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STATISTICAL ANALYSIS PLAN

VERSION: Final

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-alirocumab antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
Apo	Apolipoprotein
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
BMI	Body mass index
BUN	Blood urea nitrogen
CHD	Coronary Heart Disease
CI	Confidence interval
CMQ	Company MedDRA query
CV	Cardiovascular
DBP	Diastolic blood pressure
ECG	Electrocardiogram
e-CRF	Electronic case record form
eDISH	Evaluation of drug-induced serious hepatotoxicity
FAS	Full analysis set
GGT	Gamma-glutamyl transferase
HbA1c	Glycated haemoglobin A1c
HDL-C	High density lipoprotein Cholesterol
HLGT	High level group term
HLT	High level term
HoFH	Homozygous familial hypercholesterolemia
HR	Heart rate
hs-CRP	High-sensitivity C-reactive protein
IMP	Investigational medicinal product

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ITT	Intent-to-treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein cholesterol
LLOQ	Lower limit of quantification
LLT	Lowest level term
LMT	Lipid Modifying Therapy
LOCF	Last observation carried forward
Lp(a)	Lipoprotein a
LS	Least square
MAR	Missing-at-random
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
mITT	Modified intent-to-treat
MMRM	Mixed effect model with repeated measures
NMAR	Not-missing-at-random
PCSA	Potentially Clinically significant abnormality
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
PT	Preferred Term
Q1	First quartile
Q2W	Quoque 2 weeks
Q3	Third quartile
RDW	Red blood cell distribution width
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic blood pressure
SC	Subcutaneous

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

SD	Standard deviation
SE	Standard error
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment emergent adverse event
TG	Triglycerides
Total-C	Total Cholesterol
ULN	Upper limit of normal range
ULOQ	Upper limit of quantification
WHO-DD	World Health Organization Drug Dictionary

1. OVERVIEW

This Statistical Analysis Plan (SAP) is intended to be a detailed description (expanding on the statistical analyses described in the protocol) of the definitions and statistical techniques to be used for the analyses of data collected in the R727-CL-1628 (ODYSSEY HoFH) study. This SAP will be finalized prior to the database lock for the first-step analysis to ensure the credibility of the study results by pre-specifying the statistical methods for analyses before unblinding of treatment assignments. The content of this SAP is intended to be inclusive of both the first and second-step analyses described in the protocol.

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, and a final plan will be issued prior to the first-step database lock (i.e. before treatment assignments become known). For the purposes of this document, REGN727/SAR236553 will be referred to as "alirocumab".

1.1. Background/Rationale

The objective of this study is to evaluate the efficacy, safety and tolerability of alirocumab in patients with homozygous familial hypercholesterolemia (HoFH). Patients will be maintained on their background treatment throughout the study, supporting the choice of placebo for the control group. Considering patients are already receiving maximally tolerated lipid modifying therapy (LMT) including lipid apheresis, the choice of a parallel-group placebo-controlled study design is appropriate to provide the most unbiased assessment of the efficacy and safety of alirocumab.

1.2. Study Objectives

1.2.1. Primary Objectives

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

1.2.2. Secondary and Exploratory Objectives

The secondary objectives of the study include:

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

- To evaluate the safety and tolerability of alirocumab 150 mg SC Q2W in patients with HoFH

- To assess the pharmacokinetics (PK) of alirocumab 150 mg SC Q2W in patients with HoFH
- To assess the potential development of anti-drug (alirocumab) antibodies

The other objectives of the study include:

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

1.2.3. Modifications from the Statistical Section of Protocol Amendment 3

This SAP is based on Protocol R727-CL-1628 Amendment 3. The following modification from the protocol amendment 3 is made in this SAP:

- The analysis for new onset of diabetes in Protocol Section 9.3.3 (Adverse Events of Special Interest) is deleted since the definition for new onset of diabetes is not appropriate for this short-term study. Instead, the analysis for diabetes mellitus or diabetic complications is added in Section 4.7.1.2.

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, parallel-group study to evaluate the efficacy and safety of alirocumab in patients with HoFH.

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

The study will consist of up to 5 periods: an optional 4-week run-in period (for patients whose background medical LMT regimen or apheresis schedule and/or apheresis settings have not been stable prior to screening), a 2-week screening period, a 12-week double-blind treatment period, and a mandatory 12-week open-label treatment period during which all patients will receive alirocumab. Patients not continuing on to another lipid lowering study will undergo an 8-week follow-up period.

The analyses will be conducted in 2 steps. The first analysis will be conducted as soon as all patients have been randomized and all data through week 12 (double-blind period) have been collected and validated; this will consist of the final analysis of the double-blind primary and secondary efficacy endpoints. The safety analysis will be performed on all safety data collected and validated at the time of the first-step analysis database lock. Since the double-blind primary efficacy measure data collection will have been concluded at the time of this first analysis, the significance level for the study remains at 0.05. This first analysis may be used for the submission to health authorities or other interested parties.

The second analysis will be performed with the data from the open-label treatment period and will consist of the final analysis for the safety and efficacy measures beyond week 12 time point.

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

2.2. Sample Size and Power Considerations

Patients will be randomized in the double-blind treatment period to alirocumab or placebo in a ratio of 2:1 respectively, with the primary efficacy hypothesis comparing the alirocumab treated group to the placebo group at week 12. For the primary efficacy hypothesis during the double-blind treatment period, a total sample size of 51 patients (34 patients in the alirocumab treated group and 17 patients in the placebo group) will have 90% power to detect a difference in mean

percent change in LDL-C of 20%, with a 5% two-sided significance level and assuming a standard deviation (SD) of 20%. Assuming a 5% non-evaluable patient rate for the primary efficacy endpoint, the study sample size is 54 patients (36 patients in the alirocumab-treated group and 18 patients in the placebo group).

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

Blinded Sample Size Adjustment

Referencing the ICH E9 Guideline on Statistical Principles for Clinical Trials, the study sample size may be re-estimated after approximately 75% of the patients reach the week 12 visit in the double-blind treatment period to ensure adequate power in case of a larger-than-expected variability in the data. The sample size re-estimation will be based on the actual blinded pooled standard deviation (adjusted as described in Kieser 2003) (6) for the primary efficacy measure. Since the patients' post-baseline LDL-C levels are masked to all study participants (patients, site personnel, and sponsor staff), the blinded pooled standard deviation will be calculated by a designated unblinded CRO statistician who will have access to the lipid data. As mentioned in Kieser and Friede (Kieser 2003) (6), the blinded sample size re-estimation does not affect type I error materially for continuous endpoints.

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

The blinded sample size adjustment process was implemented in October 2018 when approximately 75% of the patients reached the week 12 visit. The Kieser adjusted pooled standard deviation for LDL-C percent change from baseline was calculated at Week 12 to be 35%, which is larger than the protocol initial planned standard deviation of 20%. Applying the Kieser adjusted pooled standard deviation of 35 (while keeping all other assumptions as described in the protocol), the sample size would increase to 156 patients. With this large sample size increase, enrollment of additional patients with HoFH, a rare disease, depends on the operational feasibility to identify eligible patients. After an assessment to identify eligible patients, a total sample size of 156 patients is not operationally feasible, but an additional 20 patients is considered realistic. Maintaining all other initial sample size assumptions, a new sample size of approximately 74 patients yields 61% power to detect a treatment group difference in mean percent change in LDL-C of 20%. Taking into account the conservative nature of the assumptions for the initial protocol sample size calculation, the new study sample size of approximately 74 patients will be implemented.

