EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2019
EMA/152718/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Praluent

International non-proprietary name: alirocumab

Procedure No. EMEA/H/C/003882/II/0042

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ACS	Acute Coronary Syndrome
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
Apo B	Apolipoprotein B
BMI	Body Mass Index
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
CI	Confidence Interval
CSED	Common Study End Date
CV	Cardiovascular
CVD	Cardiovascular disease
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
HDL-C	High Density Lipoprotein Cholesterol
HF	Heart Failure
HR	Hazard Ratio
IA	Interim Analysis
ITT	Intention to Treat
LDL-C	Low Density Lipoprotein Cholesterol
LMT	Lipid Modifying Therapy
MACE	Major Adverse Cardiac Event
MACE-plus	Endpoint defined in this report as CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, or UA requiring hospitalization
MI	Myocardial Infarction
MTD	Maximally Tolerated Dose
NOD	New Onset of Diabetes
NSTEMI	Non-ST segment Elevation Myocardial Infarction
PAD	Peripheral Artery Disease
RMP	Risk Management Plan
SAE	Serious Adverse Event
STEMI	ST-Elevation Myocardial Infarction
TEAE	Treatment-Emergent Adverse Event
TG	Triglyceride
UA	Unstable angina

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, sanofi-aventis groupe submitted to the European Medicines Agency on 28 June 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of adults with established atherosclerotic cardiovascular disease to reduce the risk of major adverse cardiovascular events and all-cause mortality by lowering LDL-C levels, alone or in combination with a statin and/or other lipid-lowering therapies, based on the final study report of Study EFC11570; a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an acute coronary syndrome. As a consequence, sections, 4.1, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is being updated accordingly. In addition, an updated RMP version 4 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0047/2018 on the agreement of a modification of the agreed paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0047/2018 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC)

726/2004 - one year of market protection for a new indication.

Scientific advice

During the CHMP Scientific Advice Working Party (SAWP) plenary meeting in April 2012, the CHMP/SAWP overall agreed with the design and objectives of the OUTCOMES study conducted to support this submission. The CHMP/SAWP also provided key advices on specific clinical efficacy and safety aspects.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alar Irs

Timetable	Actual dates
Submission date	28 June 2018
Start of procedure	21 July 2018
CHMP Co-Rapporteur Assessment Report	20 September 2018
CHMP Rapporteur Assessment Report	17 September 2018
PRAC Rapporteur Assessment Report	20 September 2018
PRAC members comments	26 September 2018
Updated PRAC Rapporteur Assessment Report	27 September 2018
PRAC Outcome	4 October 2018
CHMP members comments	10 October 2018
Updated CHMP Rapporteurs' joint Assessment Report	11 October 2018
Request for supplementary information (RSI)	18 October 2018
CHMP Rapporteurs' joint response Assessment Report	21 December 2018
PRAC Rapporteur's response Assessment Report	3 January 2019
PRAC Outcome	17 January 2019
CHMP members comments	22 January 2019
Updated CHMP and PRAC Rapporteurs' joint response Assessment Report	25 January 2019
Opinion	31 January 2019

2. Scientific discussion

2.1. Introduction

This application was submitted to provide the efficacy and safety results of the OUTCOMES study and to support the use of alirocumab for the reduction in the risk of cardiovascular (CV) events in patients with

established CV disease.

The clinical OUTCOMES study was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of CV events in patients with established CV disease (CVD) and who have experienced an acute coronary syndrome (ACS) event within 4 to 52 weeks prior to randomization. This study aimed to investigate whether the addition of alirocumab to an optimized background lipid modifying therapy (LMT) regimen, including high intensity statin, provides an additional benefit, as compared to placebo, in further reducing the risk of CV events in patients who experienced an ACS event (within 4 to 52 weeks) and who, despite high intensity LMT, were not at prespecified lipid levels (LDL-C ⩾70 mg/dL [1.81 mmol/L], or apolipoprotein B [Apo B] ⩾80 mg/dL [0.8 g/L], or non-high-density lipoprotein cholesterol [non-HDL-C] ⩾100 mg/dL [2.59 mmol/L]). The OUTCOMES study also aimed to extensively evaluate the long-term safety of alirocumab up to 5 years.

The intended wording of the extension of the indication at time of submission was:

Prevention of Cardiovascular Events in Established Atherosclerotic Cardiovascular Disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce the risk of major adverse cardiovascular events (coronary heart disease death, myocardial infarction, stroke, unstable angina requiring hospitalization) and all-cause mortality by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- *in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*

Request for an additional one year marketing protection

In accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004, the Marketing authorisation holder had applied for an additional one year marketing protection period in the framework of this application.

The applicant subsequently withdrew their request.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

Alirocumab is a protein derived from biotechnological processes. It is not expected to have an adverse effect on the environment. The Applicant has adequately justified the absence of studies to assess the environmental risk of alirocumab.

2.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, this application does not lead to a significant increase in environmental exposure further to the use of alirocumab. Considering the above, alirocumab is not expected to pose a risk to the environment

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that the clinical trial conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Clinical efficacy

2.3.2.1. Dose response studies

None

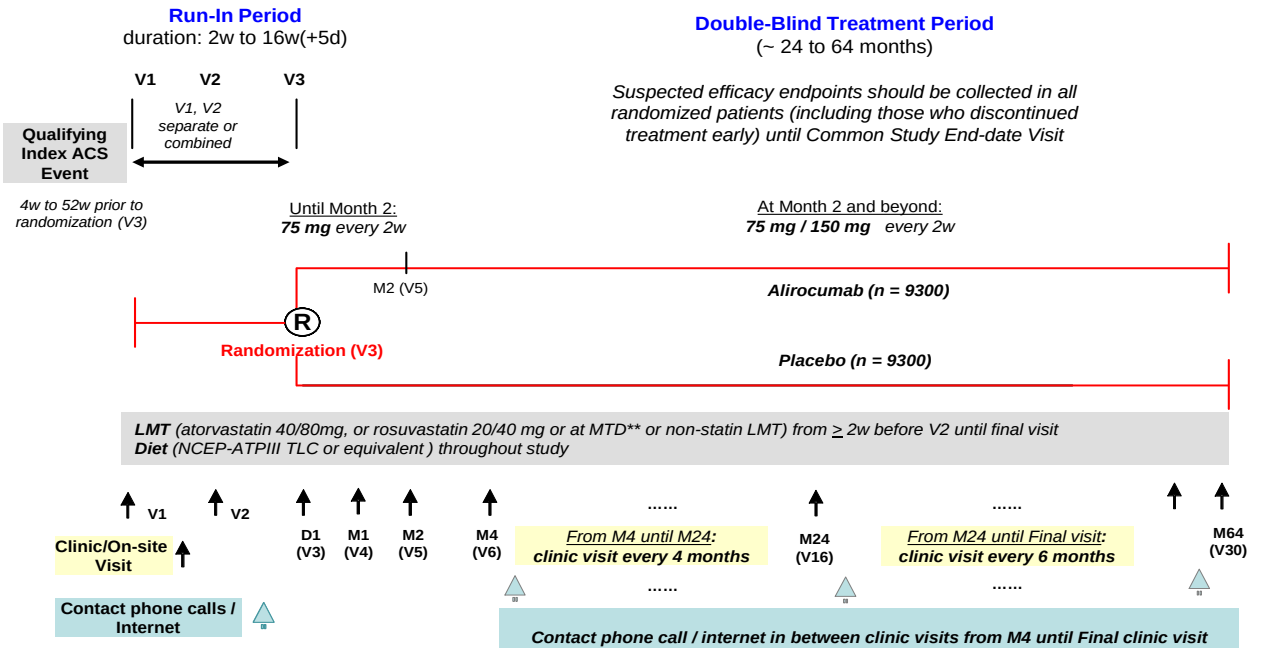
2.3.2.2. Main studies

ODYSSEY Outcomes (EFC11570): 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.

Methods

Study design

The general study design was a randomized, double-blind, placebo-controlled, parallel-group study. The study was comprised of 2 periods: a run-in period of 2 to 16 weeks and a double-blind treatment period up to 5 years (see Figure 1 below).



Run-In Period (duration between 2w and 16w+5d)
- **V1:** earliest is on day of ACS; latest is 50w post ACS (if V1, V2 separate) or 50w (+5d) post ACS (if combined V1/V2)
- **V2:** collection qualifying lipid labs after receiving lipid-modifying therapy (LMT) that is statin-intensive (atorvastatin 40/80mg, or rosuvastatin 20/40 mg or at max. tolerated dose), optimized for long-term chronic use (with addition of non-statin LMT at Inv. Discretion) and well tolerated after ≥ 2w of stable LMT dose
- **V3**: earliest is 4w and latest is 52w(+5d) post-index ACS

After randomization
- Final clinic visit (Common Study End Date Visit, V30 M64) should be completed in all randomized patients (regardless of whether they are still on treatment or had discontinued treatment early) and should occur between Common Study End Date (CSED) and CSED+30days.

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

Figure 1: Study design - EFC11570

Run-in period: The run-in period was to allow metabolic steady state after ACS and pharmacologic steady state on LMT to be achieved prior to randomization. Its duration ranged from 2 weeks to 16 weeks (+5 days) prior to randomization with randomization occurring no earlier than 4 weeks and no later than 52 weeks (+5 days) after the index ACS event. The run-in period was comprised of 2 visits, a screening visit (V1) and a qualifying visit (V2) based on the lipid criteria.

