



## **STATISTICAL ANALYSIS PLAN**

**A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Alirocumab (SAR236553/REGN727) on the Occurrence of Cardiovascular Events in Patients who have Recently Experienced an Acute Coronary Syndrome.**

**ODYSSEY Outcomes**

**SAR236553/REGN727-EFC11570**

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

|                     |                                      |
|---------------------|--------------------------------------|
| Ab:                 | antibody                             |
| ACE:                | angiotensin converting enzyme        |
| ACS:                | acute coronary syndrome              |
| ADA:                | anti-alirocumab antibodies           |
| ADP:                | adenosine diphosphate                |
| AESI:               | adverse event of special interest    |
| ALT:                | alanine aminotransferase             |
| ANCOVA:             | analysis of covariance               |
| Apo:                | apolipoprotein                       |
| AST:                | aspartate aminotransferase           |
| ATC:                | Anatomical Therapeutic Chemical      |
| BMI:                | body mass index                      |
| CABG:               | coronary artery bypass graft surgery |
| CEC:                | Clinical Events Committee            |
| CHD:                | coronary heart disease               |
| CI:                 | confidence interval                  |
| CMQ:                | company MedDRA query                 |
| CPK:                | creatine phosphokinase               |
| CSED:               | common study end date                |
| CV:                 | cardiovascular                       |
| DMC:                | data monitoring committee            |
| DVT:                | deep vein thrombosis                 |
| ECG:                | electrocardiogram                    |
| e-CRF:              | electronic case report form          |
| eGFR:               | estimated glomerular filtration rate |
| HbA <sub>1c</sub> : | glycated hemoglobin A1c              |
| HCV:                | hepatitis C virus                    |
| HDL-C:              | high-density lipoprotein cholesterol |
| HLGT:               | high level group term                |
| HLT:                | high level term                      |
| HR:                 | hazard ratio                         |
| hs-CRP:             | high-sensitivity C-reactive protein  |
| IA:                 | interim analysis                     |
| IMP:                | investigational medicinal product    |
| ITT:                | intent-to-treat                      |
| IVRS:               | interactive voice reponse system     |
| IWRS:               | interactive web response system      |
| LDH:                | lactate dehydrogenase                |
| LDL-C:              | low-density lipoprotein cholesterol  |
| LLN:                | lower limit of normal                |

|         |   |
|---------|---|
| LLOQ:   | lower limit of quantification                       |
| LMT:    | lipid modifying therapy                             |
| LMWH:   | low molecular weight heparin                        |
| Lp (a): | lipoprotein (a)                                     |
| MAR:    | missing-at-random                                   |
| MDRD:   | Modification of the Diet in Renal Disease           |
| MedDRA: | Medical Dictionary for Regulatory Activities        |
| MI:     | myocardial infarction                               |
| MMRM:   | mixed-effect model with repeated measures           |
| NOD:    | New onset of diabetes                               |
| NSAID:  | nonsteroidal anti-inflammatory drug                 |
| NSTEMI: | non ST segment elevation myocardial infarction      |
| PCI:    | percutaneous coronary intervention                  |
| PCSA:   | potentially clinically significant abnormality(ies) |
| PE:     | pulmonary embolism                                  |
| PT:     | preferred term                                      |
| Q1:     | first quartile                                      |
| Q2W:    | every 2 weeks                                       |
| Q3:     | third quartile                                      |
| RNA:    | ribonucleic acid                                    |
| SAE:    | serious adverse event                               |
| SAP:    | statistical analysis plan                           |
| SD:     | standard deviation                                  |
| SE:     | standard error                                      |
| SMQ:    | standardized MedDRA query                           |
| SOC:    | system organ class                                  |
| SPERT:  | safety planning, evaluation, and reporting team     |
| STEMI:  | ST segment elevation myocardial infarction          |
| TC:     | total cholesterol                                   |
| TEAE:   | treatment-emergent adverse event                    |
| TG:     | triglycerides                                       |
| TIA:    | transient ischemic attack                           |
| UA:     | unstable angina                                     |
| UFH:    | unfractionated heparin                              |
| ULN:    | upper limit of normal range                         |
| ULOQ:   | upper limit of quantification                       |
| WHO-DD: | World Health Organization-Drug Dictionary           |
| γGT:    | gamma glutamyl transferase                          |

# 1 OVERVIEW AND INVESTIGATIONAL PLAN

## 1.1 STUDY DESIGN AND RANDOMIZATION

This is a double-blind, randomized, placebo-controlled, balanced (1:1, alirocumab:placebo), parallel-group, multi-national, multicenter study.

Randomization takes place 4 weeks to 52 weeks after the index event and is stratified according to country.

Prior to randomization, eligible patients enter a run-in period of at least 2 weeks but no more than 16 weeks, during which they receive statin-intensive therapy defined as daily atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg. In case patients are unable to tolerate atorvastatin 40/80 mg or rosuvastatin 20/40 mg, they are allowed to receive the maximal tolerated dose of atorvastatin or rosuvastatin; or under some documented circumstances for statin-intolerant patients, receive other lipid lowering treatment other than a statin (eg, ezetimibe, or other non-statin lipid modifying therapy [LMT]), or no LMT at all.

Following this run-in period, only patients not reaching goal on their current LMT at the qualifying visit, ie, LDL-C  $\geq 70$  mg/dL ( $\geq 1.81$  mmol/L) or apolipoprotein B (Apo B)  $\geq 80$  mg/dL ( $\geq 0.8$  g/L) or non-HDL-C  $\geq 100$  mg/dL ( $\geq 2.59$  mmol/L), are randomized to either background therapy + alirocumab or background therapy + placebo. All patients randomized to alirocumab initially receive alirocumab 75 mg every 2 weeks (Q2W). After randomization, patients on alirocumab not reaching the target LDL-C level at Month 1 have their dose up-titrated to 150 mg Q2W at Month 2 in a blinded fashion (in case Month 1 LDL-C is not available or not valid for potential up-titration at Month 2, the next available LDL-C sample at Month 2 is used for potential up-titration at Month 4).

The double-blind treatment period will continue until 24 months after the closing of randomization for all countries except for China or until the target number of events (1613) is reached, whichever comes last (this date will be the Common Study End Date [CSED]). The corresponding estimated study duration is 64 months. All patients, even if they have achieved an endpoint, or have prematurely discontinued study treatment, will be asked to remain in the study until the CSED and to come back to the site as close as possible to the CSED (ie, CSED visit).

## 1.2 OBJECTIVES

### 1.2.1 Primary objective

The primary objective of this study is to compare the effect of alirocumab with placebo on the occurrence of cardiovascular events (composite endpoint of coronary heart disease [CHD] death, non-fatal myocardial infarction [MI], fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) in patients who have experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and are treated with an LMT regimen that is statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or at maximally tolerated dose of these given statins, and optimized for long-term chronic use with other non-statin LMT(s) at Investigator's discretion.

### 1.2.2 Secondary objectives

The secondary objectives are:

To compare the efficacy of alirocumab versus placebo on secondary endpoints (any CHD event, major CHD event, any cardiovascular [CV] event, composite of all-cause mortality/non-fatal MI/non-fatal ischemic stroke, all-cause mortality);

- To evaluate the safety and tolerability of alirocumab throughout the study;
- To evaluate the development of anti-alirocumab antibodies;
- To evaluate the effect of alirocumab on low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and non-high-density lipoprotein cholesterol (non-HDL-C).

A Clinical Events Committee (CEC) is established to adjudicate, in a blinded fashion, events corresponding to the primary and secondary cardiovascular endpoints as well as all causes of death.

## 1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the primary efficacy variable, with the following assumptions:

- Primary efficacy endpoint is the time from randomization to the date of first occurrence of one of the following clinical events, as determined by the CEC: CHD death, any non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization (with new high-risk electrocardiogram (ECG) findings and contemporary evidence of angiographically significant coronary disease). Based on PROVE-IT results (1) and considering adjustment based on the study design and endpoints definition, the following Kaplan-Meier probabilities of event in the placebo group have been assumed: 3.8% at 12 months, 6.4% at 24 months, 9.0% at 36 months, and 11.4% at 48 months. Probabilities of an event at other time points are estimated using a piece-wise exponential model. The primary efficacy endpoint will be analyzed on an intent-to-treat basis (all randomized



patients, including those who discontinue study medication are followed for any efficacy event until the CSED).

- Treatment hazard ratio of 0.85 (corresponding to a 15% hazard risk reduction for the test group relative to placebo), which is assumed to be constant over time;
- A log-rank test at an overall 1-sided 2.5% significance level with 90% power;
- Two interim analyses, according to a group sequential design, using for efficacy Gamma (-22)  $\alpha$ -spending function, and for futility a Gamma (-5)  $\beta$ -spending function. Non-binding spending functions are used. See [Section 4](#) for interim analysis details;
- One percent lost-to-follow-up prior to a primary efficacy endpoint at 24 months in both arms;
- Enrolment rate: sample size of 18 000 patients enrolled in 1400 sites (all sites were expected to be activated over a 12 months period). Table 1 below describes the expected enrolment rate per month; these assumptions were based on internal experience to enroll this patient population.

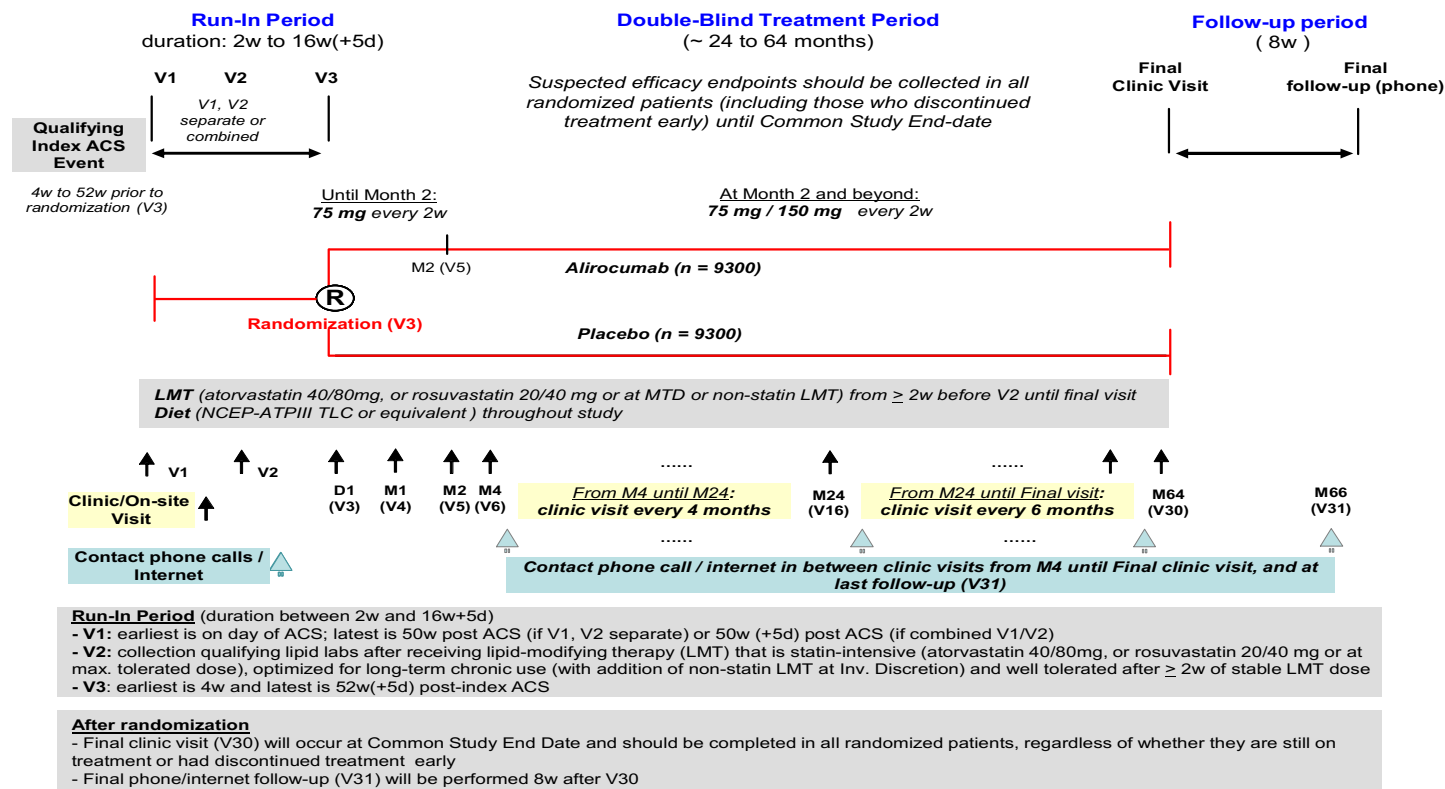
**Table 1 - Enrolment rate assumptions per month**

| Month                   | 1 to 3 | 4   | 5   | 6   | 7   | 8   | 9    | 10   | 11   | 12 to 40                   |
|-------------------------|--------|-----|-----|-----|-----|-----|------|------|------|----------------------------|
| No. patients per month  | 32     | 64  | 80  | 104 | 160 | 240 | 320  | 420  | 520  | 560                        |
| Cumulative no. patients | 96     | 160 | 240 | 344 | 504 | 744 | 1064 | 1484 | 2004 | 2564 at M12, 18 000 at M40 |

Based on the above assumptions, 1613 events are needed for 90% power. In order to achieve the 1613 targeted events, 18 000 patients (9000 per group) were initially planned to be randomized, over a period of about 40 months. However taking into account the local situation in China (regulatory requirement to randomize at least 600 patients, and anticipated delay in study start in China), the total number of patients randomized may be increased to approximately 18 600 patients (~9300 per group). At the end of the study, the overall population will include approximately 18 000 randomized patients who have either died or have been followed for a minimum of 24 months, possibly supplemented with an additional subset of Chinese patients (~600) who may be followed for less than 24 months.