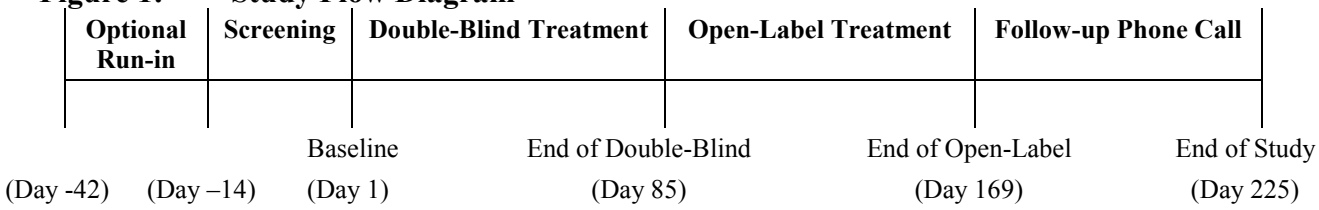
2.3. Study Plan

The study will consist of up to 5 periods: an optional 4-week run-in period (for patients whose background medical LMT regimen or apheresis schedule and/or apheresis settings have not been stable prior to screening), a 2-week screening period, a 12-week double-blind treatment period, a mandatory 12-week open-label treatment period, and an 8-week follow-up period (Figure 1).

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

Patients who do not participate in another lipid-lowering study will undergo an 8-week follow-up period. A follow-up phone call will be made at week 32 (Day 225) (corresponding to the 70-day follow-up) to collect AE and concomitant medication information.

Figure 1: Study Flow Diagram



3. ANALYSIS POPULATIONS

Two efficacy populations will be defined for this study, specifically the Intent-to-Treat (ITT) population and the Modified Intent-to-Treat population (mITT). The primary efficacy analysis population is the ITT population. Five additional patient populations are defined for safety, anti-drug (alirocumab) anti-body (ADA), pharmacokinetic (PK), quality-of-life, and open-label 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. The Efficacy Analysis Sets

3.1.1. Intent-to-treat Population

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

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

3.1.2. Modified Intent-to-Treat

The mITT population is defined as the all randomized population who took at least 1 dose or part of a dose of double-blind investigational study drug and has an evaluable primary endpoint. The endpoint is considered as evaluable when both of the following conditions are met:

- Availability of at least 1 measurement value for LDL-C before first dose of double-blind investigational study drug (i.e., baseline).
- Availability of at least 1 LDL-C value during the efficacy treatment period and within one of the analysis windows (defined in Appendix 10.2) in the double-blind period up to week 12. The efficacy treatment period is defined as the time from the first double-blind investigational study drug injection up to 21 days after the last double-blind investigational study drug injection, or the first dose of the open-label investigational study drug, whichever is earlier.

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

3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any double-blind investigational study drug (safety population). Patients will be analyzed according to the treatment actually received (i.e. as-treated treatment group, placebo or alirocumab). Below are unusual cases with the resolution for each case.

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

3.3. The Anti-alirocumab Antibody Analysis Set

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

3.4. Pharmacokinetic Analysis Set

The pharmacokinetic analysis of the double-blind period will be performed on all randomized and treated patients (safety population) with at least 1 evaluable PK sample after the first dose of double-blind study treatments (PK population).

3.5. Quality-of-life Analysis Set

The analyses for quality of life of the double-blind period will be performed on all randomized and treated patients (safety population) with a baseline and at least 1 matching post-baseline evaluation for at least one of the 5 dimensions after the first dose of double-blind study treatment (quality-of-life population).

3.6. The Open-Label Analysis Set

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

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.

Demographic Characteristics

Demographic variables will include gender (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), and ethnicity (Hispanic or Latino, Not Hispanic or Latino).

Baseline Characteristics

Baseline variables will include body mass index (BMI in kg/m²: quantitative and qualitative variable defined as <30, ≥30), weight (kg), smoking status, alcohol habit, randomization strata as reported in the IVRS, randomization strata as reported from the e-CRF, apheresis schedule at randomization (QW, Q2W, NA), HoFH genotypes (homozygotes, compound heterozygotes, double heterozygotes) and LMT at randomization.

Further baseline laboratory variables are defined below:

- Lipid parameters - quantitative variables for all efficacy parameters
- hs-CRP
- Hepatitis B surface antigen
- Hepatitis C antibody
- LDL-C : <70, ≥ 70 to <100, ≥100 to <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL (<1.81, ≥ 1.81 to <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, and ≥0.5 g/L, and category ≥ 0.3 g/L).

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 HoFH, 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 $\geq$1000 mg/day, other).
  - Number of patients at screening on a maximal tolerated dose of stain. 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.

Apheresis history information such as the frequency, treatment technique used and time from the first apheresis procedure to the screening visit in years will be summarized.

4.3. Prior and Concomitant Medications

All medications taken from the time of informed consent/assent to the final study visit, including medications that were started before the study and are ongoing during the study, are to be reported in Concomitant Medications case report form page.

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 database lock for the analysis. 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 and concomitant 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.

- Double-blind period concomitant medications are defined as any treatments received by the patient concomitantly with the double-blind study treatment, specifically from the first day of double-blind study treatment administration to the last day of double-blind study treatment +70 days (for patients who do not continue into the open-label period). For patients entering the open-label period, concomitant medications will be truncated at the day before the first open-label study treatment administration.

- Open-label period concomitant medications are defined as any treatments received by the patient concomitantly with the open-label study treatment, specifically from the first day of open-label study treatment administration to the last day of open-label study treatment +70 days.

- Double-blind period post-treatment medications are those medications received by the patient during the time period starting from 71 days after the last double-blind study treatment injection and ending when the patient completes the study or begins treatment in the open-label period (whichever comes first) as applicable.

- Open-label period post-treatment medications are those medications received by the patient during the time period starting from 71 days after the last open-label study treatment and ending when the patient completes 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, patient double-blind treatment period 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, and percentages will not be provided.
- 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
- Completed the double-blind study treatment period (i.e. as collected on the end of double blind treatment e-CRF)
- Patients who did not complete the double-blind study treatment period and patient's decision for treatment period discontinuation (as per e-CRF)
- Patients who discontinued double-blind study treatment by main reason for permanent treatment discontinuation
- Patients entering the open-label treatment period

As defined in Section 3 of this document, the patient analysis populations for the double-blind period are:

- Randomized population
- Efficacy populations: ITT and mITT populations
- Safety population
- Anti-alirocumab antibody (ADA) population
- Pharmacokinetic (PK) Population
- Quality-of-life population

For patient study status during the open-label period, patient open-label treatment period milestone categories are defined below. For all categories of patients, percentages will be calculated using the number of patients in the open-label analysis population as the denominator.

- Patients treated with open-label study treatment

- Completed the open-label study treatment period (i.e. as collected on the end of open label treatment e-CRF)
- Patients who did not complete the open-label study treatment period and patient's decision for treatment period discontinuation (as per e-CRF)
- Patient ongoing in the open-label study treatment period (applicable for first-step analysis only)
- Patients who discontinued open-label study treatment by main reason for permanent treatment discontinuation

As defined in Section 3 of this document, the patient analysis population for the open-label period are:

- Open-label analysis population

4.5. Study Treatment Exposure and Compliance Variables

Study treatment exposure variables for injections administered during the double-blind period are listed below with associated definitions:

- Duration of double-blind study treatment exposure in weeks defined as: (last double-blind study treatment administration date +14 – first double-blind study treatment administration date)/7, regardless of unplanned intermittent discontinuations. Values will be rounded to one decimal place.
- The total number of double-blind study treatment injections by patient.
- The following categories will be used for treatment exposure intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <10 weeks, ≥10 weeks.

