STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Insulin Treated Patients with Type 1 or Type 2 Diabetes and With Hypercholesterolemia at High Cardiovascular Risk Not Adequately Controlled on Maximally Tolerated LDL-C Lowering Therapy

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab:	antibody
ADA:	anti-alirocumab antibodies
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
Apo:	apolipoprotein
ASCVD:	atherosclerotic cardiovascular disease
AST:	aspartate aminotransferase
ATC:	anatomic therapeutic chemical
BMI:	body mass index
CHD:	coronary heart disease
CI:	confidence interval
CKD:	chronic kidney disease
CV:	cardiovascular
DBP:	diastolic blood pressure
e-CRF:	electronic Case Report Form
FDA:	US Food and Drug Administration
FPG:	fasting plasma glucose
GFR:	glomerular filtration rate
HbA1c:	glycated hemoglobin (A1c)
HDL-C:	high-density lipoprotein cholesterol
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IMP:	investigational medicinal product
[redacted]	[redacted]
ITT:	intent-to-treat
IVRS:	interactive voice response system
IWRS:	interactive web response system
LDL-C:	low density lipoprotein cholesterol
LMT:	lipid modifying therapy
Lp(a):	lipoprotein a
LS:	least square
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	multiple imputation
mITT:	modified intent-to-treat population
MMRM:	mixed effect model with repeated measures
non-HDL-C:	non-high-density lipoprotein cholesterol
PAD:	peripheral arterial disease

PCSA:	potentially clinically significant abnormality
PCSK9:	proprotein convertase subtilisin/kexin type 9
PT:	preferred term
Q1:	first quartile
Q2W:	quoque 2 weeks
Q3:	third quartile
RBC:	red blood cells
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
TC:	total cholestorol
TEAE:	treatment-emergent adverse event
TG:	triglyceride(s)
TGRL:	triglyceride rich lipoproteins
TIA:	transient ischemic attack
ULN:	upper limit of normal range
WBC:	white blood cell

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3b, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group, unbalanced (2:1 ratio) and stratified study.

After a screening phase of up to three weeks, patients will be centrally randomized via interactive voice response system (IVRS) or interactive web response system (IWRS) to one of the two treatment groups (alirocumab:placebo) and will be treated in a double-blind manner for approximately 24 weeks. Randomization ratio will be 2:1 (alirocumab:placebo) and patients will be stratified by diabetes type (ie, Type 1 diabetes versus Type 2 diabetes).

Approximately 500 patients will be randomized (333 in the alirocumab group and 167 in the placebo group). The recruitment of patients with Type 2 diabetes will complete when approximately 400 patients have been randomized. Recruitment of patients with Type 1 diabetes will continue until approximately 100 patients have been randomized or the end of the targeted recruitment period (summer 2016), whichever comes first.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objectives of this study are:

- To demonstrate the superiority of alirocumab in comparison with placebo in the reduction of calculated low-density lipoprotein cholesterol (LDL-C) after 24 weeks of treatment in patients with diabetes treated with insulin and with hypercholesterolemia at high cardiovascular (CV) risk not adequately controlled on maximally tolerated LDL-C lowering therapy;
- To evaluate the safety and tolerability of alirocumab in patients with diabetes treated with insulin.

1.2.2 Secondary objectives

The secondary objective of this study is:

- To demonstrate that alirocumab is superior in comparison to placebo in its effects on other lipid parameters at Weeks 12 and 24:
  - measured LDL-C;
  - non-high-density lipoprotein cholesterol (non-HDL-C);
  - apolipoprotein B (Apo B);
  - total cholesterol (TC);

- lipoprotein a (Lp(a));
- high-density lipoprotein cholesterol (HDL-C);
- triglyceride (TG) levels;
- triglyceride rich lipoproteins (TGRL);
- apolipoprotein A-1 (Apo A-1);
- apolipoprotein C-III (Apo C-III);
- LDL particle number;
- LDL particle size.

1.2.3 Other objectives

The other objectives of this study are:

- [redacted]
- To evaluate the development of anti-alirocumab antibodies (ADA);
- To describe the evolution of diabetes-related endpoints (glycated hemoglobin A1c [HbA1c], fasting plasma glucose [FPG], total daily insulin dose, daily insulin dose per kg, number of glucose lowering treatments).

While these objectives are not specified in the study protocol, they nevertheless represent additional clinically relevant objectives of the study that will be explored.

1.3 DETERMINATION OF SAMPLE SIZE

[redacted]

1.4 STUDY PLAN

This is a Phase 3b study to assess the efficacy and safety of alirocumab administered by subcutaneous injection in insulin treated patients with Type 1 or Type 2 diabetes and with hypercholesterolemia at high CV risk not adequately controlled on maximally tolerated LDL-C lowering therapy.

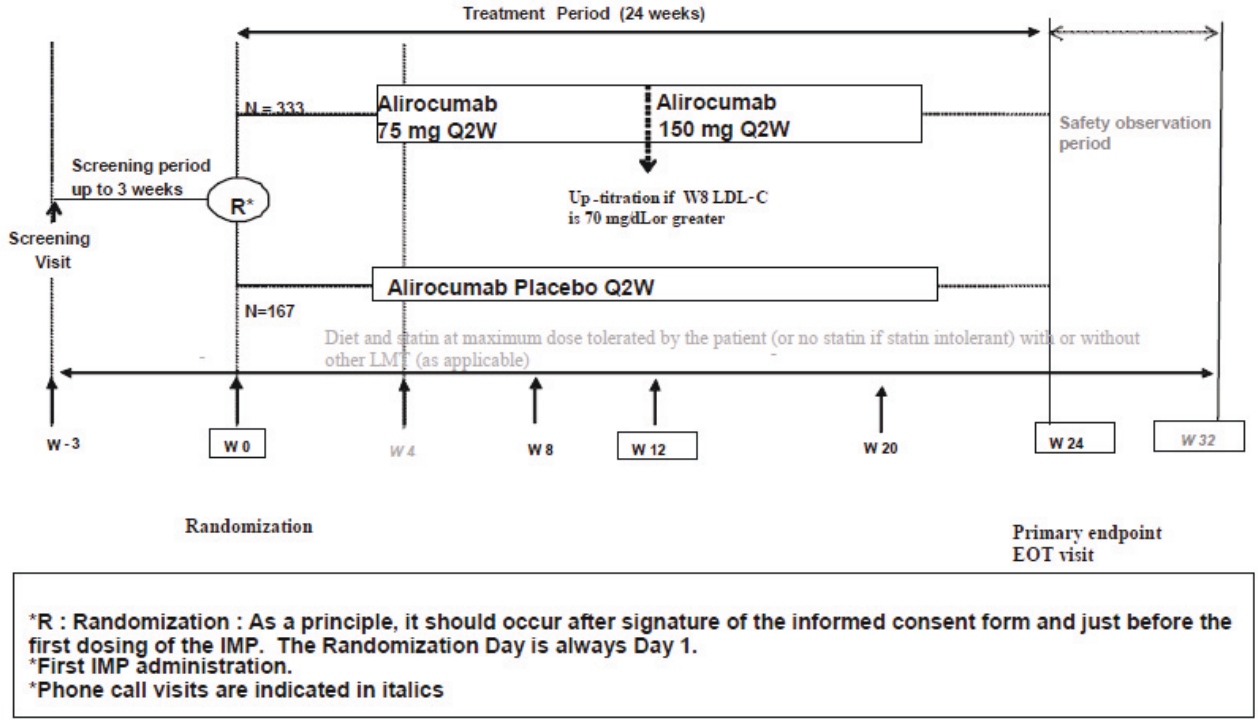
The study consists of a screening period of up to 3 weeks, a double-blind treatment period of 24 weeks, and a safety observation period of 8 weeks.