## 2 STUDY PLAN

The following figure presents graphically the study design:



ACS: acute coronary syndrome, LMT: lipid-modifying therapy, MTD: maximal tolerated dose

The study flow chart is detailed in the protocol.

## 2.1 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes made after study start (after the first patient was enrolled).

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

The first patient was randomized on 02 November 2012.

**Table 2 - Protocol amendment statistical changes**

| <b>Amendment Number</b> | <b>Date approved</b> | <b>Rationale</b>  | <b>Description of statistical changes</b>  |
|-------------------------|----------------------|---|--|
| 6                       | 05-Dec-2013          | Clarification of definition of secondary endpoints in the protocol  | The secondary endpoint of "Any hospitalization for unanticipated coronary revascularization procedure" was replaced with "Any ischemia-driven coronary revascularization procedure"                        |
| 6                       | 05-Dec-2013          | Exclusion criteria in the protocol modified to allow inclusion of patients with a qualifying index ACS event occurring more than 16 weeks and less than 52 weeks prior to randomization               | "Time from ACS event to randomization" in categorical variable (eg, 4-24 weeks, >24 weeks) is added as a subgroup factor in the Subgroups analyses of the primary efficacy endpoint                        |
| 6                       | 05-Dec-2013          | The endpoint "Cardiovascular events of interest (other than efficacy endpoints)" has been added in the protocol.  | The analysis of cardiovascular events of interest (other than efficacy endpoints) is added.  |
| 8                       | 16-Apr-2015          | Sample size may be increased up to approximately 18 600 patients to allow the inclusion of 600 Chinese patients because of the local delayed study start in China, and definition of the CSED updated | CSED definition modified to "when 1613 patients have experienced at least one primary efficacy event or 24 months after the closing of randomization for all countries except China, whichever comes last" |
| 8                       | 16-Apr-2015          | Neurologic events (including neurocognitive events) are added as AESI   | Neurologic events (including neurocognitive events) added in the safety analysis   |

ACS = acute coronary syndrome; AESI = adverse event of special interest; CSED = common study end date

## 2.2 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features

- in the first version of the statistical analysis plan dated on 25 January 2016 compared to the protocol amendment 8 (version currently in effect at this time)
- in the amended versions of the statistical analysis plan (versions 2 and 3) compared to the first version of 25 January 2016.

Changes already incorporated in a protocol amendment are listed only in [Table 2](#).

With regard to the study timelines, the first patient was enrolled on 02 November 2012. The first interim analysis occurred in April 2016 with the data cut-off for the interim analysis on 30 November 2015. The second interim analysis occurred when approximately 1210 patients had at least one positively-adjudicated primary efficacy endpoint, with review of the data by the DMC in November 2016.

**Table 3 - Statistical analysis plan statistical changes**

| <b>SAP version number</b> | <b>Date approved</b> | <b>Rationale</b>  | <b>Description of statistical changes</b>   |
|---------------------------|----------------------|---|---|
| 1                         | 25-Jan-2016          | Imputation method not planned for missing lipid values  | For patients without lipid values in the time window analyzed, multiple imputation will be used with different imputation strategies depending on the time of those missing values (during the treatment period or after treatment discontinuation) (see <a href="#">Section 3.4.7.4.1</a> )  |
| 1                         | 25-Jan-2016          | End of analysis period for the analysis of TEAEs for patients with 2 consecutive low LDL-C did not take into account down-titrations from 150 mg to 75 mg | In the specific analysis of TEAEs for the subgroup of patients with two consecutive LDL-C <25 mg/dL (respectively 15 mg/dL) within the alirocumab treatment group, the upper limit of the analysis period for patients down-titrated from 150 mg to 75 mg will end at the date of last injection of 150 mg +70 days (see <a href="#">Section 3.4.5.1</a> ).   |
| 1                         | 25-Jan-2016          | Selection of patients with 2 consecutive LDL-C <25 mg/dL (respectively 15 mg/dL) modified consistently with the other studies of the program.             | The patients will be considered as having 2 consecutive LDL-C <25 mg/dL (respectively 15 mg/dL) if these values are spaced out by at least 21 days (see <a href="#">Section 3.1.5.4</a> ).  |
| 2                         | 28-Jul-2016          | Category of patients without diabetes at baseline divided in two sub-categories, consistently with the ODYSSEY Phase 3a program.                          | The category of patients without diabetes at baseline will be sub-divided in two sub-categories: "Pre-diabetes" and "normoglycemic" (see <a href="#">Section 3.1.1</a> ). The transition to new onset of diabetes in these two subgroups will be described separately (see <a href="#">Section 3.4.5.3</a> ). The primary efficacy endpoint will also be assessed in these subgroups (see <a href="#">Section 3.4.4.1</a> ) |

| <b>SAP version number</b> | <b>Date approved</b> | <b>Rationale</b>  | <b>Description of statistical changes</b>  |
|---------------------------|----------------------|---|--|
| 2                         | 28-Jul-2016          | Per FDA's recommendation, definition of "New onset of diabetes" revised.  | The fasting glucose criterion is included in the definition of "New onset of diabetes" (see <a href="#">Section 3.4.5.3</a> ). Details about handling of specific data situations are also added.  |
| 3                         | This version         | To improve the identification of the diabetes status at baseline and during the course of the study (new onset of diabetes) for patients selected by anti-diabetic medications. | Outcome of the review by external diabetes experts considered in the definition of diabetes status for patients identified with anti-diabetic medications at baseline (see <a href="#">Section 3.1.1</a> ) and during the course of the study (see <a href="#">Section 3.4.5.3</a> ) |
| 3                         | This version         | Improve derivation of the censoring date for vital status   | Additional dates are considered to derive the censoring date for CHD deaths, CV deaths and all causes of deaths endpoints (see <a href="#">Section 3.1.3.2</a> ).  |
| 3                         | This version         | Include CHD death and CV death endpoints in the hierarchical testing to have a more robust assessment on these efficacy endpoints.  | CHD death endpoint is moved from other secondary efficacy endpoints to main secondary efficacy endpoints. In addition CV death endpoint is added in the main secondary endpoints (see <a href="#">Section 3.1.3.2.1</a> ).   |
| 3                         | This version         | Provide comprehensive assessment of diabetes.   | "New onset of diabetes" added in the list of events of interest (see <a href="#">Section 3.1.4.1</a> )   |
| 3                         | This version         | Clarification about the list of patients who will have an additional ADA sample after the end of the study.   | See <a href="#">Section 3.1.5.5</a>  |
| 3                         | This version         | Explore treatment effects on CV events before and after defined timepoints.   | Analysis with Cox Proportional hazard models, exploring if the treatment HR varies over time, added in additional analyses on CV events (see <a href="#">Section 3.4.4.4</a> ).  |
| 3                         | This version         | Avoid overlap between alirocumab period and placebo period for patients switched to placebo with incomplete/missing last active injection date.                                 | Imputation of last active injection if incomplete/missing changed from the day to the day before the first injection of placebo following the switch to placebo in IVRS (see <a href="#">Section 3.5.3</a> )   |

SAP = statistical analysis plan; TEAE = treatment-emergent adverse event;

## 3 STATISTICAL AND ANALYTICAL PROCEDURES

### 3.1 ANALYSIS ENDPOINTS

#### 3.1.1 Demographic and baseline characteristics

Unless otherwise specified, the baseline value is defined as the last available value obtained up to the first double-blind IMP injection.

For patients randomized and not treated, the baseline value will be the last available value on or before the day of randomization.

All baseline safety and efficacy parameters (apart from those listed below) will be presented along with the summary statistics in the safety and efficacy sections ([Section 3.4.5](#) and [Section 3.4.4](#)).

#### *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 (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Region (North America, South America, Western Europe, Eastern Europe, Asia, Rest of the world as defined in [Section 3.5.6](#)).

#### *Medical or surgical history*

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

Medical or surgical history includes:

- Medical history of allergies;
- Patient's family medical allergic history;
- Other relevant medical or surgical history;
- Smoking habits;
- Alcohol habits.

Medical history of specific interest includes:

- Coronary artery disease history prior to the index ACS event;
- Cardiovascular risk factors including:
  - Dyslipidemia;
  - Hypertension;
  - Family history of coronary artery disease;
  - Type 1 or Type 2 diabetes mellitus.
- Other cardiovascular disease, including:
  - Congestive heart failure;
  - Peripheral arterial disease;
  - Cerebrovascular disease (carotid endarterectomy/carotid stenting, prior stroke, transient ischemic attack).

In addition, the status of diabetes mellitus at baseline and pre-diabetes at baseline will be derived using the following definitions:

Diabetes mellitus:

- Type 1 or Type 2 diabetes reported in medical history or as an adverse event before baseline (ie, before the first IMP intake or randomization for non-treated patients) (using company MedDRA query [CMQ] “Type 1 or Type 2 diabetes” as detailed in [Appendix B, Table 11](#))
- And/or HbA<sub>1c</sub>  $\geq$ 6.5% at baseline (V3) (or at V1 if V3 is not available)
- And/or 2 values of fasting blood glucose  $\geq$ 126 mg/dL (7.0 mmol/L) (at V1 and V3)
- And/or Use of anti-diabetic medication before baseline with a confirmed diagnosis per the external diabetes experts\* (in case a partial start date for a given medication precludes determining whether it started prior or after baseline, the diabetes status will not consider anti-diabetic medications for the concerned patients).

\* Patients classified as diabetic based only on the use of anti-diabetic medication before baseline will be reviewed in a blinded manner by external experts in diabetology. The individual Diabetes cases will be reviewed based on available information (e.g., medical history, concomitant medications, concomitant AEs, laboratory data, including complementary investigations as relevant). If the diabetic mellitus status is not confirmed, the patients will be classified as pre-diabetes or normoglycemic according to the definitions below.



Pre- diabetes:

- Specific terms (CMQ “impaired glucose control” as detailed in [Appendix B Table 12](#)) reported in the medical history or as an adverse event before baseline (ie, before the first IMP intake or randomization for non-treated patients);
- And/or HbA1c  $\geq 5.7\%$  and  $< 6.5\%$  at baseline (V3) (or at V1 if V3 is not available)
- And/or two values of fasting glucose (at V1 and V3)  $\geq 100$  mg/dL (5.6 mmol/L) but no more than one  $\geq 126$  mg/dL (7.0 mmol/L).

Normoglycemic

Patients not fulfilling either of the above criteria, will be classified as normoglycemic at baseline.