Study treatment exposure variables for injections administered during the open-label period are listed below with associated definitions:

- Duration of open-label study treatment exposure in weeks defined as: (last open-label alirocumab treatment administration date +14 – first open-label alirocumab treatment administration date)/7, regardless of unplanned intermittent discontinuations. Values will be rounded to one decimal place.
- The total number of open-label alirocumab treatment injections by patient.
- The following categories will be used for treatment exposure intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <10 weeks, ≥10 weeks.

Study treatment exposure variables combining double-blind and open-label periods are listed below for all patients who received alirocumab in the double-blind period:

- Combined duration of alirocumab exposure in weeks defined as: double-blind treatment exposure plus open-label treatment exposure, regardless of unplanned intermittent discontinuations.

- Combined total number of alirocumab treatment injections by patient defined as: total number of double-blind injections plus total number of open-label injections for each patient.

- The 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 <22 weeks, ≥22 weeks.

Compliance will be assessed using the variables below with associated definitions.

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

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

All major and minor protocol deviations potentially impacting efficacy analyses, randomization and drug-dispensing irregularities, as well as other deviations, have been collected and reviewed on an ongoing basis throughout the study as described in the Protocol Deviation Definitions Document (PDDD). Both monitoring collected and programmatically derived deviations are listed and defined in the PDDD.

4.6. Efficacy Variables

Efficacy will be assessed through the following lipid parameters: calculated LDL-C (using the Friedewald formula), measured LDL-C (obtained using the beta quantification method), total-C, HDL-C, TG, non-HDL-C (calculated by subtracting HDL-C from Total-C), Apo B, Apo A-1, the ratio of Apo B / Apo A-1, and Lp(a). All lipid parameters will be collected over the course of the study and sent to a central laboratory for evaluation, including scheduled and unscheduled blood draws. For LDL-C analysis, both calculated and measured LDL-C values will be taken into account. In case both calculated and measured LDL-C values are available for the same sampling time point, the measured LDL-C will be considered.

All lipid values obtained during the study (scheduled or unscheduled), regardless of fasting status (fasting or not fasting), can be used to provide a value for the primary and secondary efficacy endpoints, with the following exceptions:

- Only fasting TG measurements will be included in the analysis. TG measurements with missing fasting status will be excluded from the analyses.
- On the day of apheresis, any lipid values collected after start of the apheresis for the respective visit will be excluded from the efficacy analyses.

All measurements will be assigned to analysis windows defined in Appendix 10.2 of this SAP, with the intent to provide an assessment for week 4 to week 24 time points. For all time points post-baseline, the value used for the analyses at a given time point (e.g. at week 12) is the value obtained within the corresponding analysis window. The baseline value is defined as the last available measurement obtained up to the date and time of the first double-blind study treatment injection. 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.

4.6.1. Primary Efficacy Variable

The primary efficacy endpoint is the percent change in LDL-C from baseline to week 12 in the ITT population for alirocumab 150 mg Q2W as compared with placebo in patients with HoFH, using all LDL-C values regardless of adherence to treatment (ITT estimand).

The percent change in LDL-C from baseline to week 12 is defined as: 100x (LDL-C value at week 12 - LDL-C value at baseline) / LDL-C value at baseline.

4.6.2. Key Secondary Efficacy Variables

The key secondary efficacy endpoints are:

- The percent change in Apo B from baseline to week 12 (ITT estimand).
- The percent change in non-HDL-C from baseline to week 12 (ITT estimand).
- The percent change in total cholesterol from baseline to week 12 (ITT estimand).
- Proportion of patients with ≥15% reduction in LDL-C at week 12 (ITT estimand).
- Proportion of patients with ≥30% reduction in LDL-C at week 12 (ITT estimand).
- The percent change in Lp(a) from baseline to week 12 (ITT estimand).
- Proportion of patients with ≥50% reduction in LDL-C at week 12 (ITT estimand).
- The percent change in HDL-C from baseline to week 12 (ITT estimand).

- The percent change in fasting TG from baseline to week 12 (ITT estimand).
- The percent change in Apo A-1 from baseline to week 12 (ITT estimand).

4.6.3. Other Secondary Efficacy Variables

The other secondary efficacy endpoints are:

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

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

4.7. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, and ECG. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of double-blind 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 double-blind study treatment injection.
- The double-blind treatment-emergent adverse event (TEAE) period: defined as the time from the first double-blind study treatment injection up to the day of the last double-blind study treatment injection + 70 days (10 weeks), or up to the day before first dose of open label investigational study drug administration, whichever is earlier.

The double-blind TEAE period will include:

- The TREATMENT period is defined as the time from the first double-blind study treatment injection up to the day of last double-blind 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. For patients entering into the open-label period, the treatment period will be truncated at the day before the first dose of open label investigational study drug administration.

- The RESIDUAL TREATMENT period is defined as the time from the day of last double-blind study treatment injection + 22 days up to the day of last double-blind study treatment injection + 70 days (10 weeks), or up to the day before first dose of open label investigational study drug administration, whichever is earlier.

- The open-label treatment-emergent adverse event (TEAE) period is defined as the time from first open label study treatment injection up to the day of the last open-label study treatment injection + 70 days.

The open-label TEAE period will include:

- The TREATMENT period is defined as the time from the first open-label study treatment injection up to the day of last open-label study treatment injection + 21 days.

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

- The POST-TREATMENT period: defined as starting the day after the end of the respective TEAE periods 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.

- Double-Blind and open-label treatment-emergent adverse events are AEs that developed or worsened or became serious during the respective TEAE period.

- Double-Blind and open-label 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 following preferred terms linked to local injection site reactions (“infusion site dermatitis”, “infusion site hypersensitivity”, “infusion site rash”, “infusion site urticaria”, “infusion site eczema”, “infusion site vasculitis”, “infusion site photosensitivity reaction”, “infusion site recall reaction”, “injection site dermatitis”, “injection site hypersensitivity”, “injection site rash”, “injection site urticaria”, “injection site eczema”, “injection site vasculitis”, “injection site photosensitivity reaction”, and “injection site recall reaction”);

- 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 (see Appendix 10.5 Table 4 for the list of terms)

- Cataract using HLT “Cataract conditions”

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

- Hepatic disorder events using SMQ “Hepatic disorder”

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

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 respective TEAE period (double-blind or open-label),

- Death post-treatment: deaths occurring during the respective post-treatment period (double-blind or open-label).

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 week -2, week 0, and weeks 8, 12/or end of double-blind treatment visit, and week 24/or end of

open-label treatment visit. 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, red blood cell distribution width (RDW)
  - 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, uric acid
  - Liver function ALT, aspartate aminotransferases (AST), alkaline phosphatase (ALP), total bilirubin, LDH
- Hepatitis screen: anti-hepatitis-C antibody collected at week -2 and week 12, and hepatitis B surface antigen collected at week -2

4.7.3. Vital Sign Variables

Vital signs parameters will include weight (kg), heart rate (bpm), systolic and diastolic blood pressure (mmHg) in a sitting position for at least five minutes (arm used for blood pressure measurement is also collected). 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 vital sign parameter values as applicable (see Appendix 10.3 for PCSA definitions).

4.7.4. Electrocardiogram Variables

Electrocardiograms were recorded automatically by the device at the Investigator site at week -2, week 12/or end of double-blind treatment visit, and week 24/or end of open-label treatment visit. Electrocardiogram assessments will be described as normal or abnormal.

