STATISTICAL ANALYSIS PLAN

Open-Label Extension Study of EFC12492, R727-CL-1112, EFC12732, & LTS11717 Studies to Assess the Long-Term Safety and Efficacy of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia

Alirocumab (SAR236553) - LTS13463

ODYSSEY OLE

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibody
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
Apo:	apolipoprotein
ATC:	anatomical therapeutic chemical
CHD:	coronary heart disease
CV:	cardiovascular
DBP:	diastolic blood pressure
e-CRF:	electronic case report form
eDISH:	evaluation of drug-induced serious hepatotoxicity
EOS:	end of study
EOT:	end of treatment
HDL-C:	high density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
ie:	id est = that is
IMP:	investigational medicinal product
LDL-C:	low-density lipoprotein cholesterol
LLOQ:	lower limit of quantification
LLT:	lowest level term
Lp (a):	lipoprotein a
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified intent-to-treat
OLE:	open label extension
PAD:	peripheral arterial disease
PT:	preferred term
Q1:	first quartile
Q2W:	every 2 weeks
Q3:	third quartile
SAE:	serious adverse event
SBP:	systolic blood pressure
SMQ:	standardized MedDRA query
SOC:	system organ class
TEAE:	treatment emergent adverse event
TG:	triglycerides
Total-C:	total cholesterol
ULOQ:	upper limit of quantification

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3, multicenter, multinational, open-label extension (OLE), uncontrolled study that includes patients diagnosed with heterozygous familial hypercholesterolemia (heFH) who have completed one of the four randomized, double-blind, 18-month parent studies: EFC12492 (ODYSSEY FH I), R727-CL-1112 (ODYSSEY FH II), EFC12732 (ODYSSEY High-FH) or LTS11717 (ODYSSEY long term).

The first study visit (Visit 1 on Day 1) of the OLE study takes place at the end of treatment (EOT) visit for patients enrolled in EFC12492, R727-CL-1112 and EFC12732 studies, or at the end of study (EOS) visit for those enrolled in the LTS11717 study.

All patients receive alirocumab 75 mg every 2 weeks (Q2W) at entry into the OLE, with the exception of patients from EFC12732 who receive 150 mg Q2W, as in the parent study. From Day 1 (Visit 1) to Week 8 (first unblinded LDL-C value), neither the treatment received at the end of double-blind treatment period of the parent study, nor the lipid parameters level, will be known by the investigator or by the patient, in order to prevent any potential blinding breaking of the parent study. From Week 12 (Visit 4), the investigator may manage adjustment of alirocumab doses (up-titration from 75 mg to 150 mg Q2W, down-titration from 150 mg to 75 mg Q2W or maintenance of dose), based on his/her own judgment and LDL-C values. Patients are to be treated for up to 168 weeks ie approximately 3.5 years with alirocumab, for the first patients enrolled, or until the product becomes commercially available for the patient in the country, whatever comes first. All patients are to be followed by phone 10 weeks after last investigational medicinal product (IMP). Patients with a Serious Adverse Events (SAEs) and or an Adverse Event of Special Interest (AESI) should be followed until resolution, stabilization, or death.

Up to approximately 1,200 heFH patients were estimated to be enrolled from approximately 200 sites worldwide.

1.2 OBJECTIVES

1.2.1 Primary objective

The primary objective of this study is to assess the long-term safety of alirocumab when added to currently available lipid-modifying drug therapy, in patients diagnosed with heterozygous Familial Hypercholesterolemia who have completed one of the four parent studies.

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To evaluate the long-term efficacy of alirocumab on lipid parameters
- To evaluate the long-term immunogenicity of alirocumab

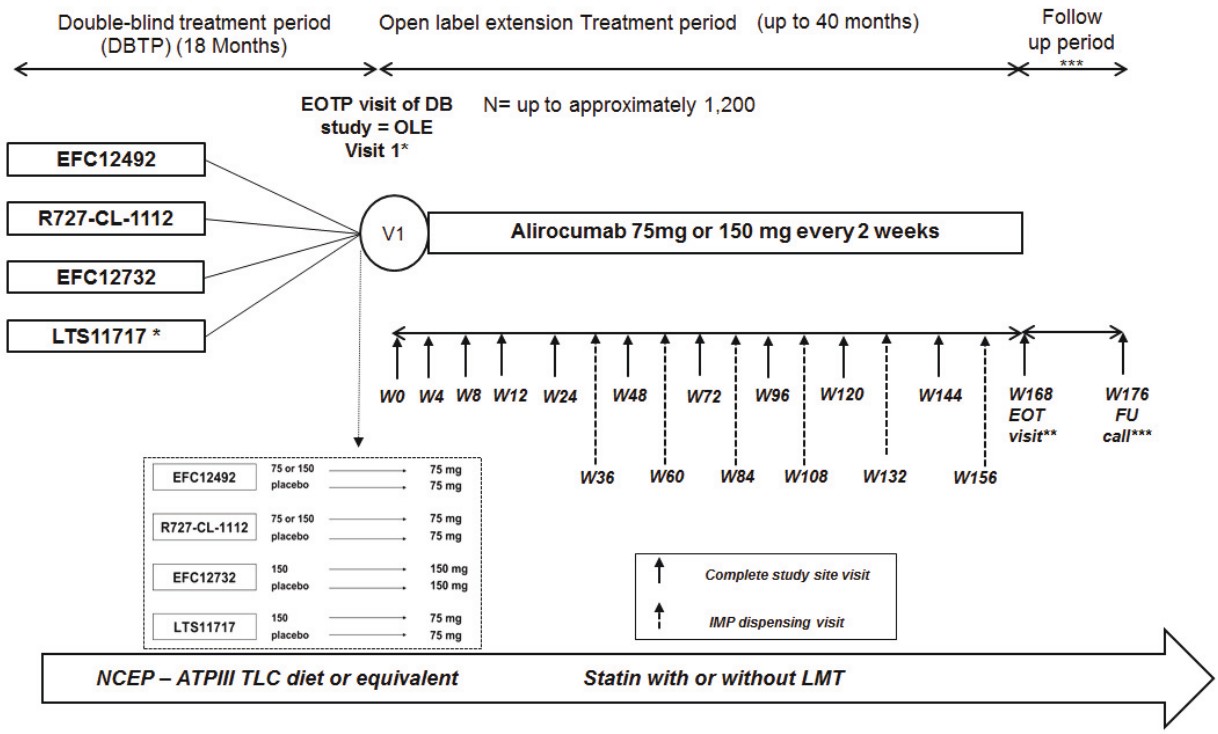
1.3 DETERMINATION OF SAMPLE SIZE

As this study is an open-label extension planning to include patients from previous studies, no calculation for sample size was performed. It is expected to enroll up to 1,200 heFH patients based on the number of patients already enrolled in the parent studies.

