STATISTICAL ANALYSIS PLAN

A Randomized, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab versus Usual Care in Patients with Type 2 Diabetes and Mixed Dyslipidemia at High Cardiovascular Risk with Non-HDL-C Not Adequately Controlled with Maximally Tolerated Statin Therapy

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

(No abbreviations defined yet)Ab: antibody

ADA:	anti-drug antibodies/ anti-alirocumab antibodies
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
ANOVA:	analysis of variance
Apo:	apolipoprotein
ASCVD:	atherosclerotic cardiovascular disease
AST:	aspartate aminotransferase
ATC:	anatomic therapeutic chemical
BMI:	body mass index
CBC:	complete blood cell count
CHD:	coronary heart disease
CI:	confidence interval
CKD:	chronic kidney disease
CV:	cardiovascular
DBP:	diastolic blood pressure
ECG:	electrocardiogram
e-CRF:	electronic case report form
eDISH:	evaluation of drug-induced serious hepatotoxicity
eGFR:	estimated glomerular filtration rate
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
GFR:	glomerular filtration rate
GGT:	gamma-glutamyl transferase
GLP-1:	glucagon-like peptide-1
HbA1c:	glycated hemoglobin A1c
HCV:	hepatitis C virus
HCV RNA:	hepatitis C virus ribonucleic acid
HDL:	high-density lipoprotein
HDL-C:	high-density lipoprotein cholesterol
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IDL:	intermediate-density lipoprotein
IMP:	investigational medicinal product
[redacted]	[redacted]
ITT:	intent-to-treat
IVRS:	interactive voice response system
IWRS:	interactive web response system
LDH:	lactate dehydrogenase

LDL:	low-density lipoprotein
LDL-C:	low-density lipoprotein cholesterol
LLOQ:	lower limit of quantification
LLT:	lowest level term
LMT:	lipid modifying therapy
LOCF:	last observation carried forward
Lp(a):	lipoprotein a
LS:	least square
MAR:	missing-at-random
MDRD:	modification of diet in renal disease
MedDRA:	medical dictionary for regulatory activities
MI:	myocardial infarction
MMRM:	mixed effect model with repeated measures
NMAR:	not-missing-at-random
NMR:	nuclear magnetic resonance
non-HDL-C:	non-high-density lipoprotein cholesterol
OLTP:	open-label treatment period
PAD:	peripheral arterial disease
PCSA:	potentially clinically significant abnormality
PCSK9:	proprotein convertase subtilisin kexin type 9
PT:	preferred term
Q1:	first quartile
Q2W:	every 2 weeks
Q3:	third quartile
QQ:	quantile quantile
RBC:	red blood cell
RDW:	red blood cell distribution width
RNA:	ribonucleic acid
SAE:	serious adverse event
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
SMQ:	standardized MedDRA query
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TG:	triglyceride
TGRL:	triglyceride rich lipoprotein
TIA:	transient ischemic attack
Total-C:	total cholestorol
TSH:	thyroid stimulating hormone
ULN:	upper limit of normal range
ULOQ:	upper limit of quantification
VLDL:	very low-density lipoprotein
WBC:	white blood cell
WHO-DD:	World Health Organization drug dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multicenter, multinational, randomized, open-label, parallel group stratified study.

After a screening phase of up to 3 weeks, patients will be centrally randomized via interactive voice response system (IVRS) or interactive web response system (IWRS) in a 2:1 ratio to one of the two treatment groups (alirocumab:usual care) and treated for 24 weeks.

Randomization will be stratified by the Investigator's selection of usual care therapy prior to randomization (5 strata: no additional lipid modifying therapy [LMT], or intent to prescribe fenofibrate, ezetimibe, omega-3 fatty acids, or nicotinic acid). Patients randomized to open-label alirocumab will continue on the maximum dose of statin that is tolerated by the patient and will administer alirocumab subcutaneously with a starting dose of 75 mg every 2 weeks for 12 weeks with a blinded up-titration to alirocumab 150 mg every 2 weeks at Week 12 visit if the non-high-density lipoprotein cholesterol (non-HDL-C) at the Week 8 visit is ≥100 mg/dL (2.59 mmol/L). Patients who have a non-HDL-C <100 mg/dL (2.59 mmol/L) at the Week 8 visit will continue with alirocumab 75 mg every 2 weeks until the end of the treatment period. Patients randomized to usual care will follow the option selected by the Investigator prior to randomization. No change during the course of the study will be made to the dose of LMT administered as part of the usual care arm except for nicotinic acid for which the Investigator may prescribe at randomization a scheduled/gradual dose titration in order to allow for the maximum dose to be achieved based on patient tolerability, or except if needed for any usual care LMT for the safety of the patient, based on the Investigator's judgment.

Approximately 420 patients will be recruited and randomized (280 in the alirocumab group and 140 in the usual care group).

1.2 OBJECTIVES

1.2.1 Primary objective

The primary objective of this study is:

- To demonstrate the superiority of alirocumab in comparison with usual care in the reduction of non-HDL-C after 24 weeks of treatment in patients with Type 2 diabetes and mixed dyslipidemia at high cardiovascular (CV) risk with non-HDL-C not adequately controlled with maximally tolerated statin therapy.

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To demonstrate whether alirocumab is superior in comparison with usual care in its effects on other lipid parameters at Weeks 12 and 24:
    - low-density lipoprotein cholesterol (LDL-C)
    - apolipoprotein B (Apo B)
    - total cholesterol (Total-C)
    - lipoprotein a (Lp(a))
    - high-density lipoprotein cholesterol (HDL-C)
    - triglycerides (TGs)
    - triglyceride rich lipoproteins (TGRLs)
    - apolipoprotein A-1 (Apo A-1)
    - apolipoprotein C-III (Apo C-III)
    - lipid subfractions by nuclear magnetic resonance (NMR) spectroscopy:
        - low-density lipoprotein (LDL) particle size
        - LDL particle number
        - very low-density lipoprotein (VLDL) particle number
        - high-density lipoprotein (HDL) particle number
        - intermediate-density lipoprotein (IDL) particle number
- To demonstrate the superiority of alirocumab in comparison with usual care in the reduction of non-HDL-C at Week 12
- To assess changes in diabetes related parameters in patients randomized to alirocumab versus usual care treatment over a period of 24 weeks
- To demonstrate the safety and tolerability of alirocumab
- [redacted]
- To evaluate changes in proprotein convertase subtilisin kexin type 9 (PCSK9) concentrations at Weeks 12 and 24
- To evaluate the development of anti-alirocumab antibodies (ADA)
- To demonstrate the superiority of alirocumab versus fenofibrate therapy on non-HDL-C and other lipid parameters

1.3 DETERMINATION OF SAMPLE SIZE

[redacted]

[redacted]

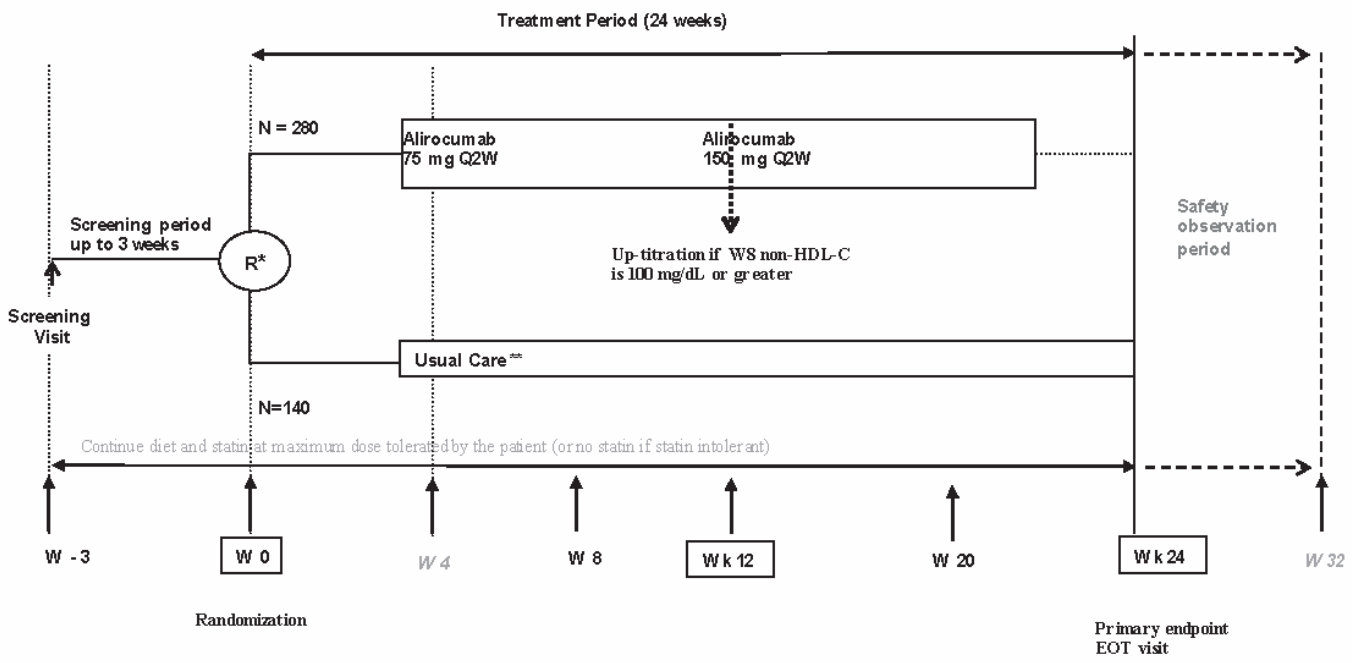
1.4 STUDY PLAN

This is a Phase 3b/4 randomized, open-label, parallel group study to assess the efficacy and safety of alirocumab administered by subcutaneous injection versus usual care in patients with Type 2 diabetes and mixed dyslipidemia at high CV risk with non-HDL-C not adequately controlled with maximally tolerated statin therapy. The study will be multinational and multicenter. The study consists of a screening period of up to 3 weeks, an open-label treatment period (OLTP) of 24 weeks, and a safety observation period of 8 weeks.

