STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients with Hypercholesterolemia Not Adequately Controlled with Non-statin Lipid Modifying Therapy or the Lowest Strength of Statin

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab:	antibody
ADA:	Anti-alirocumab antibody
AE:	adverse event
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANOVA:	analysis of variance
Apo A-1:	apolipoprotein A-1
Apo-B:	apolipoprotein B
AST:	aspartate aminotransferase
BMI:	body mass index
CEC:	Clinical Events Committee
CHD:	coronary heart disease, coronary heart disease
CI:	confidence interval
CKD:	chronic kidney disease
CMQ:	company MedDRA query
DBP:	diastolic blood pressure
DBTP:	double-blind treatment period
ECG:	electrocardiogram
e-CRF:	electronic case report form
eDISH:	evaluation of drug-induced serious hepatotoxicity
EPA:	ethyl icosapentate
GFR:	glomerular filtration rate
GGT:	gamma glutamyl transferarses
HbA1c:	glycated hemoglobin A1c
HCV:	hepatitis C virus
HCV RNA:	hepatitis C virus ribonucleic acid
HDL-C:	high density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
HR:	heart rate
IRT:	Interactive Response Technology
ITT:	intent-to-treat
IWRS:	Interactive Web Response System
LDH:	lactate dehydrogenase
LDL-C:	low-density lipoprotein cholesterol
LLN:	lower limit of normal range
LLOQ:	lower limit of quantification
Lp(a):	lipoprotein (a)
MCMC:	Markov chain Monte Carlo
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities

mITT:	modified intent-to-treat
MMRM:	mixed-effect model with repeated measures
niacin:	nicotinic acid and derivatives
non HDL-C:	non-high-density lipoprotein cholesterol
non-FH:	non-familial hypercholesterolemia
OLTP:	open-label treatment period
PCSA:	potentially clinically significant abnormality
PCSK9:	proprotein convertase subtilisin/kexin type 9
PD:	pharmacodynamics
PK:	pharmacokinetics
Q1:	first quartile
Q2W:	every 2 weeks
Q3:	third quartile
Q4W:	every 4 weeks
RDW:	red blood cell distribution width
RNA:	ribonucleic acid
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
SMQ:	standardized MedDRA query
TC:	total cholesterol
TEAE:	treatment-emergent adverse event
TG:	triglyceride
ULN:	upper limit of normal range
ULOQ:	upper limit of quantification
US:	United States of America

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a randomized, double-blind, placebo-controlled, parallel-group, balanced (1:1:1, Alirocumab 150 mg every 4 weeks (Q4W): Alirocumab 150 mg every 2 weeks (Q2W): Placebo Q2W, subcutaneous injection), multi-center phase 3 study to evaluate the efficacy and safety of alirocumab in patients with hypercholesterolemia not adequately controlled with non-statin lipid modifying therapy (LMT) or the lowest strength of statin.

After a screening phase of up to 3 weeks, patients will be centrally randomized (using permuted block randomization schedule) via Interactive Response Technology (IRT) in a 1:1:1 ratio to 1 of the 3 treatment groups. Randomization will be stratified according to background statin therapy (Yes/No). "No statin background" will be also stratified according to background fibrate/ezetimibe therapy (Yes/No), where 'Yes' represents fibrate or ezetimibe, and 'No' represents diet therapy alone.

The study consists of 5 periods: run-in, screening, double-blind treatment period (DBTP), open-label treatment period (OLTP), and follow-up.

- A run-in period of 4 weeks. Patients will be treated by stable non-statin LMTs or stable daily atorvastatin 5 mg. Patients who will have already been treated by stable non-statin LMTs or stable daily atorvastatin 5 mg for at least 4 weeks will be able to skip this period.
- A screening period of up to 3 weeks.
- A DBTP of 12 weeks. Patients will receive double-blind treatment as follows,
  - Alirocumab 150 mg Q4W alternating with placebo Q4W OR
  - Alirocumab 150 mg Q2W OR
  - Placebo for alirocumab Q2W
- An OLTP of 52 weeks. All patients will receive alirocumab 150 mg Q4W from the start of OLTP. At Week 24, the up-titration to alirocumab 150 mg Q2W will be conducted through IRT only under the following circumstances:
  - In patients with heterozygous familial hypercholesterolemia (heFH) or in patients with non-familial hypercholesterolemia (non-FH) with documented coronary heart disease (CHD), low-density lipoprotein cholesterol (LDL-C) is ≥100 mg/dL (2.59 mmol/L) at Week 20.
  - In patients with non-FH classified as primary prevention category III, LDL-C is ≥120 mg/dL (3.10 mmol/L) at Week 20.
- A follow-up period of 8 weeks.

Approximately 159 subjects (53 subjects per treatment group) will be recruited and randomized [redacted]

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the reduction of LDL-C by alirocumab 150 mg Q4W or alirocumab 150 mg Q2W regimen as add on therapy to non-statin LMT including diet therapy alone or the lowest strength of statin in comparison with placebo after 12 weeks of treatment in patients with hypercholesterolemia.

1.2.2 Secondary objectives

The secondary objectives are:

- To evaluate the effect of two treatment regimens of alirocumab on other lipid parameters: apolipoprotein B (Apo-B), non-high-density lipoprotein cholesterol (non HDL-C), total cholesterol (TC), lipoprotein (a) [Lp(a)], high density lipoprotein cholesterol (HDL-C), triglyceride (TG), apolipoprotein A-1 (Apo A-1).
- To evaluate the safety and tolerability of alirocumab 150 mg Q4W and 150 mg Q2W.
- To evaluate the development of anti-alirocumab antibodies
- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) profiles of alirocumab 150 mg Q4W and 150 mg Q2W.
- To evaluate the long-term safety in patients receiving open-label alirocumab 150 mg Q4W and 150 mg Q2W.

1.3 DETERMINATION OF SAMPLE SIZE

The study is expected to enroll approximately 159 patients.

Two pairwise comparisons will be performed (Alirocumab 150 mg Q4W versus Placebo Q2W and Alirocumab 150 mg Q2W vs. Placebo Q2W). In order to handle multiple comparisons Bonferroni adjustment will be used, i.e., the alpha level for each comparison is 0.025 to obtain an overall study alpha level of 0.05.

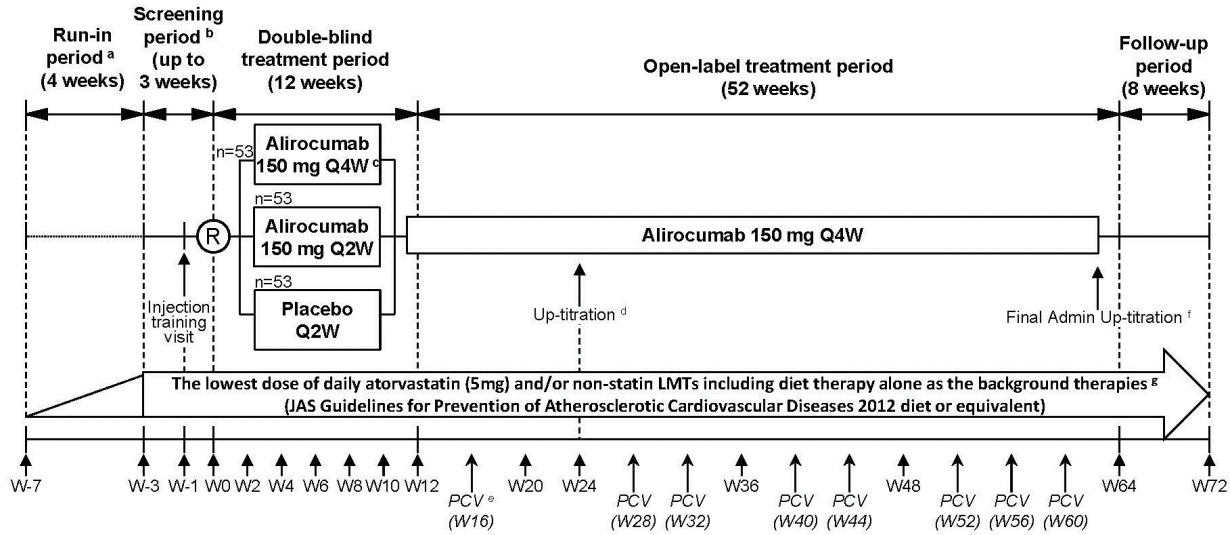
A sample size of 38 patients in the ITT population (19 in alirocumab group and 19 in placebo group) will have 90% power to detect a difference of 30% in mean percentage change in calculated LDL-C in any pairwise comparison with a 0.025 two-sided significance level and assuming a common standard deviation of 25%. [redacted] As a result, the total sample size needed for efficacy will be 57 patients (19 in each of the two alirocumab arms and 19 in the placebo arm).

