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## STATISTICAL ANALYSIS PLAN

**A randomized, open-label, blinded intravascular ultrasound analysis, parallel group, multicenter study to evaluate the effect of Praluent® (alirocumab) on coronary atheroma volume in Japanese patients hospitalized for acute coronary syndrome with hypercholesterolemia not adequately controlled with statin**

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab:	antibody
ACE:	angiotensin converting enzyme
ACS:	acute coronary syndrome
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
Apo:	apolipoprotein
AST:	aspartate aminotransferase
BMI:	body mass index
CEC:	Clinical Events Committee
CHD:	coronary heart disease
CKD:	chronic kidney disease
CMQ:	company MedDRA query
CPK:	creatine phosphokinase
EEM:	external elastic membrane
eGFR:	estimated glomerular filtration rate
GFR:	glomerular filtration rate
HbA1c:	Glycated hemoglobin A1c
HCV:	hepatitis C virus
HDL-C:	high-density lipoprotein cholesterol
HLGT:	high-level group term
HLT:	high-level term
hs-CRP:	high-sensitivity C-reactive protein
IMP:	investigational medical product
IVUS:	intravascular ultrasound
LDH:	lactate dehydrogenase
LDL-C:	low-density lipoprotein cholesterol
LLN:	lower limit of normal range
LLOQ:	lower limit of quantification
LLT:	lowest-level term
Lp (a):	lipoprotein (a)
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	myocardial infarction
NIMP:	non-investigational medical product
non-HDL-C:	non-high-density lipoprotein cholesterol
NSAID:	nonsteroidal anti-inflammatory drug
NSTEMI:	non STsegment elevation myocardial infarction
OCT:	optical coherence tomography
PAV:	percent atheroma volume
PCSA:	potentially clinically significant abnormality(ies)

PP:	per-protocol
Q1:	first quartile
Q3:	third quartile
QOL:	quality of life
RNA:	ribonucleic acid
SD:	standard deviation
SE:	standard error
SoC:	Standard of Care
SOC:	system organ class
STEMI:	ST-segment elevation myocardial infarction
TAV:	total atheroma volume
TC:	total cholesterol
TEAE:	treatment-emergent adverse event
TG:	triglycerides
UA:	unstable angina
ULN:	upper limit of normal range
ULOQ:	upper limit of quantification
WHO-DD:	World Health Organization-Drug Dictionary
$\gamma$ GT:	gamma glutamyl transferase

## 1 OVERVIEW AND INVESTIGATIONAL PLAN

### 1.1 STUDY DESIGN AND RANDOMIZATION

This is a phase IV, open-label, 1:1 randomized, blinded intravascular ultrasound (IVUS) analysis, parallel group, multicenter study.

Approximately 200 patients from approximately 40 study sites will be enrolled and randomized with a treatment period of 9 months.

These patients will be:

- Patients who suffer an acute coronary syndrome (ACS) event despite of stable statin therapy,
- Patients who have not been on any statin therapy at the time of ACS onset, but who will start either atorvastatin 10 mg/day or rosuvastatin 5 mg/day immediately after the ACS diagnosis, and whose LDL-C is not adequately controlled with statin at 2 to 4 weeks after the ACS diagnosis (in principal, LDL-C target level  $\geq 100$  mg/dL, but this may not apply if the responsible physician considers the LDL-C level inadequate on statin. Patients who have LDL-C  $< 70$  mg/dL cannot be enrolled).

Randomization will be stratified by 'on statin therapy' or 'not on statin therapy' at the time of ACS onset.

After randomization, patients will receive open-label study treatment of alirocumab 75 mg every 2 weeks (Q2W) over a period of 36 weeks on top of stable daily statin therapy or Standard of Care (SoC). A dose up-titration to alirocumab 150 mg Q2W will be performed at Week 14 for patients randomized to alirocumab group and whose LDL-C level measured at Week 12 remains  $\geq 100$  mg/dL.

### 1.2 OBJECTIVES

#### 1.2.1 Primary objectives

To compare the effect of alirocumab with standard of care (SoC) on coronary atheroma progression (percent change in normalized total atheroma volume [TAV]) after 9 months of treatment in patients who had ACS within 4 weeks prior to randomization, with hypercholesterolemia treated with any statin.

### 1.2.2 Secondary objectives

- To compare the effect of alirocumab with SoC on secondary endpoints including absolute change in percent atheroma volume (PAV) and normalized TAV after 9 months of treatment.
- To evaluate the effect of alirocumab on low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo-B), triglycerides (TGs), non-high-density lipoprotein cholesterol (non-HDL-C) and Lipoprotein(a) (Lp[a]) after 9 months treatment.
- To evaluate the safety of alirocumab including the occurrence of cardiovascular (CV) events [coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization] throughout the study.

### 1.3 DETERMINATION OF SAMPLE SIZE

The study is expected to enroll approximately 200 patients. The sample size calculations are based on the primary efficacy variable of percent change in normalized TAV from baseline to week 36.

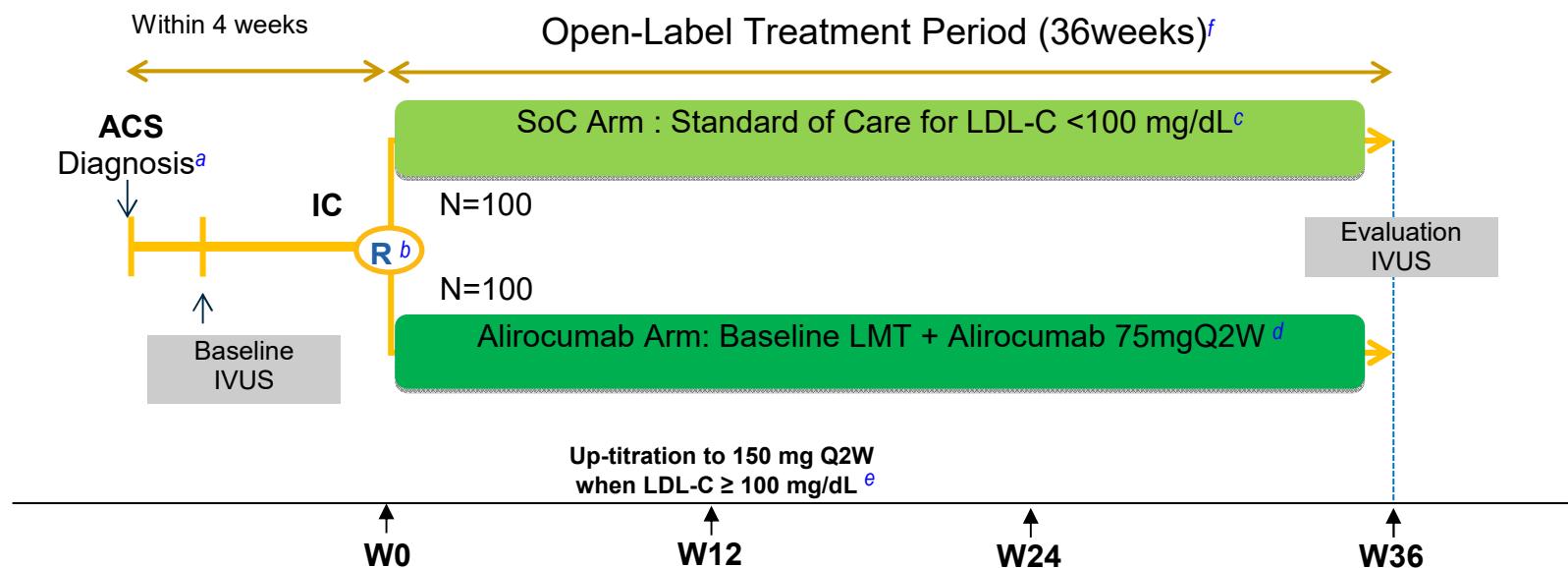
Based on the results of ZEUS (1) and PRECISE-IVUS (2) studies, it is assumed that difference in percent change in normalized TAV from baseline between alirocumab arm and SoC arm is 8%, the common standard deviation of percent change in normalized TAV is 15%.

Under the assumption, a sample size of 150 patients (75 in alirocumab arm and 75 in SoC arm) will have 90% power to detect the treatment difference with two-sided significance level of 5%. Assuming that proportion of non-evaluable primary endpoint is 25%, it is considered that 200 patients (100 in alirocumab arm, 100 in SoC arm) will be needed.

As the analysis of covariance (ANCOVA) model will be used for primary analysis, the power should be somewhat higher due to reduced estimate variability versus the two-sample t-test.

Calculations were made using SAS 9.4.

## 1.4 STUDY PLAN



**Abbreviations:** ACS, acute coronary syndrome; IC, informed consent; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol; LMT, lipid modifying therapy; Q2W, every 2 weeks; R, randomization; SoC, standard of care.

a If patients have not been on any statin therapy at ACS onset, either atorvastatin 10 mg/day or rosuvastatin 5 mg/day is started immediately after the ACS diagnosis.

b At randomization, patients should have already received stable statin therapy with either atorvastatin  $\geq$  10 mg/day or rosuvastatin  $\geq$  5 mg/day for at least 2 weeks.

c Stable dose statin monotherapy (atorvastatin  $\geq$  10 mg/day or rosuvastatin  $\geq$  5 mg/day within a range of approved statin doses by the Health Authority) will be administrated to achieve the LDL-C target level  $<$ 100 mg/dL. Adjusting of statin will occur based on above rule. Concomitant non-statin LMTs will be considered if patients have already been on them on top of statin monotherapy at the time of ACS diagnosis or if LDL-C target level  $<$ 100 mg/dL cannot be achieved by the statin monotherapy.. Adjusting of LMT will occur based on above rule, but not limited.

d Alirocumab 75mg every 2 weeks on top of dose of atorvastatin  $\geq$  10 mg/day or rosuvastatin  $\geq$  5 mg/day  $\pm$  other LMTs, in accordance with approved doses by the Health Authority. Concomitant non-statin LMTs will be considered if patients already on them on top of statin monotherapy at the time of ACS diagnosis. Background statin and/or non-statin LMT regimens should not be changed as a principle during the entire study period.

e In Alirocumab arm, if LDL-C value at Week 12 visit measured by the Central Laboratory does not reach less than 100 mg/dL, alirocumab dose uptitration to 150 mg Q2W will be carried out at Week 14.

f Patients who perform self-injection of alirocumab at home must visit the study site at least every 4 weeks, and at Week 0, Week 4, Week 12, Week 14, Week 24 and Week 36.