1.4 STUDY PLAN

The following figure presents the graphical study design:

Figure 1 - Graphical study design



* The end of treatment period visit of the Double-Blind parent study corresponds at the V1visit (Day 1) of the OLE study, except for patient having participated in the LTS11717. These latter patients will have the opportunity to enter in the OLE study, after they have completed the parent study, including the 8-week follow-up period. For these patients, the visit V1 (Day 1) of the OLE study can occur at the time of the end of study visit, after the 8-week follow-up period.

** EOT visit = to be performed 2 weeks after the last injection for the patients who complete the study or within 5 days of treatment discontinuation for the patients who early discontinue.

*** FU call= to be performed 10 weeks after the last injection for the patients who complete the study and for the patients who early discontinue.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

There were 2 global protocol amendments to the Clinical Study Protocol, introduced after the first patient was enrolled. One major change to the protocol statistical section was done by the global protocol amendment 2: the possibility of an interim analysis has been added in order either to be able to answer potential Health Authority requests, or for scientific purposes to provide analyses of available long-term safety and efficacy data before the planned end of the study.

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

Unless otherwise specified, the following demographic and baseline characteristics will be summarized for patients who entered the OLE study, at the time of entry to the parent study (i.e. parent baseline) and at the time of entry to the current study (i.e. OLE baseline) .

The parent baseline value is defined as the last available value obtained up to the date and time of the first double-blind IMP administration in the parent study.

The OLE baseline value is defined as the last available value obtained up to the date and time of the first open-label IMP administration in the OLE study, unless otherwise specified.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are gender (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, Other), age in years (quantitative and qualitative variable: <45, ≥45 to <65, ≥65 to <75, and ≥75 years; and <65, and ≥65 years), ethnicity (Hispanic or Latino, Not-Hispanic or Latino).

Medical history

All medical history and medical history of specific interest at the time of entry into the parent study as well as at the time of entry in the OLE study will be presented.

Medical history at the time of the entry in the OLE will be retrieved by combining medical history from parent study, adverse events observed during the parent study (from screening to the end of the study) and pre-treatment adverse events observed during the OLE study (up to first OLE injection).

Medical history of specific interest from the parent study includes:

- Coronary heart disease (CHD)
- CHD risk equivalents
- Cardiovascular (CV) risk factors other than hypercholesterolemia (hypertension, type 2 diabetes, type 1 diabetes, family history of premature CHD). Smoking status will be summarized separately.

- Family history of type 2 diabetes
- Patient's allergies (described using all pre-printed terms collected in the medical allergic history [e-CRF] page).

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:

CHD (regardless if it is ongoing or not)

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

CHD risk equivalents (regardless if it is ongoing or not)

Peripheral arterial disease (PAD) (as defined in Section 2.5.1)

- Ischemic stroke
- Moderate chronic kidney disease (as defined in protocol)
- Known history of diabetes mellitus (type 1 or 2) AND 2 or more additional risk factors among:
  - History of ankle-brachial index ≤ 0.90
  - History of hypertension
  - History of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening (Week -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

CV risk categories are defined for the study as high risk and very high risk as follows:

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

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 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

Medical history of specific interest at the time of entry in the OLE will include key medical history items from CHD and CHD Risk Equivalent groups as well as diabetes mellitus history and allergic history. Medical history from parent studies and adverse events from parent studies will be combined using pre-printed terms and/or grouping of Medical Dictionary for Regulatory Activities (MedDRA) terms.

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

Disease characteristics

Specific disease characteristics include:

- Time from diagnosis of heFH (years) and confirmation of diagnosis (genotyping (Yes, No), WHO/Simon Broome (certain / definite vs. probable/possible) at entry into the OLE study
- Lipid modifying therapy history, as reported in the "History of Hyperlipoproteinemia" e-CRF page of the parent study
  - 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 at screening atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg or simvastatin 80 mg daily 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 at randomization in the parent study and at enrolment in the OLE study, as reported in the dedicated prior & concomitant medications e-CRF pages of the parent and OLE studies
  - Number of patients taking atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg daily
  - Atorvastatin daily dose in mg (10, 20, 40, 80, Other)
  - Rosuvastatin daily dose in mg (5, 10, 20, 40, Other)

- Simvastatin daily dose in mg (10, 20, 40, 80, Other)
- Any LMT other than statins
  - Any LMT other than nutraceuticals (by chemical class and drug name)
  - Nutraceuticals (Omega 3 fatty acids (<1000mg/day), Phytosterols, Psyllium/plantago, Policosanol, Other nutraceuticals)

- LMT adjustment at entry in OLE study
  - Number of patients with LMT taken during the parent study and stopped at entry in OLE and reasons why the LMT was stopped, as reported in dedicated e-CRF pages. LMT interruption and LMT discontinuation will be described separately.
  - Number of patients with the LMT type changed at entry in OLE, compared to the parent study and reasons for the change, as reported in dedicated e-CRF pages
  - Number of patients with LMT dose changed at entry in OLE, compared to the parent study and reasons for the change, as reported in dedicated e-CRF pages; increase of dose and decrease of dose will be described separately.

Other baseline characteristics

Other baseline characteristics include body mass index (BMI) in kg/m² (quantitative and qualitative variable: <30, ≥30), weight (quantitative and qualitative variable: <50, ≥50 to >70, ≥70 to <100 and ≥100) (at parent baseline and OLE baseline), smoking status and alcohol habits at parent baseline.

Glycated haemoglobin A1c (HbA1c) (quantitative and qualitative variable: <5.7%, ≥5.7% to <6.5%, ≥6.5%), high sensitivity C-reactive protein (hs-CRP) will be also summarized at parent baseline.