- The main goals of the run-in period were to ensure that the patient had received prior to the qualifying visit (V2) the required LMT regimen and that LMT was well tolerated after at least 2 weeks of stable dose. The required LMT regimen could be statin-intensive (defined as atorvastatin 40 or 80 mg daily or rosuvastatin 20 or 40 mg daily) or maximally tolerated dose (MTD) of one of these 2 statins with addition of non-statin LMTs (at Investigator's discretion), or in case of documented statin intolerance, an optimized regimen with non-statins LMT.
- Following the run-in period, only patients not reaching prespecified lipid levels at the qualifying visit (V2) after receiving optimal LMT for at least 2 weeks, ie, with LDL-C ≥70 mg/dL (≥1.81 mmol/L), or apolipoprotein B (Apo B) ≥80 mg/dL (≥0.8 g/L), or non-high-density lipoprotein cholesterol (non-HDL-C) ≥100 mg/dL (≥2.59 mmol/L), were to be randomized in the double-blind treatment period.

Double-blind treatment period: At the randomization visit (V3), patients were randomized either to background LMT + alirocumab or to background LMT + placebo. Patients randomized to alirocumab initially received alirocumab 75 mg Q2W.

- Similar to the phase 3a studies conducted for the LDL-C lowering indication, after initiation of alirocumab 75 mg Q2W, an up-titration scheme in a blinded fashion was applied with possible up-titration to 150 mg Q2W at Month 2 depending on LDL-C values at Month 1 (based on an LDL-C ≥50 mg/dL (1.29 mmol/L)). Then, during the double-blind treatment period, subsequent down-titrations or switch to placebo could occur (see section treatments).
- Lipid parameter values from blood samples obtained after the randomization visit, run by the central laboratory, were not communicated to the sites so that they could not deduce the treatment group of any individual patient based on LDL-C levels.
- The planned total double-blind study duration was approximately 5 years for the first randomized patient. The common study end date (CSED) was defined as when 1613 patients had experienced at least one primary efficacy event or 24 months after the closing of randomization for all countries except China, whichever came last.

The study employed the following committees:

- An Executive Steering Committee responsible for the good conduct of the study.
- An Independent Data Monitoring Committee (referred to as CV DMC) responsible for monitoring the patients' safety by conducting formal reviews of accumulated and unblinded safety data, and for supervising the planned 2 interim analyses.
- A Clinical Events Committee (CEC) responsible for adjudicating events corresponding to the primary and secondary CV endpoints as well as all causes of death.

In addition, two experts panels were implemented in the study, a neurocognitive and a diabetes experts panel.

Study participants

Following the run-in period, only patients not reaching prespecified lipid levels at the qualifying visit after receiving optimal LMT for at least 2 weeks, ie, patients with 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) (at visit 2), were to be randomized in the double-blind treatment period.

Inclusion criteria

The population enrolled was patients with previous hospitalization for ACS, identified as either a ST-elevation myocardial infarction (STEMI), or a non-ST segment elevation myocardial infarction (NSTEMI), or a high-risk unstable angina (UA), and who were not at prespecified lipid levels (ie, either LDL-C ≥70 mg/dL [≥1.81 mmol/L], or ApoB ≥80 mg/dL [≥0.8 g/L], or non-HDL-C ≥100 mg/dL [≥2.59 mmol/L]), despite an intensive LMT.

The choice to select eligible patients on two other lipid parameters, in addition to the traditional LDL-C target lipid parameter, was based on the acceptance that ApoB and non-HDL-C can be considered to be equal to LDL-C in CV risk prediction.

Patients with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² were allowed in the study.

Exclusion criteria

Exclusion criteria were mostly related to any condition or treatment that might interfere with efficacy assessment or were related to the patients' underlying health status and especially unstable conditions that might interfere with the evaluation of efficacy and safety of alirocumab.

The most relevant exclusion criteria are:

- age <40 years.
- CV exclusion criteria including uncontrolled hypertension, history of heart failure (HF) NYHA III and IV, history of hemorrhagic stroke, new ACS within 2 weeks prior to the randomization, planned coronary revascularization (PCI or CABG).
- Exclusion criteria related to lipid profile including triglycerides (TGs) >400 mg/dL (>4.52 mmol/L) during screening and run-in, use of red yeast rice during run-in.
- Other general exclusion criteria including history of cancer < 5 years, recent hypothyroidism, previous treatment with alirocumab.

Treatments

The patients were to be on stable diet (National Cholesterol Education Program's Adult Treatment Panel III Therapeutic Lifestyle Change [NCEP-ATPIII TLC] diet or equivalent) throughout the entire study duration from screening to the end of the study.

Patients were randomized to either background LMT + alirocumab 75 mg Q2W or background LMT + placebo in a 1:1 ratio.

During the double-blind treatment period, the dosing of alirocumab was intended to achieve LDL-C levels within the range of 30 to 50 mg/dL (0.78 to 1.29 mmol/L), which is considered the physiological ideal level, and to avoid very low levels of LDL-C, ie, <15 mg/dL (0.39 mmol/L).

To achieve these intended LDL-C levels, the following up-titration or down-titration scheme (including discontinuation if needed) was applied:

- At Month 2 (or Month 4 if month 1 LDL-C was not available or not valid) patients randomized to alirocumab 75 mg Q2W, in a blinded manner, either:
  - Continued alirocumab 75 mg Q2W, when the Month 1 LDL-C was <50 mg/dL (1.29 mmol/L) OR
  - Were up-titrated to alirocumab 150 mg Q2W, when the Month 1 LDL-C was ≥50 mg/dL (1.29 mmol/L).
- At subsequent visits, for patients on alirocumab, the following blinded adjustments were to be applied depending on the dose received:
  - For patients receiving 150 mg Q2W: if LDL-C <25 mg/dL (0.65 mmol/L) on 2 consecutive measurements, down-titration to 75 mg Q2W was performed in a blinded manner at the next visit. Additional monitoring was implemented until the down-titration was done.
  - For patients receiving 75 mg Q2W:
    - When LDL-C was <25 mg/dL (0.65 mmol/L) on 2 consecutive measurements but at least 1 value ≥15 mg/dL (0.39 mmol/L): alirocumab 75 mg Q2W was continued but additional monitoring was implemented, to further confirm the safety of low LDL-C levels.

- When LDL-C was <15 mg/dL (0.39 mmol/L) on 2 consecutive measurements and confirmed with direct measurement of LDL-C, alirocumab treatment was discontinued at the next visit. In order to maintain the blind, there was blinded substitution to placebo injections for the remaining duration of the study. Additional monitoring was implemented until the switch to placebo. This threshold of 15 mg/dL (0.39 mmol/L) was arbitrarily set due to the lack of available information on LDL-C levels below 15 mg/dL (0.39 mmol/L) (except in subjects with rare genetic mutations).

Background therapy

During the run-in period, patients were required to be on high intensity statin therapy (defined as atorvastatin 40 or 80 mg daily or rosuvastatin 20 or 40 mg daily) or in case of tolerability issues, on a MTD of either of these 2 agents. All other non-statin LMTs were also authorized with the exception of fibrates (other than fenofibrate and fenofibric acid) at the Investigator's discretion.

The main objective of the run-in period was for the Investigator to identify a background LMT regimen prior to the qualifying visit (V2 or combined V1/ V2), that met all the following criteria: the required high intensity statin therapy or an MTD (as defined above), optimized treatment for long-term chronic use, and tolerability after at least 2 weeks of stable dose prior to the qualifying visit.

Patients who were not on statins could also be enrolled if documented intolerance to 2 or more statins was available and they had at least 2 weeks of non-statin LMT exposure prior to the screening visit (V1). Only after careful assessment (including after review of latest evidence and after discussion with the patient, his/her family, and the patient's primary general practitioner/cardiologist), the Investigator could have the possibility to conclude that no background chronic LMT was appropriate for the patient.

After randomization, the required background LMT regimen, as determined from the run-in period, was to be continued at a stable dose, as long as this regimen remained well tolerated. If, during the course of the study, significant tolerability concerns arose and the patient was found intolerant to any dose of atorvastatin or rosuvastatin, other statins (ie, other than atorvastatin or rosuvastatin) as well as non-statin LMTs were authorized.

Objectives

The primary objective of this study was to compare the effect of alirocumab with placebo on the occurrence of CV events (composite endpoint of coronary heart disease [CHD] death, non-fatal myocardial infarction [MI], fatal and non-fatal ischemic stroke, unstable angina [UA] requiring hospitalization) in patients who have experienced an 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.

The secondary objectives were:

- To compare the efficacy of alirocumab versus placebo on secondary endpoints (any CHD event, major CHD event, any 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 (ADA).
- To evaluate the effect of alirocumab on LDL-C, apolipoprotein B (Apo B), and non-high-density lipoprotein cholesterol (non-HDL-C).

Outcomes / endpoints

The primary efficacy endpoint was the time from randomization to the first occurrence of one of the following clinical events (major adverse cardiac event [MACE]-plus), 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);
- UA requiring hospitalization.

This composite endpoint comprised hard CV endpoints, ie CHD death, any non-fatal MI, and ischemic stroke. These endpoints are considered to be objective events easily identified. The other CV endpoint, UA requiring hospitalization, generally considered a "softer" CV endpoint is nevertheless a costly event that worsens the quality of life and therefore, treatments that reduce its frequency are clinically useful. For this specific CV endpoint stringent criteria were used to include only high-risk UA events, ie, with high-risk electrocardiogram (ECG) findings together with evidence, during that hospitalization, of angiographically significant coronary disease (ie, with need for percutaneous coronary intervention/coronary artery bypass graft, or evidence of significant coronary stenosis >70%).

The main secondary efficacy endpoints were:

- Time from randomization to first occurrence of any CHD event (major CHD event, UA requiring hospitalization, ischemia-driven coronary revascularization procedure);
- Time from randomization to first occurrence of any major CHD event (CHD death, non-fatal 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).