Patients, unless they are statin intolerant, will be taking a stable, maximally tolerated dose of statin therapy with or without other lipid modifying therapies (LMT). Statin dose and dose regimen as well as dose and dose regimen of other LMT(s) (if applicable) should be stable throughout the entire study duration including for 4 weeks prior to the screening period, during the screening period, and from screening to randomization until the Week 24 visit. Patients should be on a stable diet for glucose and lipid management throughout the entire study duration from screening to the Week 24 visit. Patients should be receiving treatment for diabetes in accordance with local/regional standards of care. Concomitant medications, including glucose lowering treatments, should be kept to a minimum during the study, however, if considered necessary for the patient's welfare they may be given at the discretion of the Investigator, with a stable dose (when possible).

Alirocumab will be administered subcutaneously with a starting dose of 75 mg every 2 weeks (Q2W) for 12 weeks with a blinded up-titration to alirocumab 150 mg Q2W at Week 12 if the LDL-C at the Week 8 visit is ≥70 mg/dL (1.81 mmol/L). Patients who have an LDL-C <70 mg/dL (1.81 mmol/L) at the Week 8 visit will continue with alirocumab 75 mg Q2W until the end of the treatment period.

The data on lipid parameters from blood samples will be masked after randomization. No attempts should be made by the Investigator or patient to have the patient's lipid values independently evaluated after randomization until after the Week 24 visit, except for the safety of the patient, as per the Investigator's judgment.

Patients will visit the study site at Weeks -3, 0, 8, 12, 20, and 24 with lab work at each visit; in addition a phone visit is scheduled at Weeks 4 and 32.



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Definition of screened patients

In protocol section 11.2, screened patients are defined as any patient who met the inclusion criteria and signed the informed consent. In SAP version 4.0 and above, definition of screened patients was updated to any patients who signed the informed consent only.

Definition of an additional compliance parameter

The overall compliance was added in assessment of extent of investigational medicinal product exposure and compliance.

Additional effects added to the analysis model of the primary efficacy endpoint

Additional effects were added to the analysis model of the primary efficacy endpoint initially defined in protocol section 11.4.2.1: the strata (ie, diabetes type), the strata-by-time point interaction, and the treatment-by-strata-by-time point interaction.

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 as the last available value obtained prior to the first double-blind investigational medicinal product (IMP) injection, including values obtained at the day of randomization since all blood samples for laboratory assessment taken on this day are performed prior to the first IMP injection. For patients randomized and not treated, the baseline value is defined as the last available value obtained up to the date and time of randomization.

[redacted]

2.1.1 Demographic and baseline characteristics

Demographic characteristics

Demographic variables are age in years (quantitative and qualitative variable: <65, [65 – 75[and ≥75 years old; <65 and ≥65 years old), gender (Male, Female), race (White/Caucasian, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported/Unknown).

Age is calculated as

$$\text{Age} = (\text{date of informed consent} - \text{date of birth} + 1) / 365.25$$

For patients in countries where date of birth is not collected, age in years is directly collected in electronic case report form (e-CRF).

History of Diabetes

History of diabetes includes:

- Type of diabetes (1 or 2) for pooled data only
- Duration of diabetes (years), quantitative and categorical: duration of diabetes <5, [5-10], >10 years
- Duration of insulin use (years)
- For patients with Type 1 diabetes, criteria used to confirm Type 1 diabetes diagnosis as indicated in the e-CRF:
  - Clinical criteria
  - Antibody testing (eg, islet cell antibodies, antibodies to glutamic acid decarboxylase, antibodies to the tyrosine phosphatases, insulin autoantibodies, antibodies to ZnT8, other antibodies)

- Historical C-peptide testing (eg, fasting, random, stimulated)
- Other

Alcohol and smoking habits

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

Hypercholesterolemia history

Hypercholesteremia characteristics are:

- Duration of hypercholesterolemia (years)
- History of hypercholesterolemia before type 2 diabetes diagnosis (only applies for patients with T2DM)
- History of LMT ever taken (eg, statin, fibrates, bile acid sequestrant, cholesterol absorption inhibitor, nicotinic acid and derivatives, omega 3 fatty acid ≥1000 mg/day, serum proprotein convertase subtilisin kexin type 9 [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 creatinine 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 (BMI)
  - Concern for cognitive impairment or experienced cognitive AEs while taking a higher dose
  - Concern for worsening of diabetes
  - Regional practice/local prescribing information
  - Other

Cardiovascular history and 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 dedicated medical history e-CRF page.

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 meeting one or more of the below (a, b, c) based on e-CRF fields
    a) Intermittent claudication (linked to PAD) with ongoing ticked 'YES' together with ankle-brachial index 0.90 or lower 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
- Additional CV risk factors among
  - Hypertension established on antihypertensive medication
  - Current cigarette smoker
  - Age ≥45 years old for men, ≥55 years old for women
  - Microalbuminuria
  - Macroalbuminuria
  - Pre–proliferative diabetic retinopathy
  - Proliferative diabetic retinopathy
  - Family history of premature CHD (before 55 years of age in male, 65 years in female, in first degree relatives)
  - Low HDL-C (male <40 mg/dL [1.0 mmol/L], female <50 mg/dL [1.3 mmol/L])
  - Chronic kidney disease (CKD) as defined by 15 < estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2

Presentation of each risk factor will include:

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

Patients with clinical atherosclerotic cardiovascular disease (ASCVD) as per protocol will be summarized. Clinical ASCVD patients are defined as patients with 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 TIA, as per the 2013 AHA/ACC guideline, will also be summarized. Clinical ASCVD as per the 2013 AHA/ACC guideline is defined by any of the following history of CV disease:

- CHD (as defined above)
- Ischemic stroke
- Transient ischemic attack (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

Family allergic history

- Asthma
- Allergic rhinitis
- Allergies to food/ pollen/ dust

Vital signs

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

Other baseline characteristics

Other baseline characteristics include:

- Other relevant medical/surgical history
- Female menopausal status:
  - occurrence,
  - For post-menopausal women: time since menopause (years), disease/symptoms controlled, type of hormone replacement therapy : estrogen only, estrogen and progesterone, no estrogen or progesterone
- HbA1c, quantitative (%, mmol/mol) and by category: <7, [7-9[, ≥9% / <7, ≥7% / <8, ≥8% /<9, ≥9%.;
- FPG, quantitative (mg/dL, mmol/L);
- C-peptide, quantitative and by category: <0.2 pmol/mL, ≥0.2 pmol/mL;
- 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);
- Non-HDL-C, quantitative and by category: <100, [100-130[, [130-160[, [160-190[, [190-220[, ≥220 mg/dL (<2.59, [2.59-3.37[, [3.37-4.14[, [4.14-4.91[, [4.91-5.7[, ≥5.7 mmol/L);
- HDL-C, quantitative and by category: for men <40, ≥40 mg/dL (<1.04, ≥1.04 mmol/L) / for women <50, ≥50 mg/dL (<1.29, ≥1.29 mmol/L);
- Fasting TG, quantitative and by category: <150, [150-200[, ≥200 mg/dL (<1.7, [1.7-2.3[, ≥2.3 mmol/L), category ≥150 mg/dL (≥1.7 mmol/L, mixed dyslipidaemia) will be also displayed;
- Lp(a), quantitative and by category: <30, [30-50[, ≥50 mg/dL (<0.3, [0.3-0.5[, ≥0.5 g/L), category ≥30 mg/dL (≥0.3 g/L) will be also displayed;
- Apo B, quantitative and by category: <80, ≥80 mg/dL (<0.8 g/L, ≥0.8 g/L);
- TGRL, quantitative and by category: <30 mg/dL, ≥30 mg/dL (<0.3 g/L, ≥0.3 g/L);
- All other quantitative lipid efficacy endpoints (TC, Apo A-1, Apo C-III, ratio Apo B/Apo A-1, ratio TC/HDL-C, LDL particle size and number);
- Total and free PCSK9 levels, quantitative;

- Estimated GFR, quantitative and by category: <15, [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 (Appendix C) (1):
  - 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

Correlations between baseline level of calculated LDL-C and HbA1c, PCSK9 (free and total) and correlation between baseline level of HbA1c and PCSK9 (free and total) will be also explored (eg, scatter plot) using a regression model adjusted on sex and type of diabetes as per IVRS as categorical covariates and age as continuous covariate.

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

2.1.2 Prior, concomitant or post-treatment medications

All medications taken within 3 months before screening visit and until the end of the study, including LMT and nutraceutical products 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 3 months prior to screening visit and prior to first double-blind IMP administration. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.

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

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

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

2.1.3 Efficacy endpoints

Efficacy parameters include lipid parameters (ie, calculated LDL-C, measured LDL-C, non-HDL-C, Apo B, TC, Lp(a), TG, HDL-C, TGRL, LDL particle size and number, Apo A-1, Apo C-III, ratio Apo B/Apo A-1, TC/HDL-C). All these parameters are measured or calculated by a Central Laboratory, for both scheduled and unscheduled time points. Calculated LDL-C is obtained using the Friedewald formula (2). Non-HDL-C is calculated by subtracting HDL-C from the TC. Measured LDL-C is obtained via beta quantification method. All measured LDL-C values provided by the Central Laboratory including those done in case of TG values exceeding 400 mg/dL (4.52 mmol/L) will not be used for the analysis of calculated LDL-C endpoints. TGRL will be calculated by total cholesterol minus HDL cholesterol minus measured LDL cholesterol. In cases where the measured LDL-C is missing and the calculated LDL-C is non-missing, the calculated LDL-C will be used for the computation of TGRL. Both fasting and non-fasting measurements will be used for calculation of TGRL.

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 2.5.4 in order to provide an assessment for Week 8 to Week 24 time points. For TG, only fasting measurements will be used. Measurements with missing fasting status will be excluded from the analyses.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to Week 24 in the intent-to-treat (ITT) population. Primary endpoint is defined as: 100 x (calculated LDL-C value at Week 24 - calculated LDL-C value at baseline) / calculated LDL-C value at baseline.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Key secondary efficacy endpoints

The key secondary endpoints are:

- Percent change in calculated LDL-C from baseline to Week 24, using all calculated LDL-C values during the efficacy treatment period (see Section 2.1.4, on-treatment estimand);
- Percent change in measured LDL-C from baseline to Week 24 (ITT estimand);
- Percent change in calculated LDL-C from baseline to Week 12 (ITT estimand);
- Percent change in measured LDL-C from baseline to Weeks 12 (ITT estimand);
- Percent change in non-HDL-C from baseline to Week 24 (ITT estimand);
- Percent change in Apo B from baseline to Week 24 (ITT estimand);
- Percent change in TC from baseline to Week 24 (ITT estimand);
- The proportion of patients reaching calculated LDL-C <70 mg/dL at Week 24 (on-treatment estimand);

- The proportion of patients reaching calculated LDL-C <50 mg/dL at Week 24 (on-treatment estimand);
- The proportion of patients reaching non-HDL-C <100 mg/dL at Week 24 (on-treatment estimand);
- The proportion of patients reaching non-HDL-C <80 mg/dL at Week 24 (on-treatment estimand);
- The percent change in Lp(a) from baseline to Week 24 (ITT estimand);
- The percent change in HDL-C from baseline to Week 24 (ITT estimand);
- The percent change in TG from baseline to Week 24 (ITT estimand);
- The percent change in LDL-C particle number from baseline to Week 24 (ITT estimand);
- The percent change in LDL-C particle size from baseline to Week 24 (ITT estimand).

2.1.3.2.2 Diabetes-related endpoints

- Absolute change in HbA1c from baseline to Weeks 12 and 24 (ITT and on-treatment estimands);
- Absolute change in FPG from baseline to Weeks 12 and 24 (ITT and on-treatment estimands);
- Absolute change in total daily insulin dose from baseline to Weeks 12 and 24 (ITT and on-treatment estimands);
- Absolute change in insulin daily dose/kg from baseline to Weeks 12 and 24 (ITT and on-treatment estimands);
- Absolute change in number of glucose-lowering treatments from baseline to Weeks 12 and 24 (ITT and on-treatment estimands).

2.1.3.2.3 Other efficacy endpoints

- Percent change in calculated LDL-C from baseline to Week 12 (on-treatment estimand);
- Percent change in measured LDL-C from baseline to Weeks 12 and 24 (on-treatment estimand);
- Percent change non-HDL, Apo B, TC, Lp(a), HDL-C, and TG from baseline to Weeks 12 (ITT and on-treatment estimands) and Week 24 (on-treatment estimand);
- Proportion of patients reaching calculated LDL-C <50 and also <70 mg/dL at Weeks 12 (ITT and on-treatment estimands) and 24 (ITT estimand);
- Proportion of patients with 50% or greater reduction from baseline in calculated LDL-C at Weeks 12 and 24 (ITT estimand);
- Proportion of patients reaching non-HDL-C <80 mg/dL and also <100 mg/dL at Weeks 12 (ITT and on-treatment estimands) and Week 24 (ITT estimand);
- Proportion of patients reaching Apo B <80 mg/dL at Weeks 12 and 24 (ITT and on-treatment estimands);
- Percent change in LDL-C particle number from baseline to Week 12 (ITT and on-treatment estimands) and Week 24 (on-treatment estimand);

- Percent change in LDL-C particle size from baseline to Week 12 (ITT and on-treatment estimands) and Week 24 (on-treatment estimand);
- Percent change in TGRL, Apo A-1, and Apo C-III from baseline to Weeks 12 and 24 (ITT and on-treatment estimands);
- Absolute change in ratio Apo B/Apo A-1 and TC/HDL-C from baseline to Weeks 12 and 24 (ITT and on-treatment estimands);
- Proportion of patients reaching calculated LDL-C <70 and <50 mg/dL at Weeks 12 and 24 according to baseline A1c of <8% or ≥8% (ITT and on-treatment estimands);
- Proportion of patients reaching calculated LDL-C <70 mg/dL and <50 mg/dL at Weeks 12 and 24 according to baseline A1c <median A1c or ≥median A1c (ITT and on-treatment estimands).