Patients, unless they are statin intolerant, will be taking a stable, maximally tolerated dose of statin therapy without other LMTs. Statin dose and dose regimen should be stable throughout the entire study duration including for 4 weeks prior to the screening period and from screening to the end of the OLTP. Patients should continue to follow a cholesterol lowering diet during the study, however, the Investigator may reinforce diet recommendations according to local/regional guidelines. Patients should be receiving treatment for diabetes in accordance with local/regional standards of care. Changes to antihyperglycemics should be limited and made only in circumstances where it is clinically needed.

The usual care arm includes the option to continue on the maximum dose of statin that is tolerated by the patient without the addition of a new LMT at randomization, or may initiate either ezetimibe, fenofibrate, omega-3 fatty acids, or nicotinic acid at randomization for the remainder of the 24-week treatment period. Initiation of usual care treatment should start as soon as possible after randomization, but no later than 7 days from the day of randomization.

The Investigator will select the most appropriate LMT for the patient prior to randomization (consisting of either no additional LMT but continuing on maximum tolerated statin, ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid) and enter this information into the IVRS. If the patient is randomized to open-label alirocumab, the Investigator will not institute the LMT option that was selected and entered into IVRS but instead treat the patient with open-label alirocumab. If the patient is randomized to usual care (non-alirocumab), the Investigator will initiate treatment with the LMT option that was selected and entered into IVRS, as applicable, in addition to continuing the patient on the maximum tolerated dose of statin.



R: Randomization : As a principle, it should occur after signature of the informed consent form and just before the first dosing of the study drug (ie, IMP or usual care). The Randomization Day is always Day 1. The randomization is stratified by intent to precribe usual care (eg, intent to prescribe ezetimibe, intent to prescribe fenofibrate).
*First study drug administration.
**Usual care includes continuing on maximum dose of statin tolerated by the patient (or no statin if statin intolerant) and one of the following: no additional LMT or initiation of either ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid.
Phone call visits are indicated in italics.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not Applicable

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not Applicable

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

The baseline value is defined generally as the last assessment obtained before the first injection of open-label alirocumab/first dose of usual care treatment or before randomization for patients randomized to usual care and not receiving additional LMT. All laboratory assessments taken the day of randomization will be considered as being performed prior to the first investigational medicinal product (IMP) administration. [redacted]

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

2.1.1 Demographic and baseline characteristics

Demographic characteristics

Demographic variables are age in years (quantitative and qualitative variables: <65, [65 - 75[and ≥75 years; <65 and ≥65 years), gender (Male, Female), childbearing potential (Yes, No; for females only), race (White/Caucasian, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or Other Pacific Island, Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported/Unknown).

Age is calculated in years as:
Age = (date of informed consent – date of birth +1) /365.25.
For patients in countries where date of birth is not collected, age in years is directly collected in the electronic case report form (e-CRF).

History of type 2 diabetes

History of type 2 diabetes includes the duration of diabetes in years (quantitative and qualitative variables: <5, [5 – 10] and >10 years).

Alcohol/smoking habits

Alcohol habits (alcohol drinking frequency, number of alcoholic drinks on a typical day when drinking) and smoking habits (never smoked, quit smoking, currently smokes); if quit smoking, time since stopped in years) will be presented.

Hypercholesterolemia history

Hypercholesterolemia characteristics are:

- Duration of hypercholesterolemia (years)

- History of hypercholesterolemia before type 2 diabetes diagnosis and duration between the diagnosis of hypercholesterolemia and the diagnosis of diabetes for patients with hypercholesterolemia diagnosed before diabetes.
- History of LMT ever taken (e.g., statin, fibrates, bile acid sequestrant, cholesterol absorption inhibitor, nicotinic acid and derivatives, omega 3 fatty acid ≥1000mg/day, PCSK9 inhibitor, other)
- History of down titration of any statin due to tolerability issues
- History of change to any different statin due to tolerability issues
- Currently taking statin
    - If currently taking statin, whether subject receives the maximum dose per the local prescribing information
    - If not currently taking statin, statin intolerance status
        - If intolerant to statin, number of statin(s) previously prescribed at a dose lower than maximum and not tolerated
    - Reasons for taking a lower dose (including no dose if statin intolerant) when subject did not receive the maximum dose will be presented overall and by category (statin intolerant and not statin intolerant but taking a dose lower than the maximum dose):
        - Experienced muscle symptoms and/or increase creatine phosphokinase while taking a higher dose
        - Has liver disease or experienced elevated liver functions test while taking a higher dose
        - Taking concomitant medications that have precautions/warnings with statins
        - Advanced age
        - Low body mass index
        - Concern for cognitive impairment or experienced cognitive adverse event(s) while taking a higher dose
        - Concern for worsening of diabetes
        - Regional practice/local prescribing information
        - Other

Cardiovascular (CV) history and CV risk factors

The coronary heart disease (CHD), CHD risk equivalents, and additional CV risk factors will be based on items or combination of items pre-listed in the 'Cardiovascular History' e-CRF page (unless otherwise specified).

Coronary heart disease and CHD risk equivalents will be detailed as follows:

- CHD (regardless if it is ongoing or not)
    - Acute myocardial infarction
    - Silent myocardial infarction
    - Unstable angina

- Coronary revascularization procedures
- 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 by the occurrence of one of the following criteria (a, b, or c) based on the e-CRF fields:
    - a) Intermittent claudication (linked to PAD) with 'Ongoing' ticked "Yes" TOGETHER WITH ankle-brachial index ≤0.90 in either leg at rest,
    - b) Intermittent claudication (linked to PAD) TOGETHER WITH either peripheral revascularization procedure (angioplasty, stenting) for PAD or peripheral revascularization surgery (arterial bypass) for PAD or both,
    - c) Critical limb ischemia TOGETHER WITH either thrombolysis for PAD or peripheral revascularization procedure (angioplasty, stenting) for PAD or peripheral revascularization surgery (arterial bypass) for PAD or any combination of the three.
  - Ischemic stroke

The following additional CV risk factors will also be considered:

- Hypertension established on antihypertensive medication
- Current cigarette smoker (as per smoking status from 'Smoking Habits' e-CRF page)
- Age ≥ 45 years old for men, ≥ 55 years old for women (age derived as detailed above in the 'Demographic characteristics' subsection)
- Microalbuminuria
- Macroalbuminuria
- Pre-proliferative diabetic retinopathy
- proliferative diabetic retinopathy
- Family history of premature (before 55 years of age in male, 65 years in female, first degree relatives) CHD
- Low HDL-C (male <40 mg/dL [1.0 mmol/L] and female <50 mg/dL [1.3 mmol/L])
- Chronic kidney disease (CKD) as defined by 15 ≤ estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for 3 months or more, including the screening visit)

Presentation of each risk factor will include:

- The occurrence
- Duration (years) of hypertension, microalbuminuria, macroalbuminuria, diabetic pre–proliferative retinopathy, diabetic proliferative retinopathy, and CKD
- Disease/symptoms controlled (if ongoing risk factor) for history of hypertension, microalbuminuria, macroalbuminuria, diabetic pre–proliferative retinopathy, and diabetic proliferative retinopathy

In addition, as per protocol, clinical atherosclerotic cardiovascular disease (ASCVD) is defined by any of the following history of CV diseases:

- CHD *(as defined above)*
- Ischemic stroke
- PAD *(as defined above)*

A second definition of clinical ASCVD including transient ischemic attack (TIA), as per the 2013 AHA/ACC guideline, is any of the following history of CV disease:

- CHD (*as defined above*)
- Ischemic stroke
- TIA
- PAD (*as defined above*)

Allergic medical history

Occurrence will be presented for each allergic medical history:

- Allergic rhinitis
- Chronic sinusitis
- Nasal polyps
- Asthma
- Drug allergy
- Food allergy
- Pollen allergy
- House dust allergy
- Hives
- Swelling (angioedema)
- Fainting episodes
- Rash
- Other allergic medical history

Occurrence will also be presented for family allergic history:

- Asthma
- Allergic rhinitis

- Allergies to food/pollen/dust

Other relevant medical/surgical history

Other relevant medical/surgical history will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Vital signs

Vital signs at baseline are weight in kg (quantitative and qualitative variables: <50, [50-70[, [70-100[, ≥100 kg), height in cm, body mass index (BMI) in kg/m^2 (quantitative and qualitative variables: <25, [25-30[, ≥30 kg/m^2), sitting systolic/diastolic blood pressures (SBP/DBP mmHg), heart rate (HR bpm).

Other baseline characteristics

- Female menopausal status:
  - occurrence
  - for postmenopausal women, time since menopause (years), menopausal symptoms controlled status and type of hormone replacement therapy (estrogen only, estrogen and progesterone, no estrogen or progesterone)

    The type of hormone replacement therapy will be obtained from concomitant treatments.
- Lipid efficacy parameters:
  - Non-HDL-C, quantitative and by category: <100, [100 - 130[, [130 - 160[, [160 - 190[, [190 – 220[, >220 mg/dL (<2.59, [2.59 - 3.36[, [3.36 - 4.14[, [4.14 - 4.91[, [4.91 - 5.70[, ≥5.70 mmol/L)
  - Calculated and measured LDL-C, quantitative and by category: <70, [70 – 100[, [100 – 130[, [130 – 160[, [160 – 190[, ≥190 mg/dL (<1.81, [1.81 – 2.59,[[2.59 - 3.37[, [3.37 – 4.14[, [4.14 – 4.91[, ≥4.91 mmol/L)
  - Apo B, quantitative and by category: <80, ≥80 mg/dL (<0.8 g/L, ≥0.8 g/L)
  - Lp(a), quantitative and by category: <30, [30 – 50[, ≥50 mg/dL (<0.3, [0.3 – 0.5[, ≥0.5 g/L); <30, ≥30 mg/dL (<0.3, ≥0.3 g/L)
  - HDL-C, quantitative and by category: <40, ≥40 mg/dL (<1.04, ≥1.04 mmol/L) for men / <50, ≥50 mg/dL (<1.29, ≥1.29 mmol/L) for women
  - Fasting TGs, quantitative and by category: <150, [150 – 200[, ≥200 mg/dL (<1.7, [1.7 - 2.3[, ≥2.3 mmol/L); <150, ≥150 mg/dL (<1.7, ≥1.7 mmol/L)
  - TGRL, quantitative and by category: < 30, ≥ 30 mg/dL (< 0.3, ≥ 0.3 g/L)
  - All other quantitative lipid efficacy parameters (Total-C, Apo A-1, Apo C-III, ratio Apo B/Apo A-1, ratio Total-C/HDL-C, ratio LDL-C/HDL-C, LDL particle number and size, VLDL, HDL, IDL particle number)
- Metabolic parameters:
  - Glycated hemoglobin A1c (HbA1c), quantitative (%, mmol/mol) and by category: <7, [7 - 9[, ≥9 %; <7, ≥7 %; <8, ≥8 %; <9, ≥9 %