***Disease characteristics at baseline***

Specific disease history includes:

- Information on index qualifying ACS event: number (%) of patients with elevated cardiac biomarkers (troponin I or T, or CKMB); with resting ECG changes consistent with ischemia or infarction (ST depression, ST elevation, T wave inversion, pathological Q waves, new tall R wave) and additional evidence of obstructive coronary disease (evidence of myocardial or infarction by perfusion imaging, regional wall motion abnormality, epicardial coronary artery stenosis  $\geq 70\%$ , need for revascularization [percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)] related to index ACS event);
- The index ACS subtype:
  - STEMI: elevated cardiac biomarkers (Troponin I or T, and/or CKMB) and new or presumed new ST elevation
  - NSTEMI: elevated cardiac biomarkers (Troponin I or T, and/or CKMB) and No new or presumed new ST elevation
  - UA: No Troponin I or T elevated, and No CKMB elevated, and “Resting ECG changed consistent with ischemia or infarction AND additional evidence of obstructive coronary disease” (ie, any combination of responses to questions “B” on the electronic case report form [e-CRF])
- Time from index ACS event to randomization (in weeks and in months), quantitatively and in category  $< 2$ ,  $\geq 2$  to  $< 4$ ,  $\geq 4$  to  $< 6$ ,  $\geq 6$  months
- Revascularization procedure associated with the index ACS event (PCI or CABG)
- Time from the revascularization procedure to randomization (in weeks and in months)
- New cardiovascular events occurring during the run-in period, selected using a list of preferred terms (PTs) from CMQ or standardized MedDRA query (SMQ).

### ***Other baseline characteristics***

Other baseline characteristics include weight in kilograms (quantitative variable), and body mass index (BMI) in kg/m<sup>2</sup> (quantitative and qualitative variable: <30, ≥30).

Lipid parameters, HbA<sub>1c</sub> (quantitative and qualitative variable: <5.7 %, ≥5.7 to <6.5%, ≥6.5%) and hs-CRP (quantitative and qualitative variable: <2, ≥2 mg/L) at baseline will be also summarized by treatment group. Lipid parameters are total cholesterol (TC), LDL-C, non HDL-C, HDL-C, fasting triglycerides (TG), Apo A-1, Apo B, and lipoprotein (a) (Lp (a)).

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

- LDL-C: <70, ≥70 to <80, ≥80 to <100, ≥100 to <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL (ie, <1.81, ≥1.81 to <2.07, ≥2.07 to <2.59, ≥2.59 to <3.37, ≥3.37 to <4.14, ≥4.14 to <4.91, ≥4.91 mmol/L)
- HDL-C: <40, ≥40 mg/dL (ie, <1.04, ≥1.04 mmol/L),
- Non-HDL-C: <100, ≥100 to <110, ≥110 to <130, ≥130 to <160, ≥160 to <190, ≥190 to <220, ≥220 mg/dL (ie, <2.59, ≥2.59 to 2.84, ≥2.84 to <3.37, ≥3.37 to <4.14, ≥4.14 to <4.91, ≥4.91 to 5.69, ≥5.69 mmol/L)
- Fasting TG: <150, ≥150 to <200, ≥200 mg/dL (ie, <1.7, ≥1.7 to <2.3, ≥2.3 mmol/L), category ≥150 mg/dL (ie, ≥1.7 mmol/L [mixed dyslipidemia]) will be also displayed,
- Lp (a): <30, ≥30 to <50, ≥50 mg/dL (ie, <0.3, ≥0.3 to <0.5, ≥0.5g/L), category ≥30 mg/dL (ie, ≥0.3 g/L) will be also displayed
- Apo B: <75, ≥75 to <90, ≥90 mg/dL (ie, <0.75, ≥0.75 to <0.9, ≥0.9 g/L)

In addition the number (%) of patients not adequately controlled at baseline as per protocol definition will be described:

- LDL-C ≥70 mg/dL (1.81 mmol/L) or Apo B ≥80 mg/dL (0.8 g/L) or non-HDL-C ≥100 mg/dL (2.59 mmol/L)
- LDL-C ≥70 mg/dL (1.81 mmol/L)
- Apo B ≥80 mg/dL (0.8 g/L)
- Non-HDL-C ≥100 mg/dL (2.59 mmol/L)

Any technical details related to computation, dates, and imputation for missing dates are described in [Section 3.5](#).

### 3.1.2 Prior or concomitant medications

All LMTs taken within 1 month before screening visit V1 and until the end of the study, are to be reported in 1 of the following specific case report form pages:

- Previous and concomitant statin drugs;
- Previous and concomitant medications lipid lowering drugs (other than statins);

Patients on chronic use of statin (ie, on any statin for at least 3 months prior to the index ACS event) and the reasons for any modification in the statin regimen post-randomization are to be reported on the following specific page:

- Additional statin information

Other concomitant medications taken since informed consent, including cardiovascular medications are to be reported on the following specific page:

- Concomitant medications (all other than statin and other than lipid lowering drugs).

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

- Prior medications are those the patient used within 1 month before screening visit V1 and prior to first investigational medicinal product (IMP) injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase;
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from first IMP injection to the last double-blind injection +70 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in [Section 3.1.4](#));
- Post-treatment medications are those the patient took in the period starting the day after the concomitant medication period 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 intake dates in relation to the date of randomization.

The following medications of specific interest will be also selected using specific coding's list:

- Aspirin or oral ADP receptor antagonists
- Injectable anticoagulants (UFH or LMWH or Bivalirudin or Selective Factor Xa inhibitor)
- Thrombolytic
- Specific oral anticoagulant
- Anti-diabetic drugs (insulin, oral anti-diabetic, other non-oral anti-diabetic)
- ACE-inhibitor or angiotensin receptor blocker
- Beta blocker

- Calcium channel blocker
- Diuretics
- Nitrates
- NSAIDs (excluding aspirin)

Any technical details related to computation, dates, imputation for missing dates are described in [Section 3.5](#).

### 3.1.3 Efficacy endpoints

#### 3.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is the time from randomization to first occurrence of 1 of the following clinical events, as determined by the CEC:

- CHD death (including “undetermined causes of death” as per the CEC);
- Any non-fatal MI;
- Fatal and non-fatal ischemic stroke (including “stroke not otherwise specified” as per the CEC);
- Unstable angina requiring hospitalization.

The rules to determine the components and the date of the event that will be considered in the analyses of the primary efficacy endpoint are detailed in [Appendix C](#).

If none of these events is observed at the time of the analysis cut-off date (final or interim, depending on the timing of the analysis, see [Section 3.4.4.1](#) and [Section 4](#) for details), the patient will be right-censored at the date of last contact when information on efficacy endpoints (presence or absence) has been retrieved, or at the date of death, or at the cut-off date/CSED, whichever comes first.

The last information on efficacy endpoint (presence or absence)” will be the latest date among:

- The date of last visit performed with “endpoints events” e-CRF page completed.
- The “Date of last information on efficacy endpoint (presence or absence)” reported in the visit e-CRF pages during the course of the study.
- The “Date of last information on efficacy endpoint (presence or absence)” reported at the end of the study for all patients (this information can also be completed during the course of the study for “lost-to-follow-up” patients, patients who discontinued the follow-up, and patients who died).

In case of no information on the presence or absence of efficacy endpoint, nor on death at time of database extraction for the interim analyses, the censoring date will be the randomization date (eg, for patients randomized but having not reached the Month 1 visit yet).

Handling of missing or incomplete dates

In the exceptional circumstances when the exact date of occurrence of the outcome event has not been established (day and/or month missing), the date will be imputed as follows:

**Table 4 - Imputation of incomplete date of events composing the primary efficacy outcome**

| Type of event   | Imputed date  |
|---|---|
| <b>Only the day is missing</b>                                  |   |
| Death   | The latter of the last contact date + 1 day and the 1 <sup>st</sup> day of the month. |
| Other primary endpoint component (CHD event or ischemic stroke) | The latter of the randomization date and the 1 <sup>st</sup> day of the month.        |
| <b>Day and month are missing</b>                                |   |
| Death   | The latter of the last contact date + 1 day and January 1 <sup>st</sup> of the year.  |
| Other primary endpoint component (CHD event or ischemic stroke) | The latter of the randomization date and January 1 <sup>st</sup> of the year.         |

CHD = coronary heart disease

**3.1.3.2 Secondary efficacy endpoint(s)**

Clinical events assessed in the analyses are those determined by the CEC. Events suspected by the investigator but not confirmed by the CEC will not be part of the outcomes. CHD death outcome will include deaths for causes that could not be determined by the CEC (adjudicated as “Undetermined cause of death”). Similarly, fatal and non-fatal ischemic stroke outcomes will include fatal and non-fatal strokes for causes that couldn’t be determined by the CEC (adjudicated as “Stroke not otherwise specified”).

Rules for censoring date and for imputation of incomplete dates of events will be the same as for the primary efficacy endpoint, for all secondary efficacy endpoints with the exception of the analyses of the time to CHD death, the time to CV death and of the time to all-cause mortality for which the censoring date will be defined as the earliest date among the “date of last known alive or Date of death” and the cut-off date/CSED.

The “date of last known alive or Date of death” will be the latest date among:

- The date of last visit performed;
- The “Date of last known alive or Date of death” reported in the visit e-CRF pages during the course of the study;
- The “Date of last known alive or Date of death” reported at the end of the study for all patients (this information can also be completed during the course of the study for “lost-to-follow-up” patients, patients who discontinued the follow-up and patients who died);

- The latest date among these dates, the last IMP injection date, the date of adverse events, the date of CV events, the date of death and the date of laboratory samples will be considered.

In case at time of database extraction for the interim analyses, only the randomization date is available, then the censoring date will be the randomization date.

#### 3.1.3.2.1 *Main secondary endpoint(s)*

- Time from randomization to first occurrence of any CHD event (major CHD event, unstable angina requiring hospitalization, ischemia-driven coronary revascularization procedure);
- Time from randomization to first occurrence of any major CHD event (CHD death, nonfatal MI);
- Time from randomization to first occurrence of any CV event (any non-fatal CHD event, any CV death, and non-fatal ischemic stroke);
- Time from randomization to first occurrence of all-cause mortality, non-fatal MI, non-fatal ischemic stroke;
- Time from randomization to CHD death;
- Time from randomization to CV death;
- Time from randomization to death (all-cause mortality).

#### 3.1.3.2.2 *Other secondary efficacy endpoint(s)*

- Component of the primary endpoint considered individually:
  - Time from randomization to first occurrence of any non-fatal MI;
  - Time from randomization to first occurrence of fatal or any non-fatal ischemic stroke;
  - Time from randomization to first occurrence of any unstable angina requiring hospitalization.
- Time from randomization to first occurrence of any ischemia-driven coronary revascularization procedure;
- Time from randomization to first occurrence of any congestive heart failure requiring hospitalization.

### 3.1.4 **Safety endpoints**

Following injections are considered as double-blind IMP injections:

- For patients randomized in the placebo group: any injection from double-blind kits;

- For patients randomized in the alirocumab group: any injection from double-blind kits excepted placebo injections given to maintain the blind in case of 2 consecutive LDL-C values <15 mg/dL.

Of note potential additional training injections after randomization using training injection kits will not be taken into account.

The period of safety observation starts from the time when the patient gives informed consent and is divided into three periods:

- PRE-TREATMENT period: defined from the signed informed consent up to the first dose of double-blind IMP injection;
- Treatment-emergent adverse event (TEAE) period: defined as the time from the first dose of double-blind IMP injection to the last dose of double-blind IMP injection +70 days (10 weeks), (as residual effect of treatment is expected until 10 weeks after the stop of double-blind IMP).

The TEAE period will include:

- The TREATMENT period defined as the time from the first dose of double-blind IMP up to the day of last dose of double-blind IMP injection +21 days, as serum concentration of alirocumab >10 µg/mL is expected for approximately 21 days following administration of 150 mg, and because throughout the previous studies it was observed that when alirocumab concentrations declined below this concentration, decrease in effect on LDL-C is observed.
- The RESIDUAL TREATMENT defined as the time from the day of last dose of double-blind IMP injection +22 days up to the day of last dose of double-blind IMP injection +70 days (10 weeks).
- POST-TREATMENT period: defined as the time starting the day after the end of the TEAE period.

