STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Asia in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy

SAR236553/REGN727-EFC13889

ODYSSEY EAST

STATISTICIAN: [redacted]

DATE OF ISSUE: 17-Oct-2017

NCT02715726

Total number of pages: 64

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab:	antibody
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotrasferase
ANCOVA:	analysis of covariance
ANOVA:	analysis of variance
Apo:	apolipoprotein
AST:	aspartate aminotransferase
ATC:	anatomic therapeutic category
CEC:	clinical events classification
CHD:	coronary heart disease
CI:	confidence interval
CKD:	chronic kidney disease
CV:	cardiovascular
CVD:	cardiovascular disease
ECG:	electrocardiogram
e-CRF:	electronic case record form
eDISH:	evaluation of drug-induced serious hepatotoxicity
EZE:	ezetimibe
GGT:	glutamyl transferase
HbA1c:	glycated hemoglobin A1c
HCV:	hepatitis C virus
HDL-C:	high density lipoprotein cholesterol
HLGT:	high level group term
HLT:	high level term
IMP:	investigational medicinal product
ITT:	intent to treat, 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
LS:	least square
MAR:	missing at random
MCMC:	Markov Chain Monte Carlo
MedDRA:	medical dictionary for regulatory activities
MI:	myocardial infarction

MMRM:	mixed effect model with repeated measures
NMAR:	not missing at random
PAD:	peripheral arterial disease, peripheral arterial disease
PCSA:	potentially clinical significant abnormality
PK:	pharmacokinetics
PT:	preferred term
Q1:	first quartile
Q2W:	every 2 weeks
Q3:	third quartile
QQ:	quantile quantile
RDW:	red blood cell distribution width
SAEs:	serious adverse events
SD:	standard deviation
SOC:	system organ class
TC:	total cholesterol
TG:	triglycerides
ULN:	upper limit of normal range
ULOQ:	upper limit of quantification
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a randomized, double-blind, parallel-group, double dummy, ezetimibe-controlled, unbalanced (2:1, alirocumab: ezetimibe), multi-center, multi-national study conducted in China, India and Thailand.

After a screening phase of up to 3 weeks, patients were centrally randomized via interactive voice response system (IVRS)/interactive web response system (IWRS) to 1 of the 2 treatment groups and treated in a double-blind manner for approximately 24 weeks.

Randomization was stratified according to:

- Prior history of myocardial infarction (MI) or ischemic stroke (Yes versus No);
- High-intensity statin treatment (Yes versus No; Yes defined as atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily, No for simvastatin whatever the dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily);
- Country (China, India or Thailand).

Starting dose of alirocumab was 75 mg every 2 weeks (Q2W). A dose up-titration at Week 12 to 150 mg Q2W, depending on Week 8 low-density lipoprotein cholesterol (LDL-C) levels, may occur for patients randomized to alirocumab group. Patients will be followed for 8 weeks after the last visit of the double-blind treatment period.

Approximately 600 patients (400 in alirocumab and 200 in ezetimibe groups) were to be randomized from approximately 69 sites.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy in comparison with ezetimibe (EZE) 10 mg daily after 24 weeks of treatment in Asia in patients with hypercholesterolemia at high cardiovascular (CV) risk.

1.2.2 Secondary objectives

The secondary objectives are:

- To evaluate the effect of alirocumab 75 mg in comparison with ezetimibe 10 mg on LDL-C after 12 weeks of treatment.

- To evaluate the effect of alirocumab on other lipid parameters: eg, Apolipoprotein B (Apo B), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), lipoprotein a (Lp[a]) ,high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and Apo A-1 levels).
- To evaluate the safety and tolerability of alirocumab.
- To evaluate the development of anti-alirocumab antibodies.
- To evaluate the pharmacokinetics (PK) of alirocumab.

1.3 DETERMINATION OF SAMPLE SIZE

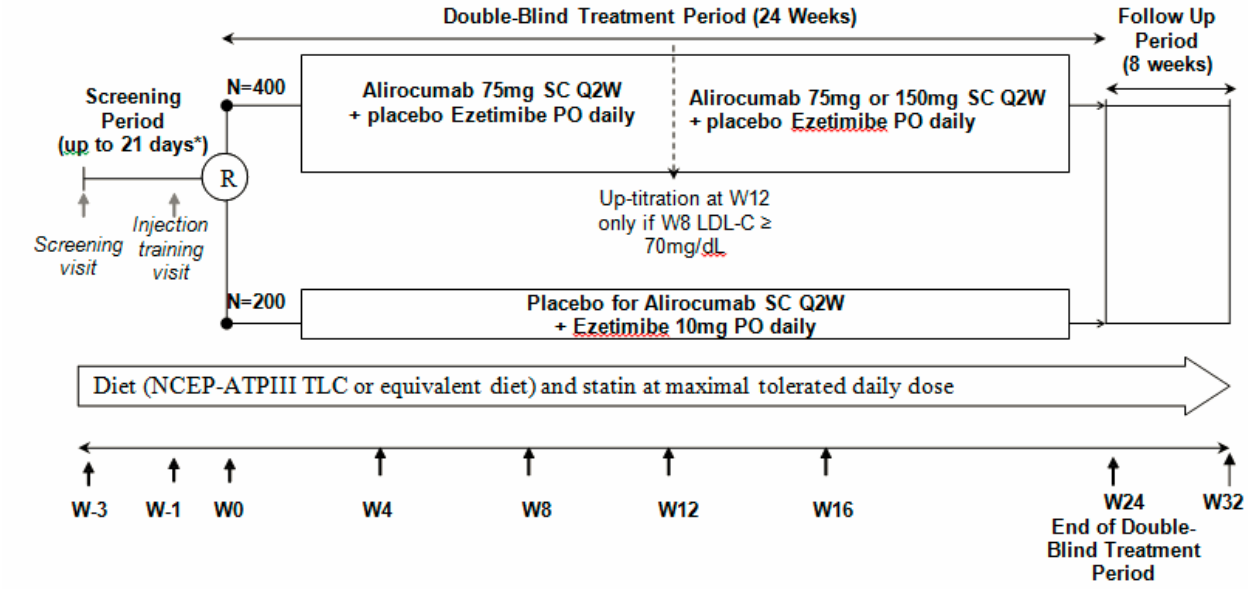
A total sample size of 96 patients (64 in alirocumab and 32 in ezetimibe arms) will have 95% power to detect a difference in mean percent change in LDL-C of 20% with a 0.05 two-sided significance level and assuming a common standard deviation (SD) of 25% and all these patients having an evaluable primary endpoint.

Nevertheless, to meet registration requirement and provide safety documentation in participating countries the final total sample size will be 600 with a randomization ratio 2:1 (alirocumab: 400, ezetimibe: 0).

1.4 STUDY PLAN

The following figure presents the graphical study design:

Figure 1 - Graphical study design



* Every effort should be made to ensure that the screening window is as short as possible and ideally within two weeks.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

There are no major changes to the protocol statistical section.

The first patient was screened on 27 July 2016(screen-failed). The first patient was randomized on 11 August 2016. There are no planned interim analyses.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value obtained up to the date and time of the first double-blind investigational medicinal product (IMP) administration. The first double-blind IMP administration is defined as the earliest administration between the first double-blind injection date and the first capsule intake. 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 summary statistics in the safety and efficacy sections (Section 2.4.4 and Section 2.4.5).

Demographic characteristics

Demographic variables are gender (Male, Female), race (Asian, other), age in years (quantitative and qualitative variable: <45, ≥45 to <65, ≥65 to <75, and ≥75 years; and <65, and ≥65 years).

Medical history

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 electronic case report form [e-CRF] page).

The CHD, CHD risk equivalents, and CV risk factors will be based on items or combination of items pre-listed in the dedicated medical history e-CRF page (unless otherwise specified).

CHD and CHD risk equivalents will be detailed as follows:

<u>CHD (regardless if it is ongoing or not)</u>

- Acute myocardial infarction
- Silent myocardial infarction
- Unstable angina
- Coronary revascularization procedure

- Other clinically significant CHD diagnosed by invasive or non-invasive testing

CHD risk equivalents

- Peripheral arterial disease (as defined in Section 2.5.1)
- Ischemic stroke
- Moderate chronic kidney disease (as defined in protocol)
- Known history of diabetes mellitus 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 -3/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.