    - Fasting plasma glucose (FPG), quantitative variable (mg/dL and mmol/L)
- Total and free PCSK9 levels as quantitative (ng/mL)
- eGFR, quantitative and by category: [15 – 30[, [30 - 60[, [60 - 90[, ≥90 ml/min/1.73 m²
- Albumin/creatinine ratio, quantitative and by category: < 30, [30 - 300[, ≥ 300 mg/g (< 3.39, [3.39 - 33.9[, ≥ 33.9 mg/mmol);
- Diabetic kidney disease category defined below (cf. Appendix C) (7):
    - Category 1: G1A1, G2A1
    - Category 2: G1A2, G2A2, G3aA1
    - Category 3: G1A3, G2A3, G3aA2, G3bA1
    - Category 4: G3aA3, G3bA2, G3bA3, G4A1, G4A2
    - Category 5: G4A3, G5A1, G5A2, G5A3

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 within 3 months before screening visit and until the end of the study are to be reported in one of the following specific e-CRF pages:

- Cardiovascular Drugs
- Lipid Modifying Therapy (Including Statin) and Nutraceutical Products that May Affect Lipids
- Other 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 are those the patient used within 12 weeks prior to screening visit and prior to first dose of open-label alirocumab injection/first dose of usual care treatment for those prescribed another LMT if allocated to the usual care arm. For those allocated to the usual care arm and for whom no other LMT is prescribed, the pre-treatment period will end on the day before randomization. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Medications taken at baseline are those the patient started before or on the day of the first dose of open-label alirocumab injection/first dose of usual care treatment (for those prescribed another LMT in the usual care arm)/randomization (for those not prescribed another LMT in the usual care arm), and ongoing or ended on or after the day of the first dose of open-label alirocumab injection/first dose of usual care treatment (for those prescribed another LMT in the usual care arm)/randomization (for those not prescribed another LMT in the usual care arm).

- Concomitant medications are any treatments received by the patient from first dose of open-label alirocumab injection to the last dose of open-label treatment + 70 days (10 weeks). For patients randomized to usual care, this will be considered as 70 days after the last dose of usual care treatment has been administered, or Study Day 225, whichever comes first. For patients randomized to usual care arm without additional LMT prescribed, the "date of last dose of usual care" is defined as the date of the last on-site visit. 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 running from the day after concomitant treatment period up to 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 (i.e., measured LDL-C, calculated LDL-C, non-HDL-C, Apo B, Total-C, Lp(a), TGs, HDL-C, TGRL, LDL particle number and size, Apo A-1, Apo C-III, ratio Apo B/Apo A-1, ratio Total-C/HDL-C, ratio LDL-C/HDL-C, VLDL, HDL, IDL particle number). These parameters (except TGRL, ratio Total-C/HDL-C and ratio LDL-C/HDL-C) are provided by the Central Laboratory. Measured LDL-C is obtained via beta quantification method. Calculated LDL-C is obtained using the Friedewald formula (5). If TG values exceed 400 mg/dL (4.52 mmol/L) then the Central Laboratory will reflexively measure (via the beta quantification method) the LDL-C rather than calculating it. All measured LDL-C values provided by the Central Laboratory including those done in case of TG values exceeding 400 mg/dL (4.52 mmol/L) will not be used for the analysis of calculated LDL-C endpoints. TGRL is derived as defined below.

Unless otherwise 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 2.5.3 in order to provide an assessment for Week 4 to Week 24 time points. For TG, only fasting measurements will be used and measurements with missing fasting status will be excluded from the analyses.

2.1.3.1 Primary efficacy endpoint

The primary efficacy endpoint is the percent change in non-HDL-C from baseline (see definition of baseline in Section 2.1) to Week 24 in the intent-to-treat (ITT) population.
Non-HDL-C is defined as Total-C minus HDL-C.
The percent change is defined as: 100 x (non-HDL-C value at Week 24 – non-HDL-C value at baseline) / non-HDL-C value at baseline.

2.1.3.2 Secondary efficacy endpoints

2.1.3.2.1 Key secondary efficacy endpoints (ITT estimand)

- Percent change in measured LDL-C from baseline to Week 24
- Percent change in non-HDL-C from baseline to Week 12
- Percent change in measured LDL-C from baseline to Week 12
- Percent change in Apo B from baseline to Week 24
- Percent change in Total-C from baseline to Week 24
- Percent change in Lp(a) from baseline to Week 24
- Percent change in TGs from baseline to Week 24
- Percent change in HDL-C from baseline to Week 24
- Percent change in LDL particle number from baseline to Week 24

2.1.3.2.2 Diabetes-related endpoints (ITT estimand)

- Absolute change in HbA1c from baseline to Weeks 12 and 24
- Absolute change in FPG from baseline to Weeks 12 and 24
- Absolute change in number of glucose-lowering treatments from baseline to Weeks 12 and 24

2.1.3.2.3 Other efficacy endpoints (ITT estimand)

- Percent change in calculated LDL-C from baseline to Weeks 12 and 24
- Percent change in Apo B, Total-C, Lp(a), TGs, HDL-C from baseline to Week 12
- Proportion of patients reaching measured LDL-C <50 mg/dL (1.30 mmol/L), <70 mg/dL (1.81 mmol/L) and <100 mg/dL (2.59 mmol/L) at Weeks 12 and 24
- Percent change in measured LDL-C according to baseline TGs of <median TG or ≥median TG at Weeks 12 and 24
- Proportion of patients reaching non-HDL-C <130 mg/dL (3.37 mmol/L), <100 mg/dL (2.59 mmol/L) and <80 mg/dL (2.07 mmol/L) at Weeks 12 and 24
- Percent change in TGs from baseline to Weeks 12 and 24 according to baseline TGs of <median TG or ≥median TG
- Percent change in LDL particle number from baseline to Week 12
- Percent change in LDL particle size from baseline to Weeks 12 and 24
- Percent change in VLDL, HDL and IDL particle number from baseline to Weeks 12 and 24
- Percent change in Apo A-1 and Apo C-III from baseline to Weeks 12 and 24

- Absolute change in TGRLs (non-HDL-C minus measured LDL-C if measured LDL-C not missing; non-HDL-C minus calculated LDL-C if measured LDL-C missing and calculated LDL-C not missing, using fasting samples first, or if fasting sample missing using non-fasting measurements) from baseline to Weeks 12 and 24
- Proportion of patients with 50% or greater reduction from baseline in measured LDL-C at Weeks 12 and 24.
- Proportion of patients reaching Apo B <80 mg/dL at Weeks 12 and 24.
- Absolute change in ratio Apo B/Apo A-1, Total-C/HDL-C and LDL-C/HDL-C from baseline to Weeks 12 and 24.

2.1.4 Safety endpoints

The safety analysis will be based on the reported AEs and other safety information, such as clinical laboratory data and vital signs.

Observation period

The observation period will be divided into 3 periods:

- Pre-treatment period is defined from the signed informed consent up to the day before the first dose of open-label alirocumab injection/first dose of usual care treatment for those prescribed another LMT if allocated to the usual care arm. For those allocated to the usual care arm for whom another LMT is not prescribed, the pre-treatment period will end on the day before randomization.
- Treatment Emergent Adverse Event (TEAE) period:
    - For patients randomized to alirocumab, the TEAE period is defined as the time from the day of the first dose of open-label alirocumab injection to the day of the last dose of open-label alirocumab injection + 70 days (10 weeks) as residual effect of treatment is expected until 10 weeks after the stop of alirocumab.
    - For patients randomized to usual care
        - and who are administered an additional LMT, the TEAE period is defined as the time from the day of the first intake of the usual care drug to 70 days after the day of the last intake or Study Day 225, whichever comes first.
        - and for whom the Investigator has not prescribed an additional LMT, the TEAE period is defined as the time from the day of randomization to the date of the last on-site visit + 70 days, or Study Day 225, whichever comes first.
- Post-treatment period is defined as the time starting the day after the end of the TEAE period up to resolution/stabilization of all serious adverse events (SAEs) and AEs of special interest (AESI), whichever comes last.

The on-study observation period is defined as the time from the day of the first dose of open-label alirocumab injection/first dose of usual care treatment (for those prescribed another LMT if

allocated to the usual care arm)/randomization (for those allocated to the usual care arm for whom another LMT is not prescribed) until the last protocol planned visit of the patient (Week 32 phone call).

Of note, neither the onset time of AEs nor the time of laboratory samples are collected in the clinical database. As a consequence it is not possible for AEs and potentially clinically significant abnormalities (PCSAs) starting the first day of the TEAE period to know if they occurred before or after the first intake of IMP. By definition of the TEAE period, they are considered to be treatment emergent even if, for example in the case of PCSA, it is not likely because laboratory samples must be collected before randomization (and thus drug administration) as per protocol.

2.1.4.1 Adverse events variables

Adverse events (including SAEs, AESI and product complaints) are recorded from the time of signed informed consent to the end of the study. All AEs diagnosed by the Investigator 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 AEs 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

An AESI is an AE (serious or non-serious) that needs to be monitored, documented, and managed in a pre-specified manner described in the protocol.

For this study, the AESI are:

- Increase in alanine aminotransferase (ALT):
    - ALT ≥ 3 times the upper limit of normal range (ULN) (if baseline ALT <ULN) or ALT ≥ 2 times the baseline value (if baseline ALT ≥ULN);
- Allergic drug reactions:
    - requiring consultation with another physician AND selected using the standardized MedDRA query (SMQ) "hypersensitivity" (broad and narrow) excluding the following PTs linked to local injection site reactions {"injection (infusion) site dermatitis", "injection (infusion) site hypersensitivity", "injection (infusion) site

oedema", "injection (infusion) site rash", "injection (infusion) site urticaria", "injection (infusion) site eczema", "injection (infusion) site vasculitis", "injection (infusion) site swelling"};

- in addition, an analysis will be performed for any general allergic event not meeting AESI criteria (not requiring consultation with another physician) but meeting the above SMQ criteria.