#### **3.1.4.1 Adverse events variables**

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

All adverse events will be coded to a “Lowest Level Term (LLT)”, “Preferred Term (PT)”, “High Level Term (HLT)”, “High Level Group Term (HLGT)”, and associated primary “System Organ Class (SOC)” using the version of MedDRA currently in effect at Sanofi at the time of the database lock.

#### **Adverse event observation periods**

- Pre-treatment adverse events are adverse events that developed or worsened or became serious during the pre-treatment period;

- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period;
- Post-treatment adverse events are adverse events 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, AESI 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”)
- Local injection site reactions, selected using e-CRF specific tick box on the adverse event page
- ALT  $\geq 3$  ULN (if baseline ALT <ULN) or ALT  $\geq 2$  times the baseline value (if baseline ALT  $\geq$ 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” and including selected PTs from SMQ "optic nerve disorders" (see [Appendix B Table 13](#) for the list of terms)
- Neurocognitive events:
  - Selected using a CMQ, based on the following 5 HLGs: “deliria (including confusion)”, “cognitive and attention disorders and disturbances”, “dementia and amnesic conditions”, “disturbances in thinking and perception”, and “mental impairment disorders”
  - A second grouping of terms for neurocognitive events was defined based on Regulatory Agency request (see [Appendix B Table 14](#) for the list of terms)
- Overdose of IMP (symptomatic or asymptomatic), selected using appropriate MedDRA codes and the tick box “Overdose with IMP” in the adverse event complementary e-CRF form
- Pregnancy (including partner of a randomized male subject) selected using appropriate MedDRA codes



In addition the additional grouping of events will be 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”
- New onset of diabetes (in the subgroup of patients not having diabetes at baseline) (see definition in [Section 3.4.5.3](#) )
- Cataract using HLT “Cataract conditions”

#### **3.1.4.2 Deaths**

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

- Deaths from first IMP injection until CSED:
  - Treatment-emergent deaths: deaths occurring during the TEAE period
  - Post-treatment emergent deaths
- Deaths post-CSED

#### **3.1.4.3 Laboratory safety variables**

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units. International units will be used in all listings and tables. Clinical laboratory values converted into conventional (US) units will be also available in the database. Analyses can be provided upon request.

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, calcium, phosphorus, bicarbonate;
  - **Renal function:** creatinine, eGFR, blood urea nitrogen, uric acid;
  - **Liver function:** alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase ( $\gamma$ GT), lactate hydrogenase (LDH), total bilirubin, and in case of total bilirubin values above the normal range, must include direct and indirect bilirubin (used for describing individual cases only);
  - **Hepatitis screen:** anti-hepatitis-C antibody.

Technical formulas are described in [Section 3.5.1](#).

#### **3.1.4.4 Vital signs variables**

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

#### **3.1.4.5 Electrocardiogram variables**

Electrocardiograms were recorded automatically by the device at the Investigator site.

Electrocardiogram assessments will be described as normal or abnormal.

#### **3.1.5 Other endpoints**

Other assessment endpoints defined below are exploratory.

##### **3.1.5.1 Lipid parameters**

The lipid parameters include values (in conventional [US] and international units), percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units) over time for the following parameters: LDL-C, TC, HDL-C, fasting TGs, non-HDL-C, Apo A-1, Apo B, ratio Apo B/Apo A-1, Lp (a), ratio TC/HDL.

All these parameters are measured or calculated by a central laboratory, for both scheduled and unscheduled time points. For LDL-C analysis, both calculated and measured LDL-C values will be taken into account. In case both calculated and measured LDL-C are provided for the same sampling, the measured LDL-C will be considered. Calculated LDL-C is obtained using the Friedewald formula. Non-HDL-C is calculated by subtracting HDL-C from the TC.

Unless otherwise specified, all central measurements (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for each timepoint, even if assessed after treatment discontinuation (intent-to-treat [ITT] approach). The analysis windows used to allocate a measurement to a time point are defined in [Section 3.5.4](#). For TG, only fasting measurements will be used. Measurements with missing fasting status will be excluded from the analyses.

For all time points post-baseline, the value used for the analyses at a given time point (eg, at Month 24) is the value obtained within the corresponding analysis window. The baseline value is the last available measurement obtained up to the date and time of the first double-blind IMP injection. For patients randomized and not treated, the baseline value is defined as the last available value obtained up to the date and time of randomization.

Percent changes from baseline to a timepoint are defined as:  $100 \times (\text{parameter value at the time point} - \text{parameter value at baseline}) / \text{parameter value at baseline}$ .

Data handling conventions for other endpoints are described in [Section 3.5](#).

### **3.1.5.2 hs-CRP**

The percent change in hs-CRP from baseline over time is defined using same definitions and rules as for LDL-C, when applicable (see section above). 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 (2).

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

### **3.1.5.3 HbA<sub>1c</sub>**

The absolute change in HbA<sub>1c</sub> (%) from baseline over time: same definitions and rules as for LDL-C (see [Section 3.1.5.1](#)).

### **3.1.5.4 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 double-blind treatment period
- The time to the first LDL-C <25 mg/dL (respectively LDL-C <15 mg/dL) for these patients.

In case both calculated and measured LDL-C are provided for the same sampling, the measured LDL-C will be considered.

### **3.1.5.5 Anti-alirocumab antibodies assessed throughout the study.**

Anti-alirocumab antibodies (ADAs) are assessed at Visit 3 (Month 0), Visit 5 (Month 2), Visit 6 (Month 4), and Visit 10 (Month 12) for the first year, then every year and at the final on-treatment visit (CSED visit for completers, or early end of treatment visit for patients who discontinued the treatment).

ADA measurements will be assigned to analysis windows as defined in [Section 3.5.4](#).

The following variables will be described:

- ADA response (Positive or Negative). For ADA positive:
  - Titer levels
  - Neutralizing status (Positive or Negative)
- Pre-existing positive ADA defined as patients with positive ADA response at baseline with less than 4-fold increase in titer in the post-baseline period
- Treatment-emergent positive ADA response defined as 1) Patients with no ADA positive response at baseline but with any positive response in the post-baseline period (up to follow-up visit) or 2) Patients with a positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period (up to follow-up visit). For treatment-emergent positive ADA, the following categories for ADA duration will be applied:
  - A persistent positive response is a treatment-emergent ADA positive response detected in at least 2 consecutive post-baseline samples separated by at least a 16-week period
  - An indeterminate duration positive response is defined as ADA present only at the last sampling time point
  - A transient positive response is defined as any treatment-emergent positive ADA response that is neither considered persistent nor indeterminate

In addition, potential ADA samples that are to be collected after CSED visit for patients with titer  $\geq 240$  at CSED visit will be listed.

### **3.1.5.6 Quality-of-life parameters**

EQ-5D™ is a standardized and generic instrument for measuring the health status and health related quality of life for clinical and economic assessment (3). EQ-5D instrument includes 5 items corresponding to the following dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression ([Appendix D](#)). 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 -0.594 (representing severe problems) and 1 (representing no problem): the single index utility score, using a regression model (4) ([Appendix E](#)). If response to one or more dimension is missing, the utility score will be missing.

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

### **3.1.5.7 Cardiovascular events of interest (other than efficacy endpoints)**

Cardiovascular events of interest (other than efficacy endpoints) include clinically significant complications or procedures (not planned at the time of randomization), related to peripheral arterial disease and venous thromboembolic events as listed below:

- Venous thromboembolic events of interest:
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Lower extremity peripheral arterial disease events of interest:
  - Peripheral lower limb revascularization (endovascular revascularization, surgical revascularization)
  - Critical limb ischemia (including ischemic imputation of lower limb for the event)

The following variables will be analyzed:

- Time from randomization to first occurrence of any other CV events of interest (venous thromboembolic events or lower extremity peripheral arterial disease events)
- Time from randomization to first occurrence of any venous thromboembolic events (DVT or PE)
- Time from randomization to first occurrence of any lower extremity peripheral arterial disease events (peripheral lower limb revascularization or critical limb ischemia)

### **3.1.6 Pharmacokinetic variables**

Not applicable.

### **3.1.7 Pharmacogenomics endpoints**

Pharmacogenetics endpoints and analyses will be detailed in a separate SAP.

### 3.2 DISPOSITION OF PATIENTS

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

Screened patients are defined as any patient who met the ACS inclusion criteria and signed the informed consent (ie, patients entering the run-in phase).

Randomized patients consist of all screened patients, with a double-blind treatment kit number allocated and recorded in the interactive voice response system (IVRS)/ interactive web response system (IWRS) database, regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a double-blind treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population.

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

- Screened patients;
- Screened failure patients and reasons for screen failure;
- Non-randomized but treated patients, if any;
- Randomized patients;
- Randomized but not treated patients and reason for not being treated;
- Randomized and treated patients;
- Patients who completed the double-blind study treatment period as per protocol (as per e-CRF end-of-treatment form);
- Patients who did not complete the double-blind study treatment period as per protocol (as per e-CRF end-of-treatment form);
- Patients who discontinued the double-blind study treatment by main reason for permanent treatment discontinuation (as per e-CRF end-of-treatment form);
- Status at last study contact.

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

Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. For blinded discontinuation due to low LDL-C level (patients who switched to placebo in blinded manner), the reason reported by the investigator will be reclassified as “2 consecutive LDL-C <15mg/dL (<0.39 mmol/L)”.

Number (%) of patients who discontinued the follow-up for CV events will be summarized over time. The main reason for study discontinuation will be summarized overall and according to whether or not the patients had a primary efficacy endpoint confirmed by CEC prior study discontinuation.

A patient will be considered as having discontinued the follow-up for CV events if the date of the last information on efficacy endpoints (presence or absence) is before the common study end date.

Kaplan-Meier plots/estimates of the cumulative incidence of premature IMP treatment discontinuation due to any reason, or due to adverse event will be provided on randomized population. Not treated patient will be considered with event at Day 1 (day of randomization). All completers will be considered as right-censored observations. Time to premature IMP treatment discontinuation and censoring time will be defined as: Date of last IMP injection – Date of randomization + 14 days.

All 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. These deviations are listed in the data review and surveillance plan.

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

- Randomized population;
- Efficacy population: intent-to-treat (ITT) population;
- Safety population;
- Anti-alirocumab antibody population.

Definition of the study populations are provided in [Section 3.3](#).

### **3.2.1 Randomization and drug dispensing irregularities**

Randomization and drug-dispensing irregularities occur whenever:

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

OR

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

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

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

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

**Table 5 - Randomization and drug allocation irregularities**

---

|   |
|---|
| Kit dispensation without IVRS/IWRS transaction  |
| Erroneous kit dispensation  |
| Patient randomized twice  |
| Stratification error  |
| A kit allocated at Day 1 or any unscheduled replacement before the up-titration visit (it may be the Month 2 or the Month 4 visit) is administered to the patient after the up-titration visit <sup>a</sup> |
| A kit allocated at any visit or unscheduled replacement from the up-titration visit, is administered to the patient after the next scheduled reallocation visit <sup>a</sup>                                |

---

a Only if dose received is different from the one expected as per IVRS/IWRS allocation

### 3.3 ANALYSIS POPULATIONS

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

Randomized population: includes all randomized patients as defined in [Section 3.2](#).

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.

#### 3.3.1 Efficacy populations

##### 3.3.1.1 Intent-to-treat population

The primary efficacy analysis population will be the intent-to-treat (ITT) population, consisting of all randomized patients. Patients in the ITT population will be analyzed according to the treatment group allocated by randomization.



### 3.3.2 Safety population

The Safety population considered for safety analyses will be the randomized patients who actually received at least 1 dose or part of a dose of the double-blind IMP injection. Patients will be analyzed according to the treatment actually received (ie, as-treated treatment group, placebo or alirocumab).

In addition:

- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population in the treatment group as randomized;
- For patients receiving double-blind IMP injection from more than one treatment group during the trial (cases reported as protocol deviation), the treatment group used for as-treated analysis will be the one to which the patient was treated with the highest number of injections; in case of the same number of injections of each treatment is received, the as-treated treatment group will be the as-randomized group.