In addition, patients' status as primary and secondary cardiovascular disease (CVD) prevention will be summarized. 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 peripheral arterial disease (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.

All medical history information pre-listed or not in the e-CRF, will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

Specific disease history includes:

- Lipid modifying therapy history, as reported in the "History of Hyperlipoproteinemia" e-CRF page:
  - Type of lipid-modifying therapy ever taken (statin, fibrates, bile acid sequestrant, cholesterol absorption inhibitor, nicotinic acid and derivates, omega 3 fatty acids ≥1000 mg/day, other);

  - Number of patients taking atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg or simvastatin 40 mg daily at screening and, for those not taking one of these agents at one of the specified doses, reasons for being on a lower dose or for not taking a statin.
- Background lipid modifying therapy (LMT) at randomization, as reported in the dedicated prior and concomitant medications e-CRF pages:
  - Number of patients taking high-intensity statin treatment (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, other);
  - Any LMT other than statins;
  - Any LMT other than nutraceuticals (by chemical class and drug name);
  - Nutraceuticals (omega 3 fatty acids (<1000 mg/day), phytosterols, psyllium/plantago, policosanol, other nutraceuticals).

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

Other baseline characteristics

Other baseline characteristics include body mass index (BMI) in kg/m^2 (quantitative and qualitative variables: <30, ≥30), smoking status, alcohol habits and randomization strata (as defined in Section 1.1) as per IVRS and e-CRF.

Statin treatment stratum as per e-CRF will be derived using the statin name and dose taken the day of the randomization. If a patient takes neither atorvastatin, rosuvastatin nor simvastatin the day of randomization, stratum will be equal to the low/moderate dose stratum defined as "simvastatin whatever the dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily". In case of combination of statins, stratum will be allocated to the high dose stratum defined as "atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily" if at least one of the statins taken is in this category. If a patient takes atorvastatin, rosuvastatin or simvastatin the day of randomization but the daily dose is missing from the e-CRF, the stratification applied at randomization (ie, IVRS strata) will be applied.

Glycated hemoglobin A1c (HbA1c) (quantitative and qualitative variable: <5.7%, ≥5.7% to <6.5%, ≥6.5%),and efficacy lipid parameters (quantitative variables for all efficacy parameters and the following qualitative variables) will be also summarized at baseline (definitions in Section 2.1.3):

- calculated LDL-C: <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: <1.04, ≥1.04 mmol/L;
- Fasting TG: <1.7, ≥1.7 to <2.3, ≥2.3 mmol/L, category ≥1.7mmol/L (mixed dyslipidaemia) will be also displayed;
- Lp(a): <0.3, ≥0.3 to <0.5, ≥0.5 g/L, category ≥0.3g/L will be also displayed.

Any technical details related to computation, dates, and imputation for missing dates is described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications taken within 12 weeks prior to screening and until the end of the study, including LMTs are to be reported in the case report form pages:

- Previous and concomitant statin drugs;
- Previous and concomitant lipid lowering drugs (other than statins);
- Previous and concomitant medications (other than statin, lipid lowering drugs).

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database locks.

Prior medications are those the patient used within 3 months to screening visit and prior to first double-blinded investigational medicinal product (IMP) administration (capsule or injection, whichever comes first). Prior medications can be discontinued before first administration or can be ongoing during treatment phase.

Concomitant medications are any treatments received by the patient concomitantly to the IMPs, from first double-blind IMP (capsule or injection, whichever comes first) to the last IMP injection +70 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in Section 2.1.4).

Post-treatment medications are those the patient took in the period starting from 71 days after the last IMP injection and ending when the patient terminates the study.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Efficacy parameters include lipid parameters (ie, TC, calculated LDL-C, measured LDL-C, HDL-C, fasting TG, non-HDL-C, Apo B, Apo A-1, Apo B/Apo A-1 ratio, Lp[a], TC/HDL-C ratio). All these parameters are measured or calculated by a Central Laboratory, for both scheduled and unscheduled time points. Calculated LDL-C is obtained using the Friedewald formula. Non-HDL-C is calculated by subtracting HDL-C from the TC. Measured LDL-C is obtained via beta quantification method. All measured LDL-C values provided by the Central Laboratory including those done in case of TG values exceeding 400mg/dL (4.52mmol/L) will not be used for the analysis of calculated LDL-C endpoints.

Unless other specified, all lipid values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the primary and secondary efficacy endpoints. All measurements scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 2 in order to provide an assessment for Week 4 to Week 24 time points. For

TG, only fasting measurements will be used. Measurements with missing fasting status will be excluded from the analyses.

For all time points post-baseline, the value used for the analyses at a given time point (eg, at Week 24) is the value obtained within the corresponding analysis window. The baseline value is the last available measurement obtained up to the date and time of the first double-blind IMP administration (capsule or injection, whichever comes first). 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.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to Week 24 in the ITT population, using all LDL-C values regardless of adherence to treatment (ITT estimand). Primary endpoint is defined as: 100 × (calculated LDL-C value at Week 24 – calculated LDL-C value at baseline) / calculated LDL-C value at baseline.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Key secondary efficacy endpoints

The key secondary endpoints are:

- The percent change in calculated LDL-C from baseline to Week 24 in the mITT population, using all LDL-C values during the efficacy treatment period (on-treatment estimand);
- The percent change in calculated LDL-C from baseline to Week 12 (ITT estimand);
- The percent change in calculated LDL-C from baseline to Week 12 (on-treatment estimand);
- The percent change in Apo B from baseline to Week 24 (ITT estimand);
- The percent change in Apo B from baseline to Week 24 (on-treatment estimand);
- The percent change in non-HDL-C from baseline to Week 24 (ITT estimand);
- The percent change in non-HDL-C from baseline to Week 24 (on-treatment estimand);
- The percent change in TC from baseline to Week 24 (ITT estimand);
- 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 TC from baseline to Week 12 (ITT estimand);
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 (ITT estimand);
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 (on-treatment estimand);
- The percent change in Lp(a) from baseline to Week 24 (ITT estimand);
- The percent change in HDL-C from baseline to Week 24 (ITT estimand);

- The percent change in fasting TG from baseline to Week 24 (ITT estimand);
- The percent change in Apo A-1 from baseline to Week 24 (ITT estimand);
- The percent change in Lp(a) from baseline to 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).

2.1.3.2.2 Other secondary efficacy endpoints

- The proportion of patients with calculated LDL-C <100 mg/dL (2.59 mmol/L) at Weeks 12 and Week 24 (ITT estimand);
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 12 (ITT estimand);
- The absolute change in calculated LDL-C (mg/dL and mmol/L) from baseline to Week 12 and Week 24 (ITT estimand);
- The absolute change in Apo B/Apo A-1 ratio from baseline to Week 12 and Week 24 (ITT estimand);
- The proportion of patients with Apo B <80 mg/dL (0.8 g/L) at Week 12 and Week 24 (ITT estimand);
- The proportion of patients with non-HDL-C <100 mg/dL (2.59 mmol/L) at Week 12 and Week 24 (ITT estimand);
- The proportion of patients with non-HDL-C <130 mg/dL (3.37 mmol/L) at Week 12 and Week 24 (ITT estimand);
- The proportion of patients with calculated LDL-C <70 mg/dL (1.81 mmol/L) and/or ≥50% reduction in calculated LDL-C (if calculated LDL-C ≥70 mg/dL [1.81 mmol/L]) at Week 12 and Week 24 (ITT estimand);
- The proportion of patients with ≥50% reduction in calculated LDL-C at Week 12 and Week 24 (ITT estimand);
- The absolute change in TC/HDL-C ratio from baseline to Week 12 and Week 24 (ITT estimand);
- The percent change in TC from baseline to Week 12 and 24 (on-treatment estimand);
- The percent change in Apo B from baseline to Week 12 (on-treatment estimand);
- The percent change in non-HDL-C from baseline to Week 12 (on-treatment estimand);
- The percent change in Lp(a) from baseline to Week 12 and 24 (on-treatment estimand);The proportion of patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 (on-treatment estimand).