- Local injection site reactions:
  - deemed to be allergic by the Investigator (or have an allergic component) AND that require consultation with another physician AND related to alirocumab (as opposed to another injectable) AND selected using the following selection of PTs from the safety complementary form for local injection site reaction or from the reported term {"Injection (infusion) site dermatitis", "Injection (infusion) site hypersensitivity", "Injection (infusion) site oedema", "Injection (infusion) site rash", "Injection (infusion) site urticaria", "Injection (infusion) site eczema", "Injection (infusion) site vasculitis", "Injection (infusion) site swelling"};
  - in addition, an analysis will be performed for any local injection site reaction not meeting AESI criteria (not allergic and not requiring consultation with another physician) but meeting the above criteria AND related to alirocumab (as opposed to another injectable).
- Pregnancy of female patient (including male patient's partner) selected using appropriate MedDRA codes.
- Symptomatic overdose with alirocumab:
  - an overdose with alirocumab is defined as at least twice of the intended dose within the intended therapeutic interval (i.e., 2 or more injections are administered in <7 calendar days), to be reported using the term "symptomatic OVERDOSE" (accidental or intentional), indicating the circumstance in parentheses (e.g., "symptomatic overdose [accidental]" or "symptomatic overdose [intentional]"). These events will be selected using the AESI category as selected by the site.
  - in addition, another analysis will be performed analysing all overdose cases (whether symptomatic or asymptomatic) related to alirocumab using the HLT for overdose.
- Neurologic events:
  - requiring additional exams/procedures or consultation AND selected using SMQ "demyelination" (broad and narrow), "peripheral neuropathy" (broad and narrow), and "Guillain Barre syndrome" (broad and narrow) excluding the following PTs "acute respiratory distress syndrome", "asthenia", "respiratory arrest", and "respiratory failure";
  - an additional analysis will be performed analyzing all events meeting the above SMQ criteria for neurologic events whether or not the criteria for an AESI are met (whether or not requiring additional exams/procedures or consultation).
- Any neurocognitive events:

- selected using the company CMQ based on HLGTs “Deliria (incl confusion)”, “Cognitive and attention disorders and disturbances”, “Dementia and amnestic conditions”, “Disturbances in thinking and perception”, “Mental impairment disorders”;
- in a second approach, neurocognitive events will be analyzed as per the CMQ developed using the FDA grouping of events based on 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”;
- in a third approach, neurocognitive events will be analysed using company CMQ or FDA CMQ.

Analyses of allergic drug reactions and local injection sites reactions and neurologic events will also be provided using the drop-down on the e-CRF AE page as a second approach.

All analyses described above as additional are not AESI, but AE groupings that will be explored.

In addition the following grouping of events will be provided:

- Hepatic disorder events using SMQ “Hepatic disorder”;
- Diabetic complications using HLGT “Diabetes Complications”, HLT “Diabetes Mellitus (incl subtypes)”, and HLT “Carbohydrate tolerance analyses (incl diabetes)”, PT “Hyperglycaemia”, PT “Hyperglycaemic unconscioussness”, PT “Hyperglycaemic seizure”, excluding PT “Blood glucose decreased”, and PT “Glycosylated haemoglobin decreased”;
- Hypoglycemia events using CMQ “Hypoglycemia” (narrow only).

2.1.4.2 Deaths

The death observation periods 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 TEAE period;
- Death post-study: deaths occurring after the last planned protocol visit.

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 as international and conventional units.

Blood samples for clinical laboratories will be taken at Week -3, Week 0 (please refer to study protocol for requirements, some safety laboratory data are only required at Week 0 per judgment of investigator), Week 8, Week 12, and Week 24/EOT. The laboratory parameters will be classified as follows:

- Hematology
    - **Red blood cells and platelets**: complete blood cell count (CBC) including hematocrit, hemoglobin, red blood cell (RBC) count, red blood cell distribution width (RDW), and platelets;
    - **White blood cells**: white blood cell (WBC) count with differential count, neutrophils, lymphocytes, monocytes, basophils and eosinophils.
- Clinical chemistry
    - **Metabolism**: plasma glucose, total protein, albumin, HbA1c, creatine phosphokinase;
    - **Electrolytes**: sodium, potassium, chloride, bicarbonate, calcium, phosphorous;
    - **Renal function**: blood urea nitrogen, creatinine, uric acid, eGFR;
    - **Liver function**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH) and total bilirubin (in case of total bilirubin values above the normal range, differentiation into conjugated and non-conjugated bilirubin will occur automatically);
    - **Pregnancy test (at screening)**: Serum β-human chorionic gonadotropin (women of childbearing potential) status (Positive/Negative);
    - **Hepatitis screen**: Hepatitis C antibody (at screening, Week 24 and in case of transaminases elevation), Hepatitis B surface antigen (screening only). If tests are repeated or confirmatory test are performed, all results will be described;
    - **Other parameters**: thyroid stimulating hormone (TSH) (for patients on thyroid hormone replacement therapy) at screening only.

Urine samples will be collected at Screening (Week -3) and Week 24/or early termination as follows:

- **Urinalysis** - quantitative analyses: pH, specific gravity, presence of blood, proteins, ketones, nitrates, leukocyte esterase, uro-bilinogen, bilirubin and glucose;
- **Spot urine testing**: albumin, creatinine for albumin/creatinine ratio calculation;
- **Standard microscopy (if abnormal dipstick)**: presence of red blood cells (RBC), RBC clumps, WBC, WBC clumps, epithelial cells (transitional, renal tubular, and

squamous), casts (hyaline, epithelial, WBC, RBC, granular, fatty, cellular, broad, waxy), crystals (triple phosphate, calcium oxalate, calcium phosphate, calcium carbonate, uric acid, amorphous, ammonium biurate, bilirubin, leucine, tyrosine, cystine), bacteria, yeast-budding, yeast-hyphae, trichomonas, oval fat body, fat, mucous, and sperm;

- **Pregnancy test** (women of childbearing potential): urine pregnancy test at Week 0 and Week 24/early termination visit.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: height (in cm at baseline), weight (in kg), BMI (in kg/m^2), HR (in bpm), SBP and DBP in sitting position (in mmHg).

2.1.4.5 Electrocardiogram variables

Not applicable.

2.1.5 Pharmacokinetic variables

Total and free PCSK9 concentrations in serum are assessed at baseline (Week 0), Week 12, and Week 24.

2.1.6 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.7 Quality-of-life endpoints

[redacted]

2.1.8 Health economic endpoints

Not applicable.

2.1.9 Diabetes related endpoints

The analyses of diabetes-related endpoints will include the following parameters:

- Absolute change in HbA1c in % and mmol/mol from baseline to Weeks 12 and 24
- Absolute change in FPG in mg/dL and mmol/L from baseline to Weeks 12 and 24

- Absolute change in number of glucose lowering treatments from baseline to Weeks 12 and 24:
    - For non-insulin treatments each unique treatment will be counted as 1, whereas for insulin treatments, insulin will be counted as 1 in total even if the patient is taking more than one insulin treatment (for example, a patient on glargine monotherapy will have "1" glucose lowering treatment, and a patient on glargine and humalog without additional glucose lowering treatments will also have "1" glucose lowering treatment).
    - For combinations of insulin and non-insulin treatment, the insulin will be counted as 1 and each non-insulin in the combination will be counted as 1 (for example, ideglira would count as "1" for the insulin degludec and "1" for the liraglutide, i.e. a total of "2" glucose lowering treatments).

2.1.10 Anti-alirocumab antibodies

Anti-alirocumab antibodies (status, neutralizing status and titer) will be collected at Week 0, Week 12, and Week 24.

2.1.11 Nutritional counseling

Nutritional counseling status will be collected at Week 0, Week 4, Week 8, Week 12, Week 20 and Week 24.

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 signed the informed consent.

Randomized patients consist of all screened patients who are recorded in the IVRS/IWRS database (if randomized to usual care) and with a treatment kit allocated (if randomized to alirocumab), regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population. The safety experience of patients treated and not randomized will be reported separately and these patients will not be in the safety population.

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.

For patient study status, the total number of patients in each of the following categories will be presented by randomization stratum (for strata with at least 10% of patients) and in the pooled data 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;
- Randomized patients;
- Randomized but not treated patients and reason for not treated (not applicable for patients randomized to usual care arm without intent to prescribe an additional LMT);
- Randomized and treated patients;
- Patients who completed the study treatment period as per protocol;
- Patients who discontinued the study treatment and main reason for permanent treatment discontinuation (not applicable for patients randomized to usual care arm without intent to prescribe an additional LMT);
- Patients who completed the study period as per protocol;
- Patients who discontinued the study and main reason for study discontinuation;
- Status at last study contact.

For all categories of patients (except for the screened and non-randomized categories) percentages will be calculated using the number of randomized patients as the denominator.

Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. A listing of patients who prematurely discontinued study treatment with further reason provided in free text will be provided.

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 treated), using Kaplan-Meier method.

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

Patients with insufficient post-treatment follow-up will be described on the safety population by treatment group. Number and percentage of patients with insufficient follow-up, quantitative (in weeks) and qualitative (<1, ≥ 1 to <3, ≥ 3 to <5, ≥ 5 to <7, ≥ 7 to <9 weeks) duration of follow-up will be presented by treatment arm. A patient is considered with insufficient post-treatment follow-up in the case of his/her last post-treatment phone-call is:

- For patients receiving alirocumab: less than 9 weeks after the last open-label alirocumab injection, unless patient died before
- For patients receiving another LMT in the usual care arm:
    - less than 9 weeks after the last dose of usual care treatment or
    - before Week 31,

whichever comes first, unless patient died before

- For patients randomized to usual care without LMT:
  - less than 9 weeks after the last on site study visit or
  - before Week 31,

  whichever comes first, unless patient died before.

All 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. Patients excluded from the ITT population will be listed as well as patients with major deviation potentially impacting efficacy analyses not resulting in exclusion from ITT population. These deviations are listed in the data review and surveillance plan.

Additionally, the following analysis populations will be summarized by treatment group:

- Randomized population;
- Efficacy population: ITT population;
- Safety population;
- PCSK9 population;
- [redacted]
- ADA population.

Definitions of the study populations are provided in Section 2.3.