Efficacy lipid parameters (quantitative variables for all efficacy parameters and the following qualitative variables) will be also summarized at parent and OLE baselines (see definitions in Section 2.1.1):

- calculated LDL-C: <70, ≥70 to <100, ≥100 to <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL, i.e <1.81, ≥1.81 to <2.59, ≥2.59 to <3.37, ≥3.37 to <4.14, ≥4.14 to <4.91, ≥4.91 mmol/L,
- HDL-C: <40 , ≥40 mg/dL, ie <1.04 , ≥1.04 mmol/L
- Fasting TGs: <150, ≥150 to <200, ≥200 mg/dL, category ≥150 mg/dL (mixed dyslipidaemia) will be also displayed, i.e. <1.7 , ≥1.7 to <2.3, ≥2.3 mmol/L
- Lp(a): <30, ≥30 to <50, ≥50 mg/dL, category ≥30 mg/dL will be also displayed, i.e. <0.3, ≥0.3 to <0.5, ≥0.5 g/L

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

2.1.2 Prior or concomitant medications

All medications taken at the time of entry into the OLE study (including those taken during the parent study and still ongoing at the time of entry in the OLE study) and until the end of the OLE study, including lipid modifying therapies and CV medications are to be reported in one of the following specific case report form pages:

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

- Prior medications at entry into the parent study are those the patient used within 3 months prior to screening visit and prior to first double-blind IMP administration. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Prior medications at entry into the OLE are those the patient used within 3 months prior to first open-label IMP administration. They can be discontinued before the first IMP administration in OLE or can be ongoing during OLE.
- Concomitant medications are any treatments received by the patient concomitantly with the open-label IMP, from first open-label IMP to the last open-label IMP injection +70 days. 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 taken by the patient in the period starting from 71 days after the last open-label 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], [Total-C], calculated LDL-C, [HDL-C], [TGs], non-HDL-C, [Apo B], Apo A-1, ratio Apo B/Apo A-1, [Lp (a)]). 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 Total-C. If TG values exceed 400 mg/dL (4.52 mmol/L), the LDL-C is measured by the Central Laboratory (via beta quantification method) rather than calculated. All measured LDL-C values provided by the Central Laboratory will not be used for the analysis of calculated LDL-C endpoints.

Unless otherwise specified, all lipid values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the efficacy endpoints. All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 1 in order to provide an assessment for each time point when the lipid values were to be collected as per protocol. For TGs, only fasting measurements will be used. Measurements with missing fasting status will be excluded from the analyses.

For all time points post open-label baseline, the value used for the analyses at a given time point is the value obtained within the corresponding analysis window.

2.1.3.1 Primary efficacy endpoints

No primary efficacy endpoints are defined since the primary objective is dedicated to safety.

2.1.3.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- The percent change in calculated LDL-C from baseline of the parent study over time in the OLE study, in the mITT population, using all LDL-C values during the efficacy treatment period defined in Section 2.3.1 (on-treatment estimand).
- The absolute change in calculated LDL-C (mg/dL and mmol/L) from baseline of the parent study over time in the OLE study (on-treatment estimand).
- The proportion of patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) over time in the OLE study (on-treatment estimand).
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L over time in the OLE study (on-treatment estimand).
- The proportion of patients with calculated LDL-C <70 mg/dL (1.81mmol/L) and / or ≥50% reduction in calculated LDL-C from baseline of the parent study (if calculated LDL-C≥70 mg/dL [1.81mmol/L]) over time in the OLE study (on-treatment estimand).
- The percent change in non-HDL-C, total-C, HDL-C, fasting TGs, Lp(a), Apo B, and Apo A-1 from baseline of the parent study over time in the OLE study (on-treatment estimand).
- The absolute change in Apo B/Apo A-1 from baseline of the parent study over time in the OLE study (on-treatment estimand).

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data 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 date up to the time of first dose of alirocumab in the OLE study. The adverse events occurring during this period were to be reported and recorded in the parent study database. However, after the lock of parent study database, some exceptional pre-treatment adverse events have been recorded in the OLE study database with a start date in the parent study period.
- The treatment-emergent adverse event (TEAE) period: defined as the time from the first dose of alirocumab in the OLE study up to the day of last dose of alirocumab received in the OLE study + 70 days (10 weeks), as residual effect of alirocumab is expected until 10 weeks after the stop of alirocumab.

  The TEAE period will include:

  - The TREATMENT period defined as the time from the first dose of alirocumab in the OLE study up to the day of last dose of alirocumab received in the OLE study + 21 days.
- The POST-TREATMENT period: defined as the time starting the day after the end of TEAE period up to the end of study

The on-study observation period is defined as the time from first dose of alirocumab in the OLE study until the last protocol planned visit of the patient in the OLE study. The last protocol planned visit is defined as the safety follow-up call if done, else 10 weeks after last injection of alirocumab.

2.1.4.1 Adverse events variables

Adverse events (including SAEs) and AESIs 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

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events are AEs that developed or worsened or became serious during the TEAE period.

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

Adverse events of special interest

AESIs are AEs (serious or non-serious) that need to be monitored, documented, and managed in a pre-specified manner described in the protocol. In this study, AESIs are the following (their complete descriptions are provided in the protocol):

- Local injection site reactions, selected using e-CRF specific tick box on the AE page;
- Allergic events:
  - General allergic events will be tabulated. Events will be selected using standardized MedDRA query (SMQ) "hypersensitivity" (broad and narrow) excluding the following preferred terms linked to local injection site reactions ("infusion site dermatitis", "infusion site hypersensitivity", "infusion site rash", "infusion site urticaria", "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");
- ALT≥3 ULN (if baseline ALT < ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN), selected using laboratory data; The baseline that will be considered will be the OLE baseline of the current study
- 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 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";
- Neurocognitive events, selected using a company MedDRA query (CMQ), based on the following 5 HLGTs: "deliria (including confusion)", "cognitive and attention disorders and disturbances", "dementia and amnestic conditions", "disturbances in thinking and perception", and "mental impairment disorders";
- Neurocognitive events, selected using FDA proposed grouping including the PTs "Amnesia", "Amnestic disorder", "Anterograde Amnesia", "Behavioural and Psychiatric Symptoms of Dementia", "Change in sustained attention", "Cognitive Disorder", "Confusional State", "Delirium", "Dementia", "Dementia Alzheimer's type", "Dementia

with Lewy Bodies", "Disorientation", "Disturbance in attention", "Executive dysfunction", "Frontotemporal Dementia", "Illogical Thinking", "Impaired reasoning", "Incoherent", "Judgement impaired", "Memory Impairment", "Mental Impairment", "Mental Status Changes", "Mini Mental Status Examination Abnormal", "Presenile Dementia", "Retrograde Amnesia", "Senile Dementia", "Thinking Abnormal", "Transient Global Amnesia ", "Vascular Dementia" and the LLTs "Mental State Abnormal Aggravated", "Thinking Slowed";