### 3.3.3 Anti-alirocumab antibody population

The ADA analysis will be performed on all randomized and treated patients (safety population) with an available ADA sample at Day 1 (baseline) and at least 1 available ADA sample post first double-blind IMP injection.

## 3.4 STATISTICAL METHODS

### 3.4.1 Demographics and baseline characteristics

Parameters described in [Section 3.1.1](#) will be summarized by treatment group and overall using descriptive statistics.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. First quartile (Q1) and third quartile (Q3) will be also provided for baseline lipid parameters, HbA<sub>1c</sub>, and 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 analyzed in the treatment group to which they were randomized. Similar analyses will be done on the safety population and will be included in the appendices if the size of the safety population is different (>10%) from the size of the randomized population for any treatment group. In the randomized population, parameters will also be summarized within each region.

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

The diagnosis of diabetes mellitus at baseline (see also [Section 3.1.1](#) for definition), as well as the source of diagnosis will be summarized in the randomized and safety populations by treatment group and overall, using the following mutually exclusive categories:

- From medical history or pre-treatment adverse events
- From anti-diabetic medications regardless of laboratory data (if no medical history of diabetes)
- From laboratory data only (if no medical history of diabetes and no anti-diabetic medications)

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.

#### **3.4.2 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 anatomical therapeutic chemical (ATC) class (anatomical 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 (anatomical or therapeutic) linked to the medication. Therefore patients may be counted in several categories for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomical 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 (anatomical or therapeutic categories), alphabetical order will be used. In addition all medications of specific interest will be presented by treatment group.

The number and percentage of patients that took any statin for at least 3 months prior to the index ACS event (as reported on the e-CRF page "Additional statin information") will be displayed by treatment group.

The background lipid modifying therapy regimen at randomization will be summarized using the following categories:

- High dose atorvastatin/rosuvastatin (defined as daily atorvastatin 40 to 80 mg, or rosuvastatin 20 to 40 mg)
- Low/moderate dose atorvastatin/rosuvastatin (defined as daily atorvastatin <40 mg, or rosuvastatin <20 mg)
- Statin other than atorvastatin or rosuvastatin, at any dose
- Only LMT other than statin
- No LMT

The reason for not being on high dose at randomization will be supplied in tables giving numbers and percentages by treatment group.

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

For atorvastatin and rosuvastatin, the dose (in mg) will be also displayed by treatment group.

- Atorvastatin daily dose in mg (10, 20, 40, 80, Other);
- Rosuvastatin daily dose in mg (5, 10, 20, 40, Other);

The LMT other than statins will be summarized by pre-specified categories, chemical class or therapeutic class, and standardized medication name.

In addition the number (%) of patients in the following background LMT categories at randomization will be displayed:

- Ezetimibe and high dose atorvastatin/rosuvastatin
- Ezetimibe and low/moderate dose atorvastatin/rosuvastatin
- Ezetimibe and statin other than atorvastatin or rosuvastatin
- Ezetimibe and other LMT other than statin
- Only ezetimibe

LMT (statins and other LMTs) used after randomization during the study will be summarized over time graphically by treatment group and LMTs intensity at randomization using the following mutually exclusive categories:

- High dose atorvastatin/rosuvastatin
- Low/moderate dose atorvastatin/rosuvastatin
- Statin other than atorvastatin or rosuvastatin
- Only LMT other than statin
- No LMT

The reason for first modification in statin regimen after randomization will be also described.

The use of ezetimibe after randomization during the study will be also summarized over time graphically by treatment group.

The number (%) of patients initiating ezetimibe after randomization will be also displayed according to background LMT status at randomization.

### **3.4.3 Extent of investigational medicinal product exposure and compliance**

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

Double-blind IMP kits contain the following:

- Placebo for the ones administered to patients randomized in the placebo group
- 75 or 150 mg of alirocumab

Placebo injections administered to patients randomized in the alirocumab following 2 consecutive LDL-C <15 mg/dL will not be considered as double-blind IMP injections in the statistical analyses.

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

The total exposure will be assessed by:

- Duration of IMP exposure in months defined as: (last dose of double-blind IMP injection date + 14 – first dose of double-blind IMP injection date) / 30.4375, regardless of intermittent discontinuations (see [Section 3.5.3](#) for calculation in case of missing or incomplete data). Non-integer values will be rounded to one decimal place;
- The total number of double-blind IMP injections by patient;

In addition the duration of the observation period in months will be analyzed. The duration of observation period is defined as: (last contact date – randomization date+1)/30.4375. Non-integer values will be rounded to one decimal place.

These parameters will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, the durations of treatment exposure and observation period will be presented according to the following categories: <2, ≥2 to <6, ≥6 to <12, ≥12 to <24, ≥24 to <36, ≥36 to <48, ≥48 to <60, ≥60 months. The total number of double-blind IMP injections by patient will be presented similarly using the following categories: <4, ≥4 to <13, ≥13 to <26, ≥26 to <39, ≥39 to <52, ≥52 to <65, ≥65 to <78, ≥78 to <104, ≥104 to <120, ≥120.

Additionally, the cumulative exposure will be provided in patient years.

### ***Titration***

The following summaries will be provided in the alirocumab group:

- The number (%) of patients with an up-titration to 150 mg, overall and according to the time of up-titration (ie, Month 2 and Month 4)
- The number (%) of patients with an up-titration followed by a down-titration to 75 mg
- The number (%) of patients with a switch to placebo
- The number (%) of patients on 75 mg, 150 mg, placebo over time (intermittent discontinuations won't be taken into account)

Cumulative exposure in patient-year by dose level (75 mg, 150 mg, placebo) will be provided, not taking into account intermittent discontinuations.

#### **3.4.3.2 Compliance**

Compliance will be assessed using the 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).

Cases of overdose (ie, 2 or more injections from the double-blind treatment kit are administered in <7 calendar days) will be summarized by treatment group. More generally, dosing irregularities are defined in [Section 3.2.1](#).

#### **3.4.4 Analyses of efficacy endpoints**

All efficacy analyses will be performed based on ITT approach that will include events occurring from randomization to the analysis cut-off date for interim analysis or CSED for the final analysis, even after the patient has discontinued the study treatment. Any CV endpoint events occurring after the cut-off date/CSED will not be included in the analyses, regardless of the adjudication status. These events, if any, will be reported in a listing separately.

##### **3.4.4.1 Analysis of primary efficacy endpoint(s)**

The analysis of the primary efficacy endpoint will be the comparison between the two treatments using a log-rank test stratified by region (North America, South America, Western Europe, Eastern Europe, Asian, Other). The randomization is stratified by country but since the number of events per individual country is expected to be low (about 50 countries), the analysis will be stratified according to a grouping of countries into regions.

This primary comparison will be the 1-sided test (at 0.0249 type 1 error for the final analysis) of the following hypotheses at the final analysis:

$$H_0: HR \geq 1 \text{ versus } H_1: HR < 1$$

The estimates of the HR and corresponding confidence interval (CI) at  $(1-2\alpha)\%$  level ( $\alpha$  being the 1-sided significance level:  $\alpha=0.0249$  at final analysis,  $\alpha=0.0001$  at second interim analysis) will be provided using a Cox Proportional Hazard model stratified by region. The underlying assumption of proportional hazards for Cox model will be checked by visual inspection of Kaplan-Meier plots. If proportionality is not observed, sensitivity analyses will be performed. In particular, the results will be presented by yearly intervals: the number of events per 100 patient-years for each yearly interval will be provided for each treatment group as well as the ratio of the two event rates. In addition, between-treatment cumulative rate ratios based on the Kaplan-Meier estimates and the corresponding 95% CIs) will be provided at yearly interval.

The cumulative incidence rate over time (at 6 months and by year) together with appropriate interval will be estimated by treatment group using Kaplan-Meier estimates.

Reasons for censoring (including patient who died before the cut-off date/CSED for other reason than CHD, lost to follow-up) will be summarized. For patients censored before the cut-off date/CSED, time from last contact when information on efficacy endpoints has been retrieved to cut-off date will be summarized.

### ***Interim analyses***

Two interim analyses will be performed. See [Section 4](#) for description of these analyses. The cut-off dates of final (ie, CSED) and interim analyses are expected to be:

- First interim analysis date (futility): when 807 patients have experienced at least 1 primary efficacy event (50% fraction information);
- Second interim analysis date (futility and overwhelming efficacy): when 1210 patients have experienced at least 1 primary efficacy event (75% fraction information);
- Final analysis date: when 1613 patients have experienced at least 1 primary efficacy event or 24 months after the last date of randomization ex-China, whichever comes last.

### ***Sensitivity analyses***

The following sensitivity analyses will be performed:

#### Primary efficacy endpoint as per investigator

A sensitivity analysis of the primary efficacy endpoint will be performed including any events up to the CSED with final diagnosis by the investigator confirming the event, whether or not confirmed by the CEC. The statistical methodology used will be the same as defined for the primary efficacy analysis.

Since Investigators are requested to report any UA regardless of whether the event fulfils the stricter protocol definition or not, a subset of the reported UA will be selected using information reported on the e-CRF on hospitalization forms, additional information reported on the UA form related to ECG findings, need for revascularization procedure, and/or the concomitance of elevation of cardiac biomarkers (see [Appendix C](#) for full details). Since the categorization of deaths as CHD death was not requested from the Investigator, CHD deaths as per Investigator will include all deaths with primary cause of death reported as “Acute myocardial infarction”, “Sudden cardiac death”, “Heart failure or cardiogenic shock” as per investigator. The category “Undetermined cause of death” as per Investigator will be also included in this endpoint.

The concordance rate between Investigator opinion and adjudication by the CEC will be provided for all CV events adjudicated, by CV event’s type.

#### Primary endpoint analysis excluding undetermined causes of death and undetermined causes of stroke

The primary efficacy analysis will be also performed excluding deaths adjudicated as “undetermined causes of death” and strokes adjudicated as “undetermined causes of stroke” by the CEC.

#### ***Supportive analyses***

The primary efficacy outcome will be analyzed on randomized and treated patients considering only events that occurred during the treatment period (ie, from the first double-blind IMP injections to the last double-blind IMP injections +21 days, or up to the date of the CSED, whichever comes first), using the same statistical methodology as for the primary efficacy analysis. If a patient does not have a primary endpoint during the treatment period, the patient will be right-censored at the date of last contact when information on efficacy endpoints (presence or absence) has been retrieved, or at the date of death, or at the CSED or at the date of last double-blind IMP injection +21 days, whichever comes first.

Analysis on all events (ie, including recurrent events after the primary efficacy endpoints) will be also performed. Risk ratios between treatments groups will be estimated by Andersen-Gill (4) mean intensity model and the robust sandwich estimate of Lin and Wei (5) for the covariance matrix. Cumulative mean function and 95% CI in each treatment group will be calculated using Nelson-Aalen estimate.

#### ***Subgroup analyses***

The consistency of the treatment effect on primary efficacy outcome will be evaluated with respect to the following demographic/baseline characteristic and prognostic factors:

- Gender;
- Age group (<65, ≥65);
- Race (Caucasian, Black, Asian/Oriental, and Other, as appropriate);
- Country (IVRS stratum, depending of the size of subgroups);

- Region (USA/Non-USA, and North America/South America/Eastern Europe/Western Europe/Asia/Rest of world);
- Time from ACS event to randomization (eg,  $\leq 24$  weeks,  $>24$  weeks).

For each factor except the region, a Cox proportional hazard model will be used, including the treatment, the region, the factor, and the treatment-by-factor interaction terms as covariates. Within each selected factor, the treatment effect hazard ratio and its CI will be estimated from this Cox model. P-values of interaction will be also provided. Results will be plotted using forests plot. The treatment effect by region will be estimated using the similar, Cox proportional model with treatment, region, and treatment-by-region interaction as the covariates.

In addition, Kaplan-Meier curves and summary statistics showing number of patients, number (%) of primary efficacy outcome events, cumulative incidence of events at 6 months and by year, and appropriate CI may be provided for each treatment arm in previously selected subgroups defined above.