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 first dose of double-blind IMP injection.
- Treatment Emergent Adverse Event (TEAE) period is defined as the time from the first dose of double-blind IMP injection to the last dose of IMP injection + 70 days (10 weeks) as residual effect of treatment is expected until 10 weeks after the stop of double-blind IMP. As the hour of IMP injection is not collected, the time of double blind IMP injection refers, here and in the rest of the document, to the date of double-blind IMP injection.

  The TEAE period will include:
  - The efficacy treatment period defined as the time from the first dose of double-blind IMP injection up to the day of last dose of double-blind IMP injection + 21 days, as serum concentration of alirocumab >10 µg/mL is expected for approximately 21 days following administration of 150 mg, and because throughout the previous studies it was observed that when alirocumab concentrations declined below this concentration, decrease in effect on LDL-C is observed.
  - The residual efficacy treatment defined as the time from the day of last dose of double-blind IMP injection + 22 days up to the day of last dose of double-blind IMP injection + 70 days (10 weeks).
- 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 (SAE) 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 double-blind IMP injection until the last protocol planned visit of the patient (Week 32 phone call).

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), selected using central laboratory data;
- Allergic drug reactions:
  - requiring consultation with another physician and selected using 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");
  - An additional 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 IMP (as opposed to another injectable) AND selected using the following selection of PT 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").

- An additional 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 IMP (as opposed to another injectable).

- Pregnancy of female patient (including male patient's partner) selected using appropriate MedDRA codes.
- Symptomatic overdose with IMP;
  - An overdose with IMP is defined as at least twice of the intended dose within the intended therapeutic interval (ie, 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 (eg, "symptomatic overdose [accidental]" or "symptomatic overdose [intentional]"). These events will be selected using the AESI category as selected by the site.
  - An additional analysis of overdoses AE will be performed: analysis of all overdose cases (whether symptomatic or asymptomatic) related to IMP using the HLT for overdose.
- Neurologic events
  - requiring additional exams/procedures or consultation 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 the 5 following high level group terms (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 using the CMQ developed using the FDA grouping of events: the PTs "Amnesia", "Amnestic disorder", "Anterograde Amnesia", "Behavioural and Psychiatric Symptoms of Dementia", "Change in sustained attention", "Cognitive Disorder", "Confusional State", "Delirium", "Dementia", "Dementia Alzheimer's type", "Dementia with Lewy Bodies", "Disorientation", "Disturbance in attention", "Executive dysfunction", "Frontotemporal Dementia", "Illogical Thinking", "Impaired reasoning", "Incoherent", "Judgement impaired", "Memory Impairment", "Mental Impairment", "Mental Status Changes", "Mini Mental Status Examination Abnormal", "Presenile Dementia", "Retrograde Amnesia", "Senile Dementia", "Thinking Abnormal", "Transient Global Amnesia ", "Vascular Dementia" and the LLTs "Mental State Abnormal Aggravated", "Thinking Slowed".

Analyses of allergic drug reactions, local injection sites reaction and neurologic events will also be provided using the drop-down on the e-CRF AE page as a second approach. All analysis 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, selected using SMQ "Hepatic disorder";
- Diabetic complications, selected using HLGT "Diabetes Complications", HLT "Diabetes Mellitus (incl subtypes)", HLT "Carbohydrate tolerance analyses (incl diabetes)", PT "Hyperglycaemia", PT "Hyperglycaemic unconscioussness" , PT "Hyperglycaemic seizure", and excluding PT "Blood glucose decreased" and PT "Glycosylated haemoglobin decreased";
- Hypoglycaemia events using SMQ "Hypoglycaemia" (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 into standard international units and conventional units, and both units will be used in all listings and tables.

Blood samples for safety assessments 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 red 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
  - **Metabolic function:** plasma glucose, total protein, albumin, HbA1c, creatinine phosphokinase;
  - **Electrolytes**: sodium, potassium, chloride, calcium, phosphorus, bicarbonate;
  - **Renal function**: creatinine, eGFR, blood urea nitrogen, uric acid;
  - **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);

Hepatitis screen: Hepatitis C antibody (at screening, Week 24 and in case of transaminases elevation), Hepatitis B surface antigen (screening only). If tests are positive/repeated (eg, confirmatory test for Hepatitis C), all results will be described (see Section 2.4.6.3).

- Other parameters: C-peptide, TSH for patients with hormone thyroid replacement only (at screening only)

Urine samples will be collected at screening and Week 24/or early termination as follows:

- **Urinalysis** - quantitative analyses: pH, specific gravity, presence of blood, protein, 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, white blood cells (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**

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: height (in cm, only at baseline), weight (in kg), BMI (in kg/m²), HR (in bpm), systolic and diastolic blood pressure (SBP and DBP) in sitting position (in mmHg).

2.1.4.5 Electrocardiogram variables

Not applicable.

2.1.5 Pharmacokinetic variables

Total and free proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations in serum are assessed at baseline (Week 0).

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:

- HbA1c, in % and in mmol/mol.
- FPG
- Total daily insulin dose and daily insulin dose per kg.
  The total daily insulin dose by patient and visit will be computed as the mean of the daily insulin dose in the last 7 days prior to visit, taken from the insulin log form. The daily insulin dose per kg will be computed from this total daily insulin dose and the weight at each visit. Total daily insulin dose and daily insulin dose per kg will be summarized overall and by regimen (basal, prandial, correction/other). Premixed daily dose will be broken down into basal and prandial daily dose according to fixed basal and prandial percentages.
- Number of glucose lowering treatments:
  - 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 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, ie, a total of “2” glucose lowering treatments).

2.1.10 Anti-alirocumab antibodies

Descriptive statistics on ADA (status, neutralizing status and titer) collected at Week 0, Week 12, and Week 24 will be provided.

2.1.11 Nutritional counseling

Descriptive statistics on the nutritional counseling status collected at Week 0, Week 4, Week 8, Week 12, Week 20 and Week 24 will be summarized by treatment group and overall.

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, with a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a double-blind treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population. 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 type of diabetes 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 (inclusion/exclusion criteria);
- Non-randomized but treated patients;
- Randomized patients;
- Randomized but not treated patients and reason for not treated (from reasons on end of study CRF form);
- 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;
- 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 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 randomized), 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 randomized), using Kaplan-Meier method.

Patients with insufficient post-treatment follow-up will be described on the safety population by treatment group. A patient is considered with insufficient post-treatment follow-up or without post-treatment follow-up at the end of the study in the following cases:

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

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/mITT population will be listed as well as patients with major deviations potentially impacting efficacy analyses not resulting in exclusion from ITT/mITT 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 and mITT;
- Safety population;
- [redacted]
- ADA population.

Definitions of the study populations are provided in Section 2.3.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

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

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as

randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis. Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

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

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). Nonrandomized, 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.

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

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 calculated LDL-C value available;
- At least one calculated LDL-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 (ie, as-randomized group).

This population will be used to assess the ITT estimands.

2.3.1.2 Modified-intent–to-treat population

The mITT population (otherwise referred to as the on-treatment population) is a subset of the ITT population defined as all randomized patients who took at least one dose or part of a dose of the double-blind IMP and have an evaluable primary efficacy endpoint during treatment period ie, Baseline calculated LDL-C value available;

- At least one calculated LDL-C value available during the efficacy treatment period and within one of the analysis windows up to Week 24.