- Ophthalmologic events selected using SMQs "optic nerve disorders" (broad and narrow), "retinal disorders" (narrow), and "corneal disorders" (narrow);
- Overdose with IMP (symptomatic or asymptomatic), selected using appropriate MedDRA codes and the tick box "Overdose with IMP" in the AE complementary e-CRF form;
- Pregnancy of female patient/subject (including male subject's partner) selected using appropriate MedDRA codes.

Analyses of allergic, neurologic and ophthalmologic events will also be provided using the tick box on the e-CRF AE page as a second approach.

In addition the following grouping of events will be provided:

- Hepatic disorder events using SMQ "Hepatic disorder";
- Diabetes mellitus or diabetic complications using HLGT "Diabetes Complications" and HLT "Diabetes Mellitus", HLT "Carbohydrate tolerance analyses (incl diabetes)" excluding PT "Blood glucose decreased" and including PT "hyperglycemia".

2.1.4.2 Deaths

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

- 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 last planned protocol visit

2.1.4.3 Laboratory safety variables

Clinical laboratory data consist of blood analysis, including hematology and clinical chemistry. Clinical laboratory values will be analyzed primarily into international units and will also be analyzed into conventional (US) units when applicable.

Unless otherwise specified below, blood samples for clinical laboratories were to be collected at Visit 1 (Week 0), Visit 3 (Week 8), Visit 5 (Week 24), Visit 7 (Week 48), Visit 9 (Week 72), Visit 11 (Week 96), Visit 13 (Week 120), Visit 15 (Week 144) and Visit 17 (Week 168)/or early termination. The laboratory parameters (excluding those considered as efficacy parameters) will be classified as follows:

- **Hematology :**
  - Red blood cells and platelets: hemoglobin, hematocrit, erythrocytes count, platelets count, reticulocyte count, red blood cell distribution width (RDW).
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- **Clinical chemistry :**
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase.
  - Electrolytes: sodium, potassium, chloride, calcium, phosphorus, bicarbonate.
  - Renal function: creatinine, eGFR, blood urea nitrogen, uric acid.
  - Liver function (also measured at Week 4, and Week 12, except GGT and LDH): alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin, and in case of total bilirubin values above the normal range, must include direct and indirect bilirubin, lactate dehydrogenase (LDH).

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital Signs parameters include Weight, Heart Rate (HR), Systolic and Diastolic Blood Pressure ([SBP] and [DBP]) in sitting position.

2.1.4.5 Electrocardiogram variables

Not applicable

2.1.5 Other variables

Other assessment variables listed below are defined using same definitions and rules as for calculated LDL-C, when applicable (see Section 2.1.3).

- The proportion of patients with two consecutive (spaced out by at least 21 days) calculated LDL-C <25 mg/dL (<0.65 mmol/L) (respectively two consecutive calculated LDL-C <15 mg/dL,i.e. < 0.39 mmol/L) during the OLE treatment period.
- For the patients with two consecutive results as described above, the time from the first study treatment administration in OLE study 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 (ADA) are assessed at Week 0 (before the IMP injection in OLE study), Week 24, Week 48, Week 72, Week 96, Week 120, Week 144 and Week 168)/or early termination .

ADA measurements will be assigned to similar analysis windows as defined for efficacy parameters (Table 1).

- 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 of the parent study with less than 4-fold increase in titer during the OLE period
- Treatment-emergent ADA positive response during the OLE period, defined as:
  - Patients with no positive ADA response at baseline of the parent study but with a positive response ADA response during the OLE period; OR
  - Patients with positive ADA response at baseline of the parent study and at least 4-fold increase in ADA titer during the OLE period.

  Treatment-emergent ADA positive responses during the OLE period will be described according to the ADA status during the double-blind period (Pre-existing, Negative and Treatment-emergent ADA status).

For treatment emergent positive ADA during the OLE period, 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 samples post first OLE injection 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 in OLE period
- A transient positive response is defined as any treatment-emergent positive ADA response that is neither considered persistent nor indeterminate

2.1.7 Pharmacokinetic variables

Not applicable.

2.1.8 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.9 Quality-of-life endpoints

EQ-5D is a standardized and generic instrument for measuring the health status and health related quality of life for clinical and economic assessment (1). EQ-5D instrument includes 5 items corresponding to the following dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression (Appendix B). Each item can take one of three responses: (1.) “no problem”, (2.) “some problems”, and (3.) “severe problems”.

Response from individual items will be converted into a single EQ-5D utility score ranging between -0.594 (representing severe problems) and 1 (representing no problem) by means of a standard regression model ((1), Appendix C). If response to one or more dimension is missing, the utility score will be missing.

Quality of life endpoints include response to each EQ-5D items over time and change in utility score over time during the OLE study from baseline of the parent study.

2.1.10 Health economic endpoints

Cost and detailed health resource utilization data will not be collected in this study. As a result, health economic endpoints, other than quality of life, will not be assessed.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations. Patient study status and the patient analysis populations will be presented overall as well as separately according to treatment (placebo versus alirocumab (regardless of dose)) received in the parent study.

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

Enrolled patients consist of all screened patients with a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether treatment kit was used or not.

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
- Enrolled patients:
  - Enrolled but not treated patients and reason for not being treated;

- Enrolled and treated patients

- Patients who did not complete the open label study treatment period as per protocol
- Patients who discontinued the open label study treatment by main reason for permanent treatment discontinuation

For the last two categories of patients percentages will be calculated using the number of treated patients in the OLE as denominator.