[redacted]

The sample size is also considered in order to obtain long-term safety data. A sample size of 159 patients (randomization ratio 1: 1: 1, i.e., 53 in Alirocumab 150 mg Q4W, 53 in Alirocumab 150 mg Q2W, and 53 in Placebo Q2W) will allow having long-term open-label safety data. With this sample size, 100 patients are expected to be exposed to alirocumab for a minimum of 12 months providing that the proportion of drop out in the entire study duration (from randomization to Week 64) is 36%, which is obtained using exponential distribution with the same hazard as that of 30% dropout rate within 12 months. Moreover, with 100 patients treated with alirocumab for at least 12 months, AEs with a rate ≥0.03 will be detected with 95% probability.

Therefore, 159 patients (53 in Alirocumab 150 mg Q4W, 53 in Alirocumab 150 mg Q2W, and 53 in Placebo Q2W) will be needed to evaluate both efficacy and safety.

1.4 STUDY PLAN



a: As a general rule, patients start the Run-in period to reach at stable daily dose of atorvastatin 5 mg or non-statin LMTs.
b: When patients have received atorvastatin 5 mg/day or non-statin LMTs at stable daily dose for at least 4 weeks, they can skip the Run-in period and start the study from the Screening period.
c: In order to keep the double-blind manner, injections of placebo will be conducted at W2, W6 and W10.
d: Up-titration to Alirocumab 150 mg Q2W at W24 is done only if LDL-C is ≥100 mg/dL or ≥120 mg/dL at W20 depending on risk category.
e: Phone Call Visit (PCV).
f: Last administration of up-titrated Alirocumab 150mg Q2W at W62
g: The permitted atorvastatin at a dose of 5mg daily, non-statin LMTs, or diet therapy should remain stable (including dose) throughout the study duration barring exceptional circumstances.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not applicable.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value obtained up to the date and time of the first double-blind investigational medicinal product (IMP) injection. For patients randomized and not treated, the baseline value is defined as the last available value obtained up to randomization.

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

Demographic characteristics

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

Medical history

Medical history of special interest includes:

- Coronary heart disease (CHD)
  - Myocardial infarction
  - Unstable angina
  - Coronary revascularization procedures
  - Other clinically significant CHD
- Risk factors as categorized in primary prevention category III
  - Ischemic stroke
  - Peripheral arterial disease
  - Diabetes
    - Type 1 diabetes
    - Type 2 diabetes
  - Chronic kidney disease
  - Other risk factors
    - 10-year fatal CHD risk score≥2%

- 10-year fatal CHD risk score≥0.5% and <2%
- Hypo HDL cholesterolemia
- Family history of premature coronary artery disease
- Impaired glucose tolerance

- Cardiovascular history and risk factors includes “Coronary heart disease (CHD)” and Risk factors as categorized in primary prevention category III” listed above”.

All medical history information pre-listed or not in the electronic case report form (e-CRF), will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), currently in effect at Sanofi at the time of database lock for the first step analysis (Timing of first step analysis is described in Section 3).

Efficacy and safety analysis performed according to “***diabetes status at baseline***” reported in the Medical history by the investigator will be done using a company MedDRA query (CMQ), based on the HLGT "Diabetes Complications", HLT "Diabetes Mellitus" and HLT "Carbohydrate tolerance analyses (incl diabetes)" excluding PT "Blood glucose decreased", and using PT "hyperglycemia".

Disease characteristics at baseline

Specific disease characteristics include:

- Type of hypercholesterolemia:
  - Heterozygous familial hypercholesterolemia (heFH)
  - Non-familial hypercholesterolemia (non-FH)
    - Secondary prevention in non-FH
    - Primary prevention category III in non-FH
- For heFH patients:
  - Time from diagnosis of heFH (years);
  - Diagnosis made by genotyping (Yes, No);
- For non-FH patients:
  - Time from diagnosis of hypercholesterolemia (years);
  - Fredrickson classification of hyperlipoproteinemia (IIa, IIb, IV);
- [redacted]
- Reason why statin is not appropriate or why statin dose cannot be increased from the lowest strength for the patients

- Background LMT at randomization, as reported in the dedicated prior and concomitant medications e-CRF pages :
  - Statin by statin name and dose
  - Any LMT other than statins
    - Ezetimibe
    - Fibrate
      - Fenofibrate
      - Bezafibrate
      - Others
  - Diet alone (defined as patients not taking any Fibrate, Ezetimibe nor Statins)

Other baseline characteristics

Other baseline characteristics include body mass index (BMI) in kg/m² (quantitative and qualitative variable: <25, ≥25), smoking status, alcohol habits, randomization strata (as defined in Section 1.1) as per IRT.

Glycated hemoglobin A1c (HbA1c) (quantitative and qualitative variable: <5.7, ≥5.7 to <6.5, ≥6.5%), eGFR (quantitative and qualitative variable: <15 , ≥15 to < 30 , ≥30 to < 60 , ≥60 to <90, ≥90 mL/min/1.73m^2), and efficacy lipid parameters (quantitative variables for all efficacy parameters and the following qualitative variables) will be also summarized at baseline (definitions in Section 2.1.3):

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

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

2.1.2 Prior or concomitant medications

All medications taken within 12 weeks prior to run-in visit (Week -7) or screening visit (Week -3) and until the end of the study.

[redacted]

[redacted]

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 for the first step analysis.

- Prior medications are those the patient used within 12 weeks prior to run-in visit or screening visit and prior to first double-blind IMP injection. Prior medications can be discontinued before first injection or can be ongoing during treatment period.
- Double-blind concomitant medications are any treatments received by the patient concomitantly with the IMP, from the first double-blind IMP injection to the last double-blind IMP injection +70 days for patient not entering into the OLTP. For patients entering into the OLTP, concomitant medications will be truncated at the day before first open-label IMP injection. A given medication can be classified both as a prior medication and as a concomitant medication. Double-blind concomitant medications do not include medications started during the post-treatment period or OLTP (as defined in the observation period in Section 2.1.4).
- Post-treatment double-blind medications are those the patient took in the period starting from 71 days after the last double-blind IMP injection and ending when the patient terminates the study.
- Open-label concomitant medications are defined as any treatments received by the patient concomitantly with the open-label IMP, from the first open-label IMP injection to the last open-label IMP injection +70 days.
- Post-treatment open-label medications are those the patient took in the period starting from 71 days after the last open-label IMP injection and ending when the patient terminates the study.

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

2.1.3 Efficacy endpoints

Efficacy parameters include lipid parameters (ie, Total-C, calculated LDL-C, HDL-C, fasting TGs, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, Lp(a)). All these parameters are measured or calculated by a Central Laboratory, for both scheduled and unscheduled time points. Calculated LDL-C is obtained using the Friedewald formula. Non-HDL-C is calculated by subtracting HDL-C from the TC. Measured LDL-C values will be provided by the Central Laboratory only if corresponding TG values exceed 400 mg/dL (4.52 mmol/L), and will not be used for the analysis of calculated LDL-C endpoints.

Unless otherwise specified, all lipid values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the primary and secondary efficacy endpoints. All measurements, scheduled or unscheduled, fasting or not fasting (except TG), will be assigned to analysis windows

defined in Section 2.5.4, Table 2 in order to provide an assessment for Week 4 to Week 64 time points.

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

For all time points post-baseline, the value used for the analyses at a given time point (eg, at Week 12) is the value obtained within the corresponding analysis window. The baseline value is the last available measurement obtained up to the date and time of the first double-blind IMP 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.

2.1.3.1 Primary efficacy endpoint

The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to Week 12 in the intent-to-treat (ITT) population (defined in Section 2.3.1.1), using all LDL-C values regardless of adherence to treatment (ITT estimand). It is defined as: 100 x (calculated LDL-C value at Week 12 - calculated LDL-C value at baseline) / calculated LDL-C value at baseline.

2.1.3.2 Secondary efficacy endpoints

2.1.3.2.1 Key secondary efficacy endpoints

The key secondary efficacy will be considered in the following order:

The percentage changes in calculated LDL-C from baseline to Week 12 in the modified ITT (mITT) population (defined in Section 2.3.1.2), using all LDL-C values during the efficacy double-blind treatment period (on-treatment estimand).