## 1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The statistical section of the protocol was not changed except that randomization strata of "statin at ACS diagnosis" was corrected to "statin at ACS onset" due to erroneous description.

## 1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The SAP version 1 was modified between the study start and database lock (DBL) for the main study in order to follow the last amended protocol, to address the further information on IVUS and optical coherence tomography (OCT) imaging analysis, to keep a consistency with the study objectives, and to correct erroneous descriptions. The changes in the SAP from version 1 to version 2 are as follows:

- **Section 2.3.1:** In the definition of mITT population, "Another one assessed during the efficacy treatment period and within the Week 36 analysis window", which is mentioned in the 3<sup>rd</sup> item of [Table 1](#) in [Section 1.7](#), was changed to "Another one assessed after 24 weeks of treatment ", since the statement in version 1 was inconsistent with the last amended protocol, and IVUS imaging outside the efficacy treatment period could not be considered as protocol deviation.
- **Section 2.3.1.1:** In the definition of PP population, the following criteria were changed:
  - "Patients with analyzed vessel length less than 10 mm" was added, since it is considered major deviation from IVUS imaging procedure and it may have an impact on IVUS parameters.
  - "LDL-C  $\geq$ 100 mg/dL" was changed to "LDL-C at patient selection  $\geq$ 100 mg/dL for patients enrolled based on the protocol amendment 1;  $\geq$ 70 mg/dL for patients enrolled based on the protocol amendment 2 or later" according to the amended protocol.
  - "Background therapy deviation" was removed, since the study team found that in the study protocol the use of background therapy including statin is eventually dependent upon the doctor and so deviation related to background therapy cannot be specified.
- Several analyses including substudy analyses for optical coherence tomography (OCT), additional efficacy analyses (Section 2.4.4.4) were removed, since they are beyond the study objectives.

## 1.7 STATISTICAL ADAPTATIONS MADE IN THE STATISTICAL ANALYSIS PLAN FROM THE PROTOCOL BEFORE STUDY START

In this section, summarize major adaptations in statistical analysis features made in approved SAP versions, with emphasis on adaptations before study start (before the first patient was enrolled)

The table below gives the timing, rationale, and key details of major adaptations made in the SAP from the protocol.

The first patient is planned to be enrolled on 16-Nov-2016. There are no planned interim analysis.

**Table 1 - Adaptations to statistical analysis plan from protocol before study start**

<b>Protocol Amendment Number</b>	<b>Date Approved</b>	<b>Rationale</b>	<b>Description of statistical changes</b>
1	19-Aug-2016	To be detailed.	The definition of normalized TAV (Median number of analyzed frames in the population) was detailed.
		To correct the erroneous description about calculation of normalized TAV.	Normalized TAV will be calculated by Sanofi or delegate, not Central Reading.
		To be detailed	The definition of primary analysis population, modified Intent-to-treat population was added to have post-baseline during efficacy treatment period
		To be detailed	Congestive heart failure will be also adjudicated by Clinical Events Committee

## 2 STATISTICAL AND ANALYTICAL PROCEDURES

### 2.1 ANALYSIS ENDPOINTS

#### 2.1.1 Demographic and baseline characteristics

Unless otherwise specified, the baseline value is defined as the last available value before randomization.

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

#### *Demographic characteristics*

Demographic variables are:

- Age in years (quantitative and qualitative variable: <65, ≥65 to <75, and ≥75 years; and <65, ≥65 years);
- Gender (Male, Female);
- Race (Asian);
- Ethnicity (Not Hispanic or Latino).

#### *Medical or surgical history*

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi or delegate at the time of database lock.

Medical history of specific interest includes:

- CHD prior to the index ACS diagnosis;
  - Myocardial infarction
  - Unstable angina
  - Coronary revascularization procedure
  - Other clinically significant CHD
- Ischemic stroke
- Peripheral arterial disease
- Hypertension
- Diabetes
  - Type 1 diabetes

- Type 2 diabetes
- Chronic kidney disease (CKD)
- Impaired glucose tolerance
- Hypo HDL cholesterolemia (<40 mg/dL)
- Family history of premature coronary artery disease
- Family history of Type 2 diabetes mellitus

“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  $\leq 0.90$   
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.

The status of hypertension at baseline will be selected using SMQ “hypertension” (narrow), based on terms reported as “ongoing” in Medical history by the investigator.

Efficacy and safety analysis performed according to “**diabetic status at baseline**” reported in the Medical history by the investigator will be done using a company MedDRA query (CMQ), based on the following PTs reported in e-CRF Medical History: “diabetes mellitus”, “diabetes mellitus inadequate control”, “fulminant type 1 diabetes mellitus”, “insulin resistant diabetes”, “insulin-requiring type 2 diabetes mellitus”, “type 1 diabetes mellitus”, “type 2 diabetes mellitus”, “diabetes mellitus malnutrition-related”, and “diabetes mellitus management”.

Diabetic status at baseline (Yes, No) will be also summarized. Besides, for diabetic patients at baseline, the following items will be summarized.

- Insulin use (Yes, No);
- Time from diagnosis of diabetes (quantitative [years] and qualitative variable:  $<\text{Median}$ ,  $\geq \text{Median}$  years).

Medical or surgical history includes:

- Medical history of allergies;
- Smoking habits (Never, Former, Current);

- Alcohol habits (Never, Occasional, At least monthly, At least weekly, At least daily).

### ***Disease characteristics at baseline***

Specific disease history includes:

- The index ACS subtype (acute ST-segment elevation myocardial infarction [STEMI], acute non ST-segment elevation myocardial infarction [NSTEMI], unstable angina [UA])
- Time from the index ACS diagnosis to randomization (in weeks), quantitatively and in category <2, ≥2 to <4, ≥4 weeks
- Revascularization procedure associated with the index ACS event (PCI or CABG)
- Time from the revascularization procedure to randomization (in weeks)
- Types of stents placed at the PCI (bare metal stent [BMS], drug eluting stent [DES] or both).
- Location of ACS culprit vessels
- Location of analyzed IVUS imaging vessels (RCA, LAD, LCX, Other)
- New cardiovascular events occurring after the index ACS diagnosis and before randomization, selected using e-CRF specific tick box on the adverse event page.
- Type of hypercholesterolemia:
  - Heterozygous familial hypercholesterolemia (heFH);
  - Non-familial hypercholesterolemia (non-FH);
  - Unknown;
- 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);
- The background lipid modifying therapy (LMT) regimen at ACS diagnosis, as reported in the “Previous Lipid Modifying Therapy” e-CRF page, will be summarized using the following categories:
  - Any LMT
  - Any statin by daily dose
    - Atorvastatin, rosuvastatin, pravastatin, simvastatin, fluvastatin, pitavastatin
  - LMT other than statin
    - Ezetimibe

Fibrate

- Fenofibrate
- Bezafibrate
- Other
- Other

- The background lipid modifying therapy regimen at randomization, as reported in the “Previous Lipid Modifying Therapy” e-CRF page, will be summarized as those at ACS diagnosis.

***Other baseline characteristics***

Other baseline characteristics include weight in kilograms (quantitative variable and qualitative variable: <Median,  $\geq$ Median), body mass index (BMI) in kg/m<sup>2</sup> (quantitative and qualitative variable: <25,  $\geq$ 25), and randomization strata (as described in [Section 1.1](#)) as per registration center.

Lipid parameters and glycated hemoglobin A1c (HbA1c) (quantitative and qualitative variable: <5.7 %,  $\geq$ 5.7 to <6.5%,  $\geq$ 6.5%), hs-CRP (quantitative [mg/L, mg/dL] and qualitative variable: <2,  $\geq$ 2 mg/L [ie, <0.2 mg/dL,  $\geq$ 0.2 mg/dL]), and eGFR (quantitative and qualitative variable: <15,  $\geq$ 15 to <30,  $\geq$ 30 to <60,  $\geq$ 60 to <90,  $\geq$ 90 mL/min/1.73m<sup>2</sup>, category <30,  $\geq$ 30, <60,  $\geq$ 60 mL/min/1.73m<sup>2</sup> will be also displayed) at baseline will be also summarized by treatment group. Lipid parameters are total cholesterol (TC), calculated LDL-C, non HDL-C, high-density lipoprotein cholesterol (HDL-C), fasting TGs, Apo A-1, Apo B, Lp (a), Apo B/Apo A-1 ratio, Fasting TGs/HDL-C ratio, and calculated LDL-C/HDL-C ratio. Lipids parameters will be summarized using standard international unit and conventional unit. Baseline values of lipid parameters are defined as the last available value from central laboratory assessed up to the date and time of randomization. eGFR will be calculated using the equation defined in [Section 2.5.1](#).