Stratification

A shift table on randomized patients will describe the strata recorded in IVRS (no additional LMT, or intent to initiate fenofibrate, ezetimibe, omega-3 fatty acids, or nicotinic acid) and the actual LMT received recorded in the e-CRF on the UC medication page. A listing of patients with discrepancies between strata will be provided.

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) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR
2. A patient is dispensed an alirocumab kit/ usual care package (e.g., blister packs, pill container) not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit/package 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. Randomization irregularities are recorded in the IVRS/IWRS. Drug dispensing irregularities come from IVRS/IWRS only for the alirocumab arm, as the process of drug supply for usual care is not handled by IVRS/IWRS and is site-specific. Therefore drug dispensing irregularities presented in this section will only concern the alirocumab arm. The corresponding information for usual care would be found in the CSR as qualitative deviations in the specific section.

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

Randomization irregularities (both treatment arms)	***Drug dispensation irregularities (alirocumab)***
Randomization by error	Alirocumab kit dispensation without IVRS transaction
Patient randomized twice	Erroneous alirocumab kit dispensation
Stratification error	Alirocumab kit not available
	An alirocumab kit allocated at Day 1 or any unscheduled replacement before Week 12 is administered to the patient after his up-titration visit (Week 12)

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Non-randomized, treated patients will be described separately. A listing of randomization and drug allocation irregularities as well as a listing of patients randomized twice (or more) or treated but not randomized will be produced.

A listing of patients with treatment group as randomized different than treatment group as treated will be produced.

2.3 ANALYSIS POPULATIONS

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

The randomized population includes all randomized patients as defined in Section 2.2.

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.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population.

2.3.1.1 Intent–to-treat population

The ITT population is defined as all randomized patients who have an evaluable primary efficacy endpoint defined as:

- Baseline non-HDL-C value available;
- At least one non-HDL-C value available 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.

2.3.2 Safety population

The safety population considered for safety analyses will be the randomized population who did actually receive at least one dose or part of a dose of the open-label alirocumab and all patients randomized to usual care.

Patients will be analyzed according to the treatment actually received (usual care or alirocumab).

The safety analysis will focus on the TEAE period defined in Section 2.1.4.

In addition:

- Non-randomized but treated patients or patients treated before the randomization will not be part of the safety population, but their safety data will be presented separately;
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized;
- For patients receiving more than one study treatment during the trial, the treatment group allocation for as-treated analysis will be the one to which the patient was treated with the longest duration.

2.3.3 Anti-alirocumab antibody population

The ADA analysis will be performed on safety population with a blood sample for antibodies at Week 0 (baseline) and at least one evaluable blood sample for antibodies post-baseline.

2.3.4 [redacted]

[redacted]

[redacted]

2.3.5 Proprotein convertase subtilisin kexin type 9 population

The PCSK9 analysis will be performed on all randomized patients with a baseline sample of PCSK9 at Week 0 (baseline) and at least one evaluable blood sample for PCSK9 level post-baseline (Week 12 and/or Week 24).

2.4 STATISTICAL METHODS

2.4.1 Demographic and baseline characteristics

Parameters described in Section 2.1.1 will be summarized by treatment group and overall using descriptive statistics. Continuous data will be summarized using the number of available data, mean, SD, median, first quartile (Q1) and third quartile (Q3), minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number of non-missing data and the number and percentage of patients (the denominator being the number of non-missing values) in each treatment group and overall.

P-values on demographic and baseline characteristic data will not be calculated.

Parameters will be summarized on the randomized population in the treatment group to which they were randomized (as per IVRS). Analyses will be repeated for the ITT population if the size of the ITT population is different (>10%) from the size of the randomized population in any treatment group. Similarly, parameters will be repeated in the safety population if the randomized population and the safety population have different size (>10%) in any of the treatment groups (defined by the actually received treatment group).

For the randomized population, parameters will also be summarized within each randomization stratum as per IVRS (for strata with at least 10% of patients).

2.4.1.1 Medical history

Patients with clinical ASCVD, defined as per protocol and as per the 2013 AHA/ACC guidelines (see Section 2.1.1) will be described using the number (%) of patients in each ASCVD component.

For the patients with no clinical ASCVD as per protocol, the following will be tabulated:

- The number (%) of patients having additional CV risk factors as defined in Section 2.1.1 (number (%) for each CV risk factor)
- The number (%) of patients with target organ damage due to diabetes (microalbuminuria, macroalbuminuria, retinopathy (pre-proliferative or proliferative) and/or CKD)
- The number (%) of patients with at least one additional CV risk factor (see Section 2.1.1):

- 1 CV risk factor
- 2 CV risk factors
- ≥3 CV risk factors

Other CV medical history, other allergic medical history and all other relevant medical/surgical history will be presented by primary SOC and HLT. The table will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on the overall incidence across treatment groups.

2.4.1.2 Correlation analysis at baseline

Linear regressions adjusted on sex, randomization strata and age (as continuous covariate) will be performed to analyze correlation between:

- baseline non-HDL-C and HbA1c,
- baseline non-HDL-C and total PCSK9,
- baseline non-HDL-C and free PCSK9,
- baseline total PCSK9 and HbA1c
- baseline free PCSK9 and HbA1c

if the variables (non-HDL-C, HbA1c and PSCK9 levels) are not normally distributed, they will be log-transformed.

Five scatter plots will be produced with regression lines plotted overall and by randomization strata (only for strata with at least 10% of patients).

2.4.1.3 Additional analyses of baseline characteristics

Additional analyses of demographics and baseline characteristics on selected endpoints will also be replicated in the subgroup of patients of the region North America, overall and in the fenofibrate stratum as per IVRS.

2.4.2 Prior or concomitant medications

The prior, concomitant and post-treatment medications will be presented for the safety population. Summaries will be repeated within each actual stratum defined by the actually received treatment (for strata with at least 10% of patients).

Medications will be coded according to the WHO-DD dictionary, considering the first digit of the anatomic therapeutical 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 by treatment group, 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), 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 (anatomic or therapeutic), alphabetical order will be used.

In addition, the following specific medications will be summarized:

- Concomitant CV drugs will be summarized by treatment group by chemical class and standardized medication name, and by therapeutic class and standardized medication name. The tables will be sorted by decreasing frequency of chemical or therapeutic class and then of standardized medication based on the incidence in the alirocumab group.
- LMTs (statins and other LMTs, including nutraceutical products that may affect lipids) will be described by treatment group, pre-specified categories and standardized medication name. The table for prior LMTs will be sorted by decreasing frequency of standardized medication name based on the overall incidence across treatment groups within categories. The tables for concomitant and post-treatment LMTs will be sorted by decreasing frequency of standardized medication name based on the incidence in the alirocumab group.

  For LMTs at randomization the following will be described:
  - Proportion of patients with any statin
  - Proportion of patients according to highest intensity of statin therapies (high intensity, moderate intensity, low intensity) according to the following table:

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg Simvastatin 80 mg	Atorvastatin 10-20 mg Fluvastatin 40 mg BID Fluvastatin XL 80 mg Lovastatin 40 mg Pitavastatin 2-4 mg Pravastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg	Fluvastatin 20-40 mg Lovastatin 20 mg Pitavastatin 1 mg Pravastatin 10-20 mg Simvastatin 10 mg

Regarding doses not included in this table:

A statin dose that falls in between two intensity classes will be counted in the class of lowest intensity (i.e. pravastatin 30 mg will be counted as low intensity, atorvastatin 30 mg will be counted as moderate intensity).

A statin dose under the lower threshold of low intensity will be counted as low intensity (i.e., lovavastatin 10 mg will be counted as low intensity).

A statin dose above the higher threshold of high intensity will be counted as high intensity (i.e., rosuvastatin 80 mg will be counted as high intensity).

Simvastatin ≥ 80 mg will be counted as high intensity, while simvastatin < 80 mg and ≥ 20 mg will be counted as moderate intensity.

- Statin therapies by name and dose

- Glucose lowering treatments (insulin and other)used at baseline, Week 12 and Week 24 will be summarized by treatment group, pre-specified category and standardized medication name. The tables will be sorted by decreasing frequency of standardized medication name within category based on the overall incidence across treatment groups at baseline and on the incidence in the alirocumab group at Week 12 and Week 24. Pre-specified categories are:
  - Insulins:
    - Fast acting
    - Intermediate (excluding premix)
    - Long acting
    - Inhaled
    - Premixed
  - Other glucose lowering treatments (non-insulin):
    - Biguanides
    - Sulfonylureas
    - Sulfonamides
    - Alpha glucosidase inhibitors
    - Thiazolidinediones
    - DPP-4 inhibitors
    - SGLT2 inhibitors
    - GLP-1 receptor agonists
    - Other blood glucose lowering drugs

  The number of glucose lowering treatments (see Section 2.1.9) will also be described as quantitative and qualitative variables: 1, 2 and ≥3.

2.4.2.1 Additional analyses of prior or concomitant medications

Additional analyses of selected concomitant medications will also be replicated in the subgroup of patients of the region North America, overall and in the fenofibrate stratum as per IVRS.

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 received within the safety population (Section 2.3.2).

For alirocumab arm, dates of injection are retrieved from e-CRF ‘Alirocumab Administration’.
For usual care arm (except when no LMT other than statin is prescribed), dates of administration are retrieved from e-CRF ‘Usual Care Medication for Lipid Modification therapy’.

2.4.3.1 Extent of investigational medicinal product exposure

Alirocumab arm

The extent of alirocumab exposure will be assessed by:

- the duration of alirocumab exposure in weeks defined as: (date of last open-label alirocumab injection – date of first open-label alirocumab injection + 14 days) / 7, regardless of unplanned intermittent discontinuations (see Section 2.5.2 for calculation in case of missing or incomplete data)
- the total number of injections by patient
- the number and percentage of patients with an up-titration; (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).

Usual care arm (except when no LMT other than statin is prescribed)

The extent of usual care treatments will be assessed by:

- The duration of exposure in weeks defined as: (last dose of open-label treatment date – first dose of open-label treatment date + 1 day) / 7, regardless of unplanned intermittent discontinuations (see Section 2.4.3 for calculation in case of missing or incomplete data)

All quantitative parameters above will be summarized using number, mean, SD, median, Q1 and Q3, minimum, and maximum (non-integer values will be rounded to 1 decimal place). In addition, duration of treatment exposure will be summarized and presented graphically using bar chart displaying the percentage of patients according to the following categories: ≥1 day to <4 weeks, ≥4 weeks to <8 weeks, ≥8 weeks to <12 weeks, ≥12 weeks to <16 weeks, ≥16 weeks to <24 weeks, and ≥24 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.

