes activities must be expressed in ULN, not in IU/L.
	>3 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
	>5 ULN	Internal DILI WG Oct 2008.
	>10 ULN	Categories are cumulative.
	>20 ULN	First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L.
		Concept paper on DILI – FDA draft Guidance Oct 2007.
		Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative.
	>2 ULN	
		Concept paper on DILI – FDA draft Guidance Oct 2007.
		Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
		Internal DILI WG Oct 2008.
		To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN	FDA Feb 2005.
	>10 ULN	Am J Cardiol April 2006.
		Categories are cumulative.
		First row is mandatory. Rows following one mentioning zero can be deleted.

Parameter	PCSA	Comments
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	Use is optional. FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	Use is optional. FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.

Parameter	PCSA	Comments
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms	

Parameter	PCSA	Comments
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula.
Borderline		
Prolonged*	Borderline: 431-450 ms (Male); 451-470 ms (Female)	
Additional		
	Prolonged: >450 ms (Male); >470 ms (Female)	*QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.
	≥500 ms	
	Increase from baseline	
	Borderline: Increase from baseline 30-60 ms	
	Prolonged: Increase from baseline >60 ms	

10.4. List of MedDRA terms for CMQs

Table 5: Selected PTs from SMQ "Optic nerve disorders" including in the CMQ for neurologic events

MedDRA Term Label
Benign neoplasm of optic nerve
Optic atrophy
Optic discs blurred
Optic nerve disorder
Optic nerve injury
Optic nerve neoplasm
Optic nerve operation
Optic neuropathy
Papillitis
Pseudopapilloedema
Subacute myelo-opticoneuropathy
Toxic optic neuropathy
Visual evoked potentials abnormal
Amaurosis fugax
Blindness
Blindness unilateral
Colour blindness acquired
Colour vision tests abnormal
Cranial nerve injury
Delayed myelination

MedDRA Term Label
Fundoscopy abnormal
Hemianopia
Hemianopia heteronymous
Hemianopia homonymous
Loss of visual contrast sensitivity
Neuro-ophthalmological test abnormal
Night blindness
Ophthalmological examination abnormal
Optic pathway injury
Optical coherence tomography abnormal
Quadrantanopia
Visual acuity reduced
Visual acuity reduced transiently
Visual acuity tests abnormal
Visual field defect
Visual field tests abnormal
Visual impairment
Visual pathway disorder

Table 6: CMQ "Neurocognitive disorders – FDA's recommendation"

MedDRA level	MedDRA Term Label
PTCD	Amnesia
PTCD	Amnestic disorder
PTCD	Anterograde Amnesia
PTCD	Neuropsychiatric symptoms
PTCD	Change in sustained attention
LLTCD	Cognitive Deterioration
PTCD	Cognitive Disorder
LLTCD	Confusion
LLTCD	Confusion Aggravated
PTCD	Confusional State
PTCD	Delirium
PTCD	Dementia
PTCD	Dementia Alzheimer's type
LLTCD	Dementia Nos
LLTCD	Dementia Nos Aggravated
LLTCD	Dementia of the Alzheimer's type NOS
PTCD	Dementia with Lewy Bodies
PTCD	Disorientation
PTCD	Disturbance in attention
PTCD	Executive dysfunction
PTCD	Frontotemporal Dementia
LLTCD	Global Amnesia

MedDRA level	MedDRA Term Label
PTCD	Illogical Thinking
PTCD	Impaired reasoning
PTCD	Incoherent
PTCD	Judgement impaired
PTCD	Memory Impairment
PTCD	Mental Impairment
LLTCD	Mental Impairment Nos
LLTCD	Mental State Abnormal Aggravated
PTCD	Mental Status Changes
PTCD	Mini Mental Status Examination Abnormal
PTCD	Presenile Dementia
PTCD	Retrograde Amnesia
PTCD	Senile Dementia
LLTCD	Senile Dementia Nos
LLTCD	Short-term Memory Loss
PTCD	Thinking Abnormal
LLTCD	Thinking Slowed
PTCD	Transient Global Amnesia
PTCD	Vascular Dementia

Table 7: CMQ "Type 1 or Type 2 diabetes"

MedDRA Term Label	Preferred Term Code
Diabetes mellitus	10012601
Diabetes mellitus inadequate control	10012607
Insulin resistant diabetes	10022491
Diabetes mellitus malnutrition-related	10050197
Diabetes mellitus management	10051599
Insulin-requiring type 2 diabetes mellitus	10053247
Type 1 diabetes mellitus	10067584
Type 2 diabetes mellitus	10067585
Fulminant type 1 diabetes mellitus	10072628

10.5. Detailed Description of the Multiple Imputation Procedure

The following is a detailed description of the multiple imputation procedure which will be used for sensitivity analysis of primary endpoint as well as the analysis of the secondary endpoints.

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

- Step 1: the MCMC method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern.

- Step 2: Using the monotone data set from step 1, missing data will be imputed using the regression method.