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, electrocardiogram (ECG) and vital signs.

Observation period

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

- The PRE-TREATMENT period: defined as the time from the signed informed consent up to the first dose of double-blind IMP;
- The treatment-emergent adverse event (TEAE) period: defined as the time from the first dose of double-blind IMP up to the day of last dose of double-blind IMP injection+70 days (10 weeks) as residual effect of alirocumab is possible until 10 weeks after the discontinuation of double-blind IMP injection.

  The TEAE period will include:
  - The TREATMENT period defined as the time from the first dose of double-blind IMP up to the day of last dose of double-blind IMP injection + 21 days, as serum concentration of alirocumab is expected to be >10 µg/mL for approximately 21 days following administration of 150 mg, and because throughout the previous studies it was observed that when alirocumab concentrations declined below this concentration, decrease in effect on LDL-C is observed.
  - The RESIDUAL TREATMENT defined as the time from the day of last dose of double-blind IMP injection + 22days up to the day of last dose of double-blind IMPinjection + 70 days (10 weeks).
- The POST-TREATMENT period: defined as the time starting the day after the end of the TEAE period (ie, 71 days after the day of last dose of double-blind IMP injection).

The on-study observation period is defined as the time from the day of first dose of double-blind IMP (capsule or injection, whichever comes first) until the last protocol planned visit of the patient. The last protocol planned visit is defined as the follow-up visit if done, or else 32 weeks after the randomization of the patient.

2.1.4.1 Adverse events variables

Adverse events (including serious adverse events [SAEs], 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, including CV events (irrespective of the result of the adjudication), will be reported and described.

All AEs will be coded to a “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 currently in effect at Sanofi at the time of database lock.

Adverse event observation period

Pretreatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of IMP.

Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period.

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

Grouping of adverse events (including adverse event of special interest)

Adverse events of special interest (AESI) are AEs (serious or non-serious) that need to be monitored, documented, and managed in a pre-specified manner described in the protocol. More generally, below are the grouping of adverse events that will be analyzed

- Alanine aminotransferase (ALT) ≥3 upper limit of normal range (ULN) (if baseline ALT<ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ULN), selected using laboratory data;
- Allergic events:
  - General allergic events, selected using 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”, “injection site dermatitis”, “injection site hypersensitivity”, “injection site rash”, “injection site urticaria”, and “injection site vasculitis”)
  - General allergic events and local allergic reactions at IMP injection site will be described. This selection will be based on the above selection for general allergic event and on the following selection of PT from the symptoms complementary form for local injection site reaction: “Injection site dermatitis”, “Injection site hypersensitivity”, “Injection site oedema”, “Injection site rash”, “Injection site urticaria”, “Injection site eczema”, “Injection site vasculitis”, “Injection site swelling“, “Infusion site dermatitis”, “Infusion site hypersensitivity”, “Infusion site oedema”, “Infusion site rash”, “Infusion site urticaria”, “Infusion site swelling“.
- Local injection site reactions, selected using e-CRF specific tick box on the AE page
- Hemolytic anemia, selected using e-CRF specific tick box on the AE page and confirmed final diagnosis provided in the AE complementary form;
- Neurologic events selected using a CMQ, based on 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 C Table 5 for the list of terms);
- Neurocognitive events:
  - Selected using a 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 C Table 6 for the list of terms)
- Ophthalmologic events selected using SMQs;

- Cataract using HLT “Cataract conditions”
- Overdose of IMP (symptomatic or asymptomatic), selected using appropriate MedDRAcodes and the tick box “Overdose with IMP” in the adverse event complementary e-CRF form
- Pregnancy of female patient/subject (including male subject’s partner) selected using appropriate MedDRA codes;
- Hepatic disorder events using SMQ “Hepatic disorder”;
- Diabetes mellitus or diabetic complications selected 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";

Cardiovascular events

Suspected CV events that occur from randomization until the follow up visit will be submitted to the Clinical Events Committee (CEC) for adjudication.

Adjudicated CV events include all CV AEs positively adjudicated as defined in the Clinical Events Committee charter. The following categories will be described:

- CHD death;
- Non-fatal MI;
- Fatal and non-fatal ischemic stroke;
- Unstable angina requiring hospitalization;
- Congestive heart failure requiring hospitalization;
- Ischemia driven coronary revascularization procedure.

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined below.

- Death on-study: deaths occurring during the on-study observation period;
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period;
- Death post-study: deaths occurring after the end of the study.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and will be used in all listings and tables.

Unless otherwise specified, blood samples for clinical laboratories will be taken at Visit 1 (Week -3), Visit 3 (Week 0), Visit 6 (Week 12), Visit 8 (Week 24), or early termination, and

during the follow-up visit (Visit 9 [Week 32]) in case of abnormality unless otherwise specified. The laboratory 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, eGFR, blood urea nitrogen, uric acid;
  - Liver function (also measured at Week 4, Week 8, and Week 16, except gamma glutamyl transferarses [GGT] and lactate dehydrogenase [LDH]): ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), GGT, total bilirubin, and in case of total bilirubin values above the normal range, must include direct and indirect bilirubin, LDH.
- Hepatitis screen: anti-hepatitis-C antibody (Ab) (at Week -3 and Week 24/or early termination).

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: heart rate (HR), systolic and diastolic blood pressure (SBP and DBP) in sitting position.

2.1.4.5 Electrocardiogram variables

The ECG parameters were recorded automatically by the device at the Investigator site at Week -3/Week -2, Week 24, or early termination.

2.1.5 Other endpoints

The assessment endpoint listed below is defined using the same definitions and rules as for calculated LDL-C, when applicable (see Section 2.1.3.1).

- The absolute change in HbA1c (%) from baseline to Week 12 and Week 24. PCSA criteria for HbA1c will be used (see Appendix A).
- The proportion of patients with 2 consecutive results, spaced out by at least 21 days, of calculated LDL-C <25 mg/dL (<0.65 mmol/L) (respectively calculated LDL-C <15 mg/dL, ie, <0.39 mmol/L) during the treatment period and the time to the first calculated LDL-C <25 mg/dL (respectively, calculated LDL-C <15 mg/dL for these patients).

2.1.6 Anti-alirocumab antibodies variables

Anti-alirocumab antibodies are assessed at baseline (before the first IMP injection), at Week 4, Week 12, Week 24/or early termination and during follow-up (Week 32). Anti-drug antibody (ADA) measurements will be assigned to similar analysis windows as defined for efficacy endpoints (Table 2), with an additional analysis window for the ADA follow-up measurement performed at Week 32.
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 (up to follow-up visit) or 2) Patients with a positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period (up to follow-up visit). For treatment-emergent positive ADA, the following categories for ADA duration will be applied:
  - A persistent positive response is a treatment-emergent ADA positive response detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period;
  - An indeterminate duration positive response is defined as ADA present only at the last sampling time point;
  - A transient positive response is defined as any treatment-emergent positive ADA response that is neither considered persistent nor indeterminate.

In addition, potential ADA samples to be collected after follow-up visit for patients with titer >240 at early end of treatment or follow-up visit will be listed.

2.1.7 Pharmacokinetics variables

Concentrations of total alirocumab, total and free proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations in serum are assessed at baseline (Week 0), Week 4, Week 12, Week 16, Week 24, and during the post-treatment follow-up visit (Week 32). To collect information on the absorption phase, an optional PK sample can be collected 5 days (±2) after the Week 22 IMP injection.

Pharmacokinetic variable is the total alirocumab concentration at each time point. Depending on the timing of the sample versus the previous injection, C_{trough}, $C_{trough,av}$, C_{max} and $C_{Follow\text{-}Up}$ will be defined as follows:

- C_{max}: alirocumab concentration sample taken 5 days ±2 days after previous injection;
- C_{trough}: alirocumab concentration sample taken 14 days ±6 days after previous injection (may be just prior the next injection):
  - $C_{trough,av}$: Alirocumab average trough concentrations ("$C_{trough,av}$") will be calculated for each patient as the mean of "$C_{troughs}$" considered at steady state. The occurrence of

steady state will be assessed graphically, by plotting "C_{trough}" throughout the study visits over all patients.