The efficacy treatment period is defined as the time period from the first double-blind IMP injection up to 21 days after the last double-blind IMP injection.

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

This population will be the basis for the on-treatment estimand evaluations.

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 double-blind IMP.

Patients will be analyzed according to the treatment actually received.

The safety analysis will focus on the TEAE period defined as the time from the first double-blind dose to the last double-blind dose of IMP + 70 days (10 weeks).

In addition:

- Nonrandomized but treated patients or patients treated with the double-blind IMP 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 1 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-double blind IMP injection.

2.3.4 [redacted]

[redacted]

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized by treatment group and overall, by diabetes type and on the pooled data, using descriptive statistics.

Continuous data will be summarized using the number of available data, mean, SD, median, Q1, Q3, minimum, and maximum for each treatment group. For lipid efficacy parameters, summary statistics will include Q1 and Q3 and medians. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

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

All reported patient's medical and surgical history will be presented by primary SOC and HLT. The tables will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on the overall incidence across treatment groups.

For the patients with no clinical ASCVD as per protocol, the following categories of CV medical history will also be summarized:

- The number (%) of patients having additional CV risk factor as defined in Section 2.1.1 (number (%) for each CV risk factor).
- The number (%) of patients with target organ damage (microalbuminuria, macroalbuminuria), CKD and/or retinopathy.
- The number (%) of patients with at least one additional CV risk factor (see Section 2.1.1), according to the following categories:
  - 1 CV risk factor
  - 2 CV risk factors
  - ≥3 CV risk factors

For the patients with clinical ASCVD, defined without TIA (as per protocol) and with TIA (as the 2013 AHA/ACC guidelines, see Section 2.1.1), the history will be described using the number (%) of patients for each of the ASCVD components.

Additional analyses of demographics and baseline characteristics on selected endpoints will also be replicated in the subgroup of patients of the region North America.

2.4.2 Diet therapy

The diet therapy data analysis will be performed on the safety population. The number (%) of patients who had a significant change in diet therapy from baseline to Week 4, Week 8, Week 12, Week 20 and Week 24 will be provided by treatment group and overall.

2.4.3 Prior, concomitant or post-treatment medications

The prior, concomitant and post-treatment medications will be presented for the safety population by category (all drugs, LMT). For CV drugs, the concomitant medications will be presented.

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

The table for all prior medications will be sorted by decreasing frequency of ATCs based on the overall incidence across treatment groups. In case of equal frequency, alphabetical order will be used.

The tables for all 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 treatment group. In case of equal frequency regarding ATCs, alphabetical order will be used.

Concomitant CV drugs will be summarized by chemical class and standardized medication name and by therapeutic class and standardized medication name. Tables will be sorted by decreasing frequency of chemical or therapeutic classes and then of standardized medications within each class based on the incidence in the alirocumab treatment group.

Lipid modifying therapies (statins and other LMTs, including nutraceutical products that may affect lipids) will be summarized by pre-specified categories and standardized medication name. The table for prior LMTs will be sorted by decreasing frequency of standardized medication incidence in the overall treatment group within categories. The tables for concomitant and post-treatment LMTs will be sorted by decreasing frequency of standardized medication incidence in the alirocumab treatment group.

In addition, background LMT use at randomization will be summarized by treatment group and overall using the following categories:

- Proportion of patients with any statin
- Proportion of patients with statin alone
- Proportion of patients with any statin in addition to other LMT
- Proportion of patients with other LMT only (without statin)
- Proportion of patients with any LMT other than statins:
  - Fibrates
  - Bile acid sequestrants
  - Cholesterol absorption inhibitor
  - Nicotinic acid and derivates
  - Omega 3 fatty acids >= 1000 mg/day
  - PCSK9 inhibitor
  - Nutraceuticals impacting lipids
  - Other
- Proportion of patients with no LMT (neither statin or other LMT)
- The statin therapies will also be presented according to intensity (high intensity, moderate intensity, low intensity) according to the below table (3):

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily dose lowers LDL-C on average by approximately ≥50 %	Daily dose lowers LDL-C on average by approximately 30 to <50 %	Daily dose lowers LDL-C on average by <30 %
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg	Simvastatin 10 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg	Pravastatin 10–20 mg
	Simvastatin 20–40 mg	Lovastatin 20 mg
	Pravastatin 40–80 mg	Fluvastatin 20–40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 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 (ie, 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 (ie, 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 (ie, 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 therapy will also be reported by type and dose

As well, glucose lowering treatment (insulin and others) use at baseline, Week 12 and Week 24 will be summarized by treatment group, categories and standardized medication name. Pre-specified categories are:

- Insulins
  - Fast acting
  - Intermediate (excluding premix)
  - Premixed
  - Long acting
  - Inhaled
- Other glucose lowering treatments
  - Biguanides
  - Sulfonylureas
  - Sulfonamides
  - Alpha glucosidase inhibitors
  - Thiazolidinediones

- DPP-4 inhibitors
- SGLT2 inhibitors
- GLP-1 receptor agonists
- Other blood glucose lowering drugs, if applicable (excluding SGLT2 inhibitors and GLP-1 receptor agonists)

Tables will be sorted by decreasing frequency of standardized medication incidence within categories in the overall treatment group at baseline and in the alirocumab treatment group at Week 12 and Week 24.

The number of glucose lowering treatments will be described by treatment arm (See Section 2.1.9).

2.4.4 Extent of investigational medicinal product exposure and compliance

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

The extent of IMP exposure will be assessed by the total number of injections by patient and the duration of IMP injection exposure in weeks is defined as: (date of last dose of double-blind IMP injection + 14 days – date of first dose of double-blind IMP injection) / 7, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data). Parameters will be summarized as quantitative variables using number, mean, SD, median, Q1, Q3, minimum, and maximum (non-integer values will be rounded to 1 decimal place). In addition, the durations of 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 and <24 weeks and ≥24 weeks. Non-integer values will be rounded to 1 decimal place.

2.4.4.1 Titration

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

2.4.4.2 Compliance

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

Compliance will be assessed using the following parameters:

- The mean injection frequency will be 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 will be defined for each patient as: 100 – (number of injections performed during the study period / number of theoretical injections to be performed during the study period), considering that injections should be performed every two weeks (+/- 3 days as per protocol).
    - 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, 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 described and for these patients, the number of injections not performed per patient will be presented by category: 1 injection, 2 injections, 3 or more injections.

Cases of symptomatic overdose with IMP (ie, 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 (ie, 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 (Section 2.1.4.1).

2.4.5 Analyses of efficacy endpoints

For statistics where international and conventional units do not impact the results (eg, 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 done and statistical models will be run using conventional units. For other statistics (eg, descriptive statistics at baseline and over time, absolute changes from baseline), derivations will be done with both international and conventional units.

2.4.5.1 Analysis of primary efficacy endpoint(s)

2.4.5.1.1 Primary efficacy analysis

Separate analyses will be performed for Type 1 diabetes patients on one hand (alpha risk = 0.05) and Type 2 diabetes patients on the other hand (alpha risk = 0.05), as well as in the pool population (alpha risk = 0.05). All outputs described below will be first described separately on the Type 1 diabetes patients and on the Type 2 diabetes patients, and then on the pooled data.