4.8. Other Variables

Other assessment endpoints are listed and defined below. As applicable, LDL-C will use the same definition as described in Section 4.6.1.

- The percent change in hs-CRP from baseline to weeks 12, and 24. 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 infections (1). PCSA (potentially clinically significant abnormalities) criteria for hs-CRP are listed in Appendix 10.3.

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

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

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

- The change in the proportion of patients who meet US apheresis eligibility criteria from baseline to week 12 (Goldberg 2011) (7).

  – A patient is considered as meeting US apheresis eligibility criteria if LDL-C ≥ 300 mg/dL (7.77 mmol/L).

- The change in the proportion of patients who meet German apheresis eligibility criteria from baseline to week 12 (Schettler 2012) (8).

  – A patient with primary CVD prevention is considered as meeting German apheresis eligibility criteria if LDL-C > 160 mg/dL (4.2 mmol/L).

  – A patient with secondary CVD prevention is considered as meeting German apheresis eligibility criteria if LDL-C > 120 mg/dL (3.1 mmol/L).

- Exploratory relationships between HoFH genotype status and lipid parameters.

4.9. Anti-alirocumab Anti-body Variables

Anti-drug (alirocumab) antibody (ADA) are assessed at baseline (before the first study treatment injection), at week 12/or end of double-blind treatment visit, and week 24/or end of open-label treatment visit. ADA measurements will be assigned to similar analysis windows as defined for efficacy endpoints in Appendix 10.2. As appropriate, patient frequencies and percentages will be depicted, and the percentages will be calculated based on the ADA population for the analysis of the double-blind period and based on the OLE population for the analysis of the open-label period.

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 for the analysis of the double-blind period:
  - 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

4.10. Pharmacokinetic (PK) Variables

Samples of drug concentration measurements are collected at baseline (week 0), weeks 4, 8, 10, 12, and 24.

Pharmacokinetic variable is the total alirocumab concentration at each time point. Alirocumab concentration, total and free PCSK9 concentration will be described following time windows as defined in Appendix 10.2 .

4.11. Quality-of-Life Variables

EQ-5D is a standardized and generic instrument for measuring the health status and health related quality of life for clinical and economic assessment (2). The EQ-5D instrument includes 5 items corresponding to the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item can take one of three responses: (1.) “no problem”, (2.) “some problems”, and (3.) “severe problems”. Overall health state is defined as a 5-digit number and will be converted into a standard utility score ranging between - 0.594 (representing severe problems) and 1 (representing no problem): the single index utility score,

using a regression model (2) (Appendix 10.4). If response to one or more dimensions is missing, the utility score will be missing.

Quality of life endpoints include response to each EQ-5D item at week 12 and week 24. The change in utility score from baseline will also be evaluated at each post-baseline week.

4.12. Genomics Variables

Plans for analysis of genomics data will be provided in a separate SAP.

5. STATISTICAL METHODS

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for the study, as well as by treatment group and overall for the study within each of the stratification factor (IVRS/IWRS defined yes/no of apheresis treatment status). Parameters described in Section 4.1 will be summarized for those patients randomized into the study, the safety population in the case of a 10% difference (in any treatment group) from the number of randomized patients, and again for the ITT population in the case of a 10% difference (in any treatment group) from the number of randomized patients.

Continuous data will be summarized using the number of patients with data, mean, SD, median, minimum and maximum for each treatment group and for each of the strata. First quartile (Q1) and third quartile (Q3) will be also provided for baseline lipid parameters, 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 Fisher exact test 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.

For the open-label population, demographic and baseline characteristics will be summarized by all patients and by treatment group of the double-blind period (i.e., alirocumab, placebo) on the open-label population in the case of a 10% difference (in any treatment group of the double-blind period) from the number of randomized patients. Parameters described in Section 4.1 will be descriptively summarized for the open-label population.

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 patients randomized into the study.

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 double-blind 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, LMT, CV), by decreasing frequency of the alirocumab 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, 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. All concomitant and post-treatment medications for the open-label period, dictionary coded by WHO-DD, will be descriptively summarized by all patients and by treatment group of the double-blind period (i.e., alirocumab, placebo) on the open-label population. Summaries will present counts (and percentages) in the open-label population.

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,
- 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),
- other statins,
- non-statin LMT only,
- no LMT.

5.4. Subject 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 for the double-blind period 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.

For the open-label period, the patient study status and patient analysis populations will be summarized by all patients and by treatment group of the double-blind period (i.e., alirocumab, placebo) on the open-label population for the variables described in Section 4.4.

5.5. Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure and study compliance parameters for the double-blind period described in Section 4.5 will be assessed and summarized by treatment group, for patients in the safety population. The extent of study treatment exposure and study compliance parameters for the open-label period described in Section 4.5 will be assessed and summarized by all patients and by treatment group of the double-blind period (i.e., alirocumab, placebo) on the open-label population.

5.5.1. Exposure to Investigational Product

Study treatment exposure for the double-blind period will be descriptively summarized for the treatment duration and patient injection total variables listed in Section 4.5. Treatment duration

will be summarized using the number of patients with data, mean, SD, median, minimum and maximum.

For the open-label period, study treatment exposure will be descriptively summarized for the treatment duration and patient injection total variables listed in Section 4.5. Alirocumab dosing exposure in the open-label period will be summarized for all patients in the open-label population. Additionally, alirocumab dosing exposure will be summarized combining double-blind and open-label periods for patients who received alirocumab in the double-blind period.

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

5.6. Analysis of Efficacy Variables

For statistics where international and conventional units do not impact the results (e.g. means and least square (LS) means for percent changes from baseline, statistical testing for both percent and absolute changes from baseline, rates of patients below a threshold), derivations will be calculated and statistical models will be run using conventional units. For other statistics (e.g. descriptive statistics at baseline and over time, absolute changes from baseline), derivations will be presented in both international and conventional units.

Statistical analyses for the primary efficacy endpoints and key secondary endpoints will be conducted in the double-blind period as described below, and will be completed during the step 1 efficacy analyses (Section 7).

With respect to the efficacy data in the open-label period, only descriptive efficacy analyses will be completed during the second-step analysis. During the open-label period, efficacy variables will be explored through descriptive statistics at each scheduled visit for the total patients administered open-label study treatment (total), as well as by the patient subgroups of study treatment received in the double-blind treatment period (i.e., alirocumab, placebo). Formal statistical testing is not planned. Descriptive statistics will include the same parameters as described for each variable in the double-blind period. The same baseline (as defined in Section 4.6) will be used for the analyses of the double-blind and open-label periods.

For patients receiving alirocumab in the double-blind period, a combined summary including both the double-blind and open-label period assessments may be considered, referencing the double-blind baseline for variable calculations. Prolonged time between last dose of double-

blind treatment and first dose of open-label treatment will need to be taken into consideration when combining longitudinal efficacy data. Again, formal testing is not planned due to the absence of control group.

5.6.1. Analysis of Primary Efficacy Variable

For the double-blind primary comparison of the alirocumab group to the placebo group, the percent change from baseline in LDL-C at week 12 will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within week 4 to week 12 analysis windows will be used and missing data are accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group (alirocumab versus placebo), randomization strata (undergoing apheresis treatment [Yes vs. No] per IVRS/IWRS), time point (weeks 4, 8, and 12), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction.