1. The percentage change in calculated LDL-C from baseline to average Week 10-12 (ITT estimand).
2. The percentage change in calculated LDL-C from baseline to average Week 10-12 (on-treatment estimand).
3. The percentage change in Apo-B from baseline to Week 12 (ITT estimand).
4. The percentage change in Apo-B from baseline to Week 12 (on-treatment estimand).
5. The percentage change in non-HDL-C from baseline to Week 12 (ITT estimand).
6. The percentage change in non-HDL-C from baseline to Week 12 (on-treatment estimand).
7. The percentage change in TC from baseline to Week 12 (ITT estimand).
8. The proportion of patients reaching LDL-C goal at Week 12, i.e., calculated LDL-C <100 mg/dL (2.59 mmol/L) for heFH or non-FH patients who have a history of documented CHD patients, or LDL-C <120 mg/dL (3.10 mmol/L) for non-FH patients

who have a history of documented diseases or other risk factors classified as primary prevention category III (ITT estimand).

9. The proportion of patients reaching LDL-C goal at Week 12, i.e., calculated LDL-C <100 mg/dL (2.59 mmol/L) for heFH or non-FH patients who have a history of documented CHD patients, or LDL-C <120 mg/dL (3.10 mmol/L) for non-FH patients who have a history of documented diseases or other risk factors classified as primary prevention category III (on-treatment estimand).
10. The percentage change in Lp(a) from baseline to Week 12 (ITT estimand).
11. The percentage change in HDL-C from baseline to Week 12 (ITT estimand).
12. The percentage change in fasting TG from baseline to Week 12 (ITT estimand).
13. The percentage change in Apo A-1 from baseline to Week 12 (ITT estimand).

2.1.3.2.2 Other Secondary Efficacy Endpoints

- The proportion of patients with calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 12 (ITT estimand).
- The proportion of patients with calculated LDL-C <120 mg/dL (3.10 mmol/L) at Week 12 (ITT estimand).
- The proportion of patients with calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 12 (ITT estimand).
- The absolute change in calculated LDL-C from baseline to Week 12 (ITT estimand).
- The change in Apo-B/Apo A-1 ratio from baseline to Week 12 (ITT estimand).
- The proportion of patients with Apo-B <80 mg/dL (0.8 g/L) at Week 12 (ITT estimand).
- The proportion of patients with non HDL-C <130 mg/dL (3.37 mmol/L) at Week 12 (ITT estimand).
- The proportion of patients achieving at least 50% reduction in LDL-C at Week 12 (ITT estimand).
- The percentage change in TC, Lp(a) from baseline to Week 12 (on treatment estimand)

2.1.4 Safety endpoints

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

Observation period

The observation period starts from the time when the patient gives informed consent and will be divided into following periods:

- The PRE-TREATMENT period is defined from the signed informed consent up to the first dose of double-blind IMP injection.

- The double-blind 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 double-blind IMP injection + 70 days (10 weeks) for patients not entering into the OLTP. For patients entering into the OLTP, the TEAE period will be truncated at the day before the first open-label IMP injection.

  The double-blind TEAE period will include:

  - The double-blind TREATMENT period: defined as the time from the first double-blind IMP injection up to the day of last double-blind IMP injection (active or placebo depending on the Q2W or Q4W dosing regimen) + 21 days. The treatment period will end approximately 35 days after last active injection for most of the patients randomized in the alirocumab 150 mg Q4W arm since last planned injection at Week 10 is a placebo injection. 35 days is considered appropriate since the effect of alirocumab 150 mg Q4W is expected to be maintained during the 4-week dosing interval.
  - The double-blind RESIDUAL TREATMENT period: 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) for patients not entering into the OLTP. For patients entering into the OLTP, the RESIDUAL TREATMENT period will be truncated at the day before the first open-label IMP injection.
- The double-blind POST-TREATMENT period: defined as the time starting the day after the end of the double-blind TEAE period (i.e., 71 days after the day of last dose of double-blind IMP injection) for patients not entering into the OLTP.
- The open-label TEAE period is defined as the time form the first dose of open-label IMP injection to the last dose of open-label IMP injection + 70 days (10 weeks).

  The open-label TEAE period will include:

  - The open-label TREATMENT period defined as the time from the first dose of open-label IMP injection up to the day of last dose of open-label IMP injection + 21 days.
  - The open-label RESIDUAL TREATMENT period: defined as the time from the day of last dose of open-label IMP injection +22 days up to the day of last dose of open-label IMP injection +70 days (10 weeks).
- The open-label POST-TREATMENT period: defined as the time starting the day after the end of the open-label TEAE period (i.e., 71 days after the day of last dose of open-label IMP injection).

Observation periods below will be analyzed at the first step analysis only.

- The alirocumab exposed TEAE period is defined as follows :
  - For alirocumab 150 mg Q4W group and alirocumab 150 mg Q2W group: The time from the first dose of double-blind IMP injection to the last dose of IMP injection (double-blind or open-label) + 70 days (10 weeks).

- For placebo Q2W group: The time from the first dose of open-label IMP injection to the last dose of open-label IMP injection + 70 days (10 weeks).

The alirocumab exposed TEAE period will include:

- The alirocumab exposed TREATMENT period: defined below:
  - For alirocumab 150 mg Q4W group and alirocumab 150 mg Q2W group: The time from the first dose of double-blind IMP injection to the last dose of IMP injection (double-blind or open-label) + 21 days.
  - For placebo Q2W group: The time from the first dose of open-label IMP injection to the last dose of open-label IMP injection + 21 days.
- The alirocumab exposed RESIDUAL TREATMENT period: defined below:
  - For alirocumab 150 mg Q4W group and alirocumab 150 mg Q2W group: The time from the day of last dose of IMP injection(double-blind or open-label) +22 days up to the day of last dose of IMP injection(double-blind or open-label) +70 days (10 weeks).
  - For placebo Q2W group: The time from the day of last dose of open-label IMP injection +22 days up to the day of last dose of open-label IMP injection +70 days (10 weeks).

The double-blind on-study observation period is defined as the time from the day of first dose of double-blind IMP injection until the last protocol planned double-blind visit of the patient. The last protocol planned double-blind visit is defined as the follow-up visit if done, or a maximum of 20 weeks after the randomization of the patient, for patients not proceeding into OLTP. For patients proceeding into OLTP, the last protocol planned double-blind visit is defined as the end of double-blind treatment period visit (Week 12).

The open-label on-study observation period is defined as the time from the first open-label IMP injection until the last protocol planned open-label visit of the patient.

The alirocumab exposed on-study observation period is defined below:

- For alirocumab 150 mg Q4W group and alirocumab 150 mg Q2W group: The time from the day of first dose of double-blind IMP injection until the last protocol planned double-blind visit for patients not entering into the OLTP or the last protocol planned open-label visit for patients entering into the OLTP.
- For placebo Q2W group: The time from the first open-label IMP injection until the last protocol planned open-label visit of the patient.

2.1.4.1 Adverse events variables

AEs (including SAEs and AESI) are recorded from the time of signed informed consent until the end of the study. All AEs diagnosed by the Investigator, irrespective of the result of the adjudication for CV events, will be reported and described.

All AEs will be coded to a lower-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 Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of the database lock for the first step analysis.

Adverse event observation period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.
- Double-blind TEAEs are AEs that developed or worsened or became serious during the double-blind TEAE period.
- Double-blind post-treatment AEs are AEs that developed or worsened or became serious during the double-blind post-treatment period.
- Open-label TEAEs are AEs developed or worsened or became serious during the open-label TEAE period.
- Open-label post-treatment AEs are AEs that developed or worsened or became serious during the open-label post-treatment period.
- Alirocumab exposed TEAEs are AEs developed or worsened or became serious during the alirocumab exposed TEAE period.

AESI include the following AEs:

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

- Local injection site reactions, selected using e-CRF specific tick box on the AE page;
- Allergic events:
  - General allergic events will be tabulated. Events will be selected using standardized MedDRA query (SMQ) “hypersensitivity” (broad and narrow) excluding the following preferred terms linked to local injection site reactions (“infusion site dermatitis”, “infusion site hypersensitivity”, “infusion site rash”, “infusion site urticaria”, “injection site dermatitis”, “injection site hypersensitivity”, “injection site rash”, “injection site urticaria” and “injection site vasculitis”);
  - General allergic events and local allergic reactions at IMP injection site will be described. This selection will be based on the above selection for general allergic event and on the following selection of PT from the symptoms complementary form for local injection site reaction ("Injection site dermatitis", "Injection site hypersensitivity", "Injection site oedema", "Injection site rash", "Injection site urticaria", "Injection site eczema", "Injection site vasculitis", "Injection site swelling", "Infusion site dermatitis", "Infusion site hypersensitivity", "Infusion site oedema", "Infusion site rash", "Infusion site urticaria", "Infusion site swelling")