Any suspected CV event suggestive of an endpoint as well as any death had to be submitted to the CEC for adjudication. Only CV events adjudicated and validated by the CEC were used for the analyses, while events suspected by the Investigator but not confirmed by the CEC were not used for the analyses, except for sensitivity analyses of the primary efficacy endpoint.

Definitions of primary and secondary efficacy endpoints related to CV events and death were based on the Food and Drug Administration (FDA)/Clinical Data Interchange Standards Consortium (CDISC) Standardized Definitions for End Point Events in Cardiovascular Trials, and on the Thygesen Universal Definition for the definition of MI.

Sample size

The sample size calculations were based on the primary efficacy variable. It was determined that 1613 events would be needed to have 90% power (with one-sided Logrank test at the overall 0.025 alpha level)

to demonstrate an effect versus placebo assuming a 15% risk reduction associated with alirocumab treatment (ie, HR of 0.85) and considering 2 interim analyses. At study set-up, a sample size of approximately 18 000 patients (9000 per treatment group) was defined considering the enrolment projections and expected event rates. Per a protocol amendment, in order to reach the target of approximately 600 randomized patients in China based on local regulatory considerations, and given the delayed study start in this country, the total number of patients to be randomized was increased to approximately 18 600 patients (approximately 9300 per group).

Randomisation

Investigational medicinal products (alirocumab 75 mg or 150 mg kit, or placebo kit) were packaged in accordance with the randomized list of treatment kit numbers generated centrally by the Sponsor. The Project Demand Manager provided the randomized list of treatment kit numbers and the Study Biostatistician provided the randomization scheme to the centralized treatment allocation system provider. Then, this centralized treatment allocation system provider generated the patient randomization list to allocate the treatments to the patients. Two types of centralized treatment allocation system were used, the IVRS and the IWRS depending on the choice of the site.

Patients were randomized to receive either alirocumab or placebo during the double-blind study treatment period using a 1:1 ratio (alirocumab: placebo), with permuted-block randomization. Randomization was stratified according to country.

The treatment kit numbers were allocated using the centralized treatment allocation system on randomization visit (Day 1, Month 0), Month 2, Month 4, every 4 months up to Month 24, and then every 6 months up to Month 64. For patients in the alirocumab treatment arm, the treatment kit allocated at Month 2 (V5) was based on their Month 1 (V4) LDL-C level, and the treatment kit allocated at Month 4 (V6) was based on their Month 1 or 2 (V4 or V5) LDL-C following the up-titration rules. Regular transfer of data was planned between the central laboratory and the centralized treatment allocation system provider in order to proceed in a blinded manner for study sites and Sponsor.

Blinding (masking)

To protect the blind, alirocumab and placebo for alirocumab were provided in identically matched autoinjectors and packaged identically which included labeling. Each double-blind treatment kit was labeled with a number generated by a computer program from the Sponsor. The treatment kit numbers were obtained by the Investigator at the time of patient randomization and subsequent visits scheduled, via a centralized treatment allocation system that was available 24 hours a day, 7 days a week. In accordance with the double-blind design, patients, Investigators, and study site personnel remained blinded to study treatment without access to the randomization.

Lipid parameter values collected at study visits and analyzed by the central laboratory were not communicated to Investigators after randomization to maintain the blind, but were communicated to IVRS/IWRS.

In addition, local laboratory testing of lipid parameters was prohibited after the patient's randomization, as specifically mentioned in both the ICF and the protocol, in order to prevent any possible unblinding by local laboratory testing. The protocol also highlighted the need for the Investigator to periodically remind and educate the general practitioner /cardiologist about the study requirements, ie, during the entire study, general practitioner/cardiologist had to refrain from checking lipid levels at a local laboratory, and were not to modify LMT regimen without discussing with the Investigator. This caution was also

emphasized in protocol training materials for monitoring teams and sites. Reminders were made at the Investigator meetings, and sent to the monitoring team and sites through newsletters and e-mail news bulletins. Caution was continuously raised to sites throughout the study. Patients who achieved 2 consecutive calculated LDL-C values <25 mg/dL (0.65 mmol/L) were monitored. In order to maintain the integrity of the blind as much as possible with this monitoring process, the following points were undertaken:

- Specific steps were in place to ensure that the work which was carried out by Covance central laboratory group, the communication between Covance central laboratory and IVRS/IWRS, and the communication with the Independent Physician(s), who was responsible for monitoring AEs in patients with 2 consecutive LDL-C levels <25 mg/dL (0.65 mmol/L), was in strict confidence.
- The Independent Physician(s) worked if needed with the dedicated member of the phase 3a DMC, subsequently replaced by the Medical Liaison, independently from the Sponsor. This dedicated phase 3a DMC member / Medical Liaison then transmitted any information as necessary to the common member involved in both DMCs (CV DMC and phase 3a DMC).
- The actual LDL-C levels (collected at study visits and analyzed by Covance central lab) were not reported to the sites.
- Monitoring by the Independent Physician(s) continued for as long as LDL-C level remained <25 mg/dL (0.65 mmol/L).

Patients' ADA results were not communicated to the sites during the study. The Sponsor had no access to ADA associated with patient identification until after the final database lock had occurred. The laboratory technicians involved in the determination of patients' ADA were excluded from the operational team and a process was set-up to prevent any potential unblinding.

The CEC reviewed and adjudicated, in a blinded manner, suspected CV events and all deaths occurring from randomization to CSED.

The NCEP (neurocognitive experts panel) reviewed in a blinded manner neurocognitive AEs reported during the study. The DEP (diabetes experts panel) reviewed in a blinded manner the potential cases of diabetes solely identified via antidiabetic medication use, occurring before, at baseline, or after baseline and not reported as "diabetes at baseline" or "new onset diabetes" AEs, nor associated with HbA1c or fasting glucose falling into the diabetes category. For the safety data review, the DMC reviewed unblinded data provided by an independent Statistician

Regular DMC safety analyses and both interim analyses were performed by the external independent CV DMC statistician and reviewed under the supervision of the CV DMC.

Statistical methods

The primary efficacy analysis **population** was the intent-to-treat (ITT) population, consisting of all randomized patients. Patients in the ITT population were analyzed according to the treatment group allocated by randomization. All analyses of efficacy endpoints were performed based on ITT approach that included all events (including those occurring after treatment discontinuation, and consequently also after switch to placebo based on 2 consecutive LDL-C values <15 mg/dL) occurring from randomization to the CSED. In addition, a supportive analysis of the primary efficacy endpoint was performed during the treatment period.

The Safety population considered for safety analyses was the randomized population who did actually receive at least one dose or part of a dose of the double-blind IMP. Patients were analyzed (in the section Clinical Safety) according to the treatment actually received (placebo or alirocumab).

The **analysis of primary efficacy endpoint** (in the section Clinical Efficacy) was the comparison between the two treatments using the log-rank test procedure stratified by region (North America, South America, Western Europe, Eastern Europe, Asia, Other). As the number of events per individual country was expected to be low (about 50 countries), the analysis were stratified according to a grouping of countries into regions.

This primary comparison is the test of the following hypotheses on the hazard ratio (HR), applying a one-sided nominal type I error of 0.0249 at the final analysis:

H0: HR ≥1 versus H1: HR <1

The estimates of the HR and corresponding confidence interval at (1-2α) % level (α being the one-sided nominal significance level: α=0.249 at final analysis, α=0.0003 at second interim analysis) were provided using a Cox Proportional Hazard Model stratified by region as for the log-rank test described above.

Consistency of the treatment effect across regions was assessed.

Underlying assumptions of the Cox Proportional Hazard Model were checked using graphical methods. If proportionality is not observed, some ad-hoc sensitivity analyses were performed depending on the data (data-driven).

The survival curves were estimated using Kaplan-Meier estimates: cumulative incidence of events at 6 months and by year, and appropriate confidence interval were presented by treatment arm using Kaplan-Meier estimates. Kaplan-Meier curves will be displayed by treatment arm.

Sensitivity analyses for the primary endpoint:

- Primary efficacy endpoint as per Investigator: including any events up to the CSED with final diagnosis by the Investigator confirming the event, whether or not confirmed by the CEC.
- Tipping point analyses: To assess the robustness of the results relative to missing information on the primary endpoint (patients without follow-up on CV events up to the CSED), a tipping-point analysis was performed to determine the imputed HR (for the period with missing information) at which the statistical significance was lost.

Supportive analyses for the primary endpoint:

- Analysis including recurrent events for MACE-plus as per CEC adjudication: analysis on all events (ie, including recurrent events after the primary efficacy endpoints).

Additional analyses for the primary endpoint:

- An analysis to evaluate the relationship between LDL-C and the risk of MACE-plus. Two models were used, one with the time-dependent covariate (time-weighted averaged LDL-C) as a continuous variable to get the reduction of MACE-plus risk per 1 mmol/L of reduction in LDL-C and one with the time-dependent covariate as a categorical variable to get the reduction of MACE-plus risk for each category compared to the reference category of LDL-C ≥100 mg/dL.

Two **interim analyses** (IA) were performed. The cut-off dates of final and interim analyses were expected to be:

- First interim analysis (futility): when 807 patients have experienced at least one primary efficacy event (50% fraction information)

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

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

Control of the type I and type II error were 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 was 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 one error in case the decision is taken to overrule the futility rule, non binding boundaries were used.