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

Let $\mu 0$ and $\mu 1$ be the population means of the percent change from baseline in LDL-C at week 12 under placebo and alirocumab, respectively. The hypothesis that will be tested is "H_0: $\mu_0 = \mu_1$" versus "H_1: $\mu_0 \neq \mu_1$". Therefore, the alirocumab treated group will be compared to the placebo group using an appropriate contrast statement tested at the 2-sided 0.05 level, with corresponding least squares estimate of mean difference, SE and 95% confidence interval.

Within treatment group least-square means and standard errors will be adjusted using weights equal to the observed proportion of patients in strata variable levels across the study population (i.e. "population weight"), rather than equal weights. Population weights are considered more appropriate that equal coefficients due to potential imbalances observed in the study population between levels of the randomization stratification factors.

Model Assumption Checks

Homogeneity of treatment effect across baseline LDL-C levels

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

- Treatment group * baseline LDL-C
- Treatment group * time-point * baseline LDL-C

Within the framework of this model with interaction terms, a graph presenting the LS means difference versus placebo at week 12 and the corresponding 95% CI will be provided by baseline LDL-C 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 (alirocumab, placebo)
  - time point (weeks 4, 8, and 12)
  - 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 efficacy analysis with regards to handling of missing data (3).

Visual examination:

- In order to explore the missing data pattern, post-baseline LDL-C observations (in the ITT population) will be described according to the following groups:

1. Ldl-C available at week 12 (i.e. primary efficacy endpoint available),
2. LDL-C available at week 8 but missing at week 12,

3. LDL-C available at week 4 but missing from week 8,

4. LDL-C missing from week 4.

A graph of mean LDL-C levels (respectively percent change from baseline in LDL-C) ± SE at baseline, and weeks 4, 8, and week 12 will be provided by missing data pattern, for each treatment group.

- In the ITT population, demographic and baseline characteristics will be described within the missing data pattern number 1 versus the pooled others. P-values from Fisher exact 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 10.6 for more details) will be used to address missing values, in the randomized 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 randomized 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 12 will be then derived from observed and imputed LDL-C 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 LDL-C value 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 efficacy analysis will be conducted using the pattern mixture model approach as described below (see Appendix 10.7 for more details).

In the pattern-mixture model approach, different imputation strategies will be applied to LDL-C values missing during the double-blind on-treatment period (i.e. within the time period from the first double-blind study treatment injection up to the day of last double-blind injection +21 days or day of the first open-label injection whichever comes first) versus LDL C values missing after treatment discontinuation (i.e. after the day of last double-blind injection +21 days) based on the following assumptions:

- Patients within 21 days of their last double-blind IMP injection would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, LDL-C values missing during the on-treatment period (e.g., samples obtained out-side the specified window, no blood sample available although visit was performed, etc.) should be considered "Missing At Random" and imputed based on other on-treatment measurements.

- Patients who stopped taking their study treatment no longer benefited from it after discontinuation, and thus tended to have LDL-C values returning to baseline. Therefore, LDL-C values missing after treatment discontinuation should be imputed based on patient's own baseline value.

Missing data from the randomized 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 efficacy analyses.

The 100 complete datasets of observed and imputed LDL-C data at week 12 will be analyzed using an ANCOVA model with treatment group and randomization strata as fixed effect, and the baseline LDL C 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. Sensitivity to the Absence of Null/Null Mutations in Both LDL Alleles

In order to assess the robustness of the primary analysis in patients excluding those with null/null mutations in both LDL alleles, the MMRM model will be re-run by excluding patients with null/null mutations in both LDL alleles in the ITT population.

5.6.1.4. 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 12 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 12 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 baseline apheresis status (Yes, No) per IVRS,

- Gender (Female, Male),

- Baseline HDL-C (<40, ≥40 mg/dL) (i.e. <1.04, ≥1.04 mmol/L),
- Baseline fasting TGs (<150, ≥150 mg/dL) (i.e. <1.7, ≥1.7 mmol/L), to be performed also on the response variable percent change in fasting TGs from baseline to week 12.
- Baseline Lp(a) (<30, ≥30 to <50, ≥50 mg/dL) (i.e. <0.3, ≥0.3 to <0.5, ≥0.5 g/L),
- Statins with versus without other LMT at randomization,
- Prior history of acute or silent myocardial infarction (MI) or ischemic stroke (Yes versus No),
- Baseline total PCSK9 level (below the median, at or above the median)

5.6.2. Analyses of Secondary Efficacy Variables

The key secondary efficacy endpoints (defined in Section 4.6.2) and other secondary efficacy endpoints (described in Section 4.6.3) for the double-blind period, descriptive summaries and analyses will be performed in the ITT population or mITT population, corresponding to the specified estimand for the endpoint.

For descriptive summaries, percent change, and when appropriate, absolute change from baseline in LDL C, total-C, HDL-C, TG, and non-HDL-C will be provided at each time point for each treatment group. All measurements, scheduled or unscheduled, will be assigned to analysis windows defined in Appendix 10.2 in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. For TGs, measurements on not-fasting patients will be excluded. The time profile of each parameter will be plotted by treatment group with the corresponding standard errors. Similar tables (with either percent change from baseline or absolute change from baseline for the ratio) and plots will be provided for other efficacy parameters: Apo B, Apo A-1, ratio Apo B/Apo A-1, Lp(a).

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

5.6.2.1. Continuous Endpoints Anticipated to have a Normal Distribution

Continuous secondary variables defined in Section 4.6.2 and 4.6.3 anticipated to have a normal distribution (i.e. lipids other than TG and Lp(a)) will be analyzed using the same MMRM model as described for the primary endpoint. Specifically, the model will contain the fixed categorical effects of treatment group, randomization strata (as per IVRS/IWRS), planned time points up to week 12, strata-by-time point and treatment-by-time point interaction, as well as, the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

5.6.2.2. Continuous Endpoints Anticipated to have a Non-normal Distribution

Continuous secondary efficacy variables defined in Section 4.6.2 and 4.6.3 anticipated to have a non-normal distribution (i.e. TG and Lp(a)) will be analyzed using the same multiple imputation approach for handling of missing values as described for primary efficacy 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 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 (5) 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.

5.6.2.3. Binary Endpoint Variables

Binary secondary efficacy endpoints defined in Section 4.6.2 and 4.6.3 will be analyzed using the multiple imputation approach for handling of missing values as described for the primary efficacy endpoint (and using the same time points in the imputation model as described above for Section 5.6.1.2).

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 such logistic regression is not applicable (e.g. the response rate is zero in one treatment arm and thus the maximum likelihood estimate may not exist), the last observation carried forward (LOCF) approach would be used for handling of missing values. 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). In case the model would not converge with stratification variables, an unstratified exact logistic regression will be performed. The LOCF imputation method will consist of using the last value obtained up to the week 12 analysis window to impute the missing week 12 value.

In case of computing issues with exact logistic regression, the baseline level(s) will be entered in the model as a categorical variable(s) using quartiles. Exact odds ratio versus placebo, 95% CI, and p-value will be provided.

5.6.2.4. Sensitivity Analyses of Key Secondary Endpoint Variables

In order to assess the robustness of more clinically relevant between-group comparisons for the analyses of the key secondary endpoints during the efficacy treatment period, the same statistical approach as described above in Section 5.6.2 will be applied during the efficacy treatment period in the mITT population.

5.6.2.5. 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, and non-HDL-C at weeks 4, 8, and week 12 time points will be summarized by treatment group in both the ITT and mITT populations as described below. 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 Lp(a), Apo-B, Apo-A1 and ratio Apo-B/Apo-A1 (absolute change from baseline) at weeks 4, 8, and week 12 points will be summarized in the ITT and mITT populations as describe 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 5.6.2.1) 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 5.6.2.2) 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.