Alirocumab arm

Compliance will be assessed using the following parameters:

- the mean injection frequency, defined for each patient as the average number of days between 2 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, defined for each patient as: (number of injections performed during the study period / number of theoretical injections to be performed during the study period)*100.

- Number of theoretical injections will be defined for each patient as: [(last injection date – first injection date) / 14] + 1

These parameters will be summarized descriptively (N, mean, SD, median, Q1 and Q3, minimum, and maximum). Percentage of patients with overall compliance <80% and ≥80% will be presented.

- Percentage of patients who discontinued temporarily in relation with an AE will be presented.
  - For patients with temporary discontinuation, the number of injections not performed will be presented by category: 1 injection, 2 injections, 3 or more injections.

Cases of symptomatic overdose with IMP (i.e., an event that is suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts), and defined as at least twice of the intended dose within the intended therapeutic interval (i.e. 2 or more injections are administered in <7 calendar days) will be specified as an AESI and will be listed and described as such in the AE analysis (see Section 2.1.4.1).

Usual care arm (except when no LMT other than statin is prescribed)

The compliance is defined by the number of days with all intakes as planned / duration of exposure x 100. The number of days with all intakes as planned will be obtained by subtracting the total number of days with at least one dose missed (from the Compliance e-CRF forms) from the duration of exposure. The compliance will be summarized descriptively (N, mean, SD, median, Q1 and Q3, minimum, and maximum) and percentage of patients with compliance <80% and ≥80% will be presented.

- Percentage of patients who discontinued temporarily in relation with an AE will be described.
  - For patients with temporarily discontinuation, the number of days without treatment will be presented.

2.4.4 Analyses of efficacy endpoints

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

All the efficacy endpoints (primary, key secondary and other efficacy endpoints) will be analyzed in the ITT population for the overall comparison (alirocumab versus usual care) and for patients intended to receive fenofibrate in order to compare the efficacy of alirocumab versus fenofibrate. However no subgroup analysis will be performed in the fenofibrate stratum.

2.4.4.1 Analysis of primary efficacy endpoint

2.4.4.1.1 Primary efficacy analysis

The percent change in non-HDL-C from baseline to 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 8 to Week 24 analysis windows will be used and missing data are accounted for by the MMRM model.

Let $\mu 0$ and $\mu 1$ be the population means of the percent change from baseline in non-HDL-C at Week 24 under usual care and alirocumab, respectively. The null hypothesis that will be tested is:

"H0: $\mu 0 = \mu 1$" versus "H1: $\mu 0 \neq \mu 1$".

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 analysis to explore the impact of non-ignorable missingness on the primary efficacy analysis will be conducted (see pattern mixture model defined in Section 2.4.4.1.3).

Overall analysis

The model will include the fixed categorical effects of treatment group (alirocumab versus usual care), randomization stratum as per IVRS, time point (Week 8, Week 12, Week 20 and Week 24), treatment group-by-time point interaction, stratum-by-time point interaction, as well as the continuous fixed covariates of baseline non-HDL-C value and baseline value-by-time point interaction. In case of non-convergence of the model, a model with less interactions terms will be explored.

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). To compare the alirocumab group to the usual care group, an appropriate contrast statement will be used to test the differences of these estimates, at the 2-sided 0.025 level. LS-mean difference versus usual care and the corresponding 97.5% confidence intervals (CIs) will be provided.

Analysis in the fenofibrate stratum

A MMRM model will also be used to compare alirocumab versus fenofibrate with additional interactions terms: treatment group-by-stratum- and treatment group-by-stratum-by-visit. The model will be run with all patients, whatever their stratum and will be also used to derive the treatment effect in the other strata (Section 2.4.4.5). In case of non-convergence of the model with the triple interaction, the same model as the primary efficacy analysis will be run in the "intent to prescribe fenofibrate" stratum.

The appropriate contrast statement will be used to test the difference between the estimate of alirocumab group and the estimate of usual care group in the fenofibrate stratum.

2.4.4.1.2 Model assumption checks

The following analyses will be performed to check the model assumptions.

Homogeneity of treatment effect across baseline non-HDL-C levels:

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

- Treatment group * baseline non-HDL-C
- Treatment group * time-point * baseline non-HDL-C

Within the framework of this model with interaction terms, a graph presenting the LS means difference versus usual care at Week 24 and the corresponding 97.5% CI will be provided by baseline non-HDL-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

2.4.4.1.3 Sensitivity analyses

On top of standard tables, forest plots will also be provided to present the results of the sensitivity analyses together with the main analysis.

Sensitivity to treatment change

A sensitivity analysis will be performed on the primary efficacy analysis excluding non-HDL-C values assessed after the first treatment change from the analyzed data. This analysis will be done as per analysis described in Section 2.4.4.1.1.

A treatment change is defined as:

- For alirocumab: permanent discontinuation
- For usual care: permanent discontinuation of the LMT initiated at randomization
- For both groups: add-on of a new LMT

Note: changes in dosage will not be considered in this analysis.

Sensitivity to randomization strata

In order to assess the robustness of the primary analysis to randomization stratum mistakes (i.e., 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. The actual stratum as per the e-CRF is defined, for the patients randomized to usual care only, as the actual usual care treatment taken for the longer time. In case no additional LMT is recorded using e-CRF page "Usual Care Medication for Lipid Modification therapy", the actual stratum will be assigned to "no intent to prescribe an additional LMT".

Sensitivity to handling of missing data - Pattern mixture model

In order to assess the robustness of the primary efficacy analysis with regards to handling of missing data, a sensitivity analysis will be conducted based on a pattern-mixture model approach.

Multiple imputation will be used with different imputation strategies applied to non-HDL-C values missing during the on-treatment period (as defined below)

- Patients randomized to alirocumab would continue to show benefit from treatment similar to that observed at the scheduled time point within 21 days of their last dose of open-label alirocumab (on-treatment period). Therefore, non-HDL-C values missing during the on-treatment period (e.g., samples obtained outside the specified window, no blood sample available although visit was performed, etc) should be considered as "Missing At Random" and imputed using a model based on other on-treatment measurements, gender, age and BMI;
- Patients randomized to usual care with additional LMT would continue to show benefit from treatment similar to that observed at the scheduled time point within 3 days of their last dose of LMT. Therefore, non-HDL-C values missing during the on-treatment period (e.g., samples obtained outside the specified window, no blood sample available although visit was performed, etc) should be considered as "Missing At Random" and imputed using a model based on other on-treatment measurements, gender, age and BMI;
- Patients, randomized to usual care and for whom the Investigator has not prescribed an additional LMT, would tend to have non-HDL-C values similar to baseline. Therefore, non-HDL-C values missing after randomization should be imputed based on patient's own baseline value;
- Patients who stopped taking their study treatment no longer benefited from it after discontinuation, and thus tended to have non-HDL-C values returning to baseline. Therefore, non-HDL-C values missing after on-treatment period should be imputed based on patient's own baseline value.

Missing non-HDL-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 non-HDL-C at this time point. The completed data sets will be analyzed using an ANCOVA model with treatment group and randomization stratum as per IVRS as fixed effects, and the baseline non-HDL-C value as continuous covariate. The results from the 100 analyses will be combined using Rubin's formulae (6).

2.4.4.1.4 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, treatment group-by-subgroup factor, time point-by-subgroup factor, and treatment goup-by-time point-by subgroup factor interaction terms and a subgroup factor term will be added as fixed factors in the primary MMRM model described in Section 2.4.4.1.1. LS means difference versus usual care at Week 24 will be provided, as well as the corresponding SE and 97.5% CI, within each subgroup. The significance level of the treatment group-by-subgroup factor interaction term at Week 24 will be also provided for each factor for descriptive purpose. Forest plots will be provided.

For each subgroup analysis, subgroups will be included in the analysis only if there are ≥10 patients by subgroup and treatment arm. Otherwise, unless specified below, the subgroups not meeting the required number of patients will be pooled to form larger subgroups if possible, or they will be excluded from analysis.

Subgroups of interest are:

- Gender: Female, Male;
- Menopausal status, for female only: Yes, No;
    - For post-menopausal women, type of hormone replacement therapy: estrogen only, estrogen and progesterone, no estrogen or progesterone;
- Age: <65, [65 - 75[and ≥75 years; 65, ≥65 years old;
- BMI: <25, [25-30[, ≥30 in kg/m2;
- Race: White/Caucasian, non-White/Caucasian;
- Ethnicity: Hispanic or Latino, non-Hispanic or Latino, Not reported/Unknown;
- Region (North America, Europe, Rest of World);
- Duration of diabetes: <5, [5-10], >10 years, if the number of patients by subgroup are sufficient; otherwise by tertiles;
    - Patients with duration of diabetes < 1 year are excluded.
- Prior history of myocardial infarction (silent or acute) or ischemic stroke: Yes, No;
- CKD: Yes, No, from cardiovascular medical history e-CRF page;
- ASCVD as per protocol (see Section 2.1.1): Yes, No;
- ASCVD including TIA (see Section 2.1.1): Yes, No;
- eGFR: <30,[30 - 60[, [60 - 90[, ≥90 mL/min/1.73m², if there are not enough patients with eGFR <30, the <30 and the [30-60[categories will be pooled together;
- Baseline albumin/creatinine ratio: <30, [30 – 300[, ≥300 mg/g (<3.39, [3.39-33.9[, ≥33.9 mg/mmol);
- Diabetic kidney disease by category (cf Appendix C)
    - Category 1: (G1A1, G2A1)

- Category 2: (G1A2, G2A2, G3aA1)
- Category 3: (G1A3, G2A3, G3aA2, G3bA1)
- Category 4: (G3aA3, G3bA2, G3bA3, G4A1, G4A2)
- Category 5: (G4A3, G5A1, G5A2, G5A3)

If the numbers of patients by subgroup don't allow this subgroup analysis, other groupings will be explored.