The incidence of premature treatment discontinuation (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically during OLE study, using Kaplan-Meier method.

The proportion of patients with insufficient post-treatment follow-up among those who prematurely discontinued or completed the treatment will be described.

A patient having permanently stopped or completed the IMP is considered with insufficient post-treatment follow-up or without post-treatment follow-up at the end of the study in the following cases:

- If the patient has no post-treatment OLE follow-up call/visit, unless patient died before.
- If the post-treatment OLE follow-up call/visit is less than 9 weeks after the last IMP injection in OLE.

All major deviations potentially impacting efficacy analyses, enrollment and drug-dispensing irregularities, and other important deviations will be summarized in tables giving numbers and percentages of deviations. These deviations are listed in the data review and surveillance plan.

Additionally, the following populations will be summarized.

- Enrolled population
- Efficacy population: mITT population
- Safety population
- Anti-alirocumab antibody population
- Quality-of-life population

Definitions of the study populations are provided in Section 2.3.

2.2.1 Enrollment and drug dispensing irregularities

Enrollment and drug-dispensing irregularities occur whenever:

1. An enrollment is not in accordance with the protocol-defined enrollment method, such as a patient is enrolled twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined allocation, such as a) a patient at any time in the study is dispensed a different treatment kit than as allocated or b) a non-enrolled patient is treated with IMP reserved for enrolled patients.

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

All enrollment and drug-dispensing irregularities will be documented in the clinical study report. The irregularities will be categorized and summarized among enrolled patients (number and percentages).

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

Enrollment and drug allocation irregularities
Kit dispensation without IVRS transaction
Erroneous kit dispensation
Kit not available
Enrolled by error
Patient enrolled twice

2.3 ANALYSIS POPULATIONS

Enrolled population: includes all screened patients with a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether treatment kit was used or not

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

2.3.1 Efficacy population

The efficacy population considered for efficacy analyses will be the mITT population.

The mITT population is defined as all patients who took at least one dose or part of a dose of the open-label IMP injection and with both of the following conditions met:

- Availability of a baseline (from parent study) calculated LDL-C
- Availability of at least one calculated LDL-C during the efficacy treatment period in one of the analysis windows from Week 8 onwards.

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

2.3.2 Safety population

The Safety population considered for safety analyses will be the population who actually received at least one dose or part of a dose of the open-label IMP injection.

Enrolled patients for whom it is unclear whether they took the study medication will be included in the safety population.

2.3.2.1 Anti-alirocumab antibody population

The anti-alirocumab antibody analysis will be performed on all treated patients (safety population) with an available ADA sample at baseline from parent study and at least one available ADA sample post first open-label IMP injection.

2.3.3 Quality-of-life population

The analyses of quality of life will be performed on all enrolled and treated patients with a baseline (from parent study) and at least one matching post-baseline evaluation for any of the 5 dimensions.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 including all medical history and all medical history of specific interest will be summarized in the safety population (overall as well as according to treatment received in the parent study (placebo versus alirocumab (regardless of dose)), using descriptive statistics, at baseline of the parent study and at baseline of the current study.

Continuous data will be summarized using the number of available data, mean, SD, median, minimum and maximum. First quartile (Q1) and third quartile (Q3) will be also provided for baseline lipid parameters. Categorical and ordinal data will be summarized using the number and percentage of patients.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the safety population (overall and according to the treatment received in the parent study (placebo or alirocumab (regardless of dose)).

Medications will be summarized according to the WHO-D dictionary, considering the first digit of the anatomical therapeutic chemical (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 in several categories for the same medication.

The table for prior and concomitant medications will be sorted by decreasing frequency of ATC followed by therapeutic class based on the overall incidence. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used.

Prior medications at entry into OLE will be summarized according to the WHO-DD.

In addition, concomitant lipid modifying therapies and CV medications will be summarized by pre-specified categories/therapeutic class and standardized medication name.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized for the safety population, overall as well as according to treatment received in the parent study (placebo versus alirocumab (regardless of dose)).

2.4.3.1 Extent of investigational medicinal product exposure

The study treatment exposure (injection) will be assessed using descriptive statistics for:

Duration of OLE IMP injection exposure in weeks defined as: (date of last OLE IMP injection +14 – date of first OLE IMP injection)/7, regardless of intermittent discontinuations (see Section 2.5 for calculation in case of missing or incomplete data). Non-integer values will be rounded to one decimal place;

- The total number of OLE IMP injections by patient.

All quantitative parameters above will be summarized using number, mean, SD, median, minimum, and maximum. In addition, the duration of treatment exposure will be summarized displaying the percentage of patients according to the following categories: ≥1 day and <4, ≥4 and <8, ≥8 and <12, ≥12 and <24, ≥24 and <36, ≥36 and < 52, ≥52 and <78, ≥78 and <104, ≥104 and <130, ≥130 and <156, ≥156 weeks.

In the event the manufacturer faces any performance or supply issues of the auto-injector, administrations would be done using prefilled syringes instead of autoinjectors until the end of the study. In case this back-up plan is used, the exposure to initial device and back-up device will be summarized. Analyses for key efficacy and safety endpoints will be presented by device to assess the impact of the device on study results: patients will be included in the device they received longer.

Up-Titration/ Down-Titration/ maintenance of dose

The number (%) of patients with an up-titration to 150 mg/down-titration to 75 mg/maintenance of 75 mg/maintenance of 150 mg of alirocumab will be described overall and by visit, on the

Safety population. The number (%) of up-titration to 150 mg will also be summarized excluding patients coming from High FH study since these patients start the OLE study with this dose.

Reasons for up- or down-titration and LDL-C used to up/down-titrate or maintain 75/150 mg dose will be summarized, overall and by visit in order to get data about real life behavior of the investigator. LDL-C will be summarized quantitatively and with the following categories: <15, ≥15 and <25, ≥25 and <50, ≥50 and <70, ≥70 and <100, ≥ 100 mg/dL.