For the open-label period, 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), LDL-C, Total-C, HDL-C, fasting TG, and non-HDL-C, Lp(a), Apo-B, Apo-A1 and ratio Apo-B/Apo-A1 (absolute change from baseline) at weeks 18,

and 24 time points will be summarized by patient counts, mean and SD by all patients and by treatment group of the double-blind period (i.e., alirocumab, placebo) on the open-label population.

For patients receiving alirocumab in the double-blind period, central laboratory values (in conventional (US) and international units) including both the double-blind and open-label period assessments, percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units), LDL-C, Total-C, HDL-C, fasting TG, and non-HDL-C, Lp(a), Apo-B, Apo-A1 and ratio Apo-B/Apo-A1 (absolute change from baseline) at weeks 4, 8, 12, 18, and 24 time points will be summarized by patient counts, mean and SD by all patients.

5.6.3. Adjustment for Multiple Comparisons

In order to handle multiple key secondary endpoints during the double-blind period for the comparison of the alirocumab group and the placebo group, the overall type-I error will be controlled by the use of a hierarchical inferential approach. Statistical significance of the double-blind primary parameter at the 0.05 alpha level is required before drawing inferential conclusions about first key secondary parameter. Inferential conclusions about successive key secondary parameters require statistical significance of the prior one. The hierarchy testing sequence is the order of endpoints as presented in Sections 4.6.1 and 4.6.2.

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

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

No adjustment will be made for the first-step and second-step statistical analyses (Section 7), since the primary and key secondary endpoints will have been concluded at the time of the first-step analysis.

5.7. Analysis of Safety Data

The summary of safety results will be presented separately for the double-blind and open-label period. The double-blind period will be presented by treatment groups (alirocumab, placebo) on the safety population (Section 3.2). The open-label period will be presented by all patients and by treatment group of the double-blind period (i.e., alirocumab, placebo) on the open-label population (Section 3.3). No formal inferential testing will be performed for either period. 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.

- For the analyses of both double-blind and open-label periods, the baseline value is defined as the last available value obtained up to the date and time of the first double-blind 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 1 and Table 2 in order to provide an assessment for week 4 to week 24 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.

- 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 presented in each of the study period, specifically the double-blind and open-label period. 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 alirocumab 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 alirocumab 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;

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;

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 alirocumab group).

- All TEAEs within diabetes grouping will be analyzed overall and according to the diabetic status 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 double-blind study treatment injections received;

- Time from first study treatment injection (double-blind or open-label depending on the analysis) 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.

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 alirocumab 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)

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. These analyses will be restricted to the respective treatment periods. The summaries of the subgroup of patients with two-consecutive LDL-C values <25 mg/dL in the double-blind treatment period will only consider TEAEs with a start date within the double-blind treatment period; summaries of the subgroup of patients with two-consecutive LDL-C values <25 mg/dL in the open-label period will only consider TEAEs with a start date within the open-label treatment period.

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 in both the double-blind and open-label periods);

- 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 both the double-blind and open-label study periods.

Analysis of Adverse Event in the Open-Label Period

For open-label period, summary of adverse events as described for the double-blind period will be used.

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).

Analysis of Clinical Laboratory Variables in Open-Label Period

For open-label period clinical laboratory parameters, summary tables as described for the double-blind period will be used.

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 vial sign measurements that meet PCSA criteria will be provided for the report appendix.

Analysis of Vital Sign Variables in Open-Label Period

For open-label period vital sign parameters, summary tables as described for the double-blind period will be used.

5.7.4. Analysis of Electrocardiogram Variables

ECG parameters will be described through an overall interpretation of ECG status. The count and percentage of patients with at least 1 abnormal post-baseline ECG during the TEAE period will be summarized by treatment group according to the following baseline status categories:

- Normal/missing;
- Abnormal

5.8. Analysis of Other Variables

The summary of other variables will be presented separately for the double-blind and open-label period. The double-blind period will be presented by treatment groups (alirocumab, placebo) on the safety population. The open-label period will be presented by all patients and by treatment group of the double-blind period (i.e., alirocumab, placebo) on the open-label population. No formal inferential testing will be performed for either period. Summaries will be descriptive in nature. All summaries of safety results described below will be presented for each period respectively, unless otherwise noted.

All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows in order to provide an assessment for week 4 to week 24 time points.

Hs-CRP parameter (Section 4.8) will be summarized for the number of patients with data, mean, SD, median, minimum, maximum, Q1 and Q3 by analysis visit during the treatment period. The medians (with Q1-Q3) will be plotted for hs-CRP. Applying the PCSA criteria at any time during the TEAE period, the number of patients (and percentages) meeting the criteria will be summarized.

Binary endpoints defined in Section 4.8 will be described through patient counts and percentages.

The change in the proportion of patients who meet US apheresis eligibility criteria form baseline to week 12 (Section 4.8) will be summarized by treatment group on the safety population for the number of patients with data, mean, SD, median, minimum, and maximum. The change in the proportion of patients who meet German apheresis eligibility criteria form baseline to week 12 will be summarized in a similar manner.

Correlations between HoFH genotype status and lipid parameters will be explored (e.g., scatter plot).

5.9. Analysis of Anti-alirocumab Antibody Variables

The summary of ADA variables will be presented separately for the double-blind and open-label period. The double-blind period will be presented by treatment groups (alirocumab, placebo) on the ADA population. The open-label period will be presented by all patients and by treatment group of the double-blind period (i.e., alirocumab, placebo) on the open-label population. No

formal inferential testing will be performed for either period. 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 (only for the double-blind period)
- Time to onset of treatment-emergent ADA positive response using descriptive statistics.

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).

5.10. Analysis of Pharmacokinetic Data

Concentrations of total alirocumab in serum and total and free PCSK9 concentrations will be summarized on the PK population by treatment group and visit using descriptive statistics. Descriptive statistics could be provided by specific sub-groups (e.g., gender, BMI, age), as needed.

Time profile for concentrations of total alirocumab and total and free PCSK9 will be provided by treatment group using graphs (mean ± SD or Median, as appropriate). Plots of the individual concentrations of alirocumab, and total and free PCSK9 may be presented versus actual time. Additional plots will be prepared, as deemed necessary (e.g., to explore the relationship with some safety or efficacy endpoints of interest).

Concentrations of total alirocumab in serum and PCSK9 levels might be used for population PK modeling if considered necessary and the results of population PK modeling will be reported separately from the study report.

5.11. Analysis of Genomics Variables

Plans for the analysis of genomics data will be provided in a separate SAP.

5.12. Analysis of Quality-of-Life Variables

The summary of quality-of-life variables will be presented separately for the double-blind and open-label period. The double-blind period will be presented by treatment groups (alirocumab, placebo) on the quality-of-life safety population. The open-label period will be presented by all patients and by treatment group of the double-blind period (i.e., alirocumab, placebo) on the open-label population. No formal inferential testing will be performed for either period. Summaries will be descriptive in nature. All summaries of safety results described below will be presented for each period respectively, unless otherwise noted.

The analysis of data from EQ-5D instrument will be performed on the quality-of-life population. Baseline is defined as the visit at Day 1 or Visit 3 (week 0) evaluation. Analysis windows for efficacy parameters will be used to assign time point visits.