- ALT ≥3 ULN (if baseline ALT <ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ULN), selected using laboratory data;
- Hemolytic anemia, selected using e-CRF specific tick box on the AE page and confirmed final diagnosis provided in the AE complementary form;
- Neurologic events selected using SMQs “demyelination” (broad and narrow), “peripheral neuropathy” (broad and narrow), and “Guillain-Barre syndrome” (broad and narrow) excluding the following preferred terms “acute respiratory distress syndrome”, “asthenia”, “respiratory arrest” and “respiratory failure”;
- Neurocognitive events, selected using a company MedDRA query (CMQ), based on the following 5 HLGTs: “deliria (including confusion)”, “cognitive and attention disorders and disturbances”, “dementia and amnestic conditions”, “disturbances in thinking and perception”, and “mental impairment disorders”
- Ophthalmologic events selected using SMQs “optic nerve disorders” (broad and narrow), “retinal disorders” (narrow), and “corneal disorders” (narrow);
- Overdose with IMP (symptomatic or asymptomatic).The selection is based on the preferred terms “Accidental overdose” and “Intentional overdose” and the tick box “Overdose with IMP auto-injectors” in the AE complementary e-CRF form;
- Overdose with NIMP (symptomatic or asymptomatic). The selection is based on the preferred terms “Accidental overdose” and “Intentional overdose” and the tick box “Other medications” in the AE complementary e-CRF form
- Pregnancy of female patient/subject (including male subject’s partner) selected using appropriate MedDRA codes.
- [redacted]

In addition the following grouping of events will be provided:

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

Cardiovascular events

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

Adjudicated CV events include all CV AEs and CV procedures positively adjudicated as defined in the CEC charter. The following categories will be described:

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

2.1.4.2 Deaths

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

- Death on-study during DBTP: deaths occurring during the double-blind on-study observation period,
- Death on-treatment during DBTP: deaths occurring during the double-blind TEAE period,
- Death on-study during OLTP: deaths occurring during the open-label on-study observation period,
- Death on-treatment during OLTP: deaths occurring during the open-label 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. International units will be used in all listings and tables. Clinical laboratory values converted into conventional (US) units will be also available in the database. Analyses can be provided upon request.

Unless otherwise specified below, blood samples for clinical laboratories were to be collected during:

- Screening period at Visit 2 (Week -3)
- DBTP at Visit 4 (Week 0), Visit 10 (Week 12) /or permanent treatment discontinuation
- OLTP at Visit 13 (Week 24), Visit 16 (Week 36), Visit 19 (Week 48), and Visit 23 (Week 64) /or permanent treatment discontinuation

- Follow-up period (Visit 24 [Week 72]) in case of abnormality at Visit 23 (Week 64).

The laboratory parameters (excluding those considered as efficacy parameters) will be classified as follows:

- Hematology:
  - Red blood cells and platelets:
    red blood cell count, hemoglobin, red blood cell distribution width (RDW), reticulocyte count, hematocrit, platelets, haptoglobin;
  - White blood cells:
    white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Clinical chemistry:
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase;
  - Electrolytes: sodium, potassium, chloride, bicarbonate, calcium, phosphorus;
  - Renal function: creatinine, glomerular filtration rate (eGFR), urea nitrogen, blood uric acid;
  - Liver function (also measured during DBTP at Week 4 and Week 8, except gamma glutamyl transferarses [GGT] and lactate dehydrogenase [LDH]):
    ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), GGT, total bilirubin, and in case of total bilirubin values above the normal range, must include direct and indirect bilirubin, LDH.
- Hepatitis screen:
  anti-hepatitis-C antibody (at Week -3 and Week 64/or permanent treatment discontinuation).

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

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

Body weight was to be measured during:

- Screening period at Week -3
- DBTP at Week 0, Week 12/or permanent treatment discontinuation
- OLTP at Week 24, Week 36, Week 64/or permanent treatment discontinuation
- Follow-up period (Week 72).

HR and blood pressure were to be measured during:

- Run-in and Screening period at Week -7, Week -3, Week -1

- DBTP at Week 0, Week2, Week 4, Week 6, Week 8, Week 10, Week 12/or permanent treatment discontinuation
- OLTP at Week 20, Week 24, Week 36, Week48, Week 64/or permanent treatment discontinuation
- Follow-up period (Week 72).

Vital signs will be described following time windows as defined in Section 2.5.4, Table 4.

2.1.4.5 Electrocardiogram variables

The ECG parameters will be recorded automatically by the device at the Investigator site during:

- Screening period at Week -3
- DBTP at Week 12/or permanent treatment discontinuation
- OLTP at Week 24, and Week 64/or permanent treatment discontinuation.

ECG assessments will be described as normal or abnormal.

2.1.5 Other endpoints

Other assessment endpoints listed below are defined using same definitions and rules as for calculated LDL-C, when applicable (see Section 2.1.3.1).

- The absolute change in HbA1c (%) from baseline (Week -3) to Week 12 (DBTP), Week 24 (OLTP), Week 36 (OLTP), Week 48 (OLTP), and Week 64 (OLTP): PCSA criteria for HbA1c will be also used (see Appendix A).
- The proportion of patients with 2 consecutives results, spaced out by at least 21 days, of calculated LDL-C <25 mg/dL (<0.65 mmol/L) [redacted] during each treatment period (double-blind and open-label) and the time to the first calculated LDL-C <25 mg/dL [redacted] for these patients within the relevant treatment period.
- Proportion of patients who are up-titrated to alirocumab 150 mg Q2W during the OLTP.

2.1.6 Anti-alirocumab antibodies variables

Anti-alirocumab antibodies (ADA) are assessed:

- At baseline (before the first IMP injection)
- During DBTP at Week 4, Week 12
- During OLTP at Week 24, Week 36, Week 48 and Week 64/or permanent treatment discontinuation
- During follow-up (Week 72).

ADA measurements will be assigned to similar analysis windows as defined for efficacy endpoints (Table 2), with an additional analysis window for the ADA follow-up measurement performed at Week 72.

The following variables will be described:

- ADA response (Positive or Negative).
  For ADA positive:
  - Titer levels;
  - Neutralizing status (Positive or Negative).
- Pre-existing positive ADA defined as patients with positive ADA response at baseline with less than 4-fold increase in titer in the post-baseline period;

  Treatment-emergent positive ADA response defined as:
  1) Patients with no ADA positive response at baseline but with any positive response in the post-baseline period (for DBTP: up to follow-up visit for patients not proceeding into OLTP, up to first open-label IMP injection for patients proceeding into OLTP, [redacted]

  or
  2) Patients with a positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period (for DBTP: up to follow-up visit for patients not proceeding into OLTP, up to first open-label IMP injection for patients proceeding into OLTP [redacted]
  For treatment-emergent positive ADA, the following categories for ADA duration will be applied:
  - A persistent positive response is a treatment-emergent ADA positive response detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period;
  - An indeterminate duration positive response is defined as ADA present only at the last sampling time point;
  - A transient positive response is defined as any treatment-emergent positive ADA response that is neither considered persistent nor indeterminate.

[redacted]

2.1.7 Pharmacokinetic variables

Concentrations of total alirocumab, total and free PCSK9 in serum are assessed at baseline (Week 0), Week 4, Week 8, Week 10, and Week 12.

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

[redacted]

Alirocumab concentration and total and free PCSK9 concentration will be described following time windows as defined in Section 2.5.4, Table 3.

2.1.8 Pharmacodynamic/genomics endpoints

[redacted]

2.1.9 Quality-of-life endpoints

[redacted]

2.1.10 Health economic endpoints

[redacted]

2.2 DISPOSITION OF PATIENTS

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

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

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

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

The following categories will be displayed for first and second step analysis:

- Screened patients
- Screen failure patients and reasons for screen failure
- Non-randomized but treated patients, if any
- Randomized patients
- Randomized but not treated patients and reason for not being treated
- Randomized and treated patients
- Patients who completed the double-blind study treatment period (at least 10 weeks of exposure with double-blind treatment and Week 12 visit performed)
- Patients who did not complete the double-blind study treatment period (as per definition above)
- Main reason for permanent double-blind treatment discontinuation (as per eCRF end-of-treatment form)

[redacted]

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

[redacted]

[redacted]

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

[redacted]

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

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

- Randomized population.
- Efficacy population: ITT and mITT populations
- Safety population
- Pharmacokinetics population
- Anti-alirocumab antibody population
- Open-label treatment population
- Alirocumab safety population

Definitions of the study populations above are provided in Section 2.3

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

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

   OR

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

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

All randomization and drug-dispensing irregularities will be documented in the clinical study report. These irregularities will be summarized by treatment group on the randomized population. Nonrandomized, treated patients will be described separately.

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

Randomization and drug allocation irregularities
Kit dispensed without IVRS transaction
Kit dispensed erroneously
Kit not available
Patient randomized twice
Stratification error

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized or treated with a double-blind or open-label 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.