Subgroup analyses

For the primary endpoint, the treatment effects across the following subgroup factors were examined:

- Gender
- Age group (<65, ≥65)
- Race (Caucasian, Black, Asian/Oriental, and Other, as appropriate)
- Country (IVRS stratum, depending on 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, 4-24 weeks, > 24 weeks)

For each parameter, a Cox proportional hazard model was used for the overall population, including the parameter and the treatment by parameter interaction. In addition, Kaplan-Meier curves and summary statistics showing number of patients, number (%) of primary efficacy outcome events, cumulative incidence of events at 6 month and by year, and appropriate confidence interval might be provided for each treatment arm in previously selected subgroups defined by the baseline characteristic/prognostic factors.

In addition, the effect of the time from ACS event to randomization (weeks) was assessed using a Cox proportional hazard model including the time from ACS event to randomization (continuous) as a covariate, the treatment group and the interaction. Time to events **secondary endpoints** were analyzed using the same statistical methodology as for the primary endpoint.

The percent change from baseline in calculated LDL-C at Month 4, at Month 24 and at the end of the study will be analyzed in the ITT population using an analysis of covariance (ANCOVA) model with treatment group and region as fixed effects, and the baseline calculated LDL-C as covariate.

Similar analyses were performed for ApoB and non-HDL. Based on previous experiences and published data on these endpoints, the assumptions of normality of the residuals, homogeneity of slopes and homoscedasticity underlying these models are usually valid.

Throughout the ANCOVA models, the alirocumab group was compared to placebo using an appropriate contrast tested at the two-sided 0.05 level, and providing the 95% confidence interval (CI) of the difference.

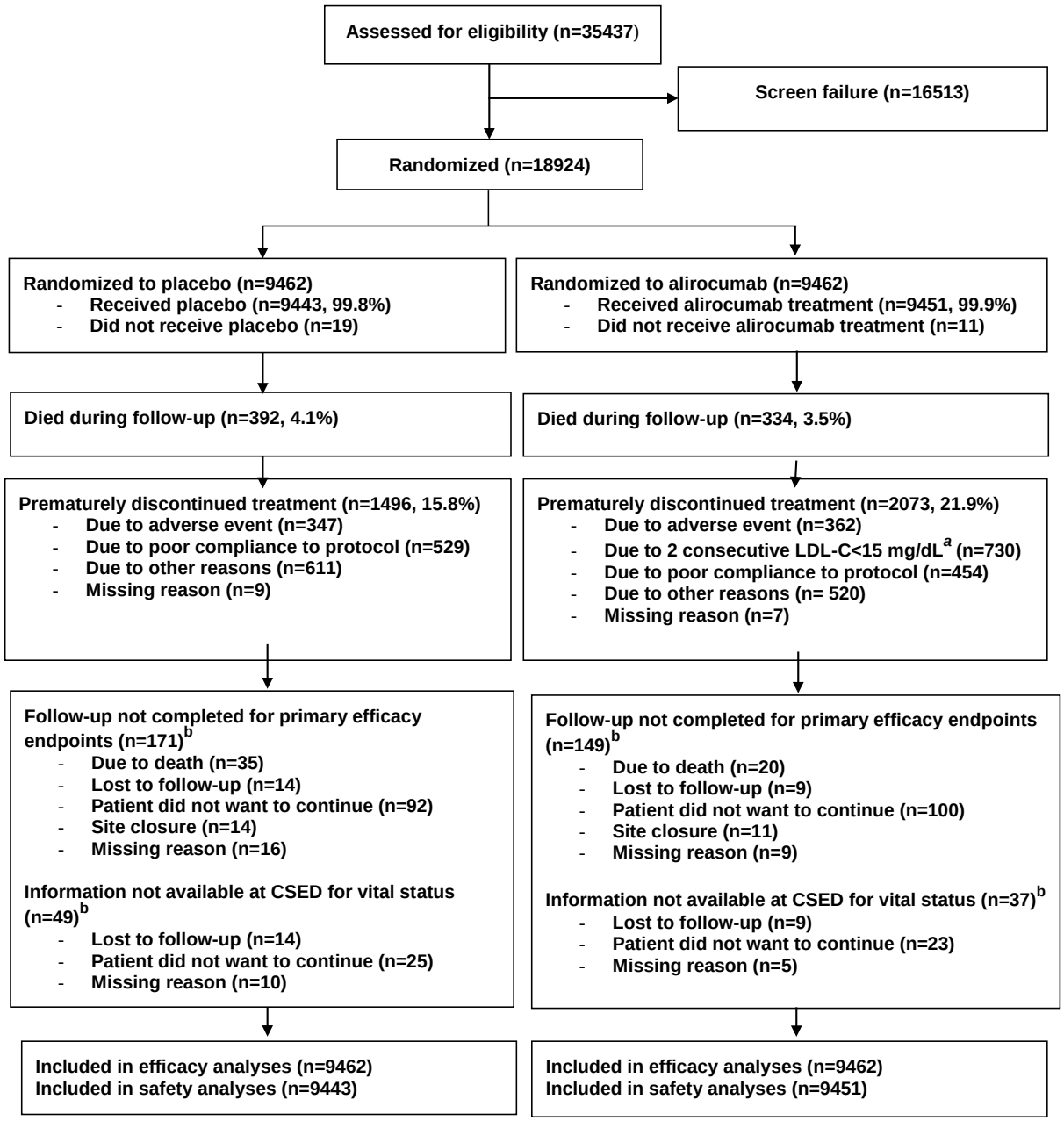
In order **to handle multiple main secondary endpoints**, the overall Type-I error was controlled by the use of a sequential inferential approach. Statistical significance of the primary parameter was required before drawing inferential conclusions about first key secondary parameter (at the 00003 one-sided alpha level at the second interim analysis or at the 0.0249 one-sided alpha level at the final analysis). Inferential conclusions about successive main secondary parameters required statistical significance of the prior one.

This fixed hierarchical approach ensured a strong control of the overall type-I error rate at the required one-sided level (0.0003 for the second interim analysis and 0.0249 at the final analysis).

No further adjustments were made for other secondary endpoints or subgroup analyses for which p-values were provided for descriptive purpose only.

Results

Participant flow



[a] In case of 2 consecutive LDL-C <15 mg/dL in the alirocumab group, alirocumab was discontinued with blinded substitution of placebo injections for the remaining study duration. These placebo injections were not considered as double-blind IMP injections.

[b] Reason not available for 25 patients for primary efficacy endpoints (9 in the alirocumab group and 16 in the placebo group) and 15 patients for vital signs status (5 in the alirocumab group and 10 in the placebo group).

Figure 2: Flow diagram of all patients – EFC11570

Table 1 - Patient disposition - Randomized population – EFC11570

	Placebo (N=9462)	Alirocumab (N=9462)
Randomized but not treated	19 (0.2%)	11 (0.1%)
Randomized and treated	9443 (99.8%)	9451 (99.9%)
Completed the study treatment period	7947 (84.0%)	7378 (78.0%)
Did not complete the study treatment period	1496 (15.8%)	2073 (21.9%)
Reason for treatment discontinuation		
Adverse event	347 (3.7%)	362 (3.8%)
Two consecutive LDL-C <15 mg/dL (<0.39 mmol/L)[a]	NA	730 (7.7%)
Poor compliance to protocol	529 (5.6%)	454 (4.8%)
Protocol became inconvenient to participate	150 (1.6%)	129 (1.4%)
Life events made continuing too difficult	171 (1.8%)	153 (1.6%)
Other reasons	208 (2.2%)	172 (1.8%)
Other reasons	611 (6.5%)	520 (5.5%)
Physician decision	77 (0.8%)	62 (0.7%)
Study terminated by sponsor	1 (<0.1%)	3 (<0.1%)
Patient moved	139 (1.5%)	104 (1.1%)
Patient withdrew consent	118 (1.2%)	91 (1.0%)
Related to IMP administration	96 (1.0%)	105 (1.1%)
Lost to Follow Up	17 (0.2%)	15 (0.2%)
Other	163 (1.7%)	140 (1.5%)
Missing reason	9 (<0.1%)	7 (<0.1%)
Patient's decision for treatment discontinuation [b]	1146 (12.1%)	988 (10.4%)

Note: Percentages are calculated using the number of patients randomized as denominator.
Only the main reason for stopping treatment was entered in e-CRF.
For detailed reasons related to IMP administration, several reasons may be provided.
Completed the study treatment period includes patients who stop IMP due to death.

a Blinded discontinuation due to low LDL-C level (patients who switched to placebo in blinded manner).

b Additional information as regard study treatment discontinuation.

23 patients in placebo group (9 identified as missing reason and 14 identified as Patient withdrew consent) are patients who discontinue the IMP at time of site closure
14 patients in alirocumab group (7 identified as missing reason and 7 identified as Patient withdrew consent) are patients who discontinue the IMP at time of site closure
PGM=PRODOPS/SAR236553/EFC11570/CSR/REPORT/PGM/dis_dispo_r_t.sas
OUT=REPORT/OUTPUT/dis_dispo_r_t_i.rtf (03MAY2018 - 14:14)

A total of 16513 subjects had a screening failure. Most important reasons for screening failure are: not meeting lipid targets (n=12068), patients who withdrew consent (n=2160), and exclusion based on (other) laboratory values (n=1414). A total of 18 924 patients were randomized to receive alirocumab or placebo (9462 patients in each group). In both treatment groups, almost all of the patients (99.8%) received at least 1 dose of the investigational medicine product (IMP).

Recruitment

The run-in period started with a screening visit (V1) (see section methods).

A patient who failed screening and left the study was allowed to undergo rescreening and re-enter the study (only once) under the following scenarios:

- If lipid inclusion criteria (LDL-C, non-HDL-C, Apo B) at V2/V2b were met during a first initial screening with a given statin dose and patient failed screening for a reason not related to these lipid inclusion criteria, then patient could be rescreened using the same statin at the same dose or, if documented intolerance, with the same statin at a lower dose or other authorized statin or no statin (latter option only if patient had documented intolerance to 2 or more statins).
- However, if lipid inclusion criteria at V2/V2b (LDL-C, non-HDL-C, Apo B) were not met during a first screening with a given statin dose, patients could not be rescreened using the same statin at the same dose. Such patients could only be rescreened if statin intolerance had developed subsequently and the statin regimen had been changed.