- $C_{Follow\text{-}up}$: alirocumab concentration sample taken more than 21 days after last injection and no more than 14 weeks after last injection.

Alirocumab concentration and total and free PCSK9 concentration will be described following time windows as defined in Section 2.5.4, Table 2.

2.1.8 [redacted]

[redacted]

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who met the inclusion criteria and signed the informed consent.

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

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients;
- Screen failure patients and reasons for screen failure;
- Non-randomized but treated patients, if any;
- Randomized patients;
- Randomized but not treated patients and reason for not being treated;
- Randomized and treated patients;
- Patients who did not complete the study treatment period as per protocol;
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation;
- Status at last study contact.

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as the denominator divided by the number of exposed patients.

Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group.

The incidence of premature treatment discontinuation (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically by treatment group on randomized and treated patients (as randomized), using Kaplan-Meier method.

Patients with insufficient post-treatment follow-up will be described. A patient is considered insufficient post-treatment follow-up at the end of the study in following cases:

- If the patient is not assessed at the post-treatment follow-up visit, or any post-treatment visit, unless patient died before;
- If the post-treatment follow-up visit is less than 9 weeks after the last double-blind IMP injection.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group. Additionally, the analysis populations will be summarized in a table by number of patients on the randomized population.

- Randomized population;
- Efficacy population: intent-to-treat (ITT) population/modified intent-to-treat (mITT) population;
- Safety population;
- Pharmacokinetics population;
- Anti-alirocumab antibody population.
- Definitions of the study population are provided in Section 2.3.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) a patient is randomized based on an incorrect stratum, b) a patient is randomized twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. These irregularities will be summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Stratification error
A kit allocated at Day 1 or any unscheduled replacement before Week 12 is administered to the patient after the up-titration visit (Week 12)

2.3 ANALYSIS POPULATIONS

Patients treated without or before being randomized will not be considered randomized and will not be included in any analysis populations. The safety experience of patients treated and not randomized will be reported separately.

The randomized population includes any patient who has been allocated to a randomized treatment by IVRS/IWRS regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population.

2.3.1.1 Intent–to-treat population

The intent-to-treat population is the randomized patients who had an evaluable primary efficacy endpoint. The primary efficacy endpoint is evaluable when the following 2 conditions are met:

- Availability of a baseline calculated LDL-C value;
- Availability of at least 1 calculated LDL-C value within one of the analysis windows up to Week 24.

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

2.3.1.2 Modified intent-to-treat population

The modified intent-to-treat population is defined as all randomized patients who took at least 1 dose or part of a dose of the double-blind IMP injection and had an evaluable primary efficacy endpoint during the efficacy treatment period. The primary efficacy endpoint is evaluable when the following 2 conditions are met:

- Availability of a baseline calculated LDL-C value;
- Availability of at least 1 calculated LDL-C value during the efficacy treatment period within one of the analysis windows up to Week 24.

The efficacy treatment period is defined as the time period from the first double-blind IMP (capsule or injection, whichever comes first) up to the day of last injection +21 days or the day of last capsule intake date +3 days, whichever comes first.

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

2.3.2 Safety population

The safety population is defined as randomized patients who actually received at least 1 dose or part of a dose of the IMP (injection or capsule). Patients will be analyzed according to the treatment actually received (ie, as-treated treatment group, alirocumab or ezetimibe).

In addition:

- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized.

For patients receiving double-blind IMP from both treatments during the trial, the treatment group used for as-treated analysis will be the one to which the patient was treated with the highest number of injections except in the case where the patient is randomized in the alirocumab group but received more placebo injections than alirocumab injections and took more placebo capsules than ezetimibe capsules. In that case the as-treated group is defined as alirocumab (see Appendix D). In case of the same number of injections of each treatment is received, the as-treated treatment group will be the as-randomized group.

2.3.3 Anti-alirocumab antibody population

The anti-alirocumab antibody analysis will be performed on all randomized and treated patients (safety population) with a blood sample on Week 0 (baseline) and at least one evaluable blood sample for antibodies after the first double-blind IMP injection.

2.3.4 Pharmacokinetic population

The PK analysis will be performed on all randomized and treated patients (safety population) with at least 1 evaluable PK sample post first double-blind IMP injection.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

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

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Similar analyses will be done on the ITT population in the as-randomized treatment group (respectively safety population in the as-treated treatment group) and will be included in the appendices if the size of the ITT population (respectively safety population) is different (>10%) from the size of the randomized population for any treatment group. In the randomized population, parameters will also be summarized within each randomization stratum as per IVRS.

All reported patient's medical and surgical history will be presented by primary SOC and HLT. The tables will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on the overall incidence across treatment groups. In addition all medical history of specific interest (see Section 2.1.1) will be presented by treatment group.

For the patients with a primary CVD prevention status, the number (%) of patients with the following comorbidities/risk factors will be tabulated:

- Diabetes mellitus with target organ damage (renal damage [microalbuminuria, or macroalbuminuria, moderate chronic kidney disease (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 2.1.1);

- Family history of premature CHD;
- Hypertension;
- Moderate CKD.

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 2.1.1);

- 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.

Besides:

- The number (%) of patients with a secondary prevention status with 1 or more associated comorbidity among hypertension, diabetes mellitus, moderate CKD will be tabulated.
- 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 presented.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the randomized population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic therapeutic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant and post-treatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the alirocumab group. In case of equal frequency regarding ATCs, alphabetical order will be used.

In addition, concomitant LMTs and CV medications will be summarized by pre-specified categories/chemical class and standardized medication name.
Lipid modifying therapy (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;

- Atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily or simvastatin at any daily dose;
- LMT other than statin only;
- No LMT.

The LMTs intensity at randomization is defined as:

- High intensity is atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily;
- Low intensity is atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily or simvastatin at any daily dose.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

Injection (alirocumab or placebo)

The extent of IMP exposure will be assessed by the duration of IMP exposure, and actual dose information.

Double-blinded IMP injections are those administered from randomization to completion or discontinuation of the study treatment. These injections contain:

- Placebo for patients randomized in the ezetimibe group;
- 75 or 150mg of alirocumab for patients randomized in the alirocumab group.

Total exposure will be assessed using descriptive statistics for:

- Duration of IMP injection exposure in weeks is defined as: (last dose of double-blind IMP injection date – first dose of double-blind IMP injection date + 14 days)/7, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data). Non-integer values will be rounded to 1 decimal place;
- The total number of injections by patient.

These parameters will be also analyzed per dose of alirocumab using similar definitions.

Titration

The number and percentage of patients with an up-titration in the alirocumab group will be described. Patients with an up-titration are defined as up-titrated patients according to IVRS/IWRS Week 12 transaction with at least 1 injection of alirocumab 150 mg afterwards.

Capsule (ezetimibe or placebo)

The total exposure of capsule will be assessed by duration in weeks defined as: (last capsule intake date – first capsule intake date + 1 day) / 7, regardless of intermittent discontinuations. Non-integer values will be rounded to 1 decimal place.

All quantitative parameters above will be summarized using number, mean, SD, median, minimum, and maximum. In addition, the durations of treatment exposure will be summarized and presented graphically using bar chart displaying the percentage of patients according to the following categories: ≥1 and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and < 22 weeks, and ≥22 weeks.

2.4.3.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Compliance will be assessed using the following parameters:

Mean injection frequency of IMP double-blind injections, is defined as the average number of days between 2 consecutive injections, that is: (last injection date – first injection date) / (number of injections – 1) for patients receiving at least 2 injections.

The **overall compliance** for injections will be defined for each patient as: 100 – (%days with under-planned dosing + %days with above-planned dosing). Under-planned and above-planned dosing will be defined as follows, considering that injections should be performed every 2 weeks (±3 days as per protocol):

Above-planned dosing percentage will be defined for each patient as the number of days with more than 1 injection administered within the 11 days before divided by the duration of IMP injection exposure in days. For example if a patient takes a dose 9 days after his/her previous injection, then 2 days are counted as days above-planned dose.