For lipid parameters, both quantitative and qualitative variables will be considered, with the following categories:

- Calculated LDL-C: <70,  $\geq$ 70 to <80,  $\geq$ 80 to <100,  $\geq$ 100 to <130,  $\geq$ 130 to <160,  $\geq$ 160 to <190,  $\geq$ 190 mg/dL (ie, <1.81,  $\geq$ 1.81 to <2.07,  $\geq$ 2.07 to <2.59,  $\geq$ 2.59 to <3.37,  $\geq$ 3.37 to <4.14,  $\geq$ 4.14 to <4.91,  $\geq$ 4.91 mmol/L), category <100,  $\geq$ 100 mg/dL (ie, <2.59,  $\geq$ 2.59 mmol/L) and <80,  $\geq$ 160 mg/dL (<2.07,  $\geq$ 4.14 mmol/L) will be also displayed,
- HDL-C: <40,  $\geq$ 40 mg/dL (ie, <1.04,  $\geq$ 1.04 mmol/L),
- Non-HDL-C: <100,  $\geq$ 100 to <110,  $\geq$ 110 to <130,  $\geq$ 130 to <160,  $\geq$ 160 to <190,  $\geq$ 190 to <220,  $\geq$ 220 mg/dL (ie, <2.59,  $\geq$ 2.59 to 2.84,  $\geq$ 2.84 to <3.37,  $\geq$ 3.37 to <4.14,  $\geq$ 4.14 to <4.91,  $\geq$ 4.91 to 5.69,  $\geq$ 5.69 mmol/L), category <110,  $\geq$ 130 mg/dL, (ie, <2.84,  $\geq$ 3.37 mmol/L) will be also displayed
- Fasting TGs: <150,  $\geq$ 150 to <200,  $\geq$ 200 mg/dL (ie, <1.7,  $\geq$ 1.7 to <2.3,  $\geq$ 2.3 mmol/L), category  $\geq$ 150 mg/dL (ie,  $\geq$ 1.7 mmol/L [mixed dyslipidemia]) will be also displayed,

- Lp (a): <30,  $\geq 30$  to <50,  $\geq 50$  mg/dL (ie, <0.3,  $\geq 0.3$  to <0.5,  $\geq 0.5$  g/L), category  $\geq 30$  , <50 mg/dL, (ie,  $\geq 0.3$ , <0.5 g/L) will be also displayed
- Apo B: <75,  $\geq 75$  to <90,  $\geq 90$  mg/dL (ie, <0.75,  $\geq 0.75$  to <0.9,  $\geq 0.9$  g/L)

Lipid parameters at patient selection and HbA1c at ACS diagnosis (quantitative and qualitative variable) will be also analyzed as those at baseline. Lipid parameters at patient selection are to be reported in the case report “Lipid Parameters at Patient Selection” form page:

Note: non-HDL-C will be calculated by subtracting HDL-C from the TC.

Ratio Apo B/Apo A-1 will be calculated by Apo B divided by Apo A-1. If LDL-C was directly measured, LDL-C will be calculated using the Friedwald formula. If TG values exceed 400 mg/dL (4.52 mmol/L), then calculated LDL-C will be missing.

IVUS parameters (quantitative variables) and analyzed vessel length at baseline will be summarized. IVUS parameters are normalized TAV, PAV, external elastic membrane (EEM) volume, lumen volume, and TAV. For normalized TAV and PAV, quantitative variables will be also considered, with the following category (<Median,  $\geq$ Median).

Any technical details related to computation, dates, and imputation for missing dates are described in [Section 2.5](#).

## 2.1.2 Prior or concomitant medications

All LMTs taken within 1 month before Visit 1 and until the end of the study are to be reported in the case report form pages. Other concomitant medications taken since informed consent until the end of study are to be reported in the case report form page:

- Previous Lipid Modifying Therapy
  - Previous lipid modifying therapies are to be reported.
- Concomitant Non-Investigational Medicinal Product
  - Concomitant Non-Investigational Medical Product (NIMP) defined in protocol are to be reported.
- Concomitant Other Medication
  - Concomitant medications except NIMPs are to be reported.

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

- Prior medications are those the patient used within 1 month prior to randomization. Prior medications can be discontinued before randomization or can be ongoing during treatment phase;
- Concomitant medications are any treatments received by the patient concomitantly to the treatment, from randomization to the last study treatment administration + 21 days, or end of study, whichever comes first. A given medication can be classified both as a prior

medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in [Section 2.1.4](#)).

- Post-treatment medications are those the patient took in the period starting the day after the end of treatment-emergent adverse event period (as defined in the observation period in [Section 2.1.4](#)) up to the end of the study.

For patients randomized but not treated, medications will be categorized as prior medications or post-treatment medications according to the date of intake in relation to the date of randomization.

The following medications of specific interest including NIMP defined in protocol will be selected using specific coding list specified in [Table 5](#), unless otherwise specified:

- Anti-platelets
  - Oral adenosine diphosphate (ADP) receptor antagonists (except aspirin)
    - Clopidogrel
    - Ticagrelor
    - Prasugrel
    - Ticlopidine
- Anticoagulants
  - Injectable anticoagulants (unfractionated heparin [UFH], low molecular weight heparin [LMWH], bivalirudin, selective factor Xa inhibitor)
  - Specific oral anticoagulants
    - Vitamin K antagonist (VKA)
    - Non-vitamin K antagonist oral anticoagulants (NOAC)
- Thrombolytic
- Anti-diabetic drugs
  - Oral hypoglycemic drugs
    - Biguanides/metformin
    - Sulfonylurea
    - Glinide
    - Thiazolidine dione (TZD)
    - Alpha-glucosidase inhibitors ( $\alpha$ -GI)
    - DPP4 inhibitor
    - SGLT2 inhibitor
  - Injectable hypoglycemic drugs
    - Glucagon-like peptide-1 receptor agonists (GLP-1 RA)
    - Insulin
- Angiotensin-converting-enzyme (ACE)-inhibitor or angiotensin receptor blocker
- Beta blocker

- Calcium channel blocker
- Diuretics
- Nitrates
- Non-steroidal anti-inflammatory drugs (NSAIDs) (excluding aspirin)
- Cholesterol absorption inhibitor
  - Ezetimibe
- Fibrate
  - Fenofibrate
  - Bezafibrate

Any technical details related to computation, dates, imputation for missing dates are described in [Section 2.5](#).

### 2.1.3 Efficacy endpoints

The EEM volume, lumen volume, TAV, normalized TAV, and PAV will be calculated by the Sponsor or delegate. These IVUS parameters will be calculated using the following equations defined using  $EEM_{CSA}$  and  $Lumen_{CSA}$  taken at pre-determined interval between each image ( $\delta=0.5$  mm):

$$TAV \text{ (mm}^3\text{)} = \sum (EEM_{CSA} - Lumen_{CSA})\delta,$$

$$\text{normalized TAV (mm}^3\text{)} = TAV \times \frac{C}{n},$$

where  $\Sigma$  is the summation over all the analyzed frames,  $n$  is the number of analyzed frames per patient,  $C$  is the median of the number of analyzed frames in patients with available baseline TAV within randomized population.  $EEM_{CSA}$  is the cross-sectional area inside the EEM border, the  $Lumen_{CSA}$  is the cross-sectional area inside the lumen border, and both parameters are measured by the central reading laboratory. Besides,

$$PAV \text{ (\%)} = \left( \frac{\sum (EEM_{CSA} - Lumen_{CSA})}{\sum EEM_{CSA}} \right) \times 100,$$

$$EEM \text{ volume (mm}^3\text{)} = \sum (EEM_{CSA})\delta,$$

$$\text{Lumen volume (mm}^3\text{)} = \sum (Lumen_{CSA})\delta,$$

where  $\Sigma$  is the summation over all the analyzed frames.

The detailed procedures of IVUS image analysis and calculation of the parameters will be specified in the procedure manual of IVUS image analysis.

For post-baseline IVUS parameters, the value used for the analyses at Week 36 is the value assessed after the  $\geq 24$  weeks of treatment and within the Week 36 analysis window defined in [Section 2.5.4.1, Table 3](#).

Efficacy parameters include lipid parameters (i.e. TC, calculated LDL-C, HDL-C, fasting TGs, non-HDL-C, Apo B, Apo A-1, Apo B/Apo A-1 ratio, Lp[a], fasting TGs/HDL-C ratio, and calculated LDL-C/HDL-C ratio). All these parameters except for fasting TGs/HDL-C ratio, and calculated LDL-C/HDL-C ratio are measured or calculated by the central laboratory, for both scheduled and unscheduled time points. The LDL-C will be calculated using the Friedewald formula. If TGs values exceed 400 mg/dL (4.52 mmol/L), the calculated LDL-C levels will not be used for any analysis. Non-HDL-C will be calculated by subtracting HDL-C from the TC. Apo B/Apo A-1 ratio will be calculated. Fasting TGs/HDL-C ratio, and calculated LDL-C/HDL-C ratio will be calculated by Sanofi or delegate.

Unless otherwise specified, all lipid values from central laboratory (scheduled or unscheduled, fasting or not fasting) will be used to provide a value for the secondary efficacy endpoints. All measurements, scheduled or unscheduled, fasting or not fasting (except for TGs), will be assigned to analysis windows as defined in [Section 2.5.4, Table 4](#) in order to provide an assessment for Week 4 to Week 36 time points. For TGs, only fasting measurements will be used. Measurements with missing fasting status will be excluded from the analyses.