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

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

2.3.1 Efficacy populations

The primary efficacy analysis population will be the Intent-to-treat (ITT) population.

2.3.1.1 Intent–to-treat population

The ITT population is defined as the randomized population who has an evaluable primary endpoint. The primary efficacy endpoint is evaluable when both of the following conditions are met:

- Availability of at least 1 value for calculated LDL-C before the first dose of double-blind IMP (i.e., baseline).
- Availability of at least 1 value for calculated LDL-C within one of the following analysis windows: Week 4, Week 8, Week 10, and Week 12.

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

2.3.1.2 Modified intent-to-treat population

The modified intent-to-treat (mITT population is defined as the randomized population who took at least one dose or part of dose of the double-blind IMP injection and has an evaluable primary efficacy endpoint during the efficacy double-blind treatment period. The primary efficacy endpoint will be considered evaluable when both of the following conditions are met:

- Availability of at least 1 value for calculated LDL-C before the first dose of double-blind IMP (i.e., baseline).
- Availability of at least 1 value for calculated LDL-C within one of the following analysis window: Week 4, Week 8, Week 10, and Week 12 during the efficacy double-blind treatment period.

The efficacy double-blind treatment period will be defined as:

- The time period from the first double-blind IMP injection up to 21 days after the last double-blind IMP injection (i.e., up to Week 12).

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

2.3.2 Safety population

The Safety population considered for the safety analyses will be the randomized patients who actually received at least one dose or partial dose of the double-blind IMP injection. Patients will be analyzed according to the treatment actually received (i.e. as-treated treatment group, Alirocumab 150mg Q4W, Alirocumab 150mg Q2W or Placebo Q2W).

In addition:

- Non-randomized but treated patients 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 double-blind IMP injection from more than one treatment group during the trial (cases reported as protocol deviation), the treatment group allocation for as-treated analysis will be the one to which the patient received the highest number of injections. In case of the same number of injections of each treatment is received, the as-treated treatment group will be the as-randomized group.

2.3.3 Anti-alirocumab antibody population

The anti-alirocumab antibody analysis will be performed on all randomized and treated patients (safety population) with an available ADA sample at Week 0 (baseline) and at least 1 available ADA sample post first double-blind IMP injection and up to follow-up visit for patients not proceeding into OLTP, up to first open-label IMP injection for patients proceeding into OLTP.

2.3.4 Pharmacokinetics population

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

2.3.5 Open-label treatment population

The open-label treatment population considered for all analyses in the open-label treatment period will be all randomized patients who received at least one dose or part of dose of open-label IMP.

2.3.6 Alirocumab safety population

The alirocumab safety population considered for the safety analyses combining exposure of alirocumab during DBTP and OLTP will be the randomized patients who actually received at least one dose or partial dose of alirocumab IMP (double-blind or open-label).

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 using descriptive statistics.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. First quartile (Q1)

and third quartile (Q3) will be also provided for baseline lipid parameters, HbA1c and eGFR. 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 as-randomized treatment group. Similar analyses will be done on the ITT population, safety population, OLT population, and alirocumab safety population [redacted]

The reason why statin is not appropriate or why statin dose cannot be increased from the lowest strength for the patients will be descriptively summarized using the number and percentage of patients by each treatment group. The reason specified in eCRF will be listed for the patient with "other reason".

[redacted]

2.4.2 Prior, concomitant, or post-treatment medications

The prior, concomitant and post-treatment medications will be presented during DBTP for the safety population.

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

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

The tables for concomitant and post-treatment medications will be sorted by decreasing frequency of ATC followed by therapeutic class based on the incidence in the Alirocumab 150mg Q4W group. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used.

All concomitant and post-treatment medications recorded during the OLTP will be summarized in the OLT population.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized for the safety population (using as-treated treatment group), OLT population and alirocumab safety population (for first step analysis only).

2.4.3.1 Extent of investigational medicinal product exposure

Injection (alirocumab or placebo)

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

- placebo Q2W for patients randomized in the Placebo Q2W group,
- placebo Q4W (to maintain the blind) or 150 mg Q4W of alirocumab for patients randomized in the Alirocumab 150 mg Q4W group.

- 150 mg Q2W of alirocumab for patients randomized in the Alirocumab 150 mg Q2W group.

The total exposure during the DBTP will be assessed using descriptive statistics for:

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

Duration of double-blind IMP injection exposure will be summarized using number, mean, SD, median, minimum and maximum. In addition, it will be summarized according to the following categories: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <10 weeks, ≥10 weeks.

The total exposure during the OLTP will be assessed using descriptive statistics for:

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

Duration of open-label IMP injection exposure will be summarized using number, mean, SD, median, minimum and maximum. In addition, it will be summarized according to the following categories: ≥1day and <12 weeks, ≥12 weeks and <24 weeks, ≥24 weeks and <36 weeks, ≥36 weeks and <48 weeks, ≥48 weeks.

The total exposure during alirocumab exposed period (defined in Section 2.4.5) for first step analysis only will be assessed using descriptive statistics for:

- Duration of alirocumab IMP injection exposure in weeks defined as:
  - For Alirocumab 150 mg Q4W group and Alirocumab 150 mg Q2W group: (date of last dose of IMP injection (double-blind or open-label) +14 – date of first dose of double-blind IMP injection) / 7, regardless of intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data). Non-integer values will be rounded to one decimal place;
  - For Placebo Q2W group: (date of last dose of open-label IMP injection +14 – date of first dose of open-label IMP injection) / 7, regardless of intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data). Non-integer values will be rounded to one decimal place;
- The total number of alirocumab IMP injections by patient.

Duration of alirocumab IMP injection exposure will be summarized using number, mean, SD, median, minimum and maximum. In addition, it will be summarized according to the following

categories: ≥1day and <12 weeks, ≥12 weeks and <24 weeks, ≥24 weeks and <36 weeks, ≥36 weeks and <48 weeks, ≥48 weeks and <60 weeks, ≥60 weeks.

Titration

For the OLTP, the number and percentage of patients with an up-titration at Week 24 will be described. Patients with an up-titration are defined as up-titrated patients according to IRT Week 24 transaction with at least 1 injection of alirocumab 150 mg Q2W afterwards.

2.4.3.2 Compliance

Compliance for the DBTP will be assessed using the following parameters:

- The mean injection frequency of IMP double-blind injections will be defined for each patient as the average number of days between 2 consecutive double-blind injections, that is: (last double-blind injection date – first double-blind injection date)/(number of double-blind injections -1) for patients receiving at least 2 injections.
- The overall compliance for double-blind injections will be defined for each patient as: 100-(%days with under-planned dosing + %days with above-planned dosing). Under-planned and above-planned dosing will be defined as follows, considering that injections should be performed every 2 weeks (±3 days as per protocol):
- The % days with under-planned dosing will be defined for each patient as the number of days with no injection administered within the previous 17 days divided by the duration of IMP injection exposure in days. For example if a patient takes a dose 18 days after his/her previous injection, then 1 day is counted as a day under-planned dosing.
- The % days with above-planned dosing will be defined for each patient as the number of days with more than one injection administered within the 11 days before divided by the duration of IMP injection exposure in days. For example if a patient takes a dose 9 days after his/her previous injection, then 2 days are counted as days above-planned dosing.

For the OLTP, only mean injection frequency will be assessed for compliance.

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

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

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

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

The mean injection frequency of IMP open-label injections (until and after Week 24 separately) will be summarized according to the up-titration status.

2.4.4 Analyses of efficacy endpoints

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

Statistical analyses for the primary and secondary efficacy endpoints will be conducted in the DBTP. [redacted]

2.4.4.1 Analysis of primary efficacy endpoint(s)

2.4.4.1.1 Primary efficacy analysis

In the primary analysis, stratification factor of statin will be considered as covariate. Consistency of treatment effects between the randomization strata will be evaluated. In case there is heterogeneity of treatment effects at Week 24, particularly treatment group-by-stratification factor of statin interaction, then analysis by the strata will be performed as secondary.

The percent change from baseline in calculated LDL-C at Week 12 as defined in Section 2.1.3.1 will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 4 to Week 12 analysis windows will be used and missing data are accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group (Placebo Q2W, Alirocumab 150 mg Q4W and Alirocumab 150 mg Q2W), stratification factor of statin (Yes/No) as per IRT, time point (Week 4, Week 8, Week 10, Week 12), treatment-by-time point interaction, and statin-by-time point interaction, as well as, the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction.

This model will be run using SAS Mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least-squares means estimates at Week 12 for each treatment groups with their corresponding standard errors (SEs). To compare each alirocumab group to the Placebo Q2W group, an appropriate contrast statement will be used to test the differences of these estimates, at the 2-sided 0.025 level.