The percent change in calculated LDL-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. The model for assessing the treatment effect in the pooled data will include the fixed categorical effects of treatment group (alirocumab versus placebo), randomization strata (ie, diabetes type, as per IVRS), time point (Week 8, Week 12, Week 20 and Week 24), treatment group-by-time point interaction, and strata-

by time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction. The model for assessing the treatment effect by diabetes type will include an additional interaction term: the treatment group-by-strata-by-time point interaction. The significance level (P-value) of the treatment group-by-strata interaction term at Week 24 will be also provided for this model for descriptive purpose. In case of non-convergence of the model, a model with less interaction terms will be fit.

These models 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 placebo group, an appropriate contrast statement will be used to test the differences of these estimates, at the 2-sided 0.05 level. LS-mean difference versus placebo and the corresponding 95% confidence intervals (CIs) will be provided. Forest plot will also be provided.

Let $\mu 0$ and $\mu 1$ be the population means of the percent change from baseline in calculated LDL-C at Week 24 under placebo and alirocumab, respectively. The null hypothesis that will be tested in each subpopulation is:

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

The MMRM model relies on the "missing-at-random" (MAR) assumption. Sensitivity analysis with the intent to evaluate the robustness of the primary analysis using a different statistical method will be conducted (see multiple imputation model definition in Section 2.4.5.1.3). 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 2.4.5.1.3).

2.4.5.1.2 Model assumption checks

The following analyses will be performed by diabetes type and in the pooled data.

Homogeneity of treatment effect across baseline calculated LDL-C levels:

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

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

Within the framework of this model with interaction terms, a graph presenting the LS means difference versus placebo at Week 24 and the corresponding 95% CI will be provided by baseline calculated LDL-C value.

Analysis of residuals:

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

- Normality of studentized residuals, presented graphically using histogram and quantile quantile (QQ)-plot;
- Plot of studentized residuals versus predicted values;

2.4.5.1.3 Sensitivity to handling of missing data

Sensitivity analyses will be conducted to assess the robustness of primary efficacy analysis with regards to handling of missing data (Section 2.5.3) (4). For all sensitivity analyses, outputs will be first described separately on the Type 1 diabetes patients and on the Type 2 diabetes patients, and then on the pooled data in ITT population. Forest plots will be also provided.

Multiple imputations:

In addition to the MMRM method, the multiple imputation method will be used to address missing values, in the randomized population, followed by the testing of treatment arms using an analysis of covariance (ANCOVA) model, with the intent to evaluate the robustness of the primary analysis using a different statistical method. Missing data from the randomized population will be imputed 100 times to generate 100 complete data sets, using the MI SAS procedure (using Markov Chain Monte Carlo). The percent change from baseline at Week 24 will be then derived from observed and imputed calculated LDL-C at this time point. The 100 complete data sets will be then analyzed using an ANCOVA model with treatment group and randomization strata (as per IVRS) as fixed effects, and the baseline calculated LDL-C value as continuous covariate, and the MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae (5, 6). The model for assessing the treatment effect by diabetes type will include an additional interaction: the treatment group-by-strata interaction.

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

The imputation model will include:

- The variables included in the ANCOVA model, including the treatment group, the randomization strata (as per IVRS) and the baseline value. The model for assessing the treatment effect by diabetes type will include an additional interaction: the treatment group-by-strata interaction.
- The baseline characteristics such as: age, BMI, and gender. Age and BMI will be included as continuous variables.
- The calculated LDL-C values at Week 8, Week 12, Week 20 and Week 24 time points. Time points are those defined in Section 2.5.4.

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

Pattern mixture model (see Appendix D for more details):

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

- Patients within 21 days of their last blind IMP injection would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, calculated LDL-C values missing during the on-treatment period (eg., samples obtained out-side the specified window, no blood sample available although visit was performed, etc.) should be considered "Missing At Random" and imputed based on other on-treatment measurements.
- Patients who stopped taking their study treatment no longer benefited from it after discontinuation, and thus tended to have calculated LDL-C values returning to baseline. Therefore, calculated LDL-C values missing more than 21 days after treatment discontinuation should be imputed based on patient's own baseline value.

Missing calculated LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to Week 24 will be derived from observed and imputed calculated LDL-C at this time point. The completed data sets will be analyzed using an ANCOVA model with treatment group and randomization strata (as per IVRS) as fixed effects, and the baseline calculated LDL-C value as continuous covariate. The model for assessing the treatment effect by diabetes type will include an additional interaction: the treatment group-by-strata interaction. The results from the 100 analyses will be combined using Rubin's formulae (6).

2.4.5.1.4 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, treatment-by-subgroup factor, time point-by-subgroup factor and treatment-by time point-by subgroup factor interaction terms and a subgroup factor term will be added as fixed factors in the primary MMRM model for the pooled data described in Section 2.4.5.1.1. For assessing the treatment effect by diabetes type, the same model will be fitted within each stratum, therefore without the strata factor and the interactions of strata with other factors. In case of non-convergence of the model, a model with less interaction coefficients will be fitted.

As for the primary efficacy analysis, all outputs will be first described separately on the Type 1 diabetes patients and on the Type 2 diabetes patients, and then on the pooled patients population.

LS means difference versus placebo at Week 24 will be provided, as well as the corresponding standard error (SE) and 95% CI, within each subgroup. The significance level of the treatment-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:

- BMI: <25, [25-30[, ≥30 kg/m²;
- Gender: Female, Male;
- Menopausal status, for female only: Yes, No;
  1. For post-menopausal women: type of hormone replacement therapy : estrogen only, estrogen and progesterone, no estrogen or progesterone;
- Race: White/Caucasian, non-White/Caucasian;
- Ethnicity: Hispanic, non-Hispanic, Not Reported/Unknown;
- Region: North America, Europe;
- Age: <65, [65–75], >75 / <65, ≥65 years old;
- Duration of diabetes : <5, [5-10], >10 years if the number of patients by subgroup meets the requirement (see above); otherwise by tertiles;
- ASCVD as per protocol: Yes, No;
- ASCVD including TIA as per the 2013 AHA/ACC guideline (see Section 2.1.1): Yes, No;
- Background LMT:
  2. Any statin versus no statin at randomization
  3. no LMT (neither statin or other LMT), versus other LMT only (without statin), versus statin alone, versus any statin plus other LMT
  4. High intensity statin at randomization vs medium or low intensity statin at randomization
- Prior history of myocardial infarction (Silent or acute MI) or ischemic stroke: Yes, No;
- CKD: Yes, No (from cardiovascular medical history CRF page);
- Estimated GFR class: <30, [30- 60[, [60-90[, ≥90 mL/min/1.73 m². 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 category as defined below (Appendix C) (1):
  1. Category 1 : G1A1, G2A1
  2. Category 2 : G1A2, G2A2, G3aA1
  3. Category 3 : G1A3, G2A3, G3aA2, G3bA1
  4. Category 4 : G3aA3, G3bA2, G3bA3, G4A1, G4A2
  5. 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 calculated LDL-C: <100, [100-130[, [130-160[, ≥160 (<2.59[, [2.59-3.37[, [3.37-4.14[, ≥4.14mmol/L) if the number of patients by subgroup meets the requirement (see above). Otherwise one of the following groupings will be explored:
  1. <100[, [100-130[, ≥130 (<2.59[, [2.59-3.37[, ≥3.37 mmol/L)
  2. by tertiles