The LDL-C value and titration/maintenance of the current dose will be associated as follows:

- For each LDL-C value (calculated or measured, from central or local Lab), IVRS calls from x days after the sample date of this LDL-C to the sample date of the next LDL-C value (included) will be considered. In case several IVRS calls (for titration and for maintenance) are made during this time period, the selected LDL-C value will be associated to the titration call.
- x will depend on the minimum time needed for the availability of the LDL-C results to Investigators and will therefore be different for local lab (i.e. 1 day) , calculated LDL-C from central lab (i.e. 3 days) and measured LDL-C from central lab (i.e. 7 days).
- In case no IVRS call is retrieved during the defined time period, the LDL-C value will be associated to maintenance of dose.

This analysis may also be done according to key factors (e.g. history of CV events at entry into the OLE study (Yes/No), geographical region) if the size of the subgroups permits.

In order to analyze the efficiency of the titration regimen to prevent low LDL-C compared to 150 mg administered throughout, the following analysis will be done in the subgroup of patients of the Safety population coming from LTS11717 study: number (%) of patients with 2 consecutive LDL-C <25 mg/dL during the OLE period (on titration regimen) will be compared to the number (%) of patients with 2 consecutive LDL-C <25 mg/dL during the double-blind period (on 150 mg). The same analysis will be done with 15 mg/dL threshold.

2.4.3.2 Compliance

Compliance will be assessed using the following parameters:

- The mean injection frequency of OLE IMP will be defined for each patient 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):
  - the %days with under-planned dosing 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.

- the %days with above-planned dosing will be defined for each patient as the number of days with more than one 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 dosing.

These parameters will be summarized descriptively (N, Mean, SD, Median, Minimum and Maximum).

The percentage of patients whose overall compliance for injections is <80% will be also summarized as well as numbers and percentages of patients with 0%, >0% and ≤5%, >5% and ≤10%, >10% and ≤20%, and >20% days with above-planned dosing and numbers and percentages of patients with 0%, >0% and ≤5%, >5% and ≤10%, >10% and ≤20%, and >20% days with under-planned dosing.

The overall compliance (quantitatively and by category (<80% vs ≥80%)) will be also summarized by the following time periods: ≥0 and <26, ≥26 and <52, ≥52 and <78, ≥78 and <104, ≥104 and <130, ≥130 and <156, and ≥156 weeks.

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

2.4.4 Analyses of efficacy endpoints

Efficacy analyses will be presented overall as well as separately according to treatment received in the parent study (placebo versus alirocumab (regardless of dose)) unless otherwise specified.

2.4.4.1 Analysis of primary efficacy endpoint(s)

Not Applicable

2.4.4.2 Analyses of secondary efficacy endpoints

No formal statistical comparisons will be performed for efficacy variables.

Central laboratory values (in conventional (US) and international units), percent changes from baseline of the parent study, and/or when appropriate absolute change from baseline of the parent study (in conventional (US) and international units), for calculated LDL-C, Total-C, HDL-C, fasting TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1(only absolute changes) and Lp (a) at time points when these lipid parameters are to be collected as per protocol will be summarized over time in the mITT population as described below.

Quantitative descriptive summaries (number of available data, mean, SD, median, minimum and maximum) by planned time point will be presented for all lipids using observed (i.e. non-missing) data. Missing data will not be imputed. In addition, standard error (SE) and the 95% confidence interval (CI) for the mean will be provided for lipids other than TGs and Lp(a) and Q1 and Q3 will be provided for TGs and Lp(a).

The time profile in percent change from baseline of each parameter (except ratio ApoB/Apo A-1 where absolute change will be used) will be plotted according to treatment received in the parent study by using mean and SE except for TGs and Lp(a). For these 2 parameters, median, Q1 and Q3 will be plotted.

In addition, binary variables for LDL-C will be also described by planned time point by presenting number and percentage of patients reaching the target.

In order to analyze the effect of forced down-titration from 150 mg Q2W at the end of the parent study to 75 mg Q2W at the entry in OLE, analyses of percent change in calculated LDL-C, ApoB, non-HDL-C, TGs and Lp(a) from Week 78 of parent study (alirocumab 150 mg) to Week 8 of OLE study (alirocumab 75 mg) will be quantitatively summarized on the 2 following categories of patients:

- patients of the mITT population who were up-titrated in EFC12492 (FH1) and R727-CL-1112 (FH2) parent studies (patients had to be up-titrated in a blinded manner, using an automated process when LDL-C at Week 8 was ≥70mg/dL)
- patients of the mITT population coming from LTS11717 who all received alirocumab 150 mg Q2W throughout the parent study.

The gain efficacy due to up-titration from 75 mg Q2W to 150 mg Q2W in the parent study will be informally compared to the loss of efficacy due to forced down-titration to 75 mg Q2W at the entry in OLE in patients of the mITT population who were up-titrated in FH1 and FH2 studies. The percent change in calculated LDL-C from Week 12 (alirocumab 75 mg) to Week 24 (alirocumab 150 mg) in parent study and the percent change in calculated LDL-C from Week 78 in parent study (alirocumab 150 mg) to Week 8 in OLE study (alirocumab 75 mg) will be quantitatively summarized (number of available data, mean, SD, median, minimum, maximum, Q1 and Q3).

The effect of alirocumab 75 mg Q2W dose will be informally compared to the effect of alirocumab 150 mg Q2W dose in patients of the mITT population coming from LTS11717 who all received alirocumab 150 mg Q2W in the parent study. The percent change in calculated LDL-C from baseline of the parent study to Week 8 (alirocumab 150 mg) in parent study and the percent change in calculated LDL-C from Day1 in OLE study (after a washout period of 10 weeks) to Week 8 in OLE study (alirocumab 75 mg) will be quantitatively summarized. Same analysis will be done for ApoB, non-HDL-C, Lp(a) and TGs.

2.4.4.3 Multiplicity issues

Not Applicable.

2.4.4.4 Additional efficacy analysis(es)

Analyses on calculated LDL-C described above may be performed by device in case different devices are used for investigational treatment, in order to assess the impact of the device on study results. Patients will belong to the device they received longer.

2.4.5 Analyses of safety data

Unless otherwise specified, safety analyses will be presented overall as well as separately according to treatment (placebo versus alirocumab (regardless of dose)) received in the parent study.