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

Let μ_0 and μ_1 be the population means of the percent change from baseline in calculated LDL-C at Week 12 under Placebo Q2W group and each alirocumab group, respectively. The hypothesis that will be tested is "$H_{0:}\ \mu_0 = \mu_1$" versus H_1: "$\mu_0 \neq \mu_1$".

Alirocumab group will be compared to placebo using an appropriate contrast tested at the two-sided 0.05 level, with corresponding least squares estimate of the mean difference between groups, SE and 97.5% CI.

In addition, the difference between the two alirocumab arms Q4W and Q2W will also be provided, with a 95% CI using an appropriate contrast from the same MMRM model.

2.4.4.1.2 Model assumption checks

Homogeneity of treatment effect across baseline LDL-C levels:

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

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

Within the framework of this model with interaction terms, a graph presenting the LS means difference versus placebo at Week 12 and the corresponding 97.5% CI will be provided by baseline LDL-C value.

Analysis of residuals:

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

- Normality of studentized residuals, presented graphically using histogram and QQ-plot;
- Plot of studentized residuals versus predicted values;
- Distribution of studentized residuals, presented graphically using boxplots, within each category of the fixed categorical effects of the MMRM:
  - Treatment group (Placebo Q2W, Alirocumab 150 mg Q4W and Alirocumab 150 mg Q2W);
  - Time point (Week 4, Week 8, Week 10, Week 12);
  - Treatment group-by-time point interaction;

- Stratification factor of statin (Yes/No);
- Stratification factor of statin - by - time point interaction.

2.4.4.1.3 Sensitivity to randomization strata

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

2.4.4.1.4 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, treatment group-by-subgroup factor, time point-by-subgroup factor and treatment group-by time point-by subgroup factor interaction terms and a subgroup factor term will be added in the primary MMRM model. LS means difference versus placebo at Week 12 will be provided, as well as the corresponding SE and 97.5% CI, within each subgroup. The significance level of the treatment group-by-subgroup factor interaction term at Week 12 will be also provided for each factor for descriptive purpose. Forest plots will be provided. In order to handle unbalances between randomization stratification factors levels, population weights will be used as for the primary analysis model.

Only subgroups with a sufficient number of patients in each level and treatment groups will be evaluated.

Subgroups of interest are:

- BMI (<25 kg/m^2, ≥ 25 kg/m^2);
- Gender (Female, Male);
- Age (<65 years, ≥ 65 years);
- Stratification factor of statin as per IRT (Yes, No)
- Randomization strata as per IRT (statin, non-statin LMT, diet alone) : for this specific subgroup factor, the MMRM model will include this randomization strata instead of stratification factor of statin as per IRT,
- Randomization strata as per LMT (statin, Ezetimibe, Fibrate, diet alone) : for this specific subgroup factor, the MMRM model will include this randomization strata instead of stratification factor of statin as per IRT,
- heFH population (Yes, No)
- Prior history of MI or ischemic stroke (Yes, No);
- Diabetes status at baseline (Yes, No), which is defined in Section 2.1;
- Chronic kidney disease (CKD) (Yes, No);
- Prior history of side effects caused by statin (Yes, No)

- Baseline calculated LDL-C (<130, ≥130 to <160, ≥160 mg/dL) (ie, <3.37, ≥3.37 to <4.14, ≥4.14 mmol/L):
  For this specific subgroup factor, the MMRM model will include fixed categorical effects for treatment group, stratification factor of statin, baseline LDL-C category, time point, and the interactions treatment group-by-time point, stratification factor of statin-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;
- Baseline HDL-C (<40 mg/dL (<1.04 mmol/L), ≥40 mg/dL (≥1.04 mmol/L)),
- Baseline fasting TG (<150 mg/dL (<1.7 mmol/L), ≥150 mg/dL (≥1.7 mmol/L) ie, mixed dyslipidemia);
- Baseline Lp(a) (<30, ≥30 to <50, ≥50 mg/dL) (ie, <0.3, ≥0.3 to <0.5, ≥0.5 g/L));
- Baseline total PCSK9 level (below the median, at or above the median);
- Baseline free PCSK9 level (below the median, at or above the median).

2.4.4.2 Analyses of secondary efficacy endpoints

Method for controlling the overall type-I error rate when testing the key secondary efficacy endpoints is described in Section 2.4.4.3.

For key secondary efficacy endpoints and other secondary efficacy endpoints (described in Section 2.1.3.2), descriptive summaries and analyses will be performed in the ITT population or mITT population depending on the estimand.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (example: percent change in calculated LDL-C), continuous measurements expected to have a non-normal distribution (example: TG), and binary measurements (example: proportion of patients reaching calculated LDL-C <100mg/dL).

2.4.4.2.1 Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables defined in Section 2.1.3.2 anticipated to have a normal distribution (ie, lipids other than TG and Lp[a]) will be analyzed using the same MMRM model as for the primary endpoint with fixed categorical effects of treatment group, stratification factor of statin as per IRT, planned time points up to Week 12, treatment-by-time point interaction and stratification factor of statin-by-time point interaction, as well as the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

The percentage change in calculated LDL-C from baseline to averaged Week 10 - 12 will be analyzed using an appropriate contrast statement (assigning a weight of 0.5 for the two time points) from the MMRM model.

2.4.4.2.2 Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy variables defined in Section 2.1.3.2 anticipated to have a non-normal distribution (ie, TG and Lp[a]) will be analyzed using multiple imputation approach described below in detail for handling of missing values, followed by the testing of treatment groups using a robust regression model (1). Missing data will be imputed 100 times to generate 100 complete data sets, using the MI SAS procedure. The percent change from baseline at time point of interest will be then derived from observed and imputed lipid values at this time point. The 100 complete data sets will be then analyzed using a robust regression model with endpoint of interest as response variable using M-estimation (using SAS ROBUSTREG procedure) with treatment group, stratification factor of statin as per IRT, and corresponding baseline value(s) as effects. Then the MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae. Combined means estimates for both treatment groups, as well as the differences of these estimates, with their corresponding SEs, 97.5% CIs and p-value will be provided.

Multiple imputation model

Since in general the missing pattern is anticipated to be non-monotone, a two-step approach will be used:

- Step 1: The MCMC (Markov chain Monte Carlo) method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern;
- Step 2: Using the monotone data set from step 1, missing data will be imputed using the regression method.

[redacted]

Data will be log-transformed before imputation process and then back-transformed to create the imputed data sets using the TRANSFORM statement of SAS MI procedure, since the distribution is assumed non-normal.

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

2.4.4.2.3 Binary endpoints

Binary secondary efficacy endpoints defined in Section 2.1.3.2 will be analyzed using multiple imputation approach for handling of missing values (see Section 2.4.4.2.2 for details about multiple imputation). In the imputations, log-transform process planned in Section 2.4.4.2.2 will not be done for the lipid parameter assuming normal distribution. The binary endpoint at time point of interest will be derived from observed and imputed lipid values at this time point. Multiple imputation will be followed by stratified logistic regression with treatment group as main effect and corresponding baseline value(s) as covariate, stratified by stratification factor of statin (as per IRT, as defined in Section 1.4). Combined estimates of odds ratio versus placebo, 97.5% CI, and p-value will be obtained through the SAS MIANALYZE procedure.

In the data dependent case such logistic regression 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 a stratified exact conditional logistic regression would be performed to compare treatment effects. The LOCF imputation method for the endpoints at Week12 will consist of using the last value obtained up to the Week 12 analysis window to impute the missing Week 12 value.

In case of computing issues with exact logistic regression, the baseline level(s) will be entered in the model as a categorical variable(s) using quartiles [redacted]

2.4.4.2.4 Sensitivity analyses of key secondary endpoints

[redacted]

2.4.4.2.5 Analyses of key secondary endpoints by subgroups

The endpoint “percent change in fasting TG from baseline to Week 12” will be analyzed according to the following subgroups:

Baseline fasting TG (<150 mg/dL (<1.7 mmol/L), ≥150 mg/dL (≥1.7 mmol/L)) ie, mixed dyslipidemia)

2.4.4.2.6 Summary of results per time point

2.4.4.3 Multiplicity issues

The multiplicity appears in two kinds in this study, due to the presence of the 2 arms of alirocumab 150 mg Q4W and 150 mg Q2W that are compared with placebo, and due to the multiple key secondary efficacy endpoints.

The overall type I error will be controlled at 0.05 by performing each pairwise test (alirocumab 150 mg Q4W vs. placebo, and alirocumab 150 mg Q2W vs. placebo) for the main efficacy endpoint at the 0.025 level.