- Baseline total PCSK9 level: <median, ≥median;
- Baseline free PCSK9 level: <median, ≥median;
- Baseline HbA1C:
  - <7, [7 – 9[, ≥9%. if the number of patients by subgroup meets the requirement (cf. above); otherwise <median, ≥median and by tertiles;
  - Controlled DM (HbA1C<7%) vs uncontrolled DM (HbA1C≥7%)
- Statin treatment at randomization:
  - Any statin versus no statin
  - High intensity statin versus medium or low intensity statin at randomization
- Baseline non-HDL-C: <130, [130 – 160[, [160 – 190[, ≥190 mg/dL (<3.37, [3.37 - 4.14[, [4.14 - 4.91[, ≥4.91 mmol/L),), if the number of patients by subgroup meets the requirement (cf. above); otherwise one of the following groupings will be explored:
  - <130, [130-160[, ≥160 mg/dL (<3.37, [3.37 – 4.14[, ≥4.14 mmol/L)
  - by tertiles (only if no sufficient patients in previous grouping)

  For this specific subgroup factor, the MMRM model will include fixed categorical effects for treatment group, randomization stratum as per IVRS, baseline non-HDL-C category, time point, and the interactions treatment group-by-time point, stratum-by-time point, baseline non-HDL-C category-by-time point, treatment group-by-baseline non-HDL-C category, and treatment group-by-baseline non-HDL-C category-by-time point;
- Baseline calculated LDL-C: <100, [100 – 130[, [130 – 160[, ≥160 mg/dL (<2.59, [2.59 - 3.37[, [3.37 - 4.14[, ≥4.14 mmol/L), if the number of patients by subgroup meets the requirement (cf. above); otherwise one of the following groupings will be explored:
  - <100, [100-130[, ≥130 mg/dL (<2.59, [2.59 - 3.37[, ≥3.37 mmol/L)
  - by tertiles (only if no sufficient patients in previous grouping)
- Baseline HDL-C: low HDL-C (<40 mg/dL (<1.04 mmol/L) for males / <50 mg/dL (<1.29 mmol/L) for females), high HDL-C ≥40 mg/dL (≥1.04 mmol/L) for males / ≥50 mg/dL (≥1.29 mmol/L) for females);
- Baseline TGRL:
  - <30, ≥ 30 mg/dL
  - by quintiles
- Baseline fasting TG:
  - <150, [150 – 200[, ≥200 mg/dL (<1.7, [1.7 – 2.3[, ≥2.3 mmol/L);

- <150, ≥150 mg/dL (<1.7, ≥1.7 mmol/L);
- by quintiles;

- Baseline Lp(a):
  - <30, [30 – 50[, ≥50 mg/dL (<0.3, [0.3 - 0.5[, ≥0.5 g/L);
  - <30, ≥30 mg/dL (<0.3, ≥0.3 g/L);

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 (i.e., lipids other than TG, TGRL and Lp(a)) will be analyzed using the same MMRM model as for the primary endpoint. Specifically, the model will contain fixed categorical effects of treatment group, randomization stratum as per IVRS, planned time points to Week 24, treatment group-by-time point interaction, stratum-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 endpoints defined in Section 2.1.3.2, anticipated to have a non-normal distribution (i.e., TG, TGRL, and Lp(a)); will be analyzed using a robust regression model (i.e., ROBUSTREG SAS procedure with M-estimation option) with treatment group, randomization stratum as per IVRS as main effects and corresponding baseline value(s) as covariate. Missing values will be addressed using a multiple imputation model. The imputation model will include:

- The variables included in the robust regression model, i.e. the treatment group, the randomization stratum, and the baseline value.
- The baseline characteristics such as: age, BMI, and gender. Age and BMI will be included as continuous variables.
- The values at Week 8, Week 12, Week 20 and Week 24 time points.

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

In the robust regression model, the analyzed endpoint at time point of interest will be derived from observed and imputed lipid values at this time point. The treatment group combined means will be provided with respective SE estimates. The combined mean difference between the treatment groups will be provided with the SE, 97.5% CI and p-value through the SAS MIANALYZE procedure.

2.4.4.2.3 Binary endpoints

Binary secondary efficacy endpoints defined in Section 2.1.3.2 (e.g., proportion of patients below a threshold) will be analyzed using logistic regression with treatment group and randomization stratum as per IVRS as main effects and corresponding baseline value(s) as covariate. Missing values will be addressed using a multiple imputation approach (see Section 2.4.4.2.2). The variables in the multiple imputation model will at least include the same variables as used in the logistic regression model. In the logistic regression model, the analyzed endpoint at time point of interest will be derived from observed and imputed lipid values at this time point. Treatment effects will be compared and the combined odds ratio estimate between the treatment groups, with their corresponding 97.5% CI and p-value will be provided via the SAS MIANALYZE procedure.

In the data dependent case that the logistic regression method is not applicable (e.g., the response rate is zero in one treatment arm and thus the maximum likelihood estimate may not exist), the last observation carried forward (LOCF) approach would be used for handling of missing values and an 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 (or Week 12 as applicable) to impute the missing Week 24 value (or 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. Exact odds ratio versus usual care, 97.5% CI, and p-value will be provided.

2.4.4.2.4 Summary of results per time point

Central laboratory values (in conventional and international units), percent change from baseline and/or when appropriate, absolute change from baseline (in conventional and international units) of all lipid efficacy endpoints (as listed in Section 2.1.3) will be provided at each time point and for each treatment group in the ITT population using:

- For lipids other than TG, TGRL, and Lp(a): LS mean and SE for each treatment group, obtained from the same MMRM models as used for endpoints above and including all 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, TGRL and Lp(a): combined mean and SE for each treatment group obtained from multiple imputation approach followed by the robust regression models as used for endpoints above and including all planned time points and with raw values or percent changes from baseline as response variable in the model as appropriate.

All measurements, scheduled or unscheduled will be assigned to analysis windows (see Section 2.5.3 on which value to select) in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded.

Summary tables and graphs over time for each parameter will be plotted by treatment group (LS mean + SEs by time point).

In addition, quantitative descriptive summaries by time point for each treatment group (value at visit and % change from baseline, and/or when appropriate absolute change from baseline) will be presented for all lipids using observed (i.e., non-missing) data and binary variables will be also provided in summary tables.

Non-HDL-C will be summarized and plotted according to up-titration status. i.e., according to whether the patients remained on the 75 mg dose or whether they were up-titrated to 150 mg.

2.4.4.3 Sensitivity analysis for the computation of TGRL values

Two sensitivity analyses will be performed to assess the impact of the computation of TGRL values on the effect of treatment:

1. In the first sensitivity computation, TGRL will be computed from measured LDL-C only, not replaced by calculated LDL-C in case of missing value for measured LDL-C.
3. In the second sensitivity computation, TGRL will be computed from fasting samples only, i.e. non-fasting samples will be excluded from analysis.

For both sensitivity computations, the percent change from baseline to Weeks 12 and 24 will be assessed in the same way than for the main computation of TGRL, using the model described in section 2.4.4.2.2.

2.4.4.4 Multiplicity issues

In order to handle multiple key secondary efficacy endpoints (for both analyses, i.e. alirocumab versus usual care and alirocumab versus fenofibrate), the overall type-I error (0.025 for each analysis) will be controlled by the use of a sequential inferential approach. Statistical significance of the primary parameter at the 0.025 alpha level is required before drawing inferential conclusions about first key secondary parameter (refer to order in Section 2.1.3.2.1).

Inferential conclusions about successive key secondary efficacy parameters require statistical significance of the prior one. This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.025 level for each analysis (alirocumab versus usual care and alirocumab versus fenofibrate).

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

2.4.4.5 Additional efficacy analyses

All analyses of the efficacy endpoints (primary, key secondary and other efficacy endpoints) will also be performed within each other randomization stratum as per IVRS (no additional LMT, or intent to prescribe ezetimibe, omega-3 fatty acids, or nicotinic acid) in order to compare the efficacy of alirocumab versus the other options of usual care. The analyses will be similar to the ones performed for the fenofibrate stratum (see Section 2.4.4.1.1) provided that there are at least 10 patients in each treatment arm in the stratum of interest.

Additional efficacy analyses on selected endpoints will also be replicated in the subgroup of patients of the region North America.

2.4.5 Analyses of safety data

The summary of safety results will be presented by actual treatment group. Summaries will be descriptive in nature. Safety analyses will be performed overall and by actual stratum defined by the actually received treatment (only for strata with at least 10% of patients).

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 (e.g., exposed but not randomized or re-randomized patients) will be listed separately.
- The baseline value is defined generally as the last available value before the first injection of open-label alirocumab/first dose of usual care treatment for patients prescribed another LMT if allocated to the usual care arm/ randomization for patients randomized to usual care and not receiving additional LMT.
- The 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]).
- PCSA criteria will determine which patients had at least one PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the TEAE period by treatment group on the safety population.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.3 in order to provide an assessment for Week 0 to Week 24 time points.
- For quantitative safety parameters based on central laboratory 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, all TEAE analyses will be provided according to up-titration status, i.e., 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.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of AEs reporting will be on TEAEs. Pre-treatment and 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 2.5.2.

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 within each treatment group.

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (pre-treatment, treatment-emergent, 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 (in the alirocumab group) 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 internationally agreed SOC 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 TEAEs 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 (patients in usual care treatment arm with no additional LMT are excluded from denominator).

- Number (%) of patients experiencing TEAEs by primary SOC, HLGT, HLT, and PT sorted by the international agreed SOC order and by alphabetical order for the other levels (HLGT, HLT, PT);
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC, HLT and PT (HLT incidence ≥2 % in any treatment group), sorted by internationally agreed SOC order and by alphabetic order for the other levels (HLT and PT);
- Number (%) of patients experiencing TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC (in the alirocumab group). This sorting order will be applied to all other tables of TEAEs by SOC and PT, unless otherwise specified;
- All TEAEs regardless of relationship in one column and, in the same table a second column with TEAEs related to IMP according to Investigator's opinion by primary SOC, HLGT, HLT and PT;
- All TEAEs by maximal intensity (i.e., 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) will be provided for all TEAEs by SOC and PT. For a patient with event, patient year is censored at time of first event; for patient without event, it corresponds to length of TEAE period;
- Kaplan-Meier curves will be provided, when appropriate, for time from first dose of open-label IMP to the first occurrence of selected TEAEs as well as incidence rates at the time of analysis (Week 24 for the first analysis, Week 32 for the final analysis). Hazard ratio versus usual care group and corresponding 95% CI will be given. Patients without any event will be censored at the end of the TEAE period. Selected TEAEs will be local injection site reactions, general allergic reactions, neurocognitive events, hepatic disorders 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;
- All serious TEAEs regardless of relationship in one column and, in the same table a second column with TEAEs related to IMP 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;
- All SAEs will be listed.