A total of 35437 patients were screened, while a number of 16513 patients failed screening (see disposition).

Conduct of the study

There were 11 protocol amendments, including 4 global amendments that applied to all patients and 7 local amendments that only applied to patients in specific countries; the changes introduced by these amendments are summarized in Table 2 below.

Both the NCEP (neurocognitive expert panel) and the DEP (diabetes expert panel) were implemented after the start of the study, respectively on 25 September 2015 and 07 September 2016.

Table 2: Summary of protocol amendments

No.	Date	Purpose of amendments
1 Global	17-Sep-2012	• Change in the wording of the exclusion criteria E07 and E23 for clarification purpose. • The waived CV efficacy endpoints (primary and secondary efficacy endpoints) were to be reported only in the specific outcome event screens of the e-CRF and no longer required to also be reported in the AE screen, to avoid duplication of data.
2 Local / France	01-Mar-2013	• Per the French Health Authorities' request, addition of the exclusion criterion "known history of active optic nerve disease".
3 Local / Latvia	22-Mar-2013	• Per the Latvian Health Authorities' request, addition of specific measures related to latent/active tuberculosis, and ECGs had to be performed at all visits of the double-blind period.

4
Local / Germany
	25-Mar-2013	• Per the German Health Authorities' request, changes related to exclusion criteria:
		  • Addition of an exclusion criterion related to known HIV infection, revision of the exclusion criterion E09 related to laboratory findings with addition of an HIV test to exclude patients who test positive for HIV
		  • Revision of the exclusion criterion E21 related to known hypersensitivity to monoclonal antibody therapeutics to specify that it related to any component of the drug product including excipients.

5 Local / China	29-Jul-2013	• Update/clarifications in the definition of the efficacy endpoints • Run-in period: clarifications and simplifications provided • Adjustment in some inclusion/exclusion criteria • Adjustment in some lipid assessments
6 Global	05-Dec-2013	• Update/clarifications in the definition of the efficacy endpoints • Adjustment of some inclusion/exclusion criteria • Run-in period: clarifications and simplifications provided • Lipid monitoring and LMT post-randomization: adjustment/clarifications • Clarification in safety (SAE) section and addition of analysis of CV events of interest related to peripheral artery disease (PAD) and venous thromboembolic events

7
Local / China
	11-Apr-2014	• Changes to be aligned with the global amendment 6 including:
		  • Adjustment of patient population
		  • Adjustment on lipid monitoring and LMT post-randomization
		  • Addition of an analysis of CV events of interest related to PAD and venous thromboembolic events

8 Global	16-Apr-2015	• Based on the need to randomize at least 600 patients in China for local regulatory purposes and since the Clinical Trial Application approval in China was delayed resulting in a late start of randomization, the closing of randomization was to be performed in 2 sequential steps. - First step was to close randomization in all countries except China shortly after a total of 18 000 patients had been randomized globally. - Second step was to close randomization in China shortly after a total of 600 patients had been randomized to China or at CSED, whichever came first. • Neurologic and neurocognitive events were considered as AESIs, and those events leading to additional examinations/procedures and/or referral to a specialist were considered as AESI with immediate notification and subject to expedited reporting (within 24 hours) to the Sponsor.
9 Local / China	10-Dec-2015	• To follow the recommendation from the Chinese Health Authorities and investigate the impact of the treatment on steroid hormones (adrenocorticotropic hormone [ACTH], follicle stimulating hormone [FSH], luteinizing hormone [LH], cortisol, testosterone, and estradiol).
10 Local / Colombia	27-Jan-2016	• Per the Colombian Health Authorities's request, addition of an annual neurologic examination to be performed by a neurologist to enhance the detection of potential neurologic or neurocognitive AEs.
11 Global	25-Feb-2016	• To streamline the requirements for the end of the study: only one final visit, called the CSED visit, was to be performed for all randomized patients, at the end of the study and within 30 days of the CSED. The additional follow-up contact that was initially planned to be performed 8 weeks after that visit for patients still on study treatment at the time of the CSED was no longer required.

There were 3 versions of the statistical analysis plan, starting with the statistical section in protocol version 8. Changes between versions are summarized in Table 3 below.

Table 3: Summary of SAP amendments

SAP version number	Date approved	Rationale	Description of statistical changes
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 Section 3.4.7.4.1)
1	25-Jan-2016	End of analysis period for the analysis of TEAEs for patients with 2 consecutives 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 Section 3.4.5.1).
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 Section 3.1.5.4).
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 "normoglyceamic" (see Section 3.1.1). The transition to new onset of diabetes in these two subgroups will be described separately (see Section 3.4.5.3). The primary efficacy endpoint will also be assessed in these subgroups (see Section 3.4.4.1)

SAP version number	Date approved	Rationale	Description of statistical changes
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 Section 3.4.5.3). 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 Section 3.1.1) and during the course of the study (see Section 3.4.5.3)
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 Section 3.1.3.2).
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 Section 3.1.3.2.1).
3	This version	Provide comprehensive assessment of diabetes.	"New onset of diabetes" added in the list of events of interest (see Section 3.1.4.1)
3	This version	Clarification about the list of patients who will have an additional ADA sample after the end of the study.	See Section 3.1.5.5
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 Section 3.4.4.4).
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 Section 3.5.3)

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

Baseline data

General baseline characteristics and CV history

General baseline characteristics are provided in the tables below. Overall prior to their index ACS event, 34.0% of patients had a history of coronary artery disease (CAD) prior to the index ACS event including 19.2% with a history of MI and 22.7% with a history of coronary revascularization procedures (coronary artery bypass graft/percutaneous coronary intervention), 3.2% with a history of stroke, 4.0% with a history of peripheral artery disease (PAD), and 14.9% reported congestive heart failure. Cardiovascular risk factors prior to the run-in period were reported for most of the randomized patients (88.9%), including hypertension (64.7% of patients), family history of CAD (35.8%), and diabetes (in 24.5% of patients when based on reported medical history, and in 28.8% of patients when based on the definition of diabetes as prespecified in the SAP). Other CV diseases prior to the run-in period include dyslipidemia

are reported in 66.7% of patients. This observation is supported by the fact that only approximately 30% of patients were taking statins for at least 3 months prior to the index ACS event.

Regarding the index ACS event, 83.2% of patients presented with MI diagnosed through cardiac biomarker elevation (ST segment elevation myocardial infarction [STEMI] in 34.6% and non-ST segment elevation myocardial infarction [NSTEMI] in 48.6% of patients), or UA in 16.8% of patients. The median time from ACS event to randomization was 2.6 months, with 72.6% of patients having been randomized less than 4 months after the index ACS event.

At the qualifying visit, almost all patients (99.5%) had lipid levels not adequately controlled. At this qualifying visit, about 8% of patients did not qualify with an LDL-C ≥70 mg/dL (≥1.81 mmol/L), but rather qualified based on Apo B (0.3% only on Apo B) and/or non-HDL-C (7.2% only on non-HDL-C).

Table 4: Demographics and patient characteristics at baseline - Randomized population

	Placebo (N=9462)	Alirocumab (N=9462)	All (N=18924)
Age (years)			
Number	9462	9462	18924
Mean (SD)	58.6 (9.4)	58.5 (9.3)	58.6 (9.3)
Median	58.0	58.0	58.0
Min : Max	39 : 92	40 : 90	39 : 92
Age Group (years) [n (%)]			
Number	9462	9462	18924
<65	6883 (72.7%)	6957 (73.5%)	13840 (73.1%)
≥65 to <75	2065 (21.8%)	2012 (21.3%)	4077 (21.5%)
≥ 75	514 (5.4%)	493 (5.2%)	1007 (5.3%)
Age Group (years) [n (%)]			
Number	9462	9462	18924
<65	6883 (72.7%)	6957 (73.5%)	13840 (73.1%)
≥65	2579 (27.3%)	2505 (26.5%)	5084 (26.9%)
Sex [n (%)]			
Number	9462	9462	18924
Male	7090 (74.9%)	7072 (74.7%)	14162 (74.8%)
Female	2372 (25.1%)	2390 (25.3%)	4762 (25.2%)
Race [n (%)]			
Number	9460	9461	18921
White	7524 (79.5%)	7500 (79.3%)	15024 (79.4%)
Black or African American	238 (2.5%)	235 (2.5%)	473 (2.5%)
Asian	1247 (13.2%)	1251 (13.2%)	2498 (13.2%)
Other	449 (4.7%)	469 (5.0%)	918 (4.9%)
Unknown	2 (<0.1%)	6 (<0.1%)	8 (<0.1%)
Ethnicity [n (%)]			
Number	9462	9462	18924
Hispanic or Latino	1555 (16.4%)	1581 (16.7%)	3136 (16.6%)
Non-Hispanic or Latino	7721 (81.6%)	7700 (81.4%)	15421 (81.5%)
Unknown	186 (2.0%)	181 (1.9%)	367 (1.9%)
Region[a]			
Number	9462	9462	18924
North America	1436 (15.2%)	1435 (15.2%)	2871 (15.2%)
South America	1295 (13.7%)	1293 (13.7%)	2588 (13.7%)
Western Europe	2091 (22.1%)	2084 (22.0%)	4175 (22.1%)
Eastern Europe	2718 (28.7%)	2719 (28.7%)	5437 (28.7%)
Asia	1143 (12.1%)	1150 (12.2%)	2293 (12.1%)
Rest of World	779 (8.2%)	781 (8.3%)	1560 (8.2%)