For laboratory parameters and vital signs, analyses of the change from baseline, PCSA according to the baseline status and analyses of PCSA based on change from baseline values, will be performed using the parent baseline and the OLE baseline.

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:

- The parent baseline value is defined as the last available value obtained up to the date and time of the first double-blind IMP injection in the parent study.
- The OLE baseline is defined as the last available value obtained up to the date and time of the first OLE IMP injection.
- 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, vital signs, and ECG (PCSA version dated January 2009 [Appendix A]). Considering that the threshold defined in the PCSA list for monocytes and basophils can be below the ULN, the following PCSA criterion will be used for the PCSA analysis :
  - PCSA criterion for monocytes: >0.7 Giga/L or > ULN (if ULN ≥0.7 Giga/L)
  - PCSA criterion for basophils: >0.1 Giga/L or > ULN (if ULN ≥0.1 Giga/L)
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations.
- The treatment-emergent PCSA denominator 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 1 in order to provide an assessment for all planned 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 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.

Analyses performed according to diabetes status at OLE baseline will be done considering diabetic patients as patients with either type 1 or type 2 diabetes (see selection below) (regardless of the ongoing status) reported in at least one of the following e-CRF pages: medical history of the parent study, AE of the parent study and AE of the current study (selecting pre-treatment AEs only).

Diabetes mellitus events from medical history of the parent study selected using a company MedDRA query (CMQ), based on the following PTs : “diabetes mellitus”, “diabetes mellitus inadequate control”, “fulminant type 1 diabetes mellitus”, “insulin resistant diabetes”, “insulin-requiring type 2 diabetes mellitus”, “type 1 diabetes mellitus”, “type 2 diabetes mellitus”, “diabetes mellitus malnutrition-related”, and “diabetes mellitus management”, will be combined with AEs of the parent study and pre-treatment AEs of the current study selected using primary and secondary HLGT 'diabetic complications', HLT 'diabetes mellitus', HLT 'carbohydrate tolerance analyses (incl diabetes)' excluding PT 'Blood glucose decreased', and including PT 'hyperglycemia'.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs. Post-treatment AEs will be described separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of AEs with missing or partial onset dates are provided in Section 2.5.1.

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

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (TEAE, and post-treatment). For that purpose, the table of all TEAEs 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 by SOC and PT, unless otherwise specified. The tables of AEs by SOC, HLGT, HLT and PT will be sorted by the SOC internationally agreed order and the other levels (HLGT, HLT, PT) will be presented in alphabetical order, unless otherwise specified.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE;
  - Serious TEAE;
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC, HLT and PT (HLT incidence ≥2 % in overall patients in the OLE), sorted by SOC internationally agreed order and by alphabetic order for the other levels (HLT and PT);
- All TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables by SOC and PT of TEAEs, unless otherwise specified;
- All TEAEs regardless of relationship in one column and, in the same table a second column with TEAEs related to alirocumab according to investigator's opinion by primary SOC, HLGT, HLT and PT;
- All TEAEs by maximal intensity (ie, mild, moderate or severe) , presented by primary SOC and PT, sorted by the sorting order defined above;
- The event rate per patient-year (the number of patients with an event in question divided by total patient-years in OLE study) will be provided for all TEAEs by SOC and PT. For a patient with event, patient year is censored at time of first event in OLE; for patient without event, it corresponds to length of OLE TEAE period;
- Kaplan-Meier curves will be provided, when appropriate, for time from first dose of OLE study treatment to the first occurrence of selected TEAEs as well as incidence rates at 24, 52, 78, 104 and 156 weeks of exposure. 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 serious TEAEs by primary SOC, HLGT, HLT, and PT and by SOC/PT;
- All serious TEAEs regardless of relationship in one column and , in the same table a second column with TEAEs related to alirocumab according to investigator's opinion, by primary SOC, HLGT, HLT, and PT;
- The event rate per patient-year will be provided for all serious TEAEs by SOC and PT.

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

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT.

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

All grouping of TEAEs including adverse events of special interest as listed in Section 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.

- Analyses of grouping of AEs for diabetes will be performed overall and according to the diabetic status at baseline.
- Serious TEAEs by PT for each grouping of AEs of special interest;
- TEAE(s) leading to permanent treatment discontinuation by PT for each grouping of AEs of special interest.

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 OLE IMP injections received;
- Time from first OLE 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 post-treatment adverse events

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

Subgroup of patients with two consecutive LDL-C <25 mg/dL

If applicable, similar summaries of TEAEs as those described above will be also provided on the safety subgroup population of patients with two consecutive results of calculated LDL-C <25 mg/dL (as defined in Section 2.1.5) during the current study. 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 will be considered.

2.4.5.2 Deaths

The following summaries of deaths will be generated.

- Number (%) of patients from the safety population who died by study period (on-study, on-treatment, post-study) and reasons for death as reported by the investigators;
- TEAEs leading to death (death as an outcome on the AE as reported by the Investigator) by primary SOC, HLGT, HLT, and PT sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC, for the safety population. TEAE leading to death are TEAE that led to death regardless of timing of death in relation to IMP injection (i.e. death occurring in the TEAE period or during the post-treatment period).
- Deaths in non-enrolled patients or enrolled but not treated patients;

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, Q1, Q3, SD, 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 value of the treatment period, last on-treatment and worst on-treatment value). In addition, for some parameters of interest, mean changes from baseline with the corresponding SE could be plotted over time (at same time points). 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), as well as ALT increase as defined as AESI and hemoglobin decrease from baseline ≥15g/L, at any time during the TEAE period will be summarized by biological function irrespective of 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 could 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.

The incidence rates of selected PCSA during TEAE period at 24, 52, 78, 104 and 156 weeks of exposure will be calculated with Kaplan-Meier methodology, using the midpoint of the time interval between the first assessment with PCSA and the previous assessment. Kaplan-Meier curves will be also provided. Only the first event (PCSA) will be counted. Patients without any event will be censored at the last assessment performed during the TEAE period.

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values or ALT increase as defined in AESI section (see Section 2.1.4) 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 (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. The selection of PTs will be based on SMQ Hepatic disorder.

2.4.5.4 Analyses of vital sign variables

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

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 TEAE period will be summarized.

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.