Under-planned dosing percentage will be defined for each patient as the number of days with no injection administered within the previous 17 days divided by the duration of IMP injection exposure in days. For example if a patient takes a dose 18 days after his/her previous injection, then 1 day is counted as a day under-planned dosing.

These parameters will be summarized descriptively (number, mean, SD, median, minimum, and maximum).
The percentage of patients whose compliance is <80% will be summarized, as well as numbers and percentages of patients with 0%, >0 to ≤5%, >5 to ≤10%, >10 to ≤20%, and >20% day with above-planned dosing and numbers and percentages of patients with 0%, >0 to ≤5%, >5 to ≤10%, >10 to ≤20%, and >20% day with under-planned dosing.

According to protocol, cases of overdose are reported in the AE e-CRF pages and will be described in AE analysis (see Section 2.1.4.1 and Section 2.4.5.1).

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

2.4.4.1.1 Primary efficacy analysis

The percent change from baseline in calculated LDL-C at Week 24 as defined in Section 2.1.3.1 will be analyzed in the ITT population using a mixed effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 4 and Week 24 analysis windows will be used and missing data are accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group (ezetimibe versus alirocumab), randomization strata (as per IVRS, as defined in Section 1.1), time point (Week 4, Week 8, Week 12, Week 16, and Week 24 as defined in Section 2.5.4), treatment -by-time point interaction, strata-by-time point interaction, and the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. In case the number of patients is lower than 10 in a given stratum (eg, MI/Ischemic Stroke = Yes), the corresponding stratum (eg, MI/Ischemic stroke) and stratum-by-time point interaction terms will be removed from the model. The same will be applied to sensitivity analyses and subgroup analyses.

This model will be run using 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 LS means estimates at Week 24 for both treatment groups with their corresponding standard errors (SEs) and 95% confidence intervals (CIs). To compare the alirocumab group to the ezetimibe group, an appropriate contrast statement will be used to test the differences of these estimates, at the 2-sided 0.05 level.

Within group least square (LS) means and SEs will be provided, using weights equal to the observed proportion of patients in strata variable levels in the study population (ie, "population weight") rather than equal weights. Population weights are considered more appropriate than equal coefficients due to unbalances between levels of the randomization stratification factors observed in the study population.

Let μ_0 and μ_1 be the population means of the percent change from baseline in calculated LDL-C at Week 24 under ezetimibe and alirocumab, respectively. The hypothesis that will be tested is "H_0: $\mu_0 = \mu_1$" versus "H_1: $\mu_0 \neq \mu_1$".

The MMRM model relies on the "missing-at-random" (MAR) assumption. As we can never exclude the possibility for a not-missing-at-random (NMAR) missingness mechanism, sensitivity analyses to explore the impact of non-ignorable missingness on the primary efficacy analysis will be conducted (see pattern mixture model defined in Section 2.4.4.1.4).

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

Within the framework of this model with interaction terms, a graph presenting the LS means difference versus ezetimibe at Week 24 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 quantile quantile (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 (ezetimibe, alirocumab);
  - Time point (Week 4, Week 8, Week 12, Week 16, Week 24);
  - Treatment-by-time point interaction;
  - Randomization strata;
  - Randomization strata-by time point interaction.

2.4.4.1.3 Sensitivity to randomization strata

In order to assess the robustness of the primary analysis to randomization stratum mistakes (ie, the stratum recorded in IVRS differs from the actual one), the MMRM model will be re-run including the actual stratum as per the e-CRF instead of the stratum recorded in IVRS.

2.4.4.1.4 Sensitivity to handling of missing data

Sensitivity analyses will be conducted to assess the robustness of primary efficacy analysis with regards to handling of missing data (1).

Visual examination:

- In order to explore the missing data pattern, post-baseline calculated LDL-C observations (in the ITT population) will be described according to the following groups:
  - Calculated LDL-C available at Week 24*(ie, primary efficacy endpoint available);
  - Calculated LDL-C available at Week 16* but missing at Week 24 *;

- Calculated LDL-C available at Week 12* but missing from Week 16*;
- Calculated LDL-C available at Week 8* but missing from Week 12*;
- Calculated LDL-C available at Week 4* but missing from Week 8*;
- Calculated LDL-C missing from Week 4*.

(*): as defined in Section 2.5.4

Then, a graph of mean LDL-C calculated levels (respectively percent change from baseline in calculated LDL-C) ± SE at baseline, Week 4, Week 8, Week 12, Week 16, and Week 24 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 1-way ANOVA test for Wilcoxon scores (Kruskal-Wallis test) for continuous data will be also provided for descriptive purposes.

Multiple imputations (under MAR assumption)

In addition to the MMRM method, the multiple imputation (MI) method 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. The imputation model described in Section 2.4.4.2.2 will be used but without log transformation. Missing data from the randomized population will be imputed 100 times to generate 100 complete data sets. The percent change from baseline at Week 24 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, as defined in Section 1.1) as fixed effects, and the baseline calculated 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 (1).

- 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 until stable estimates are obtained.

In addition, for each simulation leading to negative imputed value, another value will be redrawn using MINIMUM option of MI SAS procedure (2).

Pattern mixture model (see Appendix B for more details)

Multiple imputations will be used with different imputation strategies applied to calculated LDL-C values missing during the on-treatment period (i.e. within the time period from the first double-blind IMP injection up to the day of last injection + 21 days) versus calculated LDL-C values missing after treatment discontinuation (ie, after the day of last injection + 21 days) based on the following assumptions:

- Patients within 21 days of their last blind IMP injection would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, calculated LDL-C values missing during the on-treatment period (eg, samples obtained out-side the

specified window, no blood sample available although visit was performed) 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 calculated LDL-C values returning to baseline. Therefore, calculated LDL-C values missing more than 21 days after treatment discontinuation should be imputed based on patient's own baseline value.

Missing calculated LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to Week 24 will be derived from observed and imputed LDL-C at this time point. The completed data sets will be analyzed using an ANCOVA model with treatment group and randomization strata as fixed effects, and the baseline calculated LDL-C value as continuous covariate. The results from the 100 analyses will be combined using Rubin's formulae.

2.4.4.1.5 Sensitivity to the use of calculated versus measured LDL-C measurements

In order to assess the robustness of the primary analysis to the use of calculated versus measured LDL-C assessments, an ANCOVA model will be run using measured LDL-C within Week 24 analysis window. This model will include the treatment group, the baseline value for measured LDL-C and the randomization strata. Patients from ITT population with a measured LDL-C at baseline and at least 1 measured LDL-C available within Week 24 analysis window will be included in the analysis.

2.4.4.1.6 Subgroup 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 ezetimibe at Week 24 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 24 will also be 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.

Subgroups of interest are:

- BMI (<30 kg/m^2, ≥30 kg/m^2);
- Gender (Female, Male);
- Age (<65 years, ≥65 to <75 years, ≥75 years);
- High intensity statin treatment (atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily versus atorvastatin below 40 mg daily, rosuvastatin below 20 mg daily or simvastatin whatever the daily dose);
- Prior history of myocardial infarction (MI) or ischemic stroke (Yes, No);
- Diabetes (Yes, No);
- Moderate CKD (Yes, No);

- Baseline LDL-C (<2.59, ≥2.59 to <3.37, ≥3.37 to <4.14, ≥4.14 mmol/L): for this specific subgroup factor, the MMRM model will include fixed categorical effects for treatment group, randomization strata (as per IVRS), baseline LDL-C category, time point, and the interactions treatment-by-time point, strata-by-time point, baseline LDL-C category-by-time point, treatment group-by-baseline LDL-C category, and treatment group-by-baseline LDL-C category-by-time point;
- Baseline HDL-C (<1.04 mmol/L, ≥1.04 mmol/L);
- Baseline fasting TG (<1.70 mmol/L, ≥1.70 mmol/L, ie, mixed dyslipidemia);
- Baseline Lp(a) (<0.3, ≥0.3 to <0.5, ≥0.5 g/L);

If the subgroup factor is a randomization stratification factor, then the IVRS strata will be used.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables defined in Section 2.1.3.2 anticipated to have a normal distribution (ie, lipids other than TG and Lp[a]) will be analyzed using the same MMRM model as for the primary endpoint with fixed categorical effects of treatment group, randomization strata (as per IVRS), planned time points up to Week 24, treatment-by-time point interaction and strata-by-time point interaction, as well as, the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

2.4.4.2.2 Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy variables defined in Section 2.1.3.2 anticipated to have a non-normal distribution (ie, TG and Lp[a]) will be analyzed using multiple imputation approach for handling of missing values. 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 (3) with endpoint of interest as response variable using M-estimation (using SAS ROBUSTREG procedure) with treatment group, randomization strata (as per IVRS, as defined in Section 1.1) and corresponding baseline value(s) as effects to compare treatment effects. 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. In case the number of patients is lower than 10 in a given stratum (eg, MI/Ischemic Stroke = Yes), the corresponding stratum (eg, MI/Ischemic Stroke) term will be removed from the multiple imputation and robust regression models.