     For this specific subgroup factor, the MMRM model will include the same covariates than for other subgroup factors, except that the baseline calculated LDL-C value will be replaced by the baseline calculated LDL-C category. Therefore, the model for the overall population will include fixed categorical effects for treatment group, randomization strata (as per IVRS), baseline calculated LDL-C category, time point, and the interactions treatment-by-time point, strata-by time point, baseline calculated LDL-C category-by-time point, treatment group-by-baseline calculated LDL-C category, and treatment group-by-baseline calculated LDL-C category-by-time point. For assessing the treatment effect by diabetes type, the same model will be fitted within each stratum, therefore without the strata factor and the interaction strata-by time point.
- Baseline non-HDL-C: <130, [130-160[, [160-190[, ≥190 (<3.37, [3.37-4.14[, [4.14-4.91[, ≥4.91mmol/L)) if the number of patients by subgroup meets the requirement (see above). Otherwise one of the following groupings will be explored:
  1. <130[, [130-160[, ≥160 (<3.37, [3.37-4.14[, ≥4.14mmol/L)
  2. by tertiles (only if no sufficient patients in previous grouping)
- Baseline TGRL :
  1. <30 mg/dL, ≥30 mg/dL
  2. by quintiles if the number of patients by subgroup meets the requirement (cf. above); otherwise, by tertiles.
- Baseline HDL-C: low HDL-C (for men <40 mg/dL (<1.04 mmol/L) / for women <50 mg/dL (<1.29 mmol/L)), high HDL-C (for men ≥40 mg/dL (≥1.04 mmol/L) / for women ≥50 mg/dL (≥1.29 mmol/L));
- Baseline fasting TG:
  1. <150, [150-200[, ≥200 mg/dL (<1.7, [1.7-2.3[, ≥2.3 mmol/L) and
  2. <150, ≥150 mg/dL (<1.7, ≥1.7 mmol/L, mixed dyslipidaemia) and
  3. by quintiles if the number of patients by subgroup meets the requirement (see above); otherwise, by tertiles;
- Baseline Lp(a):
  1. <30, [30-50[, ≥50 mg/dL (<0.3, [0.3-0.5[, ≥0.5 g/L) and
  2. <30, ≥30 mg/dL ((<0.3, ≥0.3 g/L);
- Baseline total PCSK9 level: <median, ≥median ng/ml;
- Baseline free PCSK9 level: <median, ≥median ng/ml;
- 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 vs uncontrolled DM, based on baseline HbA1c: <7, ≥7%;

- Insulin daily dose per kg at baseline (only in type 2 DM patients): ≤1 U/kg/day, >1 U/kg/day

2.4.5.2 Analyses of secondary lipid efficacy endpoints

2.4.5.2.1 Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables defined in Section 2.1.3.2 anticipated to have a normal distribution (eg, lipids other than TG, TGRL and Lp(a)) will be analyzed using the same MMRM model as for the primary endpoint. Specifically, the model for assessing the treatment effect in the pooled data will contain fixed categorical effects of treatment group, randomization strata (as per IVRS), planned time points to Week 24, treatment group-by-time point interaction, and strata-by time point interaction, as well as, the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction. The significance level (P-value) of the treatment-by-strata interaction term at Week 24 will be also provided for this model for descriptive purpose. In case of non-convergence of the model, a model with less interaction coefficients will be fitted. A forest plot will be provided for percent change in calculated LDL-C from baseline to week 24 on mITT population.

2.4.5.2.2 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 (eg, TG, TGRL and Lp(a)), will be analyzed using a robust regression model (ie, ROBUSTREG SAS procedure with M-estimation option) with treatment group as main effect, and randomization strata (as per IVRS) and corresponding baseline value(s) as covariate. The model for assessing the treatment effect by diabetes type will also include the treatment group-by-strata interaction. In case of non-convergence of the model, a model with less interaction coefficients will be fit. Missing values will be addressed using a multiple imputation model (see Section 2.4.5.1.3) that will at least include the same variables as used in the robust regression model (7). 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, 95% CI and p-value through the SAS MIANALYZE procedure. The analysis will be performed by diabetes type and on the pooled data.

2.4.5.2.3 Binary endpoints

Binary secondary efficacy endpoints defined in Section 2.1.3.2 (eg, proportion of patients below a threshold) will be analyzed using logistic regression with treatment group as main effect and corresponding baseline value(s) as covariate, stratified by randomization strata. Missing values will be addressed using a multiple imputation approach (see Section 2.4.5.1.3). 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 95% CIs and p-value will be provided via the SAS MIANALYZE procedure. The analysis will be performed by diabetes type and on the pooled data.

In the data dependent case that the logistic regression method is not applicable (eg, the response rate is zero in 1 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 placebo, 95% CI, and p-value will be provided.

2.4.5.2.4 Summary of results per time point

Central laboratory values (in conventional (US) and international units), percent change from baseline and/or when appropriate absolute change from baseline (in conventional and international units) in calculated LDL-C, measured LDL-C, HDL-C, fasting TG, non-HDL-C, TC, ratio TC/HDL-C, Lp(a), Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III, TGRL, LDL-C particle size, LDL-C particle number will be provided at each time point 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 planned time points (see Section 2.4.5.2.1) 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 planned time points (see Section 2.4.5.2.2) 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 2.5.4 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 of each parameter will be plotted by treatment group (LS mean + SEs by time point). The analysis will be performed by diabetes type and on the pooled data.

In addition, quantitative descriptive summaries by time point for each treatment group (value at visit and % change from baseline, or when appropriate absolute change from baseline) will be presented for all lipids using observed (ie, non-missing) data, and binary variables for LDL-C will be also provided in summary tables. These analyses will be performed by diabetes type and on the pooled data.

Calculated LDL-C will be described and plotted according to up-titration status. ie, according to whether the patients remained on the 75 mg dose or whether they were up-titrated to 150 mg.

2.4.5.2.5 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 of measured LDL-C.
2. In the second sensitivity computation, TGRL will be computed from fasting samples only, ie, non-fasting samples will be excluded from analysis.

For both sensitivity computations, the percent change from baseline to Weeks 12 and 24 (ITT and on-treatment estimands) will be assessed in the same way than for the main computation of TGRL, using the model described in Section 2.4.5.2.2.

2.4.5.3 Multiplicity issues

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

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

2.4.5.4 Additional efficacy analysis: region North America

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

2.4.6 Analyses of safety data

The summary of safety results will be presented by actual treatment group. Summaries will be descriptive in nature. Safety analysis will be performed by diabetes type and in the pooled data.

General common rules

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

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized or re-randomized patients) will be listed separately.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (PCSA version dated January 2009 [Appendix A]).
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations. The 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 2.5.4 in order to provide an assessment for Week 0 to Week 32 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 TEAEs will be described by SOC, HLGT, HLT and PT according to up-titration status, ie, according to whether the patients remained on the 75 mg dose or whether they were up-titrated to 150 mg. These analyses will be exploratory and descriptive (no formal comparison per dose) as it is expected that there could be inherent differences in the baseline characteristics between those patients titrating to 150 mg and those remaining on 75 mg. In order to reduce the bias of this analysis, the period before the up-titration time point (planned at Week 12) will be analyzed separately since only the dose 75 mg is proposed for this time period and consequently the early events occurring before Week 12 can only be attributed to this dose. Therefore the descriptive analysis per dose will include any safety events occurring from the first injection post Week 12 IVRS/IWRS transaction to the end of the TEAE period. Baseline characteristics of patients receiving each dose will be summarized.