Individual EQ-5D items

Response for each one of the 5 EQ-5D items will be summarized for each treatment group using tables which will contain frequency and percentage of the patients reporting level 1 (no problems), level 2 (some problems) and level 3 (extreme problems) by analysis visit during the treatment period.

EQ-5D utility score

The raw value and the change from baseline of the utility score will be summarized using mean, median, Q1, Q3, SD, minimum and maximum for each post-baseline visit during the treatment period. Cumulative distribution functions for the change in utility score from baseline will be displayed by treatment groups at weeks 12 on the quality-of-life safety population.

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 double-blind study treatment. For patients randomized but not-treated, the baseline will be the last available measurement before randomization.

6.2. Data Handling Conventions for Efficacy Variables

Data handling conventions, including addressing missing data, is addressed for the efficacy endpoints in Sections 5.6.1 and 5.6.2.

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 double-blind study treatment administration or time of assessment at week 0 visit is missing

If the time of the first double-blind 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 double-blind 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 for a treatment period (double-blind or open-label) 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 for the respective treatment period:
  - double-blind treatment period: week 12 visit for completer, early end of double-blind treatment visit for patients who prematurely discontinued the study treatment,
  - open-label treatment period: week 24 visit for completer, early end of open-label 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, ECG, quality of life, PK 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, ECG, and ED-5D, 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

Efficacy and safety analyses for this study will be performed in two steps, specifically for patient data collected up to the time the last patient completes efficacy assessments at week 12 (step 1 consisting of the double-blind period) and at the end of the study (step 2 for the open-label period). No formal interim analysis for efficacy is planned since analyses of primary and key secondary efficacy endpoints will be final at the time of first-step analysis. Therefore, no multiplicity adjustment for multiple analyses is needed (see Section 5.6.3). The timing for patient data to be reported is defined below for each step:

- First-step: efficacy analyses up to week 12 and interim safety analysis
  - This analysis will be conducted on all randomized patients when all patients will have all their lipid data up to week 12 analysis window collected and validated.
  - The efficacy analyses will be performed up to week 12 time point. Analyses of endpoints up to week 12 time point will correspond to the final analyses for these endpoints. Analysis of lipid parameters beyond week 12 will be descriptive.
  - The safety analyses will be performed on all safety data (double-blind and open-label) collected up to the common cut-off date. For this analysis, the common cut-off date is defined as date of the last week 12 visit.
- Second-step: final analysis
  - This analysis will be conducted at the end of the study and will consist of the final analysis of efficacy data at time points beyond the week 12 time point and final safety analysis.

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

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply for analyses performed at first-step analysis:

- Any lipid assessments within analysis windows up to week 12 will be taken into account (may include few unscheduled lipid data soon after the cut-off date).

- Patients without end of treatment visit (double-blind or open-label) performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:

  – Patients who did not complete the respective treatment period nor prematurely discontinued the study treatment at cut-off date will be analyzed as "ongoing" in the disposition summary.

  – Their TEAE period and treatment period will end at the cut-off date.

  – Their treatment duration will be derived by considering date of cut-off as last injection date.

- Analyses of number of injections, mean injection frequency, percentage of days with under/above-planned dosing and compliance will be performed up to the last injection reported in the e-CRF up to the cut-off date.

- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an adverse event starting prior to the cut-off date will be taken into account. Medications, treatment discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.

- Post-treatment period, post-study period are not applicable for ongoing patients. Analyses of post-treatment AEs, post-study deaths and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.

- Analysis of status at last study contact and proportion of patients with insufficient follow-up will be provided for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.

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 Efficacy Analysis:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Percent change from baseline in LDL-C at week 12	ITT	MMRM	Yes, including handling of missing data	Yes	1) On-treatment estimand 2) Actual stratification factor 3) Multiple Imputations + ANCOVA 4) 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 1a Analysis Windows Definition for Double-Blind Period – All Endpoints Except Vital Signs

Time point	Targeted study day	Analysis window in study days
Week 4	29	15 to 42
Week 8	57	43 to 70
Week 12	85	71 to minimum of: 98 OR study day corresponding to the first open-label injection for patients entering open-label period

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

Table 1b Analysis Windows Definition for Double-Blind Period – Vital Signs

Time point	Targeted study day	Analysis window in study days
Week 4	29	15 to 42
Week 8	57	43 to 63
Week 10	71	64 to 77
Week 12	85	78 to minimum of: 98 OR study day corresponding to the first open-label injection for patients entering open-label period

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

Table 2 Analysis Windows Definition for Open-Label Period

Time point	Targeted study day	Analysis window in study days
Week 18	43	22 to 63
Week 24	85	64 to 105

Study days are calculated from the day of first open-label IMP injection. The day of first open-label IMP injection being Day 1.

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	To be applied for all positions (including missing) except STANDING.
	≥120 bpm and increase from baseline≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20mmHg	To be applied for all positions (including missing) except STANDING.
	≥160 mmHg and increase from baseline ≥20 mmHg	
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
	≥110 mmHg and increase from baseline ≥10 mmHg	
Orthostatic Hypotension		
Orthostatic SDB		
Orthostatic DBP	≤-20 mmHg	
	≤-10 mmHg	
Weight	≥5% increase from baseline	FDA Feb 2007.
	≥5% decrease from baseline	
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* Additional	Borderline: 431-450 ms (Male); 451-470 ms (Female)	
	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. EQ-5D Patient Questionnaire and Algorithme

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

2

EQ-5D Utility Score Algorithm

Algorithm: UK based

```
/*=====================================================================*/;
/*  Aim                      : Derive the EQ5-D index (utility)        */;
/*  Source for the algorithm : scoring EQ-5D health states (Rosalind Rabin */;
/*            (cf. G:\_HE\PRO questionnaire\EQ5D\scoring\YorkTariffx.doc)  */;
/*  Note                     : UK based population (Dolan, 1997)       */;
/*=====================================================================*/;
```

Answer to questions in numeric format, from 1 (no problem) to 3 (severe problem); Q1 (mobility), Q2 (self-care), Q3 (usual activities), Q4 (pain/discomfort), Q5 (anxiety/depression)

Result of the algorithm: Utility (EQ-5D utility score).

If at least one of the answer to questions is missing then the utility score is missing.

Start with Utility =**1** and apply the following sequential algorithm.

**********Mobility*********
if Q1=**2** then Utility = Utility - **0.069**
if Q1=**3** then Utility = Utility - **0.314**

********Self-care**********
if Q2=**2** then Utility = Utility - **0.104**
if Q2=**3** then Utility = Utility - **0.214**

******Usual activities*****
if Q3=**2** then Utility = Utility - **0.036**
if Q3=**3** then Utility = Utility - **0.094**

*****Pain/discomfort******
if Q4=**2** then Utility = Utility - **0.123**
if Q4=**3** then Utility = Utility - **0.386**

*****Anxiety/depression*****
if Q5=**2** then Utility = Utility - **0.071**
if Q5=**3** then Utility = Utility - **0.236**

if (Q1 ≠ **1** or Q2 ≠ **1** or Q3 ≠ **1** or Q4 ≠ **1** or Q5 ≠ **1**) then Utility = Utility - **0.081**
if (Q1=**3** or Q2=**3** or Q3=**3** or Q4=**3** or Q5=**3**) then Utility = Utility - **0.269**
End of the sequential algorithm

10.5. List of MedDRA terms for CMQs

Table 3 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
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 4 CMQ "Neurocognitive disorders – FDA's recommendation"

MedDRA level	MedDRA Term Label
PTCD	Amnesia
PTCD	Amnestic disorder
PTCD	Anterograde Amnesia
PTCD	Behavioural and Psychiatric Symptoms of Dementia
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
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

MedDRA level	MedDRA Term Label
PTCD	Vascular Dementia

10.6. 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 efficacy endpoint as well as the analysis of the secondary efficacy 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 12.