Then, a hierarchical procedure will be used for each pairwise comparison to control the type I error and to handle multiple endpoints. If the primary endpoint analysis is significant at the 2.5% alpha level, the key secondary efficacy endpoints will be tested sequentially at the 0.025 level, using the order defined in Section 2.1.3.2.1. Hierarchical procedure for comparisons of alirocumab 150 mg Q4W versus placebo, and alirocumab 150 mg Q2W versus placebo will be processed separately.

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

In addition, no further adjustment will be made for multiple analyses (i.e., first and second analyses), since the primary efficacy endpoint and the key secondary efficacy endpoints will all have been conducted at the time of first analysis. [redacted]

2.4.4.4 Additional efficacy analysis

Not applicable

2.4.5 Analyses of safety data

Safety analyses will be conducted using data of the DBTP and OLTP. The summary of safety results will be presented separately for the DBTP on the safety population and OLTP on the OLT population. Besides, safety analyses performed on the alirocumab exposed period (see Section 2.1.4) will be conducted on the alirocumab safety population to evaluate long-term safety at the first step analysis.

The analyses performed on the DBTP will be presented by treatment group while the analyses performed on the OLTP or the alirocumab exposed period will be presented by overall patients. No formal inferential testing will be performed. Summaries will be descriptive in nature. All summaries of safety results described below will be presented for each observation period respectively, unless otherwise noted.

General common rules

All safety analyses will be performed using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately
- The baseline value for both double-blind and open-label treatment period is defined as the last available value before the first double-blind IMP injection, except otherwise specified.
- 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, vital signs, and ECG (PCSA defined in the document “Analysis and reporting safety data from clinical trials through the Clinical Study Report (CSR) (Version Number: 3.0)” [Appendix A])
  Considering that the threshold defined in the PCSA list for monocytes and basophils can be below the ULN, the following PCSA criterion will be used for the PCSA analysis of monocytes and basophils:
  - PCSA criterion for monocytes: >0.7 Giga/L or > ULN (if ULN ≥0.7 Giga/L);

- PCSA criterion for basophils: >0.1 Giga/L or > ULN (if ULN ≥0.1 Giga/L).

- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter at least once during the TEAE period.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 2 in order to provide an assessment for Week 4 to Week 64 time points.
- In both the DBTP and the OLTP, for quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group using analysis windows. Summaries will also include the last on-treatment value and the worst on-treatment value. The last on-treatment value is defined as the last value collected during the treatment period of each observation 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 of each observation period according to the direction (minimum or maximum) of the abnormality as defined in PCSA list.

Analyses performed according to diabetes status will be done using the CMQ definition (regardless of the ongoing status) (Section 2.1.1).

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs, presented in each observation period. 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.

AE 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, TEAE, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs (in the alirocumab 150mg Q4W group) will define the presentation order for all other tables by SOC and PT, unless otherwise specified. The tables of AEs by SOC, HLGT, HLT and PT will be sorted by the SOC internationally agreed order and the other levels (HLGT, HLT, PT) will be presented in alphabetical order, unless otherwise specified

Analysis of all treatment-emergent adverse events

The following TEAEs summaries will be generated.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE;
  - Serious TEAE;
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT;
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC, HLT and PT (HLT incidence ≥2 % in any treatment group), sorted by SOC internationally agreed order and by alphabetic order for the other levels (HLT and PT);
- All TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC (in the alirocumab 150 mg Q4W group). This sorting order will be applied to all other tables by SOC and PT of TEAEs, unless otherwise specified;
- All TEAEs by treatment group regardless of relationship in one column and, in the same table a second column with TEAEs related to alirocumab according to investigator's opinion by primary SOC, HLGT, HLT and PT;
- All TEAEs by maximal intensity (ie, mild, moderate or severe), presented by primary SOC and PT, sorted by the sorting order defined above;

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 a second column with TEAEs related to alirocumab according to investigator's opinion, by primary SOC, HLGT, HLT, and PT;

Analysis of all TEAE(s) leading to treatment discontinuation

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

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

- All grouping of TEAEs including adverse events of special interest as listed in Section 2.1.4.1(except Pregnancy and overdose with NIMP) will be analyzed using selections defined in Section 2.1.4.1 and will be presented by SMQ and PT (when selection is based on SMQs) and by SOC and PT (when selection is based on the e-CRF tick box or HLGT/HLT). The summaries will be sorted by decreasing incidence of PT within each SOC/SMQ (in the alirocumab 150 mg Q4W group).
- [redacted]
- Analyses of grouping of AEs for diabetes (Section 2.1.4.1) will be performed overall and according to the diabetic status at baseline (Section 2.1.1).

In addition, the following variables will be tabulated for the local injection site reactions TEAEs:

- Intensity of the event (mild, moderate, severe);
- Number of events divided by the number of double-blind IMP injections received (number of open-label IMP injections for analysis in OLTP, number of alirocumab IMP injections for analysis in alirocumab exposed period);
- Time from first double-blind IMP injection to first injection site reaction (time from first open-label IMP injection for analysis in OLTP, from first alircumab injection for analysis in alirocumab exposed period);
- Description of the highest intensity of each symptom recorded in the specific e-CRF page with table and bar chart.

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

Analysis of cardiovascular events

Adjudication results of treatment-emergent CV events will be summarized.

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 150mg Q4W 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 150mg Q4W 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 above will be also provided on the safety subgroup population of patients with 2 consecutive results of calculated LDL-C <25 mg/dL (as defined in Section 2.1.5) . Only TEAE for which it will be confirmed or unclear that they occurred, worsened or became serious the day or after the first level of LDL-C <25 mg/dL will be considered.

[redacted]

2.4.5.2 Deaths

The following summaries of deaths will be generated for the DBTP and the OLTP.

- Number (%) of patients who died by period (on-study, on-treatment, post-study) and reasons for death as adjudicated by the CEC;
- Deaths in nonrandomized patients or randomized but not treated patients
- TEAEs leading to death (death as an outcome on the AE as reported by the Investigator) by primary SOC, HLGT, HLT, and PT sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC. TEAE leading to

death are TEAE that led to death regardless of timing of death in relation to IMP injection (ie, death occurring in the TEAE period or during the post-treatment period).

2.4.5.3 Analyses of laboratory variables

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

The incidence of PCSAs (list provided in Appendix A), as well as ALT increase as defined as AESI and hemoglobin decrease from baseline ≥15g/L (see Section 2.1.4.1), at any time during the TEAE period will be summarized by biological function and treatment group irrespective of the baseline level and/or baseline level and/or according to the following baseline status categories:

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

Glucose (quantitative summary and PCSA) will also be analyzed, overall and according to the diabetes status at baseline defined in Section 2.1.1.

CPK (PCSA) will also be analyzed, overall and according to prior history of side effects caused by statin.

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

Hepatitis C

Analysis of hepatitis C will be done for patients below according to analysis period.

- DBTP (Hepatitis C planned to be tested for patients who prematurely discontinue study treatment during DBTP) in safety population.
- Alirocumab exposed period (at first step analysis only) (Hepatitis C planned to be tested for patients who prematurely discontinue study treatment during alirocumab exposed period) in alirocumab safety population.
- OLTP: in OLT population.

The number and percentage of patients with a post-baseline seroconversion for hepatitis C test will be provided by treatment group in post-baseline (including the TEAE and post TEAE periods) as well as in the TEAE period alone. Post-baseline seroconversion is defined for patients with a negative baseline status who had either a “positive ribonucleic acid” (RNA) or a “confirmed

positive antibody (Ab) with negative RNA" post-baseline status as defined in the table below. Other situations require case by case evaluation and will be described individually if relevant.

The status as regards to hepatitis C virus (HCV) for a patient will be defined as follows for all evaluations (baseline and post-baseline).

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

	Hepatitis C				
Antibody test result	Negative		Positive		
Reflexive test [a] – hepatitis C RNA test	Not available or HCV RNA not detected	HCV RNA detected	HCV RNA not detected [b]	HCV RNA detected	Not available
Hepatitis C status - label	Negative	Positive RNA	Negative [b]	Positive RNA	Positive Ab – no RNA available

a Test performed at the same time or after the antibody test in the pre-treatment period (for baseline evaluation), or post-baseline, respectively

b For post-baseline evaluation, a second antibody test with a different type of assay is to be done at the same date or after the first antibody test. The result of this test will modify the final hepatitis C status of the patient in some cases (see details in the text below the table)

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

In case of multiple hepatitis C tests available for the post-baseline evaluation, the positive status of the patient will be defined as follows:

- "Positive RNA" status if at least one post-baseline positive RNA is detected, regardless of status of the patient at the end of treatment.
- Else "Positive Ab – no RNA available" status if no post-baseline reflexive RNA test is available for at least one post-baseline positive antibody test.

If no antibody test is available or with "indeterminate" as result pre-treatment or post-baseline, respectively, the RNA test (if available) will be used alone to determine the status of the patient. If no RNA is available then the hepatitis C status of the patient will be missing.