[a]: the region is derived using the stratum country from IVRS
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Table 5 - Medical history of specific interest: Cardiovascular history and risk factors - Randomized population – EFC11570

	Placebo (N=9462)	Alirocumab (N=9462)	All (N=18924)
Coronary artery disease prior to index ACS event	3245 (34.3%)	3183 (33.6%)	6428 (34.0%)
Angina	2075 (21.9%)	1979 (20.9%)	4054 (21.4%)
Myocardial infarction	1843 (19.5%)	1790 (18.9%)	3633 (19.2%)
Coronary artery bypass graft surgery	526 (5.6%)	521 (5.5%)	1047 (5.5%)
Percutaneous coronary intervention	1615 (17.1%)	1626 (17.2%)	3241 (17.1%)
Cardiovascular risk factors prior to run-in period	8418 (89.0%)	8413 (88.9%)	16831 (88.9%)
Dyslipidemia	6287 (66.4%)	6340 (67.0%)	12627 (66.7%)
Hypertension	6044 (63.9%)	6205 (65.6%)	12249 (64.7%)
Family history of coronary artery disease	3365 (35.6%)	3408 (36.0%)	6773 (35.8%)
Type 1 or type 2 diabetes mellitus	2340 (24.7%)	2305 (24.4%)	4645 (24.5%)
Type 1 diabetes mellitus	19 (0.2%)	18 (0.2%)	37 (0.2%)
Type 2 diabetes mellitus	2321 (24.5%)	2287 (24.2%)	4608 (24.4%)
Other cardiovascular disease prior to run-in period	2039 (21.5%)	1956 (20.7%)	3995 (21.1%)
Congestive heart failure	1449 (15.3%)	1365 (14.4%)	2814 (14.9%)
Peripheral arterial disease	386 (4.1%)	373 (3.9%)	759 (4.0%)
Cerebrovascular disease	467 (4.9%)	477 (5.0%)	944 (5.0%)
Carotid endarterectomy / carotid stenting	67 (0.7%)	62 (0.7%)	129 (0.7%)
Prior stroke	305 (3.2%)	306 (3.2%)	611 (3.2%)
Ischemic	256 (2.7%)	268 (2.8%)	524 (2.8%)
Hemorrhagic	1 (<0.1%)	0	1 (<0.1%)
Unknown	47 (0.5%)	37 (0.4%)	84 (0.4%)
Transient ischemic attack	148 (1.6%)	161 (1.7%)	309 (1.6%)

Note: A patient can be counted in several categories according to the items pre-listed in the e-CRF

Table 6 - Index qualifying ACS event - Randomized population – EFC11570

	Placebo (N=9462)	Alirocumab (N=9462)	All (N=18924)
Index ACS event [n (%)]			
A) Either of A1 or A2 (i.e., biomarker positive qualifying event)	7836 (82.8%)	7875 (83.2%)	15711 (83.0%)
A1 Elevated troponin I or T	7155 (75.6%)	7202 (76.1%)	14357 (75.9%)
A2 Elevated CK-MB	3674 (38.8%)	3725 (39.4%)	7399 (39.1%)
Neither of the above (i.e., no biomarker positive qualifying event)	1624 (17.2%)	1587 (16.8%)	3211 (17.0%)
B) Resting ECG changes consistent with ischemia or infarction (B1) AND additional evidence of obstructive coronary disease, based upon the following criteria (B2)	6689 (70.7%)	6750 (71.3%)	13439 (71.0%)
B1. Resting ECG changes consistent with ischemia or infarction	6791 (71.8%)	6857 (72.5%)	13648 (72.1%)

	Placebo (N=9462)	Alirocumab (N=9462)	All (N=18924)
a) ST depression (new or presumed new)	2115 (22.4%)	2158 (22.8%)	4273 (22.6%)
b) ST elevation (new or presumed new)	4050 (42.8%)	4047 (42.8%)	8097 (42.8%)
c) T wave inversion (new or presumed new)	2004 (21.2%)	2008 (21.2%)	4012 (21.2%)
d) Pathological Q waves (new or presumed new)	348 (3.7%)	351 (3.7%)	699 (3.7%)
e) New tall R wave (V1, V2)	17 (0.2%)	18 (0.2%)	35 (0.2%)
B2. Additional evidence of obstructive coronary artery disease	7258 (76.7%)	7264 (76.8%)	14522 (76.7%)
a) Evidence of myocardial ischemia or infarction by perfusion imaging (new or presumed new)	627 (6.6%)	625 (6.6%)	1252 (6.6%)
b) Regional wall motion abnormality (new or presumed new)	2474 (26.1%)	2364 (25.0%)	4838 (25.6%)
c) Epicardial coronary artery stenosis > or = 70% by coronary angiography	5891 (62.3%)	5818 (61.5%)	11709 (61.9%)
d) Need for revascularization (PCI or CABG) related to index ACS event[a]	4053	4012	8065
Time from ACS event until randomization (weeks)			
Number	9462	9462	18924
Mean (SD)	15.9 (12.1)	15.8 (12.0)	15.8 (12.1)
Median	11.4	11.3	11.4
Q1 : Q3	7.6 : 18.7	7.6 : 19.0	7.6 : 18.9
Min : Max	1 : 235	2 : 86	1 : 235
Time from ACS event until randomization (months)			
Number	9462	9462	18924
Mean (SD)	3.6 (2.8)	3.6 (2.8)	3.6 (2.8)
Median	2.6	2.6	2.6
Q1 : Q3	1.7 : 4.3	1.7 : 4.4	1.7 : 4.3
Min : Max	0 : 54	0 : 20	0 : 54
Time from ACS event until randomization (months) [n (%)]			
Number	9462	9462	18924
<2	3061 (32.4%)	3117 (32.9%)	6178 (32.6%)
≥2 to <4	3820 (40.4%)	3736 (39.5%)	7556 (39.9%)
≥4 to <6	969 (10.2%)	993 (10.5%)	1962 (10.4%)
≥6	1612 (17.0%)	1616 (17.1%)	3228 (17.1%)

	Placebo (N=9462)	Alirocumab (N=9462)	All (N=18924)
Index ACS subtype [n (%)]			
Number	9450	9443	18893
STEMI	3235 (34.2%)	3301 (35.0%)	6536 (34.6%)
NSTEMI	4601 (48.7%)	4574 (48.4%)	9175 (48.6%)
UA	1614 (17.1%)	1568 (16.6%)	3182 (16.8%)

Note: 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" (i.e any combination of responses to questions "B" on the eCRF)

a Information collected only for patients randomized after protocol Amendement 6

LDL-C levels at baseline

Overall, mean LDL-C at baseline was 92.4 mg/dL (2.392 mmol/L), mean non-HDL-C was 122.3 mg/dL (3.169 mmol/L), and mean Apo-B was 83.1 mg/dL (0.8 g/L).

A total of 19.8% (3751) of patients had a LDL-C <70 mg/dL (<1.81 mmol/L) at baseline. This proportion was higher than that observed at the qualifying visit (about 8%) and is likely explained by the known variability of LDL-C within individuals over short periods of time, more particularly for patients who do not have yet a confirmation in the diagnosis of hypercholesterolemia due to these fluctuations.

Concomitant treatment including statin use

Overall, only one-third (32.6%) of patients who were randomized in the study were treated with statin for at least 3 months prior to the index ACS event.

At randomization patients were receiving the best standard of care with LMT. Treatment groups were well balanced with regard to the background LMT regimen. Most patients (88.8%) were receiving high dose statin (ie, atorvastatin 40 mg or 80 mg daily or rosuvastatin 20 mg or 40 mg daily), 8.5% were receiving low/moderate dose statin (ie, atorvastatin <40 mg daily and/or rosuvastatin <20 mg daily), and 0.2% were receiving another statin. The other patients were receiving only LMT other than statins (1.5%) or were not receiving any LMT (0.9%). The main reason for not receiving high dose statin was muscle symptoms and/or increased CPK while taking statin (5.8% of patients).

During the course of the study, the proportion of patients receiving intensive statin slightly decreased in both treatment groups. This decrease was greater in the alirocumab group (from 88.6% at baseline to 81.9% at Month 48) than in the placebo group (from 89.1% at baseline to 86.3% at Month 48). The percentage of patients not receiving statins increased from 2.5% at randomization to 5.8% at Month 48 in the alirocumab group and from 2.4% at randomization to 4.2% at Month 48 in the placebo group.

A total of 460 patients were not taking statin at randomization (see table below). The reasons for not taking statin are described.