In addition, the effect of the time from ACS to randomization (in weeks) will be assessed using a Cox Proportional Hazard model including the time from ACS event (continuous) as a covariate, the treatment group and the interaction.

In addition, homogeneity of treatment effect in the following subgroups will be explored (providing sufficient number of events per subgroups):

- BMI ( $<30$ ,  $\geq 30$  kg/m<sup>2</sup>)
- Age ( $<65$ ,  $\geq 65$  to  $<75$ ,  $\geq 75$ )
- Ethnicity (hispanic or latino/not hispanic nor latino)
- Statin treatment at randomization in three categories (high dose atorvastatin/rosuvastatin; any other statin [ie, low/moderate doses of atorvastatin/rosuvastatin, any dose of other statins]; no statin)
- Diabetes mellitus status at baseline (diabetes, pre-diabetes/ normoglycemic)
- Diabetes mellitus status at baseline (diabetes, pre-diabetes, normoglycemic)
- Baseline LDL-C ( $<80$ ,  $\geq 80$  to  $<100$ ,  $\geq 100$  mg/dL)
- Index ACS event (STEMI, NSTEMI, UA)
- Prior stroke
- Baseline non-HDL-C ( $<110$ ,  $\geq 110$  to  $<130$ ,  $\geq 130$  mg/dL)
- Baseline Apo B ( $<75$ ,  $\geq 75$  to  $<90$ ,  $\geq 90$  mg/dL)
- Baseline Lp (a) ( $<50$ ,  $\geq 50$  mg/dL)
- Baseline hs-CRP ( $<2$ ,  $\geq 2$  mg/L)



#### **3.4.4.2 Analyses of secondary efficacy endpoints**

Method for controlling the overall type-I error rate when testing the main secondary efficacy endpoints is described in [Section 3.4.4.3](#).

Secondary endpoints will be analyzed using the same statistical methodology as for the primary endpoint.

#### **3.4.4.3 Multiplicity issues**

In order to handle multiple main secondary endpoints, the overall type-I error will be controlled by the use of a sequential inferential approach. Statistical significance of the primary endpoint is required before drawing inferential conclusions about first main secondary endpoint (at the 0.0001 1-sided alpha level at the second interim analysis or at the 0.0249 1-sided alpha level at the final analysis). Inferential conclusions about successive main secondary parameters require statistical significance of the prior one. The order of tests is detailed in [Section 3.1.3.2.1](#).

This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the required 1-sided level (0.0001 for the second interim analysis and 0.0249 at the final analysis).

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

#### **3.4.4.4 Additional efficacy analyses**

Additional efficacy analyses, endorsed by the steering committee, may be defined in an exploratory SAP, before the unblinding of the treatment code. In particular the relationship between lipid lowering effects and the outcome of cardiovascular efficacy endpoints will be assessed.

Additional analyses will be performed to explore if the randomized treatment effects on cardiovascular efficacy endpoints are statistically different before and after a specified timepoint (e.g. 0-1 year vs. >1 year). These analyses will be performed with Cox proportional hazard models. Specifically, for a given endpoint, the model fit that allows the treatment HR to vary before and after the specified timepoint (with adjustment for region) will be compared to the corresponding model where the treatment HR is not allowed to vary over time.

#### **3.4.5 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 3.3.2](#), unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (ie, exposed but not randomized) will be listed separately;
- The baseline value is defined as the last available value before first double-blind IMP injection, except otherwise specified;
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (see [Appendix A](#)). In case the PCSA threshold is within the normal laboratory ranges, the analysis will be done using “<LLN” or “>ULN” threshold instead of “<PCSA threshold” or “>PCSA threshold” respectively. Of note, for HbA<sub>1c</sub>, usual PCSA criteria will not be applied as specific analysis for the incidence of diabetes during the TEAE period will be provided, combining information from adverse event, laboratory parameters, and antidiabetic medications (see detail in [Section 3.4.5.3](#)).
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during this period, including nonscheduled, local 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 3.5.4 Table 8](#).
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit (using analysis windows defined in [Section 3.5.4 Table 8](#)) and treatment group. 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.
- For exploratory purpose, safety analyses could also be provided according to up-titration status, ie, according to whether the patients remained on the 75 mg dose or whether they were up-titrated to 150 mg. These analyses will be exploratory and descriptive (no formal comparison per dose) as it is expected that there could be inherent differences in the baseline characteristics between those patients titrating to 150 mg and those remaining on 75 mg. In order to reduce the bias of this analysis, the period before the up-titration for patients up-titrated and the period before the first up-titration time point (ie, Month 2) for patients not up-titrated will not be included in the analysis since only the dose 75 mg is proposed for this time period and consequently the early events can only be attributed to

this dose. Therefore the descriptive analysis per dose will include any safety events occurring from the first injection post up-titration time point IVRS/IWRS transaction to the end of the TEAE period or to 70 days after down-titration to 75 mg (if any), whichever comes first. Event-rate per patient-year will also be provided after up-titration time point to take into account variable duration of exposure.

- Analyses performed according to diabetes mellitus status at baseline will be done using the definition provided in [Section 3.1.1](#).

### **3.4.5.1 Analyses of adverse events**

#### ***Generalities***

The primary focus of adverse event reporting will be on TEAEs. Pre- and post-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in [Section 3.5.3](#).

Adverse event incidence tables will present by SOC, HLG, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. 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 should ensure the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the alirocumab group.

As recommended by the safety planning, evaluation, and reporting team (SPERT, [6]) the analysis of all TEAEs will be split into 3 tiers for signal detection and analysis of adverse events.

- Tier 1: TEAEs with pre-specified detailed analysis: TEAEs for which hypothesis and comprehensive analytical approach are prospectively defined.
- Tier 2: signal detection among common TEAE: (not prespecified).
- Tier 3: descriptive analysis of infrequent TEAEs: TEAEs which are infrequent. This could include some AESI predefined in the protocol (eg, pregnancy, hemolytic anemia) to ensure close monitoring but which are expected to be so rare that statistical analysis is not meaningful. For those events, medical judgment should prevail.

### ***Prospective analysis for Tier 1 events***

Tier 1 events will include the AESIs and grouping of adverse events as defined in [Section 3.1.4.1](#). Some of these events may be analyzed as Tier 3 in case their occurrence is infrequent. For each selected Tier 1 event, comprehensive analytic approach will be conducted, as described below, in order to evaluate whether the incidence is higher in the alirocumab group versus the placebo group.

#### Descriptive summaries of Tier 1 events

The number (%) of patients with an event in the TEAE period will be summarized in each treatment group: 95% CIs of the incidence rate (%) will be provided (CI calculated using the mid-p method) for each Tier 1 grouping of terms. The event rate per 100 patient-years (the number of patients with an event in question divided by total 100 patient-years), as well as 95% CI will be also provided. For a patient with an event, patient year is censored at time of first event; for patient without event, it corresponds to the length of the TEAE period. If the event is defined as a grouping of terms, the table will be presented by SMQ/CMQ and PT (when selection is based on SMQ/CMQ) and by PT (when selection is based on the e-CRF tick box or HLG/HLT), showing the number (%) of each PT included in the grouping of terms. The summaries will be sorted by decreasing incidence of PT within each SMQ/CMQ (in the alirocumab group). In addition, above description will be provided according to diabetes mellitus status at baseline for the diabetes mellitus or diabetic complications grouping.

An overview of each Tier 1 TEAE will be also provided in each treatment group: number (%) of TEAE, of treatment-emergent SAE, of TEAE leading to death and of TEAE leading to permanent treatment discontinuation. In addition, a summary of the following characteristics at grouping level will be provided: the severity grade (mild, moderate, severe), the outcome (Recovered/Resolved, Recovering/Resolving, Unknown, Recovered/Resolved with sequelae, Stabilized, Not recovered/Not Resolved, Fatal), the seriousness, the outcome status of Tier 1 TEAE leading to premature treatment discontinuation. In addition, summary by SMQ/CMQ and PT will be provided for serious TEAEs and TEAEs leading to permanent treatment discontinuation.

Time to liver-related treatment discontinuation and time to liver death may also be provided using hepatic disorder SMQ.

#### Additional statistical analyses for Tier 1

In order to compare treatment groups, the hazard ratio (HR) will be provided together with the corresponding 95% CI. Hazard ratio will be calculated using a Cox model. Patient without any event will be censored at the end of the TEAE period.

Kaplan-Meier curves for time from first dose of double-blind IMP to the first occurrence of Tier 1 TEAE will be provided for each Tier 1 (grouping of terms). Patient without any event will be censored at the end of the TEAE period.

In addition, HR and Kaplan-Meier curves and estimates will be provided according to diabetes mellitus status at baseline for the diabetes mellitus or diabetic complications grouping.

To assess the homogeneity of the treatment effect across age groups (<65 years versus  $\geq 65$  years, and <75 years versus  $\geq 75$  years), the treatment-by-age interaction will be tested in a Cox model including the age factor term and the treatment-by-age interaction term. Hazard ratio and the corresponding 95% CI within each age subgroup (calculated using a Cox model), as well as the significance level of the treatment-by-age interaction term will be also provided for descriptive purpose.

#### Additional summaries for local injection site reaction

The following description of local injection site reaction will be tabulated:

- Number of local injection site reaction per patient: 1, >1;
- Mean duration;
- Number of events divided by the number of double-blind IMP injections received;
- Time from first double-blind IMP injection to first local injection site reaction;
- Number of double-blind IMP injections received up to the first event;
- Intensity of the event (mild, moderate, severe);
- Description of the highest intensity of each symptom recorded in the specific e-CRF page.

#### ***Analysis of all “common” TEAE(s) - Tier 2 events***

“Common” events are defined as those for which there are more (>) than n patients with an event overall in the safety population. This threshold will be defined as the number of patients with events (n) observed overall (whatever the treatment group) for which the extreme case scenario (n for alirocumab versus 0 for the placebo) doesn't allow the p-value to be less than 0.05.

All common TEAEs (by HLT and PT), showing the number (%) of TEAE, the event rate per 100 patient-years, HR (estimated using a Cox model) with the corresponding 95% CI, sorted by decreasing incidence rate in alirocumab group in one table, and by decreasing HR in the another table, will be analyzed.

If any clinically significant signal is detected and need further characterization, additional analyses similar to Tier 1 analyses, will be provided.

#### ***Descriptive analysis of infrequent adverse events – Tier 3 events***

All infrequent TEAEs (Tier 3) will be reported with descriptive statistics (n, %) and event rate per 100 patient year, without comparative statistics since with so rare event statistical comparisons are not meaningful and medical judgment should prevail.

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

The following TEAE summaries, including all TEAEs (common or not, Tier 1 or not) will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any:
  - TEAE;
  - Serious TEAE;
  - TEAE leading to death;
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT, sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order;
- All TEAEs regardless of relationship and related to IMP by primary SOC, HLGT, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order;
- All TEAEs regardless of relationship and related to statin/other lipid lowering drug by primary SOC, HLGT, HLT, and PT, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order;
- 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 event rate per 100 patient-years (the number of patients with an event in question divided by total patient-years) will be provided for all TEAEs by SOC and PT. For a patient with event, patient-year is censored at time of first event; for patient without event, it corresponds to length of TEAE period;
- All TEAEs that occurred with HLT and PT incidence  $\geq 2\%$  in alirocumab group and at incidence at least 0.5% higher in alirocumab than placebo, by primary SOC, HLT, and PT;
- All TEAEs that occurred with incidence  $\geq 5\%$  in any treatment group, by primary SOC and PT, with event rate per 100 patient-years;
- All TEAEs by maximal severity (ie, mild, moderate, or severe), presented by primary SOC and PT.

### ***Subgroup of patients with 2 consecutive LDL-C <25 mg/dL (<0.65 mmol/L)***

A 2-step approach will be used to analyze the safety in relation to low LDL-C.