The imputation model for step 1 will include the treatment group and the values of the analyzed parameter at baseline and planned time-points up to week 96.

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

- the randomization strata (age and statin use strata);
- age, BMI, and gender (age and BMI included as continuous variables).

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

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

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

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

10.6. Detailed Description of the Pattern Mixture Model

As a sensitivity analysis of the primary neurocognitive endpoint (i.e. CANTAB cognitive domain SWM strategy z-score change from baseline to Week 96), a pattern-mixture model approach will be used to explore missing data patterns. Specifically, a different imputation strategy is planned for missing SWMS values during the TEAE period (i.e. within the time period from the first double-blind IMP injection up to the day of the last double-blind injection +70 days) in contrast to those missing after the TEAE period. Presented below are the reasons for considering differences in the impact of alirocumab dependent on the timing of the last study treatment administration:

- Patients who discontinued study treatment due to adjudicated neurocognitive events but are still within the TEAE period would continue to show impact from treatment similar to that observed for other patients who also had adjudicated neurocognitive events.

Note: The neurocognitive events recorded on the AE eCRF by the investigator are defined below, by any of the following programmatical procedures:

- Sponsor neurocognitive events CMQ;
- FDA neurocognitive events CMQ;
- Investigator identified NC events, as entered in the eCRF.

- Patients who discontinued study treatment due to reasons other than adjudicated neurocognitive events but are still within the TEAE period would continue to show impact from treatment similar to that observed for patients without any adjudicated neurocognitive events.

- Patients who discontinued study treatment (alirocumab or placebo) but are after the TEAE period would no longer be impacted by study treatment, and thus would have SWMS values similar to patients receiving placebo.

In addition, SWMS data missing prior to last study treatment administration (i.e., intermittent missing) are considered "Missing At Random".

Missing SWMS values from the primary safety population will be imputed 100 times to generate 100 complete data sets. The change from baseline to Week 96 will be derived from observed and imputed SWMS at this time point. The completed data sets will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and randomization strata as fixed effects, and the baseline SWMS value as continuous covariate. The results from the 100 analyses will be combined using Rubin's formulae. If necessary, the number of imputations (100) will be increased until stable estimates are obtained.

Imputation Strategy 1: Missing data during the TEAE period for patients who discontinued study treatment due to adjudicated neurocognitive events

The imputation strategy for missing SWMS values following discontinuation of study treatment due to adjudicated neurocognitive events but still within the TEAE period, is to impute by patients who had at least one adjudicated neurocognitive event during the TEAE period. Specifically, data collected during the TEAE period for patients who had at least one adjudicated neurocognitive event during the TEAE period will be used to impute missing data.

For each patient, missing SWMS values will be imputed 100 times, using a random draw from a normal distribution, with mean equal to the mean of the observed SWMS values, and variance equal to the conditional variance of observed SWMS values given the baseline value, at the specific time-point from patients in the same treatment group who had adjudicated neurocognitive events during the TEAE period.

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

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

Where σ_1^2 denotes the variance of Y1 and ρ the coefficient of correlation between Y_0 and Y_1.

During the random generation process, a minimum value of 4 and a maximum of 28 will also be applied in order to avoid imputed SWMS values out of range.

Imputation Strategy 2: Imputation of missing data during the TEAE period for patients who discontinued study treatment due to reasons other than adjudicated neurocognitive events

The imputation strategy for missing SWMS values following discontinuation of study treatment due to reasons other than adjudicated neurocognitive event, but still within the TEAE period, is to impute by patients who did not have any adjudicated neurocognitive events during the TEAE period. Specifically, data collected during the TEAE period for patients who did not have any adjudicated neurocognitive events during the TEAE period will be used to impute missing data.

For each patient, missing SWMS values will be imputed 100 times, using a random draw from a normal distribution, with mean equal to the mean of the observed SWMS values, and variance equal to the conditional variance of observed SWMS values given the baseline value, at the specific time-point from patients in the same treatment group who did not have any adjudicated neurocognitive events during the TEAE period.

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

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

Where σ_1^2 denotes the variance of Y1 and ρ the coefficient of correlation between Y_0 and Y_1.

During the random generation process, a minimum value of 4 and a maximum of 28 will also be applied in order to avoid imputed SWMS values out of range.

Imputation of missing data after the TEAE period

The imputation strategy for missing SWMS values following discontinuation of study treatment, and after the TEAE period, is to impute by patients who are in the placebo treatment group. Specifically, all data collected (whether during TEAE period or after TEAE period) for patients who are in the placebo treatment group will be used to impute missing data.

For each patient, missing SWMS values will be imputed 100 times, using a random draw from a normal distribution, with mean equal to the mean of the observed SWMS values , and variance equal to the conditional variance of observed SWMS values given the baseline value, at the specific time-point from patients in the placebo treatment group.

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

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

Where σ_1^2 denotes the variance of Y1 and ρ the coefficient of correlation between Y_0 and Y_1.

During the random generation process, a minimum value of 4 and a maximum of 28 will also be applied in order to avoid imputed SWMS values out of range.

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