For all time points, the value of post-baseline lipid parameters used for the analyses at a given time point (eg, at Week 36) is the value assessed and within the corresponding analysis window. The baseline value is the last available value from central laboratory assessed up to the date and time of randomization.

### **2.1.3.1 Primary efficacy endpoint**

The primary efficacy endpoint is the percent change in normalized TAV from baseline to Week 36, which is defined as:  $100 \times (\text{normalized TAV value at Week 36} - \text{normalized TAV value at baseline}) / \text{normalized TAV value at baseline}$  and calculated by Sponsor or delegate.

The baseline normalized TAV value is the one assessed before the randomization.

The normalized TAV at Week 36 will be the one assessed after the  $\geq 24$  weeks of treatment and within the Week 36 analysis window, defined in [Section 2.1.3](#).

### **2.1.3.2 Secondary efficacy endpoint(s)**

#### **2.1.3.2.1 Key secondary efficacy endpoint**

- Absolute change in PAV from baseline to Week 36.

#### 2.1.3.2.2 *Other secondary efficacy endpoints*

- Absolute change in normalized TAV from baseline to Week 36.
- Absolute and percent changes in EEM volume from baseline to Week 36.
- Absolute and percent changes in lumen volume from baseline to Week 36.
- Absolute and percent changes in TAV from baseline to Week 36.
- Absolute and percent changes in calculated LDL-C from baseline to Week 12, and Week 36.
- Absolute and percent changes in Apo B from baseline to Week 36.
- Absolute and percent changes in non-HDL-C from baseline to Week 36.
- Absolute and percent changes in TC from baseline to Week 36.
- Absolute and percent changes in Lp(a) from baseline to Week 36.
- Absolute and percent changes in HDL-C from baseline to Week 36.
- Absolute and percent changes in fasting TGs from baseline to Week 36.
- Absolute and percent change in Apo A-1 from baseline to Week 36.
- Absolute change in Apo B/Apo A-1 ratio from baseline to Week 36.
- Absolute change in fasting TGs/HDL-C ratio from baseline to Week 36.
- Absolute change in calculated LDL-C/HDL-C ratio from baseline to Week 36.
- The proportion of patients with calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 36
- The proportion of patients with calculated LDL-C <50 mg/dL (3.37 mmol/L) at Week 36
- The proportion of patients achieving at least 50% reduction in calculated LDL-C at Week 36

#### 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 and vital signs.

##### ***Observation period***

The observation period of safety data will be as follows:

- **Pre-treatment** period is defined as the time from the signed informed consent date up to the day of randomization.
- **Treatment-emergent adverse event (TEAE)** period is defined as the time from the day of randomization to the last study treatment administration + 21 days, or end of study, whichever comes first in both the alirocumab and SoC groups.

- **Post-treatment** period is defined as the time starting the day after the end of the TEAE period up to the end of the study.
- **On-study observation** period is defined as the time from the day of randomization until the end of the study.

#### **2.1.4.1 Adverse events variables**

Occurrence of adverse events (including SAEs and adverse events of special interest [AESIs]) are recorded from the time of signed informed consent until the end of study.

All AEs (including SAEs and AESIs) will be coded to a lowest-level term (LLT), PT, high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of MedDRA currently in effect at Sanofi or delegate at the time of database lock.

#### ***Adverse event observation period***

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period
- TEAEs are AEs that developed or worsened or became serious during the TEAE period
- Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period

#### ***Adverse events of special interest***

Adverse events of special interest (AESIs) are adverse events (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):

- General allergic events, selected using SMQ “hypersensitivity” (broad and narrow) excluding the following preferred terms linked to local injection site reactions (“infusion site dermatitis”, “infusion site hypersensitivity”, “infusion site rash”, “infusion site urticaria”, “injection site dermatitis”, “injection site hypersensitivity”, “injection site rash”, “injection site urticaria”, and “injection site vasculitis”)
- General allergic events and local allergic reactions at IMP injection site, selected based on the above selection for general allergic event and on the following selection of PT from the symptoms complementary form for local injection site reaction (“Injection site dermatitis”, “Injection site hypersensitivity”, “Injection site oedema”, “Injection site rash”, “Injection site urticaria”, “Injection site eczema”, “Injection site vasculitis”, “Injection site swelling”, “Infusion site dermatitis”, “Infusion site hypersensitivity”, “Infusion site oedema”, “Infusion site rash”, “Infusion site urticaria”, “Infusion site swelling”).
- Local injection site reactions, selected using e-CRF specific tick box on the adverse event page
- ALT >3 ULN, selected using laboratory data

- Hemolytic anemia, selected using e-CRF specific tick box on the adverse event page and confirmed final diagnosis provided in the adverse event complementary form
- Neurologic events selected using a CMQ, based on SMQs “demyelination” (broad and narrow), “peripheral neuropathy” (broad and narrow), and “Guillain-Barre syndrome” (broad and narrow) excluding the following preferred terms “acute respiratory distress syndrome”, “asthenia”, “respiratory arrest” and “respiratory failure”
- Neurocognitive events selected using a CMQ, based on the following 5 HLGTs: “deliria (including confusion)”, “cognitive and attention disorders and disturbances”, “dementia and amnestic conditions”, “disturbances in thinking and perception”, and “mental impairment disorders”
- Ophthalmologic events selected using SMQs “optic nerve disorders” (broad and narrow), “retinal disorders” (narrow), and “corneal disorders” (narrow);
- Skeletal muscle-related adverse events using a CMQ based on the following PTs ”Myalgia”, ”Muscle contractions involuntary”, ”Muscle spasms”, ”Muscle twitching”, ”Muscle fatigue”, ”Muscle tightness”, ”Myofascial spasm”, ”Muscular weakness”, ”Limb discomfort”, ”Musculoskeletal discomfort”, ”Musculoskeletal pain”, ”Pain in extremity”, ”Back pain”, ”Muscle contracture”, ”Musculoskeletal stiffness”
- Overdose of Investigational Medical Product (IMP) (symptomatic), selected using the preferred terms "Accidental overdose" and "Intentional overdose" and the tick box "Overdose with IMP" and "Symptomatic Overdose" in the adverse event complementary e-CRF form
- Pregnancy (including partner of a randomized male subject) selected using appropriate MedDRA codes

The additional grouping of events will be also provided:

- Hepatic disorder events using SMQ “Hepatic disorder”
- Diabetes mellitus or diabetic complications using HLT “diabetes complications” (including PTs pertaining to the secondary SOC included in the HLT), 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 “Hyperglycaemic 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:

- CV death (including undetermined cause),
- MI,
- Ischemic stroke,
- Unstable angina requiring hospitalization,
- Congestive heart failure requiring hospitalization,
- Ischemia driven coronary revascularization procedure.

#### **2.1.4.2 Deaths**

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

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the TEAE period
- Death post-study: deaths occurring after the end of the study

#### **2.1.4.3 Laboratory safety variables**

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

Blood samples for clinical laboratories will be taken as described in the study flow chart in the protocol. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets:** hemoglobin, hematocrit, red blood cell count, platelet count;
  - **White blood cells:** white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Clinical chemistry
  - **Metabolism:** fasting plasma glucose, total protein, albumin, creatine phosphokinase (CPK);
  - **Electrolytes:** sodium, potassium, chloride;
  - **Renal function:** creatinine, uric acid, estimated glomerular filtration rate (eGFR);
  - **Liver function:** alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase ( $\gamma$ GT), lactate dehydrogenase (LDH), total bilirubin;
  - **Hepatitis screen:** anti-hepatitis-C antibody.

Technical formulas are described in [Section 2.5.1](#).

#### **2.1.4.4 Vital signs variables**

Vital signs include: weight, heart rate, systolic and diastolic blood pressure in the sitting position.

#### **2.1.5 Other endpoints**

Other assessment endpoints defined below are exploratory.

##### **2.1.5.1 HbA1c**

The absolute change in HbA1c (%) from baseline over time: same definitions and rules as for normalized TAV (see [Section 2.1.3.1](#)).

##### **2.1.5.2 hs-CRP**

The percent change in hs-CRP from baseline at Week 36 is defined using same definitions and rules as for normalized TAV, when applicable (see [Section 2.1.3.1](#)). hs-CRP values greater or equal to 10 mg/L will be excluded from analyses in a second approach, since these are suggestive of concurrent infections, MI, or other events provoking an acute phase response ([3](#)).

PCSA criteria for hs-CRP are defined in [Appendix A](#).

##### **2.1.5.3 Patients with LDL-C <25 mg/dL (0.65 mmol/L)**

The assessment will include:

- The proportion of patients with two consecutive results, spaced out by at least 21 days, of LDL-C <25 mg/dL (<0.65 mmol/L) (respectively LDL-C <15 mg/dL, ie, <0.39 mmol/L) during the treatment period
- The time to the first LDL-C <25 mg/dL (respectively LDL-C <15 mg/dL) for these patients.

Only calculated LDL-C will be used for this endpoint.

#### **2.1.6 Quality-of-life endpoints**

EQ-5D is a standardized and generic instrument for measuring the health status and health related quality of life (QOL) for clinical and economic assessment ([4](#)). EQ-5D instrument includes 5 items corresponding to the following dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression ([Appendix B](#)). Each item can take 1 of 3 responses: (1.) “no problem”, (2.) “some problems”, and (3.) “severe problems”. Overall health status is defined as a 5-digit number and will be converted into a standard utility score ranging between -0.111 (representing severe problems) and 1 (representing no problem): the single index utility score, using a regression model ([, Appendix C](#)). If response to one or more dimension is missing, the utility score will be missing.

QOL parameters include response to each EQ-5D items and change in utility score over time from baseline.