Multiple imputation model

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

- Step 1: The Markov Chain Monte Carlo (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 time-points up to Week 24.

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

- The randomization strata;
- Age, BMI, and gender (age and BMI included as continuous variables).

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.

2.4.4.2.3 Binary endpoints

Binary secondary efficacy endpoints defined in Section 2.1.3.2 will be analyzed using multiple imputation approach for handling of missing values as described for non-normally distributed endpoints but without log-transformation (see Section 2.4.4.2.2 for details about multiple imputation).

For each simulation leading to negative imputed value, another value will be redrawn using MINIMUM option of MI SAS procedure.

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 treatment group as main effect and corresponding baseline value(s) as covariate, stratified by randomization factors (as per IVRS, as defined in Section 1.1). Combined estimates of odds ratio versus ezetimibe, 95% CI, and p-value will be obtained through the SAS MIANALYZE procedure.

In case the number of patients is lower than 10 in a given stratum (eg, MI/Ischemic Stroke = Yes), the corresponding stratum (eg, MI/Ischemic Stroke) term will be removed from the multiple imputation and logistic regression models.

In the data dependent case when such logistic regression is not applicable (eg, the response rate is zero in one treatment arm and thus the maximum likelihood estimate may not exist), the last observation carried forward (LOCF) approach would be used for handling of missing values and a stratified exact conditional logistic regression would be performed to compare treatment effects. The LOCF imputation method will consist of using the last value obtained up to the Week 24 analysis window (Week 12 respectively) to impute the missing Week 24 value (Week 12 respectively).

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. In case the model would not converge with

stratification variables, an unstratified exact logistic regression will be performed. Exact odds ratio versus ezetimibe, 95% CI, and p-value will be provided.

2.4.4.2.4 Sensitivity analyses of key secondary endpoints

In order to assess secondary endpoints during the efficacy treatment period, the same statistical approach as described above from Section 2.4.4.2.1 to Section 2.4.4.2.3 will be applied during the efficacy treatment period in the mITT population (see Section 2.3.1.2).

2.4.4.2.5 Analyses of key secondary endpoints by subgroups

The endpoint "the percent change in fasting TG from baseline to Week 24" will be analyzed according to the following subgroups:

- Baseline fasting TG (<150 mg/dL [<1.70 mmol/L], ≥150 mg/dL [≥1.70 mmol/L] ie, mixed dyslipidemia).

2.4.4.2.6 Summary of results per time point

Central laboratory values, percent change from baseline, and/or when appropriate absolute change from baseline, for calculated LDL-C, TC, HDL-C, fasting TG, non HDL-C, and T C/HDL-C ratio at Week 4, Week 8, Week 12, Week 16, Week 24 time points, for Lp(a), Apo B, Apo A-1 at Week 12 and Week 24 time points will be summarized in the ITT population using:

- 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 including planned time points and with raw values, changes from baseline, or percent change from baseline as response variable in the model as appropriate.
- 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 including planned time points and with raw values or percent changes from baseline as response variable in the model as appropriate.

In addition, quantitative descriptive summaries by time point (value at visit and % change from baseline) will be presented for all lipids using observed (ie, non-missing) data. In addition binary variables for LDL-C will be also described by time point.

2.4.4.3 Multiplicity issues

In order to handle multiple key efficacy secondary endpoints, the overall type-I error will be controlled by the use of a sequential inferential approach. Statistical significance of the primary parameter at the 0.05 alpha level is required before drawing inferential conclusions about first key secondary parameter (refer to the order in Section 2.1.3.2.1). Inferential conclusions about successive key secondary parameters require statistical significance at the 0.05 alpha level of the prior ones.

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

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

2.4.4.4 Additional efficacy analysis(es)

Not applicable.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group. No formal inferential testing will be performed. Summaries will be descriptive in nature.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately;
- The baseline value is defined as the last available value obtained up to the date and time of the first double-blind IMP administration (capsule or injection, whichever comes first), except otherwise specified.
- The potentially clinical significant abnormality (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 A]). In case the threshold defined in the PCSA list for a given lab parameter is below the ULN, the following PCSA criterion will be used for the PCSA analysis: >PCSA threshold or > ULN (if ULN ≥PCSA threshold).
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during TEAE period, including nonscheduled or repeated evaluations.
- The treatment-emergent PCSA denominator by 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 Section 2.5.4, Table 2 in order to provide an assessment for Week 4 to Week 24 time points.

- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group using analysis windows. Summaries will also include the last on-treatment value and the worst on-treatment value. The last on-treatment value is defined as the last value collected during the treatment period (see Section 2.1.4). The worst on-

treatment value is defined as the nadir and /or the peak value during the treatment period according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.

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

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

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event (AE) reporting will be on treatment-emergent adverse events (TEAEs). Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables 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, and PT) will be presented in alphabetical order, unless otherwise specified.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- 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, showing number (%) of patients with at least 1 TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order;
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified;
- 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, sorted by the sorting order defined above;
- All TEAEs by maximal intensity (ie, mild, moderate, or severe), presented by primary SOC and PT, sorted by the sorting order defined above;
- Kaplan-Meier curves will be provided, when appropriate, for time from first dose of double-blind IMP (capsule or injection, whichever comes first) to the first occurrence of selected TEAEs. Patients without any event will be censored at the end of the TEAE period. Selected TEAEs could be local injection site reactions, general allergic reactions, hepatic disorders, diabetes among non-diabetic patients at baseline and TEAE related to any clinically significant signal that needs further characterization.

Analysis of all treatment emergent serious adverse event(s)

- All TEAEs by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order;
- 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 administration 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 treatment discontinuation, by primary SOC, HLGT, HLT, and PT.

Analysis of groupings of adverse event(s) including selected adverse events of special interest

- All grouping of TEAEs including adverse events of special interest as listed in Section 2.1.4.1 will be analyzed using selections defined in Section 2.1.4.1 and will be presented by SMQ and PT (when selection is based on SMQs) 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).
- Analyses of grouping of AEs for diabetes will be performed overall and according to the diabetic status at baseline.

In addition, the following variables will 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 IMP injections received;
- Time from first double-blind IMP injection to first injection site reaction;
- Description of the highest intensity of each symptom recorded in the specific e-CRF page with table and bar chart.

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

Analysis of cardiovascular events

Adjudication results of treatment-emergent CV events will be summarized on the safety population.

Analysis of pre-treatment and post-treatment adverse events

- All pre-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 pre-treatment AEs leading to treatment discontinuation by primary SOC and PT, sorted by the sorting order defined above;
- 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 2 consecutive LDL-C <25 mg/dL (<0.65 mmol/L)

If applicable, similar summaries of TEAEs as those described above will be also provided on the safety subgroup population of patients with 2 consecutive results of calculated LDL-C <25 mg/dL (<0.65 mmol/L, as defined in Section 2.1.5) in both treatment groups. Only TEAE for which it will be confirmed or unclear that they occurred, worsened or became serious the day or after the first level of LDL-C <25 mg/dL (<0.65 mmol/L) will be considered.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients from the safety population who died by study period (on-study, on-treatment, post-study) and reasons for death as adjudicated by the clinical events classification (CEC);
- Deaths in nonrandomized patients or randomized but not treated patients;
- TEAEs leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC. TEAE leading to death are TEAE that led to death regardless of timing of death in relation to IMP injection (ie, death occurring in the TEAE period or during the post-treatment period).