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 AESI as listed in Section 2.1.4.1 will be analyzed using selections defined in Section 2.1.4.1. They will be presented by SOC, HLGT and PT. The summaries will be sorted by decreasing incidence of PT within each SOC and HLGT (in the alirocumab group).
- Overview of AESI and grouping of hepatic disorders will be presented summarizing number (%) of patients with any
    - AE;
    - TEAE;
    - TEAE leading to death;
    - TEAE leading to permanent treatment discontinuation (patients in usual care treatment arm with no additional LMT are excluded from denominator).
- In addition, the following variables will be tabulated for the local injection site reactions TEAEs:
    - Highest intensity of the event (mild, moderate, severe);
    - Mean duration (days);
    - Number of events divided by the number of open-label treatment injections received;
    - Time from first open-label treatment injection to first injection site reaction;
    - Number of open-label IMP injections up to the first injection site reaction;
    - Description of the highest intensity of each symptom recorded in the specific e-CRF page with tables and bar chart.
- Besides, description of symptoms and possible etiologies for general allergic reaction TEAE reported by Investigator will be presented.

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.

Subgroups of patients with 2 consecutive LDL-C <25 mg/dL or 2 consecutive LDL-C <15 mg/dL

- 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, 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, i.e., <0.39 mmol/L). 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 (respectively <15 mg/dL) will be considered.

Analysis of non-serious treatment emergent adverse events

- All non-serious TEAEs by primary SOC and PT presented in alphabetical order within each SOC with PT >5% in any treatment arm.

Analysis of product complaints

- Number (%) of patients experiencing product complaints;
- Number (%) of patients experiencing product complaints associated with a TEAE;

2.4.5.2 Deaths

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

- Number (%) of patients who died by study period (on-study, on-treatment, post-study);
- Deaths in non-randomized patients or randomized but not treated patients
- Treatment-emergent AEs leading to death (death as an outcome on the AE e-CRF page as reported by the Investigator) by primary SOC and PT showing number (%) of patients sorted by internationally agreed SOC order, with 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 (i.e., death occurring in the TEAE period or during the post-treatment period).
- All deaths will be listed, with reason.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, standard deviation, median, Q1 and Q3, 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 of the treatment period, last on-treatment and/or worst on-treatment) by treatment group. In addition, for some parameters of interest, mean changes from baseline with the corresponding SE will 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 treatment group whatever the baseline level and/or according to the following baseline status categories:

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

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 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 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.

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 period (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 (Ab) with negative RNA", a "confirmed positive antibody (Ab) with no RNA available" 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 described for all evaluations (baseline and post-baseline).

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

1st Ab	**Positive**						**Negative**				
RNA	Positive	Negative			Missing		Positive	Negative		Missing	
2nd Ab	*Any result*	*Positive*	*Negative*	*Missing*	*Positive*	*Negative / missing*	*Any result*	*Positive*	*Negative / missing*	*Positive*	*Negative / missing*
HCV infection status	Positive RNA	Conf. positive Ab with neg. RNA	Negative	Negative RNA, conf. Ab missing	Conf. Positive Ab no RNA available	Positive Ab no RNA available	Positive RNA	Negative	Negative	Positive Ab no RNA available	Negative

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

If no Ab 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.

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 2.1.4.1) at any post-baseline visit by baseline status will be displayed by treatment group for each parameter.

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

Listing of possible Hy's law cases identified by treatment group (i.e., patients with any elevated ALT >3 x ULN, and associated with an increase in bilirubin >2 x ULN, concomitantly or not) with AST, ALT, ALP, GGT, 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 2.3.5.1). Time to liver-related treatment discontinuation will be analyzed using Kaplan-Meier estimates presented by treatment group.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, standard deviation, median, Q1 and Q3, minimum and maximum) of all vital signs variables (raw values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point of the treatment period, last on-treatment and/or worst on-treatment 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.

- The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group.

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 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.

2.4.5.6 Additional safety analyses: region North America

Additional safety analyses on selected endpoints will be replicated in the subgroup of patients of the region North America.

2.4.6 [redacted]

[redacted]

2.4.7 Analyses of diabetes-related endpoints

The analyses of diabetes-related endpoints will be performed on the ITT population and will be descriptive only. Summary statistics, including the mean, SD, median, Q1 and Q3, minimum, and maximum of the 3 endpoints (HbA1c, FPG, and number of glucose lowering treatments, see Section 2.1.9) will be calculated for each visit and presented by treatment group, for the raw values as well as the change from baseline. The analysis will be performed overall and by randomization stratum as per IVRS (for strata with at least 10% of patients) and also in the subgroup of patients of the region North America.

2.4.8 Analyses of anti-alirocumab antibody variables

The following summaries will be performed on the ADA population (see Section 2.3.3), taking into account all samples regardless of timing in relation to injections:

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

Additional analyses of ADA parameters may also be replicated in the subgroup of patients in the region North America.

2.4.9 Analyses of proprotein convertase subtilisin kexin type 9 levels

PCSK9 levels (total and free), percent change from baseline at each time point for each treatment group will be provided. All measurements, scheduled or unscheduled will be assigned to analysis windows (see Section 2.4.4 on which value to select) in order to provide an assessment for these time points. The time profile of mean PCSK9 levels will be plotted by treatment group with the corresponding SEs.

Analyses of PCSK9 will be performed overall and by randomization stratum as per IVRS (for strata with at least 10% of patients) and may be replicated in the subgroup of patients in the region North America.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Time since/duration of event

Time since/duration of [event] (years) = (Date of informed consent – Date of [event]*) / 365.25.

[event] can be diagnoses, quit smoking, menopause, …

*: In case the month of event would be missing, it will be put equal to JANUARY if the year of event equals the year of informed consent; it will be put equal to JULY otherwise. In case only the day of event would be missing, it will be put equal to 1.

Date of last dose of alirocumab

The date of the last injection is equal to the last date of administration reported on injection administration e-CRF page, or missing if the last administration date is unknown.

Date of last usual treatment care

The date of the last usual treatment care is equal to the last date of usual care reported on usual care medication for LMT e-CRF page, or missing if the last medication date is unknown.

HbA1c formula

The master equation for converting National Glycohemoglobin Standardization Program (NGSP) units into International Federation of Clinical Chemistry (IFCC) units (8) is:

HbA1c mmol/mol = 10.93 x HbA1c % - 23.5

Renal function formulas

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

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

Lipids variables and laboratory safety variables

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 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 computation of treatment duration if open-label alirocumab/usual care treatment first or end of treatment date is missing

If the first or last administration of open-label alirocumab/usual care treatment 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 date of administration of open-label alirocumab/usual care treatment 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;

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 onset dates/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. 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 open-label alirocumab/usual care treatment administration is missing, all AEs that occurred on or after the day of randomization will be considered as TEAEs.

When the time of the first open-label alirocumab/usual care treatment administration is missing, all AEs that occurred on the day of the first open-label alirocumab/usual care treatment administration will be considered as TEAEs.

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

If the assessment of the relationship to open-label alirocumab/usual care treatment is missing, then the relationship to open-label alirocumab/usual care treatment has to be assumed as possibly related in the frequency tables, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline, he/she will be grouped in the category “normal/missing at baseline.”

For PCSAs with two conditions:

- The first one based on a change from baseline value
- The other one based on a threshold value or a normal range.

If the first condition is missing, PCSA will be based only on the second condition.

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

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

[redacted]

[redacted]

2.5.3 Windows for time points

Data analyzed by time point (including efficacy data, laboratory safety data, vital signs, PCSK9, [redacted] diabetes-related parameters, ADA) will be summarized using the analysis windows given in Table 2 - Analysis windows definition. 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 98 for usual care 71 to minimum (98; study day corresponding to the first injection with IMP from kit allocated at up-titration IVRS contact) for alirocumab group
Week 20	141	127 to 154
Week 24	169	155 to 182
Week 32	225	211 to 238

Study day is calculated from the day of randomization. Day 1 is the day of randomization.

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.

2.5.4 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.

2.5.5 Pooling of centers for statistical analyses

Not applicable.

2.5.6 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No formal interim analysis for efficacy is planned since analysis of primary and key secondary efficacy endpoints will be final at the time of first-step analysis described below.

All efficacy data will be available for final analysis at a cut-off date corresponding to the Week 24 visit of the last patient and both the efficacy and safety analyses will be performed in a first-step analysis. Since safety data are being collected until the end of the study (Week 32), an update of the safety analysis will be performed at the end of the study. If analyses are not needed at Week 24, then they will be included in a second-step analysis at the end of the study.

The first-step analysis will be conducted as soon as all patients have been randomized and have at least all their data up to Week 24 collected and validated, and will consist of a final analysis of the primary and secondary efficacy endpoints up to Week 24, as well as safety analysis performed on all safety data collected and validated up to the common cut-off date, defined as the date of the last Week 24 visit.

The second-step analysis will be conducted at the end of the study and will consist in the updated analysis of safety endpoints until Week 32.

No multiplicity adjustment for multiple analyses is needed because all efficacy analyses will be completed at the time of the first-step analysis.

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

- Any lipid assessments within analysis windows up to Week 24 will be taken into account (may include few unscheduled lipid data soon after the cut-off date).
- 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 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 IMP/usual care 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 AE starting prior to the cut-off date will be taken into account. Medications, treatment discontinuations/completions, and deaths occurring after the cut-off date will not be included in the analyses.

- Post-treatment period, post-study period are not applicable for ongoing patients. Analyses of post-treatment AEs, post-study deaths, and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.
- Analysis of status at last study contact and proportion of patients with insufficient follow-up will be provided for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.

4 DATABASE LOCK

The database for Week 24 analysis is planned to be locked at 40 calendar days after last patient last on-site Week 24 visit. The database for Week 32 analysis is planned to be locked at 20 calendar days after last patient last Week 32 phone call.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

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