## 2.2 DISPOSITION OF PATIENTS

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

Included population consists of the patients who signed the informed consent.

Randomized patients consist of all patients who have been randomly allocated to a treatment group and recorded in the registration center, regardless of whether the study drug was used or not. Patients treated without being randomized 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:

- Patients who signed the informed consent
- Non-randomized patients and reasons for non-randomized, if any;
- Non-randomized but treated patients, if any
- Randomized patients
- Randomized but not treated patients and reason for not being treated;
- Randomized and treated patients
- Patients who did not complete the study treatment period as per protocol;
- Main reason for permanent treatment discontinuation;
- Status at last study contact,

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

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

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

All critical and major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, the following populations will be summarized by treatment group. Definition of the study populations are provided in [Section 2.3](#).

- Randomized population
- Efficacy population: modified intent-to-treat (mITT) population/per-protocol population
- Safety population
- QOL population

### **2.2.1 Randomization irregularities**

Randomization 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,

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

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

Randomization irregularities to be prospectively identified include but are not limited to:

<b><i>Randomization irregularities</i></b>
<i>Patient randomized twice</i>
<i>Stratification error</i>

## **2.3 ANALYSIS POPULATIONS**

Patients treated without being randomized will not be considered 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**

#### **2.3.1.1 *Modified intent-to-treat population***

The primary efficacy analysis population will be the modified intent-to-treat (mITT) population, defined as the randomized population who took at least one dose or part of dose of study drug, and has 2 analyzable normalized TAV, as defined below.

- One assessed before randomization
- Another one assessed after 24 weeks of treatment.

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

#### **2.3.1.2 *Per-protocol population***

The per-protocol (PP) population is a subset of the mITT population excluding patients with any major protocol deviations that have significant impact on the primary study objective, analyzed according to the treatment actually received.

Major protocol deviations that do not cause exclusion from mITT population, but have significant impact on the primary study objective are as follows:

- Poor adherence to the study protocol
- IVUS not performed from Week 34 to Week 38 during efficacy treatment period, which is defined as the time from the day of randomization to the last study treatment administration + 21 days.
- Patients with analyzed vessel length less than 10 mm.
- Patients who do not meet the following inclusion criteria.
  - Patient hospitalized for any ACS
  - LDL-C at patient selection (either Friedewald method or direct methods measured at each study site)  $\geq 100$  mg/dL for patients enrolled based on the protocol amendment 1;  $\geq 70$  mg/dL for patients enrolled based on the protocol amendment 2 or later.
  - Patient who undergoes IVUS imaging with at least  $>50\%$  stenosis angiographically within 1 week after the ACS onset. The IVUS imaging should be performed in the culprit vessels with some levels of atherosclerosis/stenosis.
  - Patients aged  $\geq 20$  years old at ACS diagnosis.
- Patients who meet the following exclusion criteria.
  - Patient who has been previously treated with at least one dose of any anti-PCSK9 monoclonal antibody.
  - Patient on LDL apheresis

- Patient who has withdrawn consent before enrolment/randomization (starting from signed informed consent form).

### **2.3.2 Safety population**

The safety population considered for the safety analyses will be the randomized population who actually received at least 1 dose or part of a dose of the study drug (alirocumab or standard of care). Patients will be analyzed according to the treatment actually received (i.e. as-treated treatment group, Standard of Care or Alirocumab).

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 drug will be included in the safety population as randomized.
- The treatment group allocation for “as-treated analysis” will be defined as follows:
  - Alirocumab group if IMP injection proportion is  $\geq 50\%$ .
  - SoC group if IMP injection proportion is  $<50\%$ .

IMP injection proportion (%) defined as  $100 \times (\text{Number of IMP injection}) / [(\text{the date of last study treatment administration} - \text{the date of randomization}) / 14 + 1]$

### **2.3.3 Quality-of-life population**

The analyses of QOL will be performed on all randomized and treated patients (safety population) with a baseline and at least 1 matching post-baseline evaluation for any of the 5 dimensions. Patients will be analyzed according to the treatment actually received.

## **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 IVUS parameters, lipid parameters, HbA<sub>1c</sub>, hs-CRP. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Unless otherwise specified, parameters will be summarized on the randomized population and mITT population analyzed in the treatment arm to which they were randomized. Similar analyses

will be done on the PP population (respectively safety population) in the treatment arm to which they are actually received if the size of the PP population (respectively safety population) is different (>10%) from the size of the mITT population (respectively randomized population) for any treatment group. In the randomized population and mITT population, parameters will also be summarized within each randomization strata as per the registration center and within each diabetic status at baseline.

All reported patient's medical and surgical history and all ongoing reported patients' these histories at the start of study will be presented by primary SOC and HLT. The tables will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on the overall incidence across treatment groups. In addition all medical history of specific interest will be presented by treatment group.

P-values comparing the 2 treatment groups on demographic characteristics, disease characteristics and other baseline characteristic data will be provided for descriptive purpose, as a screening tool, using the Fisher exact test for categorical data and Wilcoxon rank sum test for continuous data.

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

#### **2.4.2 Prior, concomitant or post-treatment medications**

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

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

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

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

### **2.4.3 Extent of study treatment exposure and compliance**

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

#### **2.4.3.1 Extent of investigational medicinal product exposure**

The total exposure will be assessed by:

- Duration of IMP exposure in weeks defined as: (last dose of IMP injection date – first dose of IMP injection date + 14 days) / 7, regardless of intermittent discontinuations (see [Section 2.5.3](#) for calculation in case of missing or incomplete data);
- The total number of IMP injections by patient.

These parameters will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, the durations of treatment exposure will be presented according to the following categories:  $\geq 1$  day to  $< 4$  weeks,  $\geq 4$  weeks to  $< 12$  weeks,  $\geq 12$  weeks to  $< 24$  weeks,  $\geq 24$  weeks to  $< 34$  weeks,  $\geq 34$  weeks.

#### ***Titration***

The following summaries will be provided in the alirocumab group:

- The number (%) of patients with an up-titration to 150 mg at Week 14 as per kit number recorded in eCRF page "Praluent Administration"
- The number (%) of patients with calculated LDL-C not achieving  $< 100$  mg/dL at Week 12

#### **2.4.3.2 Compliance of investigational medicinal product exposure**

Compliance of IMP will be assessed using the following parameters:

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

duration of IMP injection exposure in days. For example if a patient takes a dose 9 days after his/her previous injection, then 2 days are counted as days above-planned dosing.

These parameters will be summarized descriptively (N, Mean, SD, Median, Minimum and Maximum). In addition, the parameters will be presented according to the following categories: <80%, ≥80%.

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 underplanned dosing.

Cases of overdose will be reported in AE e-CRF pages and described in the AE analysis defined in [Section 2.1.4.1](#).

#### **2.4.3.3 *Extent of non-investigational medicinal product exposure***

NIMPs are assessed according to the following categories:

- Statin (Atorvastatin, Rosuvastatin)
- Non-statin LMT (Ezetimibe, Fibrate)
- Anti-platelets
- Anticoagulants

Statin and Non-statin LMT are selected using the eCRF tick box in Previous lipid modifying therapy form or “Concomitant Non-investigational Medicinal Product”.

Anti-platelets and anticoagulants are selected using eCRF form “Concomitant Non-investigational Medicinal Product” and the specific coding list specified in [Table 5](#).

The total exposure will be assessed by:

- Duration of NIMP exposure in weeks defined as: (last NIMP administration date in study – first NIMP administration date after randomization + 1 days) / 7, regardless of intermittent discontinuations (see [Section 2.5.3](#) for calculation in case of missing or incomplete data).
- If more than 1 NIMP in a category are taken, duration of exposure will be calculated using the earliest start date and the latest end date.

These parameters will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, the durations of treatment exposure will be presented according to the following categories: ≥1day to <4 weeks, ≥4 weeks to <12 weeks, ≥12 weeks to <24 weeks, ≥24 weeks to <34 weeks, ≥34 weeks.

#### **2.4.3.4 Compliance of non-investigational medicinal product exposure**

Compliance for each NIMP medications is used Compliance/Adherence Rate in eCRF Concomitant Non-investigational Medicinal Product form.

For each category of NIMP defined the above, the percentage of patients with <50%, ≥50 % to <80%, ≥80 %, and <80% compliance will be also summarized. If more than 1 NIMP in the category are taken or compliance of the medication was changed during the TEAE period, the lowest compliance should be used.

Details (i.e., all drug names, duration, compliance) for patients who had received at least 1 NIMP with <50% compliance (if any) will be listed.

#### **2.4.4 Analyses of efficacy endpoints**

##### **2.4.4.1 Analysis of primary efficacy endpoint**

The primary efficacy endpoint, percent change in normalized TAV from baseline to Week 36 defined in [Section 2.1.3.1](#) will be analyzed in the mITT population using an analysis of covariance (ANCOVA) model with treatment group (SoC arm, Alirocumab arm) and randomization strata (statin at ACS onset [Yes / No]), as fixed effects, and the baseline normalized TAV as covariate.

Throughout the ANCOVA model run using SAS Mixed procedure, Alirocumab group will be compared to SoC group at the two-sided 0.05 level for superiority, and baseline adjusted least squares means (LS means) estimates at Week 36 for each treatment group with their corresponding standard errors (SEs) and the 95% confidence interval (CI) of the difference between treatment groups will be provided.

Let  $\mu_0$  and  $\mu_1$  be the population means of the percent change in normalized TAV from baseline to Week 36 under SoC group and alirocumab group, respectively. The null hypothesis that will be tested is " $H_0 : \mu_0 = \mu_1$ " versus " $H_1 : \mu_0 \neq \mu_1$ ".