2.4.6.1 Analyses of adverse events

Generalities

The primary focus of AE 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 2.5.3.

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

Analysis of all treatment-emergent adverse events

The following 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.
- Number (%) of patients experiencing TEAEs by primary SOC, HLGT, HLT, and PT;
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC, HLT and PT (HLT incidence ≥2% in any treatment group), sorted by SOC internationally agreed 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 order will be applied to all other TEAEs tables by SOC and PT, unless otherwise specified;

- All TEAEs by treatment group regardless of relationship in one column and, in the same table, in a second column, related to IMP according to investigator's opinion by primary SOC, HLGT, HLT and PT;
- All TEAEs by maximal intensity (ie, mild, moderate or severe), presented by primary SOC and PT, sorted by the sorting order defined above;
- The event rate per patient-year (the number of patients with an event in question divided by total patient-years) 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 double-blind IMP to the first occurrence of selected TEAEs as well as incidence rates at the time of analysis (Week 24 for the first step analysis, Week 32 for the final analysis). Hazard ratio versus placebo 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 disorder events 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 by treatment group regardless of relationship in one column and, in the same table, in a second column, 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 SMQ and PT (when selection is based on SMQs) or by SOC and PT (when selection is based on the e-CRF tick box or HLGT/HLT). The summaries will be sorted by decreasing incidence of PT within each SOC/SMQ (in the alirocumab group).
- Overview of each AESI and grouping of hepatic disorder events will be presented, summarizing number (%) of patients with any
  - AE;
  - TEAE;
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.

- 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;
  - Number of events divided by the number of double-blind IMP injections received;
  - Time from first double-blind IMP injection to first injection site reaction;
  - Number of double-blind 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.
- 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.

Subgroup of patients with 2 consecutive LDL-C <25 mg/dL

- If applicable, similar summaries of TEAEs as those described previously will be also provided on the safety subgroup population of patients with 2 consecutive results of calculated LDL-C <25 mg/dL. 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 calculated LDL-C <25 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 group.

Analysis of product complaints

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

2.4.6.2 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 (ie, death occurring in the TEAE period or during the post-treatment period).
- All deaths will be listed.

2.4.6.3 Analyses of laboratory variables

The summary statistics (including number, mean, standard deviation, median, Q1, 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 value of the treatment period, last on-treatment and/or worst on-treatment) by treatment group, by diabetes type and in the pooled data. In addition, for some parameters of interest, mean changes from baseline with the corresponding SE could be plotted over time (at same time points) in each treatment group. This section will be organized by biological function as specified in Section 2.1.4.3. For glucose, only fasting samples will be summarized.

The incidence of PCSAs (list provided in Appendix A) at any time during the TEAE period will be summarized by 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.

Glucose (quantitative summary and PCSA) will also be analyzed, by diabetes type and in the pooled data.

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), a “confirmed positive antibody (Ab) with negative RNA” or 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 in Table 1 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 (ie, patients with any elevated ALT >3 x ULN, and associated with an increase in bilirubin >2 x ULN, concomitantly or not) with ALT, AST, ALP, 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 2.4.5.1). Time to liver-related treatment discontinuation will be analyzed using Kaplan-Meier estimates presented by treatment group.

2.4.6.4 Analyses of vital sign variables

The summary statistics (including number, mean, standard deviation, median, Q1, 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 value 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

2.4.6.5 Analyses of electrocardiogram variables

Not applicable.

2.4.6.6 Additional safety analysis: region North America

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

2.4.7 [redacted]

[redacted]

2.4.8 Analyses of diabetes-related endpoints

The analyses of diabetes-related endpoints will be performed on the ITT and mITT populations and will be descriptive only. Summary statistics of raw values and of change from baseline of the five endpoints (see Section 2.1.9), including the mean, SD, median, Q1, Q3, minimum, and maximum, will be calculated for each visit and presented by treatment group, by diabetes type and in the pooled data .

Additional analyses of diabetes-related endpoints may also be replicated in the subgroup of patients of the region North America.

2.4.9 Analyses of ADA 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, Q1, Q3, minimum and maximum) for positive ADA by time point and by treatment group and also according to up-titration status;
- Number (%) of patients with pre-existing ADA and number (%) of patients with treatment-emergent ADA positive response by treatment group, overall and according to up-titration status;
- Number (%) of patients with persistent/transient/indeterminate treatment-emergent ADA positive response by treatment group, overall and according to up-titration status;
- Time to onset of treatment-emergent ADA positive response using descriptive statistics by treatment group, overall and according to up-titration status.

Correlations between ADA parameters (eg, titers, status, neutralizing status) and calculated LDL-C will be also explored (eg, box plot, scatter plot):

- % change from baseline in calculated LDL-C vs neutralizing negative/positive ADA status at last value up to Week 24
- % change from baseline in calculated LDL-C vs persistent/transient/indeterminate treatment-emergent ADA positive response at last value up to Week 24
- % change from baseline in calculated LDL-C vs ADA titers at last value up to Week 24

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

2.5 DATA HANDLING CONVENTIONS

2.5.1 Conventions

The following formulas will be used for computation of parameters.

Time since event / duration

Time since [event]/duration (years) = (Date of informed consent – Date of [event][1]) / 365.25.

[event] can be quit smoking, menopause. Duration can be for diabetes, hypercholesterolemia, insulin use, hypertension...

Date of last dose of IMP

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.

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 (estimated Glomerular Filtration Rate) value will be derived using the Modification of Diet in Renal Disease (MDRD) equation:

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

Lipids variables and laboratory safety variables

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

2.5.2 Data handling conventions for secondary efficacy variables

See Section 2.4.5.2.

[1] 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 the day of event would be missing, it will be put equal to 1.

2.5.3 Missing data

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Handling of potentially clinically significant abnormalities

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

For PCSAs with 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 only based 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; eg, for eosinophils, if no ULN is available or if ULN is <0.5 GIGA/L then the PCSA is >0.5 GIGA/L, while if ULN is available and ≥0.5 GIGA/L then the PCSA is >ULN.

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

[redacted]

[redacted]

2.5.4 Windows for time points

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

Table 2 - Analysis windows definition

Time point	Targeted study day	Analysis window in study days
Week 4	29	15 to 42
Week 8	57	43 to 70
Week 12	85	71 to minimum (98; study day corresponding to the first injection with IMP from kit allocated at up-titration IVRS contact)
Week 20	141	127 to 154
Week 24	169	155 to 182
Week 32	225	211 to 238

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

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

Not applicable.

2.5.7 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 collected until the end of the study (Week 32), an update of the safety analysis will be performed 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 analysis window collected and validated. It 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 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. Selected individuals who are not involved in the conduct of the study after the first step analysis will perform the second step analysis; individual patient identification will not be released to anyone who is directly involved in the ongoing conduct of the study.

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 injection date and last capsule date.
- Analyses of number of injections, mean injection frequency, percentage of days with under/above-planned dosing and compliance (for injections and capsules) will be performed up to the last injection and capsule reported in the e-CRF up to the cut-off date.
- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an 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 is planned to be locked at 30 working days after last patient last Week 24 visit. The second final database lock is planned at 20 working days after last patient last Week 32 visit.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

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