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, first quartile (Q1), third quartile (Q3), standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, last on-treatment, worst on-treatment value) by treatment group. In addition, for some parameters of interest, mean changes from baseline with the corresponding SE could be plotted over time (at same time points) in each treatment group. This section will be organized by biological function as specified in Section 2.1.4.3. For glucose, only fasting samples will be summarized.

The incidence of PCSAs (list provided in Appendix A), at any time during the TEAE period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

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

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

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

If any clinically significant signal is detected and need further characterization, exploration of time to onset will be performed for selected PCSAs assessed during the TEAE period as described below to account for the differential exposure time in all patients.

Kaplan-Meier curves during TEAE period will be also provided using the midpoint of the time interval between the first assessment with PCSA and the previous assessment. Only the first event

(PCSA) will be counted. Patients without any event will be censored at the last assessment performed during the TEAE period.

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 ribonucleic acid" (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 to hepatitis C virus (HCV) 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 (Ab) 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 the 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" status if at least one 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 one 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 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 applied by replacing post-baseline by TEAE period.

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase (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 in AESI section (see Section 2.1.4.1) 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 (ie, 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 2.4.5.1).

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables in sitting position (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, last on-treatment, worst on-treatment value, and follow-up visit) by treatment group. In addition for some parameters of interest; mean changes from baseline with the corresponding SE could be plotted over time (at same time points) in each treatment group.

Vital signs without position filled in will only be used for the PCSA analysis described below.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

If any clinically significant signal is detected and needs further characterization, exploration of time to onset will be performed for selected PCSAs assessed during the TEAE period as described below to account for the differential exposure time in all patients.

Kaplan-Meier curves during TEAE period will be also provided using the midpoint of the time interval between the first assessment with PCSA and the previous assessment. Only the first event

(PCSA) will be counted. Patients without any event will be censored at the last assessment performed during the TEAE period.

2.4.5.5 Analyses of electrocardiogram variables

The count and percentage of patients with at least 1 abnormal ECG will be summarized by treatment group during TEAE period according to the following baseline status categories:

- Normal/missing;
- Abnormal.

2.4.6 Analyses of other endpoints

All analyses for other endpoints will be performed on the Safety population. All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 2 in order to provide an assessment for Week 4 to Week 24 time points.

HbA1c parameter will be summarized by analysis visit using number of available data, mean, SD, median, minimum, and maximum for each treatment group during the treatment period. Summary will also be provided according to the diabetes mellitus status at baseline. The time profile will also be plotted by treatment group with the means and the corresponding SEs. The incidence of PCSA at any time during the TEAE period will also be summarized by treatment group using descriptive statistics, overall and according to diabetes mellitus status at baseline.

Binary endpoints defined in Section 2.1.5 will be described using count and percentage. Kaplan-Meier curves will be provided for the "Time to" variables. Patient without event will be censored at the end of the treatment period. For the analysis of the time to the first of the 2 consecutive LDL-C, patients without post-baseline LDL-C result or with only 1 post-baseline LDL-C result will not be included.

2.4.7 Analyses of anti-alirocumab antibodies variables

The following summaries will be performed on the ADA population, taking into account all samples regardless of timing relative to the injections:

- ADA results (negative or positive) by time point and by treatment group and also according to up-titration status;
- Neutralizing status (negative or positive) by time point for positive ADA and by treatment group and also according to up-titration status;
- ADA titers using descriptive statistics (median, minimum and maximum) for positive ADA by time point and by treatment group and also according to up-titration status;
- Number (%) of patients with pre-existing ADA and number (%) of patients with treatment-emergent ADA positive response by treatment group, overall and according to up-titration status;
- Number (%) of patients with persistent/transient/indeterminate treatment-emergent ADA positive response by treatment group, overall and according to up-titration status;

- Time to onset of treatment-emergent ADA positive response using descriptive statistics by treatment group, overall and according to up-titration status.

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

2.4.8 Analyses of pharmacokinetics variables

Concentrations of total alirocumab in serum (C_{trough}, C_{max} and $C_{Follow\text{-}up}$), free and total PCSK9 concentrations will be summarized on the PK population by treatment group and visit using descriptive statistics. $C_{trough,av}$ will be summarized on the PK population by treatment group using descriptive statistics. These summaries will be also provided by dose in the alirocumab group to explore the impact of up-titration on concentrations (C_{trough}, C_{max} and $C_{Follow\text{-}up}$). Descriptive statistics could be provided by specific sub-groups (eg, gender, BMI, age), as needed.

Time profiles for C_{trough} concentration, total and free PCSK9 will be also provided by treatment group using graphs (mean ± SE or Median, as appropriate).

Additional plots will be prepared, as deemed necessary (eg, 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.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

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.

Medical History

“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.

Date of last dose of IMP

The date of 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.

Lipid variable, laboratory safety variables

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

2.5.2 Data handling conventions for secondary efficacy variables

See Section 2.4.4.2 Analysis of secondary endpoints.

2.5.3 Missing data

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 administration or time of assessment at Week 0 visit is missing

If the time of the first double-blind administration or time assessment at Week 0 visit is missing then the baseline value is defined as the last available value obtained before or on the day of the first double-blind IMP administration.

Handling of computation of treatment duration and compliance if investigational medicinal product end of treatment date is missing

If the last or first injection date (capsule administration respectively) is missing, the injection (capsule respectively) exposure duration and compliance will be left as missing.

Handling of safety and efficacy analysis periods and survival analysis if investigational medicinal product end of treatment date is missing

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

- The last day of the month and year, when applicable or else the 31st of December of the year;
- The date of the end of treatment visit (Week 24 visit for completer, early end of treatment visit for patients who prematurely discontinued the IMP);
- And the date of the last contact;

in order to determine the end of the safety and efficacy analysis periods.

If the last capsule intake date is missing, the last known capsule intake date is used to define the end of the efficacy treatment period.

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 onset dates and times will be imputed so that if the partial AE onset 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. No imputation of AE end dates/times will be performed. 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 investigational medicinal product administration is missing

When the date and time of the first IMP administration (capsule or injection, whichever comes first) is missing, all AEs that occurred on or after the day of randomization should be considered as treatment-emergent adverse events.

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

If the assessment of the relationship to IMP is missing, then the relationship to IMP 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 he will be grouped in the category “normal/missing at baseline.”

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, 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; eg, 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.

2.5.4 Windows for time points

Data analyzed by time point (including efficacy, laboratory safety data, vital signs, and ADA) will be summarized using the analysis windows given in Table 2. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses.

Table 2 - Analysis windows definition

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 (98; study day corresponding to the first injection with IMP from kit allocated at up-titration IVRS contact)
Week 16	113	99 to 126
Week 24	169	155 to 182
Follow-up[a]	Last double-blind IMP injection + 10 weeks	Last double-blind IMP injection +10 weeks ± 4weeks

Study days are calculated from the day of first double-blind IMP (capsule or injection, whichever comes first), the day of first double-blind IMP being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.
a Only for ADA and vital signs.

If multiple valid values of a variable exist within an analysis window, the nearest one 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 the same day, the first value of the day will be selected when time is available, or the scheduled visit will be selected.

2.5.5 Unscheduled visits

For efficacy, safety laboratory data, and vital signs, 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/PCSA.

2.5.6 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 is already controlled. Therefore, the center will not be added as factor in the primary analysis model.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The database is planned to be locked at 4 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

6 REFERENCES

1. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012 Oct;367(14):1355-60.