Main result of this study is the result using the primary analysis.

##### ***Model assumption checks***

##### **Treatment group-by-statin dose interaction:**

A treatment group-by-randomization strata interaction term will be added in the primary ANCOVA model, and the Least Square Means Difference versus SoC group of alirocumab group will be provided, as well as the corresponding standard error and 95% confidence interval, within each randomization strata.

### Homogeneity of slope:

Given the low sample sizes in each treatment group, the homogeneity of slopes assumption will be explored by means of the following outputs:

- The treatment group-by-baseline normalized TAV interaction term will be added in the primary ANCOVA model and its significance level will be examined.
- A separate-slopes model with terms for treatment group, randomization strata, and treatment group-by- baseline normalized TAV interaction will be fitted to the data, and the graph presenting the observed and predicted values by baseline normalized TAV values will be provided. Predicted values within a same treatment group and randomization strata will be joined to form the 2 twins of regression lines of the separate slopes model.
- Within the framework of the above separate-slopes model, a graph presenting the Least Square Means Difference of alirocumab arm versus SoC arm and the corresponding 95% confidence interval, by baseline normalized TAV value, will be provided.

### Homogeneity of variance:

The homogeneity of variances will be checked by displaying the variance of the residuals within each level of the treatment group. A scatter plot of predicted versus residual values will be also provided.

### **Sensitivity analyses**

A sensitivity analysis will be performed on randomized population to explore the potential impact of the missing post-baseline normalized TAV. This will include analyses using multiple imputation methods. Missing data will be imputed 100 times to generate 100 complete data sets, using SAS MI procedure. The MI procedure assumes that the data are from a continuous multivariate distribution and contain missing values that can occur on any value. Baseline normalized TAV and other baseline characteristics such as age, gender, weight, statin at ACS onset as randomization strata and laboratory markers (HDL-C, calculated LDL-C, fasting TGs) at baseline, diabetic status at baseline, and treatment group will be used in the imputation procedure. The imputation procedure will only be performed on the primary endpoint. The 100 complete data sets will be then analyzed using ANCOVA model above. Then the MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae (5). Combined means estimates for both treatment groups, as well as the differences of these estimates, with their corresponding SEs, 95% CIs and p-value will be provided.

### **Supportive analyses**

The primary efficacy endpoint will be analyzed on PP population to assess the effect due to major protocol deviation and/or premature discontinuation.

### ***Subgroup analyses (Stratified analyses)***

To assess the homogeneity of the treatment effect across various subgroups, treatment group-by-subgroup factor interaction terms and a subgroup factor term will be added in the primary ANCOVA model. LS means difference versus SoC will be provided, as well as the corresponding SE and 95% CI, within each subgroup. The significance level of the treatment group-by-subgroup factor interaction term will be also provided for each factor for descriptive purpose. Forest plots will be provided.

Subgroups of interest are (providing sufficient number of patients per subgroups):

- Baseline normalized TAV(<Median,  $\geq$  Median) for this specific subgroup factor, the ANCOVA model will include this categorical baseline instead of continuous baseline;
- BMI (<25,  $\geq$  25 kg/m<sup>2</sup>);
- Weight (<Median,  $\geq$ Median kg) ;
- Gender;
- Age (<65,  $\geq$ 65 years);
- Randomization strata as per registration center (With/Without statin at ACS onset);
- Diabetic status at baseline (Yes, No);
- Diabetic status at baseline relevant to insulin use (No diabetes, diabetes without insulin, diabetes with insulin);
- Diabetic status at baseline relevant to time from diagnosis of diabetes (No diabetes, diabetes for <Median years, diabetes for  $\geq$  Median years);
- Index ACS event (STEMI, NSTEMI, UA);
- Prior ischemic stroke(Yes, No);
- eGFR (<60,  $\geq$ 60 mL/min/1.73m<sup>2</sup>) ;
- eGFR (<30,  $\geq$ 30 to <60,  $\geq$ 60 mL/min/1.73m<sup>2</sup>); if sufficient number of patients in category  $\geq$  30 to <60, then combine category  $\geq$  30 to <60 and  $\geq$ 60; i.e. eGFR(<30,  $\geq$ 30);
- Baseline calculated LDL-C (<80,  $\geq$ 80 to <100,  $\geq$ 100 to <130,  $\geq$ 130 to <160,  $\geq$ 160 mg/dL) (ie, <2.07,  $\geq$ 2.07 to <2.59,  $\geq$ 2.59 to <3.37,  $\geq$ 3.37 to <4.14,  $\geq$ 4.14 mmol/L);
- Baseline calculated LDL-C (<100,  $\geq$ 100 to <130,  $\geq$ 130 to <160,  $\geq$ 160 mg/dL) (ie, <2.59,  $\geq$ 2.59 to <3.37,  $\geq$ 3.37 to <4.14,  $\geq$ 4.14 mmol/L);
- Baseline HDL-C (<40,  $\geq$ 40 mg/dL) (ie, <1.04,  $\geq$ 1.04 mmol/L);
- Baseline fasting TGs (<150,  $\geq$ 150 mg/dL) (ie, <1.7,  $\geq$ 1.7 mmol/L [mixed dyslipidemia]);
- Baseline Lp(a) (<30,  $\geq$ 30 to <50,  $\geq$ 50 mg/dL) (ie, <0.3,  $\geq$ 0.3 to <0.5,  $\geq$ 0.5 g/L);
- Baseline Lp(a) (<50,  $\geq$ 50 mg/dL) (ie, <0.5,  $\geq$ 0.5 g/L);
- Baseline non-HDL-C (<110,  $\geq$ 110 to <130,  $\geq$ 130 mg/dL) (ie, <2.84,  $\geq$ 2.84 to <3.37,  $\geq$ 3.37 mmol/L);

- Baseline Apo B (<75,  $\geq$ 75 to <90,  $\geq$ 90 mg/dL) (ie, <0.75,  $\geq$ 0.75 to <0.9,  $\geq$ 0.9 g/L);
- Baseline hs-CRP (<2,  $\geq$ 2 mg/L);
- Baseline HbA1c (<6.5,  $\geq$ 6.5 %).

#### **2.4.4.2 Analyses of secondary efficacy endpoints**

Method for controlling the overall type-I error rate when testing the key secondary efficacy endpoint is described in [Section 2.4.4.3](#).

For the key secondary efficacy endpoint (defined in [Section 2.1.3.2.1](#)) and the other secondary efficacy endpoints (described in [Section 2.1.3.2.2](#)), descriptive summaries and analyses will be performed in the mITT population.

For lipids parameters (calculated LDL-C, TC, HDL-C, fasting TGs, non-HDL-C, Apo B, Apo A-1, ApoB/Apo A-1 ratio, Lp(a), calculated LDL-C/HDL-C ratio, and fasting TGs/HDL-C ratio), all measurements, scheduled or unscheduled will be assigned to analysis windows defined in [Section 2.5.4.2, Table 4](#) in order to provide an assessment for time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. For TGs, measurements on not-fasting patients will be excluded. Analyses will be performed using standard international unit and conventional unit.

##### ***Continuous endpoints anticipated to have a normal distribution with only 1 post-baseline value collected***

Continuous secondary endpoints anticipated to have a normal distribution (i.e., normalized TAV, PAV, Apo B, Apo A-1, Apo B/Apo A-1 ratio, fasting TGs/HDL-C ratio, calculated LDL-C/HDL-C ratio) will be analyzed using the same ANCOVA model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value.

##### ***Continuous endpoints anticipated to have a non-normal distribution with only 1 post-baseline value collected***

Continuous secondary endpoints anticipated to have a non-normal distribution (i.e., lumen volume, EEM volume, TAV, Lp[a]) will be analyzed in the mITT population using a robust regression model (6) (i.e., ROBUSTREG SAS procedure with M-estimation option) with treatment group, and randomization strata (statin at ACS onset [Yes / No]) as main effect and corresponding baseline value(s) as covariate.

##### ***Continuous endpoints anticipated to have a normal distribution with multiple post-baseline values collected***

Continuous secondary endpoints anticipated to have a normal distribution with multiple post-baseline values collected (i.e., calculated LDL-C, TC, HDL-C, non-HDL-C) will be analyzed in the mITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 4, Week 12, Week 24, and Week 36 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 (SoC group, Alirocumab group), time point (Week 4, Week 12, Week 24, and Week 36), randomization strata (statin at ACS onset [Yes / No]), treatment-by-time point interaction, randomization strata-by-time point interaction, as well as, the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

***Continuous endpoints anticipated to have a non-normal distribution with multiple post-baseline values collected***

Continuous secondary efficacy endpoints anticipated to have a non-normal distribution (ie, TGs), will be analyzed in the mITT population using multiple imputation approach described in detail for handling of missing values, followed by the testing treatment groups using a robust regression model (6). 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, randomization strata (statin at ACS onset [Yes / No]), 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 (5). Combined means estimates for both treatment groups, as well as the differences of these estimates, with their corresponding SEs, 95% CIs and p-value will be provided.

**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 method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern;
- Step 2: Using the monotone data set from step 1, missing data will be imputed using the regression method.

The imputation model for step 1 will include the treatment group and the values of the analyzed parameter at baseline and all pre-specified time-points from baseline up to Week 36.