Table 7 - Background LMT regimen at randomization - Randomized population - Patients not taking statins at randomization

	Placebo (N=227)	Alirocumab (N=233)	All (N=460)
Background lipid modifying therapy at randomization [n (%)]			
Number	227	233	460
Only LMT other than statin	136 (59.9%)	146 (62.7%)	282 (61.3%)
No statin and no other LMT	91 (40.1%)	87 (37.3%)	178 (38.7%)
Reason for not being on statin			
Number	227	233	460
Muscle symptoms and/or increased CPK while taking statin	131 (57.7%)	143 (61.4%)	274 (59.6%)
Active liver disease	1 (0.4%)	1 (0.4%)	2 (0.4%)
Elevated LFTs while taking statin	15 (6.6%)	15 (6.4%)	30 (6.5%)
Taking concomitant medications that have precautions/warnings with statins	1 (0.4%)	1 (0.4%)	2 (0.4%)
Advanced age	3 (1.3%)	1 (0.4%)	4 (0.9%)
Subject unable to tolerate 2 different statins	150 (66.1%)	154 (66.1%)	304 (66.1%)
Other documented reason that the subject is unable to take the maximum statin dose	10 (4.4%)	14 (6.0%)	24 (5.2%)
Other	5 (2.2%)	13 (5.6%)	18 (3.9%)
LMT combination treatment			
Any combination	27 (11.9%)	29 (12.4%)	56 (12.2%)
Does not include a statin	27 (11.9%)	29 (12.4%)	56 (12.2%)
Any LMT other than statins	136 (59.9%)	146 (62.7%)	282 (61.3%)
Ezetimibe	67 (29.5%)	79 (33.9%)	146 (31.7%)
Other LMT other than nutraceuticals (except ezetimibe)	30 (13.2%)	38 (16.3%)	68 (14.8%)
Omega 3 Fatty Acids	44 (19.4%)	33 (14.2%)	77 (16.7%)
Niacin (Nicotinic Acid)	12 (5.3%)	14 (6.0%)	26 (5.7%)
Other nutraceuticals	12 (5.3%)	14 (6.0%)	26 (5.7%)

PGM=PRODOPS/SAR236553/EFC11570/PUB_2018/REPORT/PGM/dem_lmt_nostatin_r_t.sas
OUT=REPORT/OUTPUT/dem_lmt_nostatin_r_t_i.rtf (02OCT2018 - 16:49)

At randomization the majority of patients were very well treated according to the post-ACS guideline-recommended treatment, including aspirin or oral adenosine diphosphate (ADP) receptor antagonists in 98.8% of patients, angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker in 77.8% of patients, and beta blocker in 84.5% of patients.

Table 8: Background LMT regimen at randomization - Randomized population

	Placebo (N=9462)	Alirocumab (N=9462)	All (N=18924)
Background lipid modifying therapy at randomization [n (%)]			
Number	9462	9462	18924
High dose atorvastatin/rosuvastatin[a]	8431 (89.1%)	8380 (88.6%)	16811 (88.8%)
Low/moderate dose atorvastatin/rosuvastatin[b]	777 (8.2%)	830 (8.8%)	1607 (8.5%)
Other statin[c]	27 (0.3%)	19 (0.2%)	46 (0.2%)
Only LMT other than statin	136 (1.4%)	146 (1.5%)	282 (1.5%)
No statin and no other LMT	91 (1.0%)	87 (0.9%)	178 (0.9%)
Reason for not being on High statin dose[a]			
Number	1000	1052	2052
Muscle symptoms and/or increased CPK while taking statin	530 (5.6%)	568 (6.0%)	1098 (5.8%)
Active liver disease	22 (0.2%)	22 (0.2%)	44 (0.2%)
Elevated LFTs while taking statin	81 (0.9%)	84 (0.9%)	165 (0.9%)
Taking concomitant medications that have precautions/warnings with statins	14 (0.1%)	12 (0.1%)	26 (0.1%)
Advanced age	79 (0.8%)	74 (0.8%)	153 (0.8%)
Low BMI	3 (<0.1%)	6 (<0.1%)	9 (<0.1%)
Subject unable to tolerate 2 different statins	192 (2.0%)	207 (2.2%)	399 (2.1%)
Other documented reason that the subject is unable to take the maximum statin dose	210 (2.2%)	216 (2.3%)	426 (2.3%)
Other	201 (2.1%)	205 (2.2%)	406 (2.1%)

Numbers analysed

The number of patients included in each analysis population is provided in Table 9 below. The randomized population consisted of 18 924 patients, 9462 in the alirocumab group and 9462 in the placebo group. All patients were included in the ITT population. Almost all patients (18 894, 99.8%) received at least one dose of double-blind IMP and were included in the safety population. The ADA population included 18 188 patients.

Table 9: Analysis populations

	Placebo	Alirocumab	All
Randomized population	9462 (100%)	9462 (100%)	18924 (100%)
Efficacy populations			
Intent-to-Treat (ITT)	9462 (100%)	9462 (100%)	18924 (100%)
Safety population	9443	9451	18894
Anti-alirocumab antibody population	9097	9091	18188

Note: For the safety and anti-alirocumab antibody populations, patients are tabulated according to treatment actually received (as treated).
For the other populations, patients are tabulated according to their randomized treatment.
PGM=PRODOPS/SAR236553/EFC11570/CSR/REPORT/PGM/dis_std_populations_r_t.sas
OUT=REPORT/OUTPUT/dis_std_populations_r_t_i.rtf (03MAY2018 - 14:14)

Outcomes and estimation

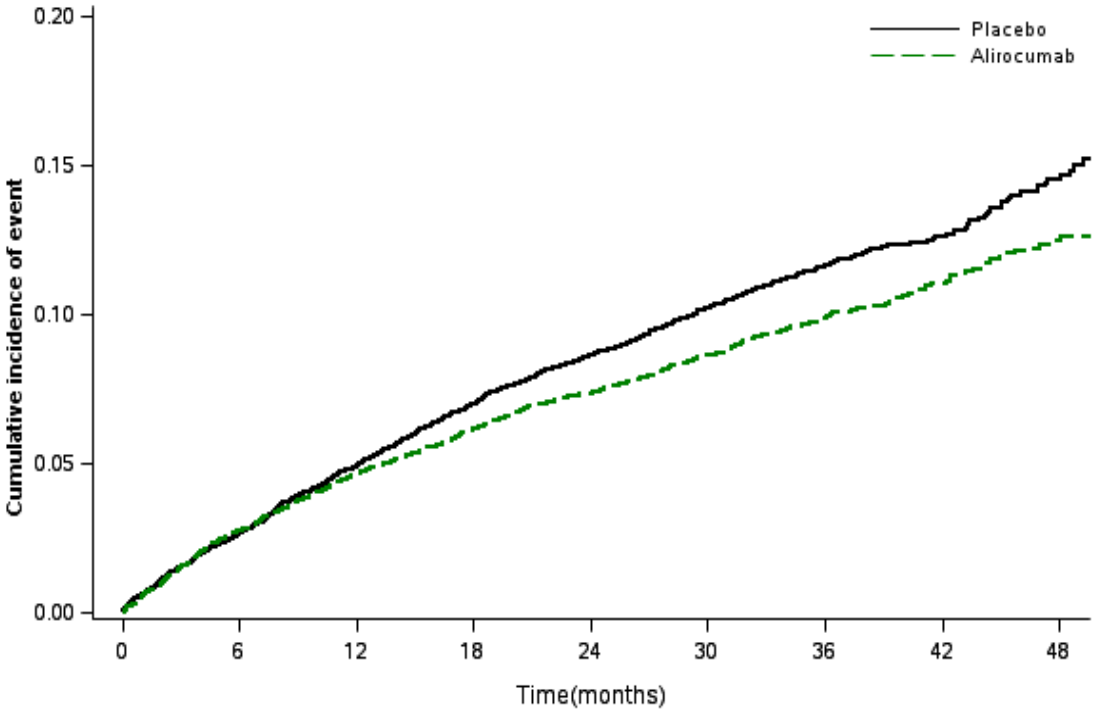
Study treatment

Of the 9451 patients randomized and treated in the alirocumab group, 2615 (27.7%) had their dose up-titrated to 150 mg. Of these 2615 patients, 805 (8.5% of the total number of patients) had their dose subsequently down-titrated to 75 mg. A total of 730 (7.7%) patients while receiving alirocumab 75 mg Q2W were switched to placebo due to 2 consecutive LDL-C values <15 mg/dL (0.39 mmol/L), most of them between 4 to 12 months after initiation of treatment with alirocumab.

The median duration of follow-up for CV events/vital status was approximately 33 months which resulted in more than 53 000 patient-years of follow-up. Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and death, respectively, highlighting the robustness in the collection of the data and consequently in the results.

Primary endpoint

Alirocumab significantly reduced the risk of MACE-plus (composite endpoint of CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, or UA requiring hospitalization) as compared to placebo. The primary endpoint occurred in 903 (9.5%) patients in the alirocumab group and in 1052 (11.1%) patients in the placebo group, corresponding to a relative risk reduction of 15.0% (HR: 0.85; 95% CI: 0.78 to 0.93, p=0.0003) as illustrated in Figure 3 below. The Kaplan-Meier cumulative incidence curves for first occurrence of MACE-plus for the alirocumab and placebo groups began to diverge at approximately 1 year after randomization and continued to diverge up to the end of the study.



Number at Risk

Placebo	9462	9172	8802	8390	8198	5558	3471	1794	629
Alirocumab	9462	9178	8843	8500	8343	5687	3574	1856	653

Figure 3: Time to first occurrence of MACE-plus (primary efficacy endpoint) as per CEC - Kaplan-Meier cumulative incidence curve ITT population - EFC11570

The most common first event of the composite endpoint in the study was non-fatal MI for 68.1% (615/903) and 66.3% (698/1052) of the cases of MACE-plus in the alirocumab and placebo groups, respectively. For the other events contributing to the composite endpoint of MACE-plus, the occurrence was by decreasing frequency as follows: CHD death (including undetermined causes of death), fatal or non-fatal ischemic stroke (including “stroke not otherwise specified”), and UA requiring hospitalization (with this component accounting for only 3.2% [29/903] and 4.9% [52/1052] of cases in the alirocumab and placebo groups, respectively). Significant reductions of 14%, 27%, and 39% were observed in the risk of non-fatal MI, ischemic stroke, and UA requiring hospitalization, respectively. A positive trend in the risk of CHD death (also main secondary endpoint) with a reduction of 8% was also observed.