2. SAS Institute Inc. 2009. SAS/STAT® 9.2 User's Guide. 2nd Ed. Cary, NC: SAS Institute Inc.

3. Mehrotra DV, Li X, Liu J, Lu K. Analysis of longitudinal clinical trials with missing data using multiple imputation in conjunction with robust regression. Biometrics. 2012 Dec;68(4):1250-9.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: Detailed statistical methodology for pattern mixture model

Appendix C List of MedDRA terms for CMQs

Appendix D As treated treatment group definition

Appendix A Potentially clinically significant abnormalities criteria

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 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. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 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. Categories are cumulative. 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 >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. 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.

Parameter	PCSA	Comments
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	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 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
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.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.

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

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

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	≥500 ms	
QTc	Absolute values (ms) >450 ms >480 ms >500 ms Increase from baseline Increase from baseline]30-60] ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.

Appendix B Detailed statistical methodology for pattern mixture model

As a sensitivity analysis of the primary efficacy endpoint (i.e. percent change from baseline to Week 24 in calculated LDL-C), a pattern-mixture model approach will be used, with a different imputation strategy applied for missing calculated LDL-C values during the on-treatment period (ie, within the time period from the first double-blind IMP injection up to the day of the last injection +21 days) and missing calculated LDL-C values after treatment discontinuation (ie, 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, calculated LDL-C 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 calculated LDL-C values returning to baseline. Thus calculated 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
  - Calculated LDL-C not measurable due to technical reasons

  In addition, these missing data are often intermittent, i.e. followed by calculated 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 alirocumab treatment.

Missing calculated LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to Week 24 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 model with treatment group and randomization strata as fixed effects, and the baseline calculated LDL-C value as continuous covariate. The results from the 100 analyses will be combined using Rubin's formulae.

Imputation of missing data during the on-treatment period

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

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

The imputation model will include the treatment arm, baseline calculated LDL-C value and all calculated LDL-C values at pre-specified visits. Since the pattern of missing data is necessarily non-monotone, a Monte-Carlo Markov Chain (MCMC) method is 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;
var ARM LDL_BASE LDL_W4 LDL_W8 LDL_W12 LDL_W16 LDL_W24;
run;
```

As stated above, the input dataset DATAIN will include only calculated LDL-C values collected during the on-treatment period. Any calculated LDL-C values collected during the post-treatment period will be excluded from the input dataset. In practice, the MI procedure generates 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 calculated LDL-C values during the post-treatment period will be imputed assumingLDL-C values would on average return to baseline values.

For each patient, missing post-treatment calculated 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 Y_1 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.

Appendix C List of MedDRA terms for CMQs

Table 3 - CMQ "Type 1 or Type 2 diabetes"

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

Table 4 – CMQ "Impaired Glucose Control"

MedDRA Term Label	Preferred Term Code
Glucose tolerance impaired	10018429
Insulin resistance	10022489
Insulin resistance syndrome	10022490
Impaired fasting glucose	10056997

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

MedDRA Term Label	Preferred Term Code
Benign neoplasm of optic nerve	10057424
Optic atrophy	10030910
Optic discs blurred	10030923
Optic nerve disorder	10061322
Optic nerve injury	10030938
Optic nerve neoplasm	10053645
Optic nerve operation	10053272
Optic neuropathy	10061323
Papillitis	10033708
Pseudopapilloedema	10037141

MedDRA Term Label	Preferred Term Code
Subacute myelo-opticoneuropathy	10058009
Toxic optic neuropathy	10044245
Visual evoked potentials abnormal	10047549
Amaurosis fugax	10001903
Blindness	10005169
Blindness unilateral	10005186
Colour blindness acquired	10010051
Colour vision tests abnormal	10010056
Cranial nerve injury	10061094
Delayed myelination	10076456
Fundoscopy abnormal	10017520
Hemianopia	10019452
Hemianopia heteronymous	10019455
Hemianopia homonymous	10019456
Loss of visual contrast sensitivity	10064133
Neuro-ophthalmological test abnormal	10029256
Night blindness	10029404
Ophthalmological examination abnormal	10056836
Optic pathway injury	10030949
Optical coherence tomography abnormal	10073561
Quadranopia	10075427
Visual acuity reduced	10047531
Visual acuity reduced transiently	10047532
Visual acuity tests abnormal	10047534
Visual field defect	10047555
Visual field tests abnormal	10047567
Visual impairment	10047571
Visual pathway disorder	10061411

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

MedDRA level	MedDRA Code	MedDRA Term Label
PTCD	10001949	Amnesia
PTCD	10061423	Amnestic disorder
PTCD	10002711	Anterograde Amnesia
PTCD	10066842	Behavioural and Psychiatric Symptoms of Dementia

MedDRA level	MedDRA Code	MedDRA Term Label
PTCD	10008398	Change in sustained attention
LLTCD	10009843	Cognitive Deterioration
PTCD	10057668	Cognitive Disorder
LLTCD	10010300	Confusion
LLTCD	10048321	Confusion Aggravated
PTCD	10010305	Confusional State
PTCD	10012218	Delirium
PTCD	10012267	Dementia
PTCD	10012271	Dementia Alzheimer's type
LLTCD	10012290	Dementia Nos
LLTCD	10012291	Dementia Nos Aggravated
LLTCD	10012292	Dementia of the Alzheimer's type NOS
PTCD	10067889	Dementia with Lewy Bodies
PTCD	10013395	Disorientation
PTCD	10013496	Disturbance in attention
PTCD	10070246	Executive dysfunction
PTCD	10068968	Frontotemporal Dementia
LLTCD	10058669	Global Amnesia
PTCD	10021402	Illogical Thinking
PTCD	10071176	Impaired reasoning
PTCD	10021630	Incoherent
PTCD	10023236	Judgement impaired
PTCD	10027175	Memory Impairment
PTCD	10027374	Mental Impairment
LLTCD	10027376	Mental Impairment Nos
LLTCD	10048345	Mental State Abnormal Aggravated
PTCD	10048294	Mental Status Changes
PTCD	10065424	Mini Mental Status Examination Abnormal
PTCD	10036631	Presenile Dementia
PTCD	10038965	Retrograde Amnesia
PTCD	10039966	Senile Dementia
LLTCD	10039967	Senile Dementia Nos
LLTCD	10040602	Short-term Memory Loss
PTCD	10043431	Thinking Abnormal
LLTCD	10043438	Thinking Slowed
PTCD	10044380	Transient Global Amnesia
PTCD	10057678	Vascular Dementia

Appendix D As treated treatment group definition

Randomized Treatment group	Kit Type	Allocated kit decode	Actual kit	As treated group
ALIROCUMAB	Injection Capsule	Alirocumab Placebo	Placebo injections > alirocumab injections Placebo, or more placebo capsules taken than ezetimibe capsules	ALIROCUMAB
ALIROCUMAB	Injection Capsule	Alirocumab Placebo	alirocumab, or alirocumab 3 injections > Placebo injections More ezetimibe capsules taken than Placebo capsules	ALIROCUMAB
ALIROCUMAB	Injection Capsule	Alirocumab Placebo	Placebo injections > alirocumab injections More ezetimibe capsules taken than Placebo capsules	EZETIMIBE
ALIROCUMAB	Injection Capsule	Alirocumab Placebo	alirocumab, or alirocumab injections > Placebo injections Placebo, or more placebo capsules taken than ezetimibe capsules	ALIROCUMAB
EZETIMIBE	Injection Capsule	Placebo EZETIMIBE	alirocumab injections > Placebo injections ezetimibe, or more ezetimibe capsules taken than Placebo capsules	ALIROCUMAB
EZETIMIBE	Injection Capsule	Placebo EZETIMIBE	Placebo, or placebo injections > alirocumab injections More Placebo capsules taken than ezetimibe capsules	EZETIMIBE
EZETIMIBE	Injection Capsule	Placebo EZETIMIBE	alirocumab injections > Placebo injections More Placebo capsules taken than ezetimibe capsules	ALIROCUMAB
EZETIMIBE	Injection Capsule	Placebo EZETIMIBE	Placebo, or placebo injections > alirocumab injections ezetimibe, more ezetimibe capsules taken than Placebo capsules	EZETIMIBE

EFC13889 16.1.9 Statistical analysis plan

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	02-Nov-2017 08:37 GMT+0100
[redacted]	Clinical Approval	01-Dec-2017 15:04 GMT+0100