The first step will screen events for potential signal using 2 approaches. The first approach will be a direct comparison of patients with 2 consecutive LDL-C <25 mg/dL versus  $\geq 25$  mg/dL (ie, patients without 2 consecutive LDL-C <25 mg/dL) within the alirocumab treatment group. Since these 2 groups are based on post-randomization data with a potential for bias, a second approach will compare the alirocumab effect versus placebo according to categories based on baseline LDL-C. The frequency of patients with 2 consecutive LDL-C <25 mg/dL is expected to be the largest in the category with the lowest baseline LDL-C and be lower and lower in the categories with higher baseline LDL-C. Therefore, an event induced by low LDL-C should be associated with a higher alirocumab effect versus placebo (ie, higher HR) in the first baseline LDL-C category(ies) than in the subsequent categories. Details of these 2 approaches are provided below.

The second step will consist in the comparison of patients with 2 consecutive LDL-C <25 mg/dL versus  $\geq 25$  mg/dL within the alirocumab group for the events detected in the first step, as well as for pre-specified events.

Similar analyses will be provided considering 15 mg/dL (0.39 mmol/L) as threshold instead of 25 mg/dL.

#### First step

##### *First screening approach*

TEAE summary by primary SOC, HLGT, HLT, and PT as well as groupings of events (ie, cataract, neurological events, neurocognitive disorders and “new onset of diabetes” [see [Section 3.4.5.3](#) for the definition]) will be provided on the safety population in the groups below:

- Placebo group
- Alirocumab group
- Alirocumab LDL-C  $\geq 25$  mg/dL (ie, alirocumab patients without 2 consecutive LDL-C <25 mg/dL)
- Alirocumab patients with 2 consecutive LDL-C <25 mg/dL

For patients with 2 consecutive LDL-C <25 mg/dL, analyses will be done on the period starting from the first of the 2 consecutive LDL-C lower than 25 mg/dL to the upper limit of the TEAE period excepted for patients down-titrated from 150 mg to 75 mg for whom the analysis period will end at the date of last injection of 150 mg +70 days (as patients down-titrated from 150 mg to 75 mg are likely to come back above 25 mg/dL).

The time to the first TEAE/event will be compared for patients with 2 consecutive LDL-C <25 mg/dL versus  $\geq 25$  mg/dL, within the alirocumab group, using a Cox model, including the covariate for 2 consecutive LDL C <25 mg/dL (Yes/No). Hazard ratio (and 95% CI) from this model will be provided. The event rate per 100 patient-years (the number of patients with an event in question divided by total 100 patient-years) will also be provided.

### *Second screening approach*

TEAE summary by primary SOC, HLGT, HLT, and PT as well as groupings of events (ie, cataract, neurological events, neurocognitive disorders and “new onset of diabetes” will be provided on the safety population according to baseline LDL-C categories (eg, <70,  $\geq 70$  to <90,  $\geq 90$  to <110,  $\geq 110$  mg/dL).

Hazard ratio (and 95% CI) for alirocumab effect versus placebo within each baseline LDL-C subgroup will be provided using a Cox model with baseline LDL-C (in categories), treatment group and the treatment-by-baseline LDL-C interaction term.

To assess the impact of baseline LDL-C on hazard ratio, a Cox model including the baseline LDL-C (as continuous factor), treatment group and treatment-by-baseline LDL-C interaction term will be used. The p-value from the interaction term will be provided for descriptive purpose to evaluate if there is a potential relationship between baseline LDL-C and hazard ratio.

### Second step

For each pre-specified event (cataract, neurological events, neurocognitive disorders, new onset of diabetes) as well as for each event with a potential signal detected in the first step, the time to the first TEAE/event will be compared for patients with 2 consecutive LDL-C <25 mg/dL versus  $\geq 25$  mg/dL, within the alirocumab group, using a Cox model, including the covariate for 2 consecutive LDL-C <25 mg/dL (Yes/No) and prognostic factors of the event analyzed. Adjusted HR (and 95% CI) from this model will be provided.

The list of prognostic factors will be established based on the literature and on study data (as applicable).

### ***Subgroups of patients with treatment-emergent ADA positive response***

All TEAEs by primary SOC, HLGT, HLT, and PT as well as local injection site reactions will be described in the alirocumab group according to the following ADA parameters:

- Treatment-emergent ADA positive response (yes/no)
- Persistent/transient/indeterminate treatment-emergent ADA positive response.



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

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

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

### ***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.

#### **3.4.5.2 Deaths**

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

- Number (%) of patients who died from the first IMP injection until CSED and reasons for death as adjudicated by the CEC;
- Deaths occurring after CSED (adjudicated or not);
- 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 sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC;

- All post-treatment adverse events leading to death by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC;
- In addition, deaths in non-randomized patients or randomized but not treated patients will be displayed.

### **3.4.5.3 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 diabetes 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 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 diabetes 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.

PCSA summaries will also be provided in patients from alirocumab group with 2 consecutive LDL-C  $< 25$  mg/dL in case a signal detected in the adverse events analyses (see [Section 3.4.5.1](#)) warrants further investigations. Only PCSA occurring after the first occurrence of LDL-C  $< 25$  mg/dL will be considered (see [Section 3.4.5.1](#), sub-section “Subgroup of patients with two consecutive LDL-C  $< 25$  mg/dL ( $< 0.65$  mmol/L)” for the definition of the analysis period).

### ***Analysis of new onset of diabetes (NOD)***

The incidence of new onset of diabetes during the TEAE period will be analyzed in the subgroup of patients not having diabetes at baseline as well as in the subgroups of patients with pre-diabetes and normal glycemic at baseline (see [Section 3.1.1](#)). New onset diabetes will be defined as follows, combining information from adverse events, medication, and laboratory parameters:

- Type 1 or 2 diabetes TEAE (CMQ "Type 1 or type 2 diabetes", [Table 11](#)).
- And/or anti-diabetic medication initiated during the TEAE period with a confirmed diagnosis per the external diabetes experts\*.

\* Patients classified as NOD based only on the use of anti-diabetic medication during the TEAE period will be reviewed in a blinded manner by external experts in diabetology. If the diabetic mellitus status is not confirmed, the patients will not be classified as NOD.

- And/or at least 2 HbA<sub>1c</sub>  $\geq 6.5\%$  during the TEAE period
  - For patients with a single measurement available during the TEAE period, a single value  $\geq 6.5\%$  will be considered and qualify the patient as NOD by default
  - For patients with several HbA<sub>1c</sub> measurements but only with the last one  $\geq 6.5\%$ , this single value  $\geq 6.5\%$  will be considered and qualify the patient as NOD by default.
- And/or at least two fasting glucose measurements  $\geq 126$  mg/dL (7.0 mmol/L):
  - For patients with only a single measurement available during the TEAE period, a single value  $\geq 126$  mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD.
  - For patients with several fasting glucose measurements but only with the last one  $\geq 126$  mg/dL (7.0 mmol/L), this single value  $\geq 126$  mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD.

### ***Hepatitis C antibody***

The number and percentage of patients with a post-baseline seroconversion for hepatitis C test will be provided by treatment group in post-baseline (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 6 - Definition of the patient status regarding hepatitis C virus**

| Hepatitis C Antibody (Ab) test result              |                                       |                  |                                   |                  |                                |
|--|---------------------------------------|------------------|-----------------------------------|------------------|--------------------------------|
| 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 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

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

#### **3.4.5.4 Analyses of vital sign variables**

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum, and maximum) of all vital signs 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.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

#### **3.4.6 Analyses of other safety parameters**

Events initially suspected by investigators, and reported as such in endpoints forms, may finally not be confirmed by investigators and possibly classified into another category that is not a component of the primary efficacy endpoint. In addition, per protocol all suspected UAs have to be sent for adjudication regardless of whether the event fulfils the stricter protocol definition or not, therefore a high proportion of the reported UAs are expected to be finally not retained as an endpoint.

Since those events are not reported as adverse events either, they will be described separately as follows:

The number (%) of patients with events below during the TEAE period will be displayed by treatment group on the safety population:

- With final diagnosis as per investigator of stable coronary disease,
- With final diagnosis as per investigator of unstable angina regardless of whether the event fulfils the stricter protocol definition or not;
- With final diagnoses as per investigator of hemorrhagic stroke, transient ischemic attack (TIA), and subdural hematoma.

The number (%) of patients with hemorrhagic strokes or silent MI as per CEC during the TEAE period will also be summarized on the safety population

### **3.4.7 Analyses of other endpoints**

All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in [Section 3.5.4](#), in order to provide an assessment for Month 1 to Month 64 time points.

#### **3.4.7.1 Analyses of hs-CRP**

hs-CRP parameter 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.

#### **3.4.7.2 Analyses of HbA<sub>1c</sub>**

HbA<sub>1c</sub> parameter will be summarized on the safety population by analysis visit using number of available data, mean, SD, median, minimum, and maximum for each treatment during the treatment period. Summary will be also provided according to the diabetes mellitus status at baseline (see [Section 3.1.1](#)). The time profile will be plotted by treatment group with the means and the corresponding standard errors (SEs).

In case the proportion of initiation of anti-diabetic medications is different between the 2 treatment groups, further analysis of HbA<sub>1c</sub> over time would be performed.

#### **3.4.7.3 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.

#### **3.4.7.4 Analyses of lipid parameters**

The lipids variables (see [Section 3.1.5.1](#)) will be analyzed using an ITT approach (based on the ITT population) including all lipid values, regardless of whether the patient was continuing therapy or not. In addition, analyses will also be conducted using an on-treatment approach (based on the randomized and treated population) only including lipid data collected during the treatment period.

#### 3.4.7.4.1 ITT analyses

A pattern-mixture model approach (see [Appendix F](#)) will be used with a different imputation strategy applied for missing lipid values during the treatment period (ie, within the time period from the first double-blind IMP injection up to the day of the last double-blind injection +21 days) and missing lipid values after treatment discontinuation (ie, after the day of last injection +21 days) based on the following assumptions:

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

Missing lipid values will be imputed 10 times using the MI SAS® procedure, to generate 10 complete data sets. The percent change from baseline and/or the absolute change from baseline at a pre-specified time point will be derived from observed and imputed lipid value at this time point. Imputed values for time points after CSED will be discarded.

TGs and Lp (a) data will be log-transformed before imputation process and then back-transformed to create the imputed data sets.

The completed data sets will be analyzed using an analysis of covariance (ANCOVA) model for continuous lipid variables other than Lp (a) and TGs or a robust regression (6) model for Lp (a) and TGs continuous variables with treatment group as fixed effect, and the baseline lipid value as continuous covariate. The MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 10 analyses using Rubin’s formula.

The number of imputations (10) will be informally verified by replicating sets of 10 imputations and checking whether the combined results are stable. If not stable, the number of imputations will be increased and informally checked as above, and thus until stable estimates are obtained.

The value at the CSED will be the value obtained at the CSED visit. For patients without CSED visit, the last lipid value observed or imputed up to CSED will be taken into account.

Throughout the ANCOVA and robust regression models, the alirocumab group will be compared to placebo using appropriate contrasts tested at the two-sided 0.05 level, and providing the 95% CI of the difference, for the different time points as well as at the CSED.

No adjustment will be made for lipid variables for which p-values will be provided for descriptive purpose.

#### 3.4.7.4.2 *On-treatment analyses*

Analysis of lipid variables will be conducted during the treatment period. Post-treatment data will not be considered.

The lipid variables other than Lp (a) and TGs will be analyzed in the randomized and treated population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline on-treatment data available within Month 1 to Month 64 analysis windows will be used and missing data will be accounted for by the MMRM model.

The model will include the fixed categorical effects of treatment group (placebo, alirocumab), planned time point (Month 1 to Month 64), treatment-by-time point interaction, as well as, the continuous fixed covariate of baseline lipid value and baseline lipid value-by-time point interaction. This model will be run using SAS Mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least-squares means estimates over time for both treatment groups with their corresponding SEs and 95% CI. To compare the alirocumab group to the placebo group, appropriate contrasts statement will be used to test the differences of these estimates, at the 2-sided 0.05 level, for the different time points.

**Note:** in case of computation issue for this approach, multiple imputation under missing-at-random (MAR) assumption will be conducted, followed by an ANCOVA model.

The Lp (a) and TGs will be analyzed in the randomized and treated population using multiple imputation (same imputations as in [Section 3.4.7.4.1](#) without discarding imputations of missing values during the post-treatment period (see [Appendix F](#)).