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

- the randomization strata (apheresis treatment status 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.

10.7. Detailed Description of Pattern Mixture Model

As a sensitivity analysis of the primary efficacy endpoint (i.e. percent change from baseline to Week 12 in LDL-C), a pattern-mixture model approach will be used, with a different imputation strategy applied for missing LDL-C values during the on-treatment period (i.e. within the time period from the first double-blind IMP injection up to the day of the last double-blind injection +21 days or to the day before the first open-label injection, whichever comes first) and missing LDL-C values after treatment discontinuation (i.e. after the day of last injection +21 days) based on the following assumptions:

- Patients within 21 days of their last IMP injection would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, LDLC values missing during the on-treatment period will be considered "Missing At Random" and imputed using a model estimated using all samples collected on treatment.

- Patients who stopped taking their study treatment no longer benefited from it in the future, and thus tended to have LDL-C values returning to baseline. Thus LDL-C values missing after treatment discontinuation will be imputed based on patient's own baseline value.

The assumptions for this approach are based on the following considerations:

- Missing values during the on-treatment period are mostly consecutive to:
  - Visits performed outside of the pre-specified time-window
  - No blood sample available although visit was done
  - LDL-C not measurable due to technical reasons

In addition, these missing data are often intermittent, i.e. followed by LDL-C values collected at subsequent visits. It is therefore considered reasonable to assume that these missing data were "At Random".

Phase 2 studies DFI11565 and R727-CL-1003 included a prospective assessment of calculated LDL-C during the follow-up period after a 12-week treatment period. These studies showed that after treatment discontinuation, the average calculated LDL-C returned to baseline level within 4 weeks after ceasing Praluent treatment (see Figure 2 and Figure 3).

Figure 2 - Study DFI11565: calculated LDL-C mean (+/- SE) percent change from baseline

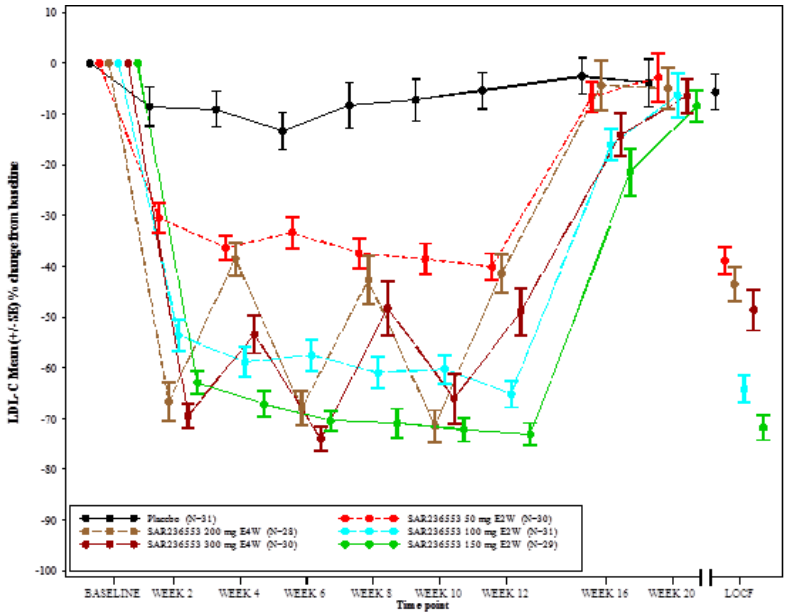
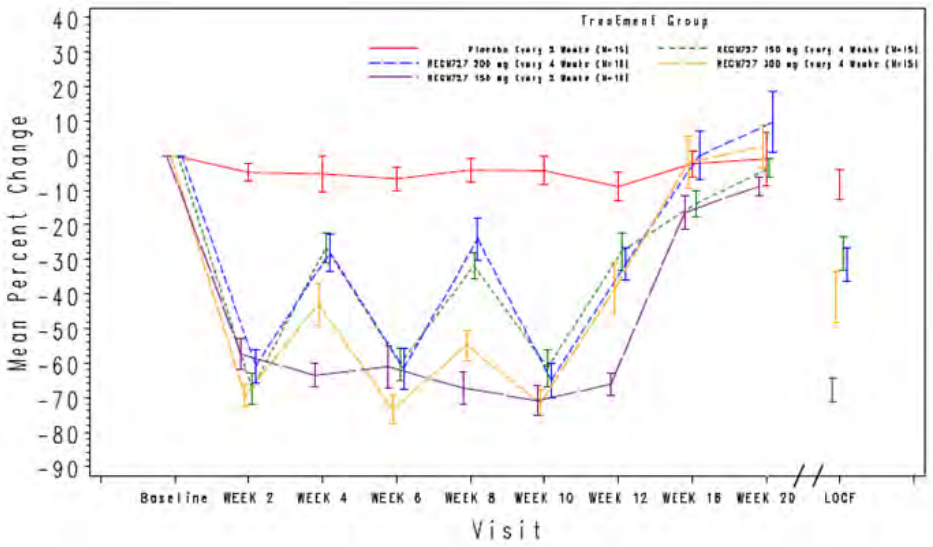


Figure 3 - Study R-727-CL-1003: calculated LDL-C mean (+/- SE) percent change from baseline



Missing LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to Week 12 will be derived from observed and imputed LDL-C 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 LDL-C 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 of missing data during the on-treatment period

Missing LDL-C values during the on-treatment period will be imputed from other on-treatment measurements assuming Missing At Random, using SAS® MI procedure.

Only LDL-C values collected during the on-treatment period will be included in the imputation model. This way, missing LDL-C values during the on-treatment period will be imputed based solely on observed on-treatment LDL-C values.

The imputation model will include the treatment arm, baseline LDL-C value, and all LDL-C values at pre-specified visits. Since the pattern of missing data will necessarily be non-monotone, a Monte-Carlo Markov Chain (MCMC) method will be used. A minimum value of 0 will be specified in order to avoid negative imputed LDL-C values.

A sample SAS code is provided below:

```
proc mi data=DATAIN out=DATAOUT nimpute=100 minimum=0;

    mcmc impute=monotone;

    var ARM LDL_BASE LDL_W4 LDL_W8 LDL_W12;

run;
```

As stated above, the input dataset DATAIN will include only LDL-C values collected during the on-treatment period. Any LDL-C values collected during the post-treatment period will be excluded from the input dataset. In practice, the MI procedure will generate imputed values for all missing values (whether on-treatment or post-treatment), but only imputed values during the-on-treatment period will be kept in the final datasets that will be analyzed using ANCOVA. Imputed values during the post-treatment period will be discarded and replaced by imputed values described in the next paragraph.

Imputation of missing data after treatment discontinuation

Missing LDL-C values during the post-treatment period will be imputed assuming LDL-C values would on average return to baseline values.

For each patient, missing post-treatment LDL-C values will be imputed 100 times, using a random draw from a normal distribution, with mean equal to patient's own baseline value and variance equal to the conditional variance at the specific time-point, given the baseline value.

Let Y_0 and Y_1 denote the LDL-C 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.

The conditional variance will be estimated from observed data within the same treatment arm at the specific time-point.

During the random generation process, a minimum value of 0 will also be applied in order to avoid negative imputed LDL-C values.

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