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

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

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

### ***Binary endpoints***

Binary secondary endpoints defined in [Section 2.1.3.2.2](#) (i.e. The proportion of patients with calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 36, The proportion of patients with calculated LDL-C <50 mg/dL (3.37 mmol/L) at Week 36., and The proportion of patients achieving at least 50% reduction in calculated LDL-C at Week 36) will be analyzed using multiple imputation approach for handling of missing values(See above for details about multiple imputation). In the imputations, log-transform process planned above 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 randomization strata (as per registration center, as defined in [Section 1.1](#)). Combined estimates of odds ratio versus placebo, 95% 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 Week 36 will consist of using the last value obtained up to the Week 36 analysis window to impute the missing Week 36 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. In case the model would not converge with stratification variables, an unstratified exact logistic regression will be performed. Exact odds followed by logistic regression. In the data dependent case that the logistic regression method is not applicable (e.g., the response rate is zero in 1 treatment arm and thus the maximum likelihood estimate may not exist).

### ***Descriptive summaries***

For descriptive summaries (N, Mean, SD, Median, Minimum, Maximum, Q1 and Q3), raw value, percentage change (except for ratio and PAV), and absolute change from baseline in IVUS and lipids parameters will be provided at each time point for each treatment group. The time profile of each parameter will be plotted by treatment group with the corresponding SDs. For IVUS parameters, TG, and Lp(a), the time profile of each parameter will be plotted using box whisker plot by treatment group. For calculated LDL-C, the same descriptive summaries will also be provided for the following patients:

- Patients with up-titration;
- Patients without up-titration;

together with the spaghetti plots corresponding to the summaries.

In addition, for calculated LDL-C, TC, HDL-C, non-HDL-C, and fasting TG (in conventional (US) and international units), raw value, percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units), will be summarized in the mITT population using:

- For calculated LDL-C, TC, HDL-C, non-HDL-C: LS mean and SE for each treatment group, obtained from the same MMRM models as used for endpoints above and with raw values, absolute change from baseline, or percent change from baseline as response variable in the model as appropriate.
- For fasting TG: mean and SE for each treatment group obtained from multiple imputation approach followed by the robust regression models as used for endpoints above and with raw values or percent changes from baseline as response variable in the model as appropriate.

#### ***Sensitivity analyses of key secondary efficacy endpoint***

A sensitivity analysis of key secondary efficacy endpoint will be performed on randomized population as the same method as sensitivity analysis of primary efficacy endpoint described in [Section 2.4.4.1](#), using the baseline PAV instead of baseline normalized TAV.

#### ***Supportive analyses of secondary efficacy endpoints of IVUS parameters***

The secondary efficacy endpoints of IVUS parameters will be analyzed on PP population to assess the effect due of major protocol deviation and/or premature discontinuation. Descriptive summaries of IVUS parameters will be also performed on PP population.

#### ***Analyses of secondary efficacy endpoints by subgroups***

Subgroup analyses of the key secondary efficacy endpoint and percent change from baseline in calculated LDL-C at Week 36 will be performed using the same subgroup factor and in the same way as in primary efficacy endpoint described in [Section 2.4.4.1](#).

Subgroup analyses of the secondary efficacy endpoints of interest and subgroups of interest are the followings (providing sufficient number of patients per subgroups):

- The secondary efficacy endpoint : percent change in Lp(a) from baseline to Week 36
  - Interest subgroup: Baseline Lp(a) (<30,  $\geq$ 30 to <50,  $\geq$ 50 mg/dL) (ie, <0.3,  $\geq$ 0.3 to <0.5,  $\geq$ 0.5 g/L);
- The secondary efficacy endpoint : percent change in fasting TGs from baseline to Week 36
  - Interest subgroup: Baseline fasting TGs (<150 mg/dL,  $\geq$ 150 mg/dL) (ie, <1.7,  $\geq$ 1.7 mmol/L [mixed dyslipidemia]);

#### **2.4.4.3 Multiplicity issues**

In order to handle the key secondary efficacy endpoint, the overall type-I error will be controlled by the use of a sequential inferential approach. Statistical significance of the primary efficacy endpoint at the 0.05 alpha level is required before drawing inferential conclusions about the key secondary efficacy endpoint (defined in [Section 2.1.3.2.1](#)). This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.05 level.

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

#### **2.4.5 Analyses of safety data**

The summary of safety results will be presented by treatment group.

##### ***General common rules***

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

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately;
- The baseline value is defined as the last available value before randomization, unless 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 (PCSA defined in the document “Analysis and reporting safety data from clinical trials through the Clinical Study Report (CSR) (Version Number: 3.0)” [\[Appendix A\]](#))
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the TEAE period by treatment group on the safety population.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in [Section 2.5.4.2, Table 4](#).
- For quantitative safety parameters, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group using analysis windows defined in [Section 2.5.4.2, Table 4](#). Summaries will include the last on-treatment value and the worst on-treatment value. The worst value is defined as the nadir and/or the peak value during the treatment period according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.

Analyses performed according to diabetic 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. 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, HLTG (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 group) will define the presentation order for all other tables by SOC and PT, unless otherwise specified. The tables of AEs by SOC, HLTG, HLT and PT will be sorted by the SOC internationally agreed order and the other levels (HLTG, HLT, and PT) will be presented in alphabetical order, unless otherwise specified

##### ***Analysis of all treatment-emergent adverse events***

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any:
  - TEAE;
  - Treatment emergent serious adverse event (SAE);
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLTG, HLT, and PT, sorted by the SOC internationally agreed order. The other levels (HLTG, HLT, and PT) will be presented in alphabetical order;

- All TEAEs regardless of relationship and related to IMP by primary SOC, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, and PT) will be presented in alphabetical order;
- All TEAEs regardless of relationship and related to LMT-NIMP by primary SOC, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, and PT) will be presented in alphabetical order;
  - AE related to LMT-NIMP is defines all AEs checked “Related” in “Atorvastatin/Rosuvastatin?” or “Lipid Modifying Therapy?” on the adverse event case report form page.
- All TEAEs regardless of relationship and related to LMTs by primary SOC, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order;
  - AE related to LMTs is defines all AEs checked “Related” in “IMP/Praluent?”, or “Atorvastatin/Rosuvastatin?”, or “Lipid Modifying Therapy?” on the adverse event case report form page.
- 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 group). This sorting order will be applied to all other tables by SOC and PT of TEAEs, unless otherwise specified.
- The frequency of AEs by SOC/PT and selected AEs over time during TEAE period (number of patients experiencing AE and percentage by patient-months) will be provided by time intervals defined as:  $\leq 12$  weeks,  $>12$  to  $\leq 24$  weeks,  $>24$  weeks using the actuarial method. Only the first event will be counted. Those intervals will be calculated from the randomization.
- All TEAEs that occurred with HLT incidence  $\geq 2\%$  in any treatment group, by primary SOC, HLT, and PT, sorted by internationally agreed SOC order and by alphabetic order for the other levels (HLT and PT);
- All TEAEs by maximal intensity (ie, mild, moderate, or severe), presented by primary SOC and PT.

#### ***Analysis of all treatment emergent serious adverse event(s)***

- All treatment-emergent SAEs by primary SOC, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, and PT) will be presented in alphabetical order;
- All treatment-emergent SAEs regardless of relationship and related to IMP, by primary SOC, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, and PT) will be presented in alphabetical order.
- All treatment-emergent SAEs regardless of relationship and related to LMT-NIMP, by primary SOC, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, and PT) will be presented in alphabetical order.

- All treatment-emergent SAEs regardless of relationship and related to LMTs, by primary SOC, HLGT, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, and PT) will be presented in alphabetical order.
- All treatment-emergent SAEs by primary SOC and PT.

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

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, and PT) will be presented in alphabetical order.
- All TEAEs leading to treatment discontinuation by primary SOC and PT;

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

All grouping of TEAEs including adverse events of special interest as listed in [Section 2.1.4.1](#) will be analyzed using selections defined in [Section 2.1.4.1](#) and will be presented by SMQ and PT (when selection is based on SMQs) and by SOC and PT (when selection is based on the e-CRF tick box or HLGT/HLT). The summaries will be sorted by decreasing incidence of PT within each SOC/SMQ (in the alirocumab group).

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 IMP injections received;
- Time from randomization to first injection site reaction;
- Description of the highest intensity of each symptom recorded in the specific e-CRF page with table and bar chart.

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

#### ***Analysis of cardiovascular events***

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

#### ***Analysis of pre-treatment and post-treatment adverse events***

- All pre-treatment adverse events by primary SOC and PT sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC;
- All pre-treatment adverse events leading to treatment discontinuation (if any) by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC;

- All post-treatment adverse events by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC;
- All post-treatment SAEs by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

### ***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 2.1.5.3](#)) . Only TEAE for which it will be confirmed or unclear that they occurred, worsened or became serious the day or after the first level of calculated LDL-C <25 mg/dL will be considered.

Analysis of AESI including neurocognitive and neurological events and cataract (see selections in [Section 2.1.4.1](#)) will also be provided on the safety subgroup population of patients with 2 consecutive results of calculated LDL-C <25 mg/dL (as defined in [Section 2.1.5.3](#)).

#### **2.4.5.2 Deaths**

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

- Number (%) of patients who died by study period (on-study, on-treatment, post-study) and reasons for death adjudicated by the CEC
- Deaths in non-randomized patients or randomized but not treated patients
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC .

#### **2.4.5.3 Analyses of laboratory variables**

##### ***Descriptive statistics over time***

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

For glucose, this summary will be also provided according to the diabetic status at baseline. Only fasting samples will be summarized.

In addition, for some parameters of interest, mean changes from baseline with the corresponding standard error could be plotted over time in each treatment group.