#### 3.4.7.5 *Analyses of anti-alirocumab antibody variables*

The following summaries will be performed on the ADA population, taking into account all samples regardless of timing in relation to injections. ADA results will be summarized by treatment group and up-titration status (see [Section 3.4.5](#)).

- ADA results (negative or positive) by time point;
- Neutralizing status (negative or positive) by time point for positive ADA;
- ADA titers using descriptive statistics (median, minimum, and maximum) for positive ADA by time point;
- Number (%) of patients with pre-existing ADA and number (%) of patients with treatment-emergent ADA positive response;
- Number (%) of patients with persistent/transient/indeterminate treatment-emergent ADA positive response;
- Time to onset of treatment-emergent ADA positive response using descriptive statistics;



- Number (%) of patients with at least 1 neutralizing ADA.

Correlations between ADA parameters (eg, titers, treatment-emergent ADA positive status, neutralizing status), safety and/or efficacy endpoints will be also explored (eg, scatter plot).

#### **3.4.7.6 Analyses of quality of life/health economics variables**

The analysis of data from EQ-5D instrument will be performed on the ITT population.

Baseline is defined as the Visit 3 (Day 1) evaluation. Analysis window will be used to assign the measurements to time points (see [Section 3.5.4](#)).

##### Individual EQ-5D items

Response for each one of the 5 EQ-5D items will be summarized by time point for each treatment group with number (%) of patients reporting level 1 (no problems), level 2 (some problems), and level 3 (extreme problems) by item.

##### EQ-5D utility score

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

The change from baseline in utility score over time will be analyzed using a MMRM model with fixed categorical effects of treatment group, planned time points up to the CSED, treatment-by-time point interaction, as well as, the continuous fixed covariates of baseline value and baseline value-by-time point interaction.

**Note:** In case of computation issue for this approach, multiple imputation under MAR assumption will be conducted, followed by an ANCOVA model.

#### **3.4.7.7 Analysis of cardiovascular events of interest (other than efficacy endpoint)**

Other cardiovascular events of interest (see [Section 3.1.5.7](#)) will be analyzed using a time-to-event approach (Kaplan-Meier methodology) in the ITT population. Patients without any event will be censored using the same methodology as for the primary efficacy endpoint.

#### **3.4.8 Analyses of pharmacokinetic and pharmacodynamic variables**

Not applicable.

## 3.5 DATA HANDLING CONVENTIONS

### 3.5.1 General conventions

The following definitions/formulas will be used for computation of parameters.

#### *Common study end date*

The common study end date is defined as the date when 1613 patients have experienced at least 1 primary efficacy event or 24 months after the last date of randomization ex-China, whichever comes last.

#### *Date of last dose of investigational medicinal product*

The date of the last dose of IMP is equal to the last date of administration reported on the IMP administration case report form page, or missing if the last administration date is unknown. For patients on the alirocumab arm who will switch to placebo injection due to blinded treatment discontinuation, the date of last administration reported associated to an active injection will be considered.

#### *Renal function formulas*

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

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

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

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

The above rules won't be applied for the calculated LDL-C and non-HDL-C when HDL-C value is below the LLOQ. The value of LLOQ/2 for HDL-C will be used to obtain the non-HDL-C and calculated LDL-C used for quantitative analyses.

Below is an example of data for a dummy patient reported in the database, with the values that will be used in quantitative analyses for each parameters.

**Table 7 - Example of lipid data for a dummy patient**

| Parameter                     | Value reported in the database | Value used in the analysis |
|-------------------------------|--------------------------------|----------------------------|
| TC                            | 255 mg/dL                      | 255 mg/dL                  |
| HDL-C                         | <10 mg/dL                      | 5 mg/dL                    |
| Calculated LDL-C <sup>a</sup> | <221 mg/dL                     | 216 mg/dL                  |
| NON-HDL-C                     | <255 mg/dL                     | 250 mg/dL                  |
| TRIG                          | 172 mg/dL                      | 172 mg/dL                  |

<sup>a</sup> Friedewald formula for calculated LDL-C (when lipid expressed in mg/dL:  $LDL-C = NON-HDL-C - 0.2 * TG$ )

### 3.5.2 Data handling conventions for secondary efficacy variables

Rules defined for the primary efficacy variable will apply to time-to-event secondary efficacy variables.

### 3.5.3 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 missing or incomplete dates of primary endpoint events*

Rules for imputations are detailed in [Table 4](#).

#### *Handling of baseline definition if time of first double-blind injection or time of assessment at visit 3 is missing*

If the time of the first double-blind injection or the time of assessment at Visit 3 is missing then the baseline value is defined as the last available value obtained before or on the day of the first double-blind IMP injection.

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

If the IMP first or end of treatment date is missing, the exposure duration and compliance will be left as missing.

***Handling of treatment/TEAE analysis periods and survival analysis if IMP end of treatment date is unknown***

If the last injection (last active injection for patients randomized in the alirocumab group, last injection from a double-blind kit for patients randomized in the placebo group) date is missing or incomplete, this date will be imputed to the earliest of the dates below to define the upper bound of the treatment/TEAE analysis periods and to define the censoring date for survival analyses performed on these periods:

- The last day of the month and year, when only the day is missing, or the 31<sup>st</sup> of December of the year, when only the year is known;
- The date of the end of treatment visit (CSED visit for completer, early end of treatment visit for patients who prematurely discontinued the IMP);
- The date of the last contact;
- The date of death (if any);
- The day before the date of first injection of placebo following the switch to placebo in IVRS (if any).

Exception: In case the last active injection for a patient allocated to the alirocumab group was inadvertently received after the first injection of placebo following the switch to placebo in IVRS, the last active injection date (missing or incomplete) will be imputed to the earliest of the dates below:

- The last day of the month and year, when only the day is missing, or the 31<sup>st</sup> of December of the year, when only the year is known;
- The date of the end of treatment visit (CSED visit for completer, early end of treatment visit for patients who prematurely discontinued the IMP);
- The date of the last contact;
- The date of death (if any);
- The day before the date of the placebo injection (if any) following the last active injection.

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

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

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

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the TEAE period, the adverse event will be classified as treatment-emergent. No imputation of adverse event 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 IMP administration is missing***

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization will be considered as TEAEs.

### ***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 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 (eg, “>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.

## **3.5.4 Windows for time points**

Data analyzed by time point (including lipid data, laboratory safety data, vital signs, ECG, ADA, EQ-5D) will be summarized using the time windows given in [Table 8](#) below. These time windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses.

**Table 8 - Time windows definitions**

| <b>Time point</b>    | <b>Targeted study days</b>   | <b>Time windows</b>              |
|----------------------|--|----------------------------------|
| Month 1              | 30   | 16 to 44                         |
| Month 2              | 60   | 45 to 75                         |
| Month 4              | 122  | 107 to 137                       |
| Month 8              | 244  | 229 to 259                       |
| Month 12 to Month 24 | Number of months of the planned visit x 30.4375 and rounded to the nearest entire number of days | Targeted study day $\pm 21$ days |
| Beyond Month 24      | Number of months of the planned visit x 30.4375 and rounded to the nearest entire number of days | Targeted study day $\pm 28$ days |

If multiple valid values of a variable exist within a time window, the nearest from the targeted study day will be selected for the statistical analysis by time point. 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.

### 3.5.5 Unscheduled visits

For lipid data, safety laboratory data, ECG, 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.

### 3.5.6 Pooling of centers for statistical analyses

The randomization scheme was not stratified by center to avoid risk of unbalance between treatment groups within a country induced by the large number of centers that will participate to the study. Nevertheless, as the primary efficacy and main secondary endpoints are centrally adjudicated by the CEC, these outcomes are not expected to be influenced by the center. Therefore, the center will not be added as factor in the primary analysis model.

Centers will be pooled into region (see [Table 9](#)) to describe the study population and to perform the primary efficacy analysis and subgroup analyses.

**Table 9 - Definition of geographic regions**

| <b>North America</b> | <b>South America</b> | <b>Western Europe</b> | <b>Eastern Europe</b> | <b>Asia</b> | <b>Rest of the World</b> |
|----------------------|----------------------|-----------------------|-----------------------|-------------|--------------------------|
| Canada               | Argentina            | Austria               | Bosnia Herzegovia     | Hong Kong   | Australia                |
| United States        | Brazil               | Belgium               | Bulgaria              | India       | Israel                   |
|                      | Chile                | Denmark               | Croatia               | Japan       | New Zealand              |
|                      | Colombia             | Finland               | Czech Republic        | Korea       | Republic of South Africa |
|                      | Mexico               | France                | Estonia               | Malaysia    |                          |
|                      | Peru                 | Germany               | Georgia               | Philippines |                          |
|                      | Guatemala            | Italy                 | Hungary               | Singapore   |                          |
|                      |                      | Netherlands           | Latvia                | Sri Lanka   |                          |
|                      |                      | Norway                | Lithuania             | Thailand    |                          |
|                      |                      | Portugal              | Macedonia             | Taiwan      |                          |
|                      |                      | Spain                 | Poland                | China       |                          |
|                      |                      | Sweden                | Romania               |             |                          |
|                      |                      | Switzerland           | Russian Federation    |             |                          |
|                      |                      | United Kingdom        | Serbia                |             |                          |
|                      |                      | Greece                | Slovakia              |             |                          |
|                      |                      |                       | Slovenia              |             |                          |
|                      |                      |                       | Turkey                |             |                          |
|                      |                      |                       | Ukraine               |             |                          |

### 3.5.7 Statistical technical issues

Not applicable.

## 4 INTERIM ANALYSIS

Two interim analyses (IA) are planned, when 50% and 75% of the total number of expected events have occurred:

- Interim analysis for futility will be conducted, when approximately 807 events (50% of the targeted number of primary endpoint events) have occurred;
- Interim analysis for futility and overwhelming efficacy will be conducted, when approximately 1210 events (75% of the targeted number of primary endpoint events) have occurred.

Both IAs will be performed by the external independent CV DMC Statistician and will be reviewed under the supervision of the CV DMC. The CV DMC will also review secondary efficacy endpoints and safety data (adverse events, laboratory data, vital signs) available at the time of the IA.

Control of the type I and type II error will be ensured using gamma (-5) spending function for type II error (futility) and Gamma (-22) for type I error (efficacy) at each IA (the type I error spending function is also applied at the first IA, even if the objective of this first IA is only futility). It has to be noted that, in order to protect the global type I error in case the decision is taken to overrule the futility rule, non-binding boundaries were used.

The following table shows the stopping rules at each interim analysis (using the sample size assumptions described in [Section 1.3](#)):

**Table 10 - Interim analyses stopping boundaries corresponding to Gamma (-22) type I error and Gamma (-5) type II error spending functions**

| Timing of analyses                | Stopping boundaries<br>(1-sided p-value and hazard ratio) |   |
|-----------------------------------|---|---|
|                                   | Futility  | Overwhelming efficacy                     |
| First IA: 50% of targeted events  | p > 0.548<br>(⇔ HR > 1.008)                               | NA  |
| Second IA: 75% of targeted events | p > 0.19<br>(⇔ HR > 0.951)                                | p < 0.0001 <sup>a</sup><br>(⇔ HR < 0.802) |

HR = hazard ratio; IA = interim analysis; NA = not applicable

<sup>a</sup> Should the second interim analysis be triggered just before or after 1210 events have been reached, the exact nominal significance level to be used at the second IA would be re-computed based on a Gamma(-22) spending function.

Calculations done using EAST® 5.4



The CV data monitoring committee (DMC) could consider early stopping of the study for overwhelming efficacy at the second IA, if the following conditions are met:

- Stopping boundaries for overwhelming efficacy are crossed;
- Positive trend observed for secondary efficacy endpoints, including all cause mortality, and no excess of non-CV mortality;
- Consistency of the treatment effect on the primary efficacy endpoint across the following subgroups: gender, age, race, country (depending on the size of subgroups), time from index ACS event to randomization, and regions (see [Section 3.4.4.1](#)).

## **5 DATABASE LOCK**

The final database is planned to be locked approximately 3 months after the last patient last visit.

## **6 SOFTWARE DOCUMENTATION**

All summaries and statistical analyses will be generated using SAS version 9.1 or higher.

Sample size calculations were done using EAST® 5.4 version.

## 7 REFERENCES

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