The incidence rates of selected PCSA during TEAE period at 24, 52, 78, 104 and 156 weeks of exposure will be calculated with Kaplan-Meier methodology, using the midpoint of the time interval between the first assessment with PCSA and the previous assessment. Kaplan-Meier curves will be also provided. 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

Not applicable

2.4.6 Analyses of other endpoints

Binary endpoints defined in Section 2.1.5 will be described through patient counts and percentages in the safety population, overall and according to the treatment received during the parent study (placebo versus alirocumab (regardless of dose)). Kaplan-Meier curves will be provided for the "Time to" variables. Patients not meeting the event will be censored at the end of the treatment period. For the analysis of the time to the first of the two consecutive LDL-C events, patients without post-baseline LDL-C result or with only one post-baseline LDL-C result will not be included in the analysis.

2.4.7 Analyses of anti-alirocumab antibodies variables

The following summaries will be performed on the ADA population, overall as well as according to treatment received in the parent study (placebo versus alirocumab (regardless of dose)), taking into account all samples collected during the current study regardless of timing in relation to injections:

- ADA results (negative or positive) by time point;
- Neutralizing status (negative or positive) by time point for positive ADA;
- ADA titers using descriptive statistics (median, minimum and maximum) for positive ADA by time point;
- Number (%) of patients with treatment-emergent ADA positive response during the OLE period, overall and according to ADA status during the double-blind period (Pre-existing ADA, Negative ADA status and Treatment emergent ADA status)
- Number (%) of patients with persistent/transient/indeterminate treatment-emergent ADA positive response, overall and according to ADA status during the double-blind period (Pre-existing ADA, Negative ADA status and Treatment emergent ADA status)
- Time to onset of treatment-emergent ADA positive response during the OLE period using descriptive statistics.

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 pharmacokinetic and pharmacodynamic variables

Not applicable

2.4.9 Analyses of quality of life/health economics variables

The analysis of data from EQ-5D instrument will be performed on quality-of-life population, overall as well as separately according to treatment received in the parent study (placebo versus alirocumab (regardless of dose)). Baseline is defined as the baseline of the parent study. Analysis window for efficacy parameters will be used to assign time points (see Section 2.5.4, Table 1).

Individual EQ-5D items

Response for each one of the 5 EQ-5D items will be summarized by visit using tables which will contain frequency and proportion of the population reporting level 1 (no problems), level 2 (some problems) and level 3 (extreme problems) and by item.

EQ-5D utility score

The raw value and the change from baseline of the utility score will be summarized using mean, median, Q1, Q3, SD, minimum and maximum for each post-baseline visit. Cumulative distribution functions for the change in utility score from baseline will be displayed over time.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

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" of the parent study:

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

Renal function formulas

eGFR value will be derived using the Modification of the Diet in Renal Disease (MDRD) equation:
175 × (creatinine in µmol/L / 88.4)-1.154 × (age in years)-0.203 (x 0.742 if female, x 1.212 if race is "black or african american").

Lipids variables, laboratory safety variables, Hs-CRP

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

2.5.2 Data handling conventions for secondary efficacy variables

See Section 2.1.3.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified.

Handling of baseline definition if time of first double-blind administration or time of assessment at Week 0 visit of parent study is missing

If the time of the first double-blind administration or the time of assessment at Week 0 visit of parent study 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 baseline definition of the current study if time of first open-label administration or time of assessment at Week 0 visit of the current study is missing

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

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

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

Handling of safety and efficacy analysis periods and survival analysis if 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,
- and the date of the last contact,

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

Handling of medication missing/partial dates

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

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

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

Handling of adverse events when date and time of first OLE investigational medicinal product administration is missing

When the date and time of the first OLE IMP administration is missing, all AEs that occurred on or after the day of visit 1 will be considered as TEAEs.

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

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

If the assessment of the relationship to 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 value he will be grouped in the category "normal/missing at baseline."

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

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; 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, quality of life, ADA) will be summarized using the analysis windows given in Table 1. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses.

Table 1 - Analysis windows definition

Time point	Targeted study day	Analysis window in study days from OLE entry
Week 4	29	15 to 42
Week 8	57	43 to 70
Week 12	85	71 to minimum (98, study day corresponding to first the injection with IMP from kit allocated at Week 12 re-supply IVRS contact)
Week 24	169	155 to 182
Week 36	253	239 to 266
Week 48	337	316 to 357
Week 60	421	400 to 441
Week 72	505	484 to 525
Week 84	589	568 to 609
WeeK 96	673	652 to 693
Week 108	757	729 to 784
Week 120	841	813 to 868
Week 132	924	896 to 951
Week 144	1008	980 to 1035

Time point	Targeted study day	Analysis window in study days from OLE entry
Week 156	1092	1064 to 1119
Week 168	1176	1148 to 1203

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

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If multiple valid values of a variable exist within an analysis window, the nearest from the targeted study day will be selected. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values of a variable exist within a same day, then the first value of the day will be selected when time is available, else the scheduled visit will be selected.

2.5.5 Unscheduled visits

For efficacy, safety laboratory data, or 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

No pooling of centers will be performed for safety nor for efficacy analyses.

3 INTERIM ANALYSIS

Interim analyses may be performed before the end of the study if requested by Health Authorities or if needed for the purpose of scientific communication.

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

- Patients without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:
  - Patients who did not complete treatment period nor prematurely discontinued the study treatment at cut-off date will be analyzed as “ongoing” in the disposition summary.
  - Their TEAE period, treatment period, efficacy treatment period and on-study observation period will end at the cut-off date.
  - Their treatment duration will be derived by considering date of cut-off as last injection date.
- Analyses of number of injections, mean injection frequency, percentage of days with under/above-planned dosing and compliance will be performed up to the last injection reported in the e-CRF up to the cut-off date.
- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an adverse event starting prior to the cut-off date will be taken into account. Medications, treatment discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.
- Post-treatment period, post-study period are not applicable for ongoing patients. Analyses of post-treatment AEs, post-study deaths and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.
- Analysis of proportion of patients with insufficient follow-up will be provided for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.

4 DATABASE LOCK

The database is planned to be locked approximately 4 weeks after common cut-off date (for interim analysis) or last patient last visit (for final analysis).

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

1. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997 Nov;35(11):1095-108.