### ***Potentially clinically significant abnormalities***

The incidence of PCSAs (list provided in [Appendix A](#)) as well as ALT increase as defined as AESI and hemoglobin decrease from baseline  $\geq 15$  g/L at any time during the TEAE period will be summarized by biological function (specified in [Section 2.1.4.3](#)) and treatment group whatever the baseline level and/or according to the following baseline status categories:

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

For glucose, this summary will also be provided according to the diabetic status at baseline. Only fasting samples will be summarized.

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

### ***Hepatitis C***

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). Post-baseline seroconversion is defined for patients with a negative baseline status who had either a “positive ribonucleic acid” (RNA) or a “confirmed positive antibody with negative RNA” post-baseline status as defined in the table below. Other situations require case by case evaluation and will be described individually if relevant.

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

**Table 2 - Definition of the patient status regarding hepatitis C virus**

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

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

<sup>b</sup> 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 1 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 1 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.

#### ***Possible drug-induced liver injury***

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter.

A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. 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  $3 \times \text{ULN}$  for ALT and a horizontal line corresponding to  $2 \times \text{ULN}$  for total bilirubin.

Graph and listing of possible Hy’s law cases identified by treatment group (eg, patients with any elevated  $\text{ALT} > 3 \times \text{ULN}$ , and associated with an increase in bilirubin  $\geq 2 \times \text{ULN}$ ) with ALT, AST, alkaline phosphatase, total bilirubin, and, if available, direct and indirect bilirubin, will be provided.

#### ***2.4.5.4 Analyses of vital sign variables***

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum, and maximum) of all vital sign variables (values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, last on-treatment and worst on-treatment value) by treatment group during the treatment period. In addition, for some parameters of interest, mean changes from baseline with the corresponding standard error could be plotted over time 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.

#### **2.4.6 Analysis of other endpoints**

All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in [Section 2.1.5](#).

##### **2.4.6.1 Analyses of hs-CRP**

hs-CRP parameter (values and percent change from baseline) will be summarized on the safety population by analysis visit using number of available data, mean, SD, median, Q1, Q3, minimum, and maximum for each treatment group during the treatment period. The time profile will be plotted by treatment group with the medians, Q1 and Q3. The incidence of PCSA at any time during the TEAE period will be summarized by treatment group using descriptive statistics.

hs-CRP values greater or equal to 10 mg/L will be excluded from analyses in a second approach, since these are suggestive of concurrent infections.

##### **2.4.6.2 Analyses of HbA1c**

HbA1c parameter (values and change from baseline) will be summarized on the safety population by analysis visit using number of available data, mean, SD, median, Q1, Q3, minimum, and maximum for each treatment during the treatment period. Summary will be also provided according to the diabetic status at baseline (see [Section 2.1.1](#)). The time profile will be plotted by treatment group with the means and the corresponding standard errors (SEs). The incidence of PCSA at any time during the TEAE period will be summarized by treatment group using descriptive statistics.

##### **2.4.6.3 Analyses of patients with LDL-C <25 mg/dL (<0.65 mmol/L)**

The number and percentage of patients with 2 consecutive LDL-C <25 mg/dL (respectively, LDL-C <15 mg/dL, ie, 0.39 mmol/L) will be provided by treatment group on the safety population. Kaplan-Meier curves will be provided for the time to the first LDL-C <25 mg/dL (respectively 15 mg/dL) for these patients. For this analysis, 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 quality of life/health economics variables**

The analysis of data from EQ-5D instrument will be performed on QOL population. Baseline is defined as the visit 1 (Week 0) evaluation. Analysis window for efficacy parameters will be used to assign time points (see [Section 2.5.4.2, Table 4](#)).

### ***Individual EQ-5D items***

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

### ***EQ-5D utility score***

The raw value and the absolute change from baseline of the utility score will be summarized using mean, median, Q1, Q3, SD, minimum, and maximum for each post-baseline visit. Cumulative distribution functions for the absolute change in utility score from baseline will be displayed by treatment groups, at Week 4, Week 12, Week 24, and Week 36.

The absolute change from baseline in utility score to Week 4, Week 12, Week 24, and Week 36 will be analyzed using a MMRM model with fixed categorical effects of treatment group, randomization strata as per the registration center, treatment-by-time point interaction, strata-by-time point interaction, as well as, the continuous fixed covariates of baseline value and baseline value-by-time point interaction.

## **2.5 DATA HANDLING CONVENTIONS**

### **2.5.1 General conventions**

The following formulas will be used for computation of parameters.

#### ***Time***

1 month = 30.4375 days,

1 year = 365.25 days.

#### ***Age***

Age (years) = (Date of ACS diagnosis – Date of birth) / 365.25.

Age will be rounded using SAS INT function. In case date of ACS diagnosis and date of birth have the same month and day, then Age = year of ACS diagnosis – Year of birth.

#### ***BMI***

BMI (kg/m<sup>2</sup>) = weight (kg)/ height (m)/ height (m).

For reporting such as Patients Profiles, or Listing of validation, the value will be rounded with 2 significant digits. But for calculating the summary, it will not be rounded.

### ***Time from index ACS diagnosis to randomization***

Time from index ACS diagnosis to randomization (weeks) = (Date of randomization – Date of index ACS diagnosis) / 7.

### ***Time from revascularization procedure to randomization***

Time from revascularization procedure to randomization (weeks) = (Date of randomization – Date of revascularization procedure) / 7.

### ***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. In case that the day of the date is missing, the day will be put equal to "1st".

### ***Calculated LDL-C using the Friedwald formula***

$$\text{calculated LDL-C(mg/dL)} = \text{TC} - \text{HDL-C} - \text{TGs}/5$$

If TG values exceed 400 mg/dL (4.52 mmol/L), then calculated LDL-C will be missing.

### ***Conversion to standard international unit***

Should not be rounded at the time of calculation for conversion to standard international unit.

### ***Date of last administration of study treatment***

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

### ***Renal function formulas***

eGFR value will be derived using the Japanese equation:

$194 \times (\text{serum creatinine in mg/dL})^{-1.094} \times (\text{age in years})^{-0.287}$  (x 0.739 if female). Serum creatinine rounded off to two decimal places will be used.

### ***Lipid variables, laboratory safety variables, hs-CRP***

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

## **2.5.2 Data handling conventions for secondary efficacy variables**

See [Section 2.1.3](#).

## **2.5.3 Missing data**

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

### ***Handling of computation of treatment duration and compliance if IMP or NIMP first or end of treatment date is missing***

If the last or first administration date is missing, the exposure duration and compliance will be used theoretical date.

### ***Handling of medication missing/partial dates***

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

### ***Handling of adverse events with missing or partial date/time of onset***

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

### ***Handling of adverse events when date and time of first administration is missing***

The exposure duration should be kept as missing.

### ***Handling of missing assessment of relationship of adverse events to IMP***

If the assessment of the relationship to IMP is missing for an adverse event, the adverse event will be considered as related to the IMP in the tables of possibly related adverse events, but no imputation will be done at the data level

### ***Handling of missing assessment of relationship of adverse events to LMTs***

If the assessment of the relationship to LMTs is missing for an adverse event, the adverse event will be considered as related to the LMTs in the tables of possibly related adverse events, but no imputation will be done at the data level

### ***Handling of missing assessment of relationship of adverse events to LMT-NIMP***

If the assessment of the relationship to LMT-NIMP is missing for an adverse event, the adverse event will be considered as related to the LMT-NIMP in the tables of possibly related adverse events, but no imputation will be done at the data level

### ***Handling of potentially clinically significant abnormalities***

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

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

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing (e.g., “>0.5 GIGA/L” criterion will be used for eosinophils for the PCSA “>0.5 GIGA/L or >ULN if  $ULN \geq 0.5$  GIGA/L” when ULN is missing.

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 IVUS and OCT variables**

Data analyzed by time point for IVUS and OCT variables will be summarized using the analysis window given in [Table 3](#). This analysis window will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses.

**Table 3 - Analysis windows definition**

Time point	Targeted study day	Analysis window in study days
Week 36	253	$\geq 169$

Study days are calculated from the day of randomization, the day of randomization being Day 1.

##### **2.5.4.2 Time points for data except OCT and IVUS variables**

Data analyzed by time point for all variables except OCT and IVUS variables will be summarized using the analysis windows given in [Table 4](#). These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses.

**Table 4 - Analysis windows definition**

Time point	Targeted study day	Analysis window in study days
Week 4	29	15 to 42
Week 12	85	78 to 98
Week 24	169	155 to 182
Week 36	253	239 to 266

Study days are calculated from the day of randomization, the day of randomization being Day 1.

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

### **2.5.5 Unscheduled visits**

For IVUS data, OCT data, lipid data, QOL, safety laboratory data, or vital signs, unscheduled visit measurements may be used to provide a measurement for a time window, a baseline, a time point, or a worst value, if appropriate according to their definition. The measurements may also be used to determine abnormal/PCSA values.

### **2.5.6 Pooling of centers for statistical analyses**

The randomization scheme was not stratified by center because the number of patients in some center is expected to be low. Therefore, the center will not be added as factor in the primary analysis model.

### **2.5.7 Statistical technical issues**

Not applicable.

### **3 INTERIM ANALYSIS**

No interim analysis is planned.

## 4 DATABASE LOCK

The database is planned to be locked at 2 months after last patient last visit.

## 5 SOFTWARE DOCUMENTATION

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

## 6 REFERENCES

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3. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003 Jan 28;107(3):499-511.
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6. Mehrotra DV, Li X, Liu J, Lu K. Analysis of longitudinal clinical trials with missing data using multiple imputation in conjugation with robust regression. *Biometrics*. 2012;68(4):1250-9.