The post-baseline status "confirmed positive antibody with negative RNA" will replace "Negative" status as defined above in the case where no RNA was detected post-baseline and the 2 antibody tests surrounding the same visit (from 2 different types of assay) are positive.

For a conservative approach, the post-baseline status "Positive Ab – no RNA available" will not be modified by the availability of a second antibody test from a different assay.

For the description of the positive hepatitis C virus test during the TEAE period, all above rules applied by replacing post-baseline by TEAE period.

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values or ALT increase as

defined in AESI section (see Section 2.1.4.1) during TEAE period by baseline status will be displayed by treatment group for each parameter.

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

Listing of possible Hy's law cases identified by treatment group (ie, patients with any elevated ALT >3 x ULN, and associated with an increase in bilirubin >2 x ULN, concomitantly or not) with ALT, AST, ALP, total bilirubin, and if available, direct and indirect bilirubin will be provided.

The incidence of liver-related TEAEs will be summarized by treatment group. The selection of PTs will be based on SMQ Hepatic disorder (see Section 2.4.5.1).

Analysis of clinical laboratory variables in the open-label treatment period

For OLTP, summary tables as described for the DBTP above will be used with the following exception:

- Analyses by visit (unless data warrants further investigation)

Analysis of clinical laboratory variables in the alirocumab exposed period (first step anlaysis only)

For alirocumab exposed period, summary tables as described for the DBTP above will be used with the following exception:

- Analyses by visit (unless data warrants further investigation)

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, SD, minimum and maximum) of all vital signs variables (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, worst on-treatment value and follow-up visit) by treatment group. In addition for some parameters of interest; mean changes from baseline with the corresponding SE could be plotted over time (at same time points) in each treatment group.

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

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

Analysis of vital signs variables in the open-label treatment period

For OLTP, summary tables as described for the DBTP above will be used with the following exception:

- Analysis by visit (unless data warrants further investigation)

Analysis of vital signs variables in the alirocumab exposed period (first step analysis only)

For alirocumab exposed period, summary tables as described for the DBTP above will be used with the following exception:

- Analyses by visit (unless data warrants further investigation)

2.4.5.5 Analyses of electrocardiogram variables

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

- Normal/missing;
- Abnormal.

2.4.6 Analyses of other endpoints

All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 2 in order to provide an assessment for Week 4 to Week 64 time points.

HbA1c parameters will be summarized by analysis visit using number of available data, mean, SD, median, minimum, and maximum for each treatment group during the DBTP and OLTP. For HbA1c in DBTP, summary will be also provided according to the diabetes status at baseline defined in Section 2.1.1. The time profile of each parameter will be also plotted by treatment group with the means and the corresponding SEs for HbA1c in DBTP. The incidence of PCSA at any time during the double-blind TEAE period will be also summarized on safety population by treatment group using descriptive statistics. PCSA for HbA1c will be also provided according to the diabetes status at baseline. The incidence of PCSA at any time during the open-label TEAE period (on OLT population) and during alirocumab exposed TEAE period (on alirocumab exposed population, at first step analysis only) will be also summarized using descriptive statistics. PCSA for HbA1c will be also provided according to the diabetes status at baseline.

Binary endpoints defined in Section 2.1.5 will be described using count and percentage. [redacted] For the analysis of the time to the first of the 2 consecutive LDL-C, patients without post-baseline LDL-C result or with only 1 post-baseline LDL-C result will not be included.

2.4.7 Analyses of anti-alirocumab antibodies variables

The summary of ADA variables will be presented separately for the DBTP (on ADA population) and [redacted]

The following summaries will be performed, taking into account all samples regardless of timing in relation to injections but within each study period separately:

- [redacted]
- [redacted]
- [redacted]

- Number (%) of patients with pre-existing ADA and number (%) of patients with treatment-emergent ADA positive response

  Number (%) of patients with persistent/transient/indeterminate treatment-emergent ADA positive response (for alirocumab exposed period and [redacted] ;
- Time to onset of treatment-emergent ADA positive response using descriptive statistics.beginning from the first IMP administration within the relevant period [redacted]

[redacted]

2.4.8 Analyses of pharmacokinetic and pharmacodynamic variables

Serum total alirocumab concentration (alirocumab concentration, C_{trough} and $C_{follow\text{-}up}$), free and total PCSK9 concentrations will be summarized on the PK population by treatment group and visit using descriptive statistics. $C_{trough,av}$ will be summarized on the PK population by treatment group using descriptive statistics. Descriptive statistics could be provided by specific sub-groups (eg, gender, BMI, age), as needed.

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

[redacted]

[redacted]

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Time from diagnosis

Time from diagnosis (years) = (Date of informed consent – Date of diagnosis*) / 365.25.

(*): In case the month of diagnosis would be missing, it will be put equal to JANUARY if the year of diagnosis equals the year of informed consent; it will be put equal to JUNE otherwise.

Medical history

"Peripheral Arterial Disease" history is defined as follows, using combinations of the corresponding pre-listed medical history items of the e-CRF page "Cardiovascular history and cardiovascular risk factors":

- Intermittent claudication (linked to PAD) TOGETHER WITH ankle-brachial index ≤0.90

  Or

- Intermittent claudication (linked to PAD) TOGETHER WITH peripheral revascularization procedure (angioplasty, stenting) for PAD or peripheral revascularization surgery (arterial bypass) for PAD

  Or

- Critical limb ischemia TOGETHER WITH peripheral revascularization procedure (angioplasty, stenting) for PAD or thrombolysis for PAD or peripheral revascularization surgery (arterial bypass) for PAD.

Date of last dose of IMP (for double-blind and for open-label)

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

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

Renal function formulas

estimated Glomerular filtration rate (eGFR) value will be derived using the Modification of the Diet in Renal Disease (MDRD) equation:

$175 \times (\text{creatinine in } \mu\text{mol/L} / 88.4)^{-1.154} \times (\text{age in years})^{-0.203}$ (x 0.742 if female, x 1.212 if race is "black or african american").

Lipids variables, 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.

Pharmacokinetic variables

Data below the LLOQ are set to zero.

2.5.2 Data handling conventions for secondary efficacy variables

See Section 2.1.3.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. 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 the time of assessment at Week 0 visit is missing then the baseline value is defined as the last available value obtained before or on the day of the first double-blind IMP administration.

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

If the last or first 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 of DBTP or OLTP 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 of the period (DBTP: Week 12 visit for patients who completed the double-blind study treatment period as per protocol, early end of treatment visit for patients who prematurely discontinued the IMP; OLTP: Week 64 visit for patients who completed the open-label study treatment period as per protocol, 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.

The last dose intake should be clearly identified in the case report form and will not be approximated by the last returned package date.

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 posttreatment 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 double-blind IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

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 TEAEs.

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 and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

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

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

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

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

2.5.4 Windows for time points

2.5.4.1 Time points for efficacy data, laboratory safety data, ADA, and PK

[redacted]

[redacted]

2.5.4.2 Time points for vital signs

[redacted]

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

The randomization scheme was not stratified by center because the primary efficacy variable is centrally assessed and expected to not be influenced by the center when other factors such as diet is already controlled. Therefore, the center will not be added as factor in the primary analysis model.

3 TWO-STEP ANALYSIS

The analysis will be conducted in 2 steps, although no formal interim analysis for efficacy is planned in this study. No multiplicity adjustment for multiple analyses is needed as explained in Section 2.4.4.3.

- First step: Efficacy and safety analyses using data up to 24 weeks after randomization (including 12 weeks double-blind).
  - This analysis will be conducted as soon as all patients have been randomized and have at least all their data up to Week 24 (including 12 weeks DBTP and 12 weeks OLTP) collected and validated.
  - The final analysis of the primary and secondary efficacy endpoints will be performed up to Week 12 time point. The results of this analysis will not be used to change the conduct of the ongoing study in any aspect.
  - [redacted]
  - The safety analyses will be performed on all safety data up to the patient's cut-off date defined as the date of Week 24 visit or the date corresponding to 169 days (i.e. 6 months) after first double-blind IMP injection for patients with no Week 24 visit.
- Second step: Long-term safety and efficacy exploratory analysis
  - This analysis will be conducted at the end of the study with all data including the data of the OLTP, and will consist in the final analysis of the safety endpoints and exploratory efficacy assessment during the OLTP.

[redacted]

4 DATABASE LOCK

Two database locks will be done:

- First database lock (for first analysis): will include all available data on all randomized patients up to date of Week 24 visit for each patient as defined in Section 3. [redacted]
- Final database lock (for second analysis): will include all data, including follow-up, for all randomized patients. [redacted]

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

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