Table 10: Time to first occurrence of MACE-plus (primary efficacy endpoint) as per CEC - ITT population – EFC11570

	Placebo (N=9462)	Alirocumab (N=9462)
Any MACE-plus [n (%)]	1052 (11.1%)	903 (9.5%)
Incidence rate per 100 patient years (95% CI)	4.2 (3.9 to 4.4)	3.5 (3.3 to 3.8)
Censorings [n (%)]	8410 (88.9%)	8559 (90.5%)
Reason for censoring		
No event at CSED	8164 (97.1%)	8339 (97.4%)
Death for reason other than MACE-plus	107 (1.3%)	90 (1.1%)
Post-CSED death	1 (<0.1%)	1 (<0.1%)
Lost to follow-up	14 (0.2%)	9 (0.1%)
Patient did not want to continue	94 (1.1%)	100 (1.2%)
Site terminated by sponsor	14 (0.2%)	11 (0.1%)
Missing reason	16 (0.2%)	9 (0.1%)
Comparison vs. placebo		
Hazard ratio (95.02 % CI)		0.85 (0.78 to 0.93)
Hazard ratio (95 % CI)		0.85 (0.78 to 0.93)
Stratified log-Rank test two-sided p-value		0.0003*
First event of the composite endpoint		
Non-fatal MI	698 (66.3%)	615 (68.1%)
CHD death (including undetermined cause)	168 (16.0%)	161 (17.8%)
Fatal or non-fatal ischemic stroke (including stroke not otherwise specified)	131 (12.5%)	98 (10.9%)
Unstable angina requiring hospitalization	52 (4.9%)	29 (3.2%)
Non-fatal MI/Ischemic stroke (including stroke not otherwise specified)	3 (0.3%)	0

Incidence rate per 100 patient years calculated as number of patients with an event divided by total patient years (up to date of the first event if any, else up to censoring date) and multiplied by 100
Hazard ratio, p-value come from Cox regression model and log-rank test stratified on geographical region (North America, South America, Western Europe, Eastern Europe, Asia, Rest of the world)
The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at final analysis at the 0.0498 level

Table 11 - Primary efficacy endpoint and its components – Time to first occurrence – ITT population - EFC11570

Endpoint, n (%)	HR (95% CI)	Log-rank p-value
MACE-plus	0.85 (0.78, 0.93)	0.0003
CHD death	0.92 (0.76, 1.11)	0.3824
Non-fatal MI	0.86 (0.77, 0.96)	0.0058
Ischemic stroke	0.73 (0.57, 0.93)	0.0097
UA with hospitalization	0.61 (0.41, 0.92)	0.0177

Extracted from 16-2-6-eff-data [16.2.6.1.1.1], [16.2.6.2.5.1], [16.2.6.2.8.1], [16.2.6.2.9.1], and [16.2.6.2.10.1]

HR = hazard ratio, MACE-plus = composite endpoint of CHD death, non-fatal MI, fatal and non-fatal ischaemic stroke, or UA requiring hospitalization, CHD = coronary heart disease, MI = myocardial infarction, UA = unstable angina

Secondary endpoints

A hierarchical testing procedure was used to test the main secondary endpoints while controlling for multiplicity. Statistical significance was reached down through the composite endpoint "all-cause mortality, non-fatal MI, non-fatal ischemic stroke". For this composite endpoint including all-cause mortality instead of CHD or CV death and 2 other hard endpoints, all the components individually demonstrated nominal statistical significant reductions in the alirocumab versus placebo groups.

CHD death was the first endpoint for which statistical significance was not reached. P-values for the subsequent endpoints in the hierarchy, starting from CV death, were provided for descriptive purpose. Although this hierarchical procedure was stopped when the main secondary endpoint CHD death did not reach statistical significance despite a risk reduction of 8%, the subsequent 2 main secondary endpoints, CV death and all-cause death, also showed risk reductions of 12% and 15% in favor of alirocumab, respectively, with nominal p-values of 0.1528 for CV death and 0.026 for all-cause death (Table 12).

Table 12 - Hierarchical testing strategy applied - ITT population - EFC11570

Endpoint	Analysis	Hazard ratio (95.02% CI)	P-value
Time to first occurrence of any CHD event as per CEC	ITT	0.88 (0.81 to 0.95)	0.0013*
Time to first occurrence of any major CHD event as per CEC	ITT	0.88 (0.80 to 0.96)	0.0060*
Time to first occurrence of any CV event as per CEC	ITT	0.87 (0.81 to 0.94)	0.0003*
Time to first occurrence of all-cause mortality, non-fatal MI, non-fatal ischemic stroke as per CEC	ITT	0.86 (0.79 to 0.93)	0.0003*
Time to CHD death as per CEC	ITT	0.92 (0.76 to 1.11)	0.3824
Time to CV death as per CEC	ITT	0.88 (0.74 to 1.05)	0.1528
Time to all-cause death	ITT	0.85 (0.73 to 0.98)	0.0261

The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.0498 level

For the first 4 endpoints up to the composite endpoint "all-cause mortality, non-fatal MI, non-fatal ischemic stroke" where a significant reduction in the risk was observed, a consistent profile of the Kaplan-Meier cumulative incidence curve was seen, with the 2 curves starting to diverge from about 1 year after randomization.

Overall, the analysis of all-cause death indicated that CV death accounted for 63.9% of the total 726 deaths from any cause. Thus the treatment effect observed on all-cause death was partially driven by

the treatment effect observed on non-CV deaths (HR: 0.77; 95% CI: 0.59 to 1.01). During the treatment-emergent adverse event (TEAE) period the reduction of all-cause death with alirocumab over placebo (233 [2.5%] in the alirocumab groups versus 273 [2.9%] in the placebo group) was driven by CV death (169 [1.8%] in the alirocumab group versus 202 [2.1%] in the placebo group) and not by non-CV deaths (54 [0.6%] in the alirocumab group versus 59 [0.6%] in the placebo group). In the post-treatment period up to the CSED, the reduction in all-cause death was primarily driven by non-CV death (40 [0.4%] in the alirocumab group versus 62 [0.7%] in the placebo group).

For non-CV death, the effect was driven by pulmonary events (mainly pneumonia and lung cancer; 33 [0.3%] and 47 [0.5%] patients in the alirocumab and placebo groups, respectively), gastrointestinal events (6 [<0.1%] and 13 [0.1%] patients, respectively), and other non-CV causes (including cancers; 22 [0.2%] and 28 [0.3%] patients, respectively) with a difference in favour of alirocumab.

Table 13 - Deaths during efficacy period according to adjudication - ITT population – EFC11570

Primary cause of death as per adjudication n(%)	Placebo (N=9462)	Alirocumab (N=9462)
CHD death (excluding undetermined cause of death)	196 (2.1%)	184 (1.9%)
Acute myocardial infarction	51 (0.5%)	41 (0.4%)
Sudden cardiac death	117 (1.2%)	109 (1.2%)
Heart failure or cardiogenic shock	23 (0.2%)	25 (0.3%)
Cardiovascular procedure	2 (<0.1%)	3 (<0.1%)
Other cardiovascular causes	3 (<0.1%)	6 (<0.1%)
Any cardiovascular (excluding undetermined cause of death)	245 (2.6%)	219 (2.3%)
Acute myocardial infarction	51 (0.5%)	41 (0.4%)
Sudden cardiac death	117 (1.2%)	109 (1.2%)
Heart failure or cardiogenic shock	33 (0.3%)	29 (0.3%)
Stroke	24 (0.3%)	19 (0.2%)
Ischemic	14 (0.1%)	10 (0.1%)
Hemorrhagic	8 (<0.1%)	9 (<0.1%)
Undetermined	2 (<0.1%)	0
Cardiovascular procedure	4 (<0.1%)	5 (<0.1%)
Cardiovascular hemorrhage	2 (<0.1%)	0
Other cardiovascular causes	14 (0.1%)	16 (0.2%)
Any non-cardiovascular	121 (1.3%)	94 (1.0%)
Pulmonary	47 (0.5%)	33 (0.3%)
Renal	2 (<0.1%)	5 (<0.1%)
Gastrointestinal	13 (0.1%)	6 (<0.1%)
Hepatobiliary	4 (<0.1%)	3 (<0.1%)
Pancreatic	2 (<0.1%)	6 (<0.1%)
Hemorrhage	6 (<0.1%)	3 (<0.1%)
Non-cardiovascular procedure or surgery	2 (<0.1%)	3 (<0.1%)
Accidental	8 (<0.1%)	10 (0.1%)
Suicide	5 (<0.1%)	2 (<0.1%)
Neurological process	4 (<0.1%)	1 (<0.1%)
Other non-cardiovascular	28 (0.3%)	22 (0.2%)
Non cardiovascular: Malignant	56 (0.6%)	43 (0.5%)

Primary cause of death as per adjudication n(%)	Placebo (N=9462)	Alirocumab (N=9462)
Worsening prior malignancy	9 (<0.1%)	3 (<0.1%)
New malignancy	47 (0.5%)	40 (0.4%)
Non cardiovascular: Infection	31 (0.3%)	24 (0.3%)
Undetermined	26 (0.3%)	21 (0.2%)

Note: Only the primary cause of death is adjudicated.

Lipid reduction

Lipid parameters were analyzed using an ITT approach (based on the ITT population) including all lipid values, regardless of whether the patient was continuing therapy or not (therefore included lipid values of the 730 patients who switched to placebo due to 2 consecutive LDL-C values <15 mg/dL [0.39 mmol/L]). In case of missing values, different imputations were performed according to whether the missing value was during the treatment period or post-treatment.

In addition, analyses were also conducted using an on-treatment approach (based on the randomized and treated population) only including lipid data collected during the treatment period (up to 21 days after the last alirocumab injection for patients prematurely discontinued as well as patients switched to placebo). In case of missing values, imputations were performed from the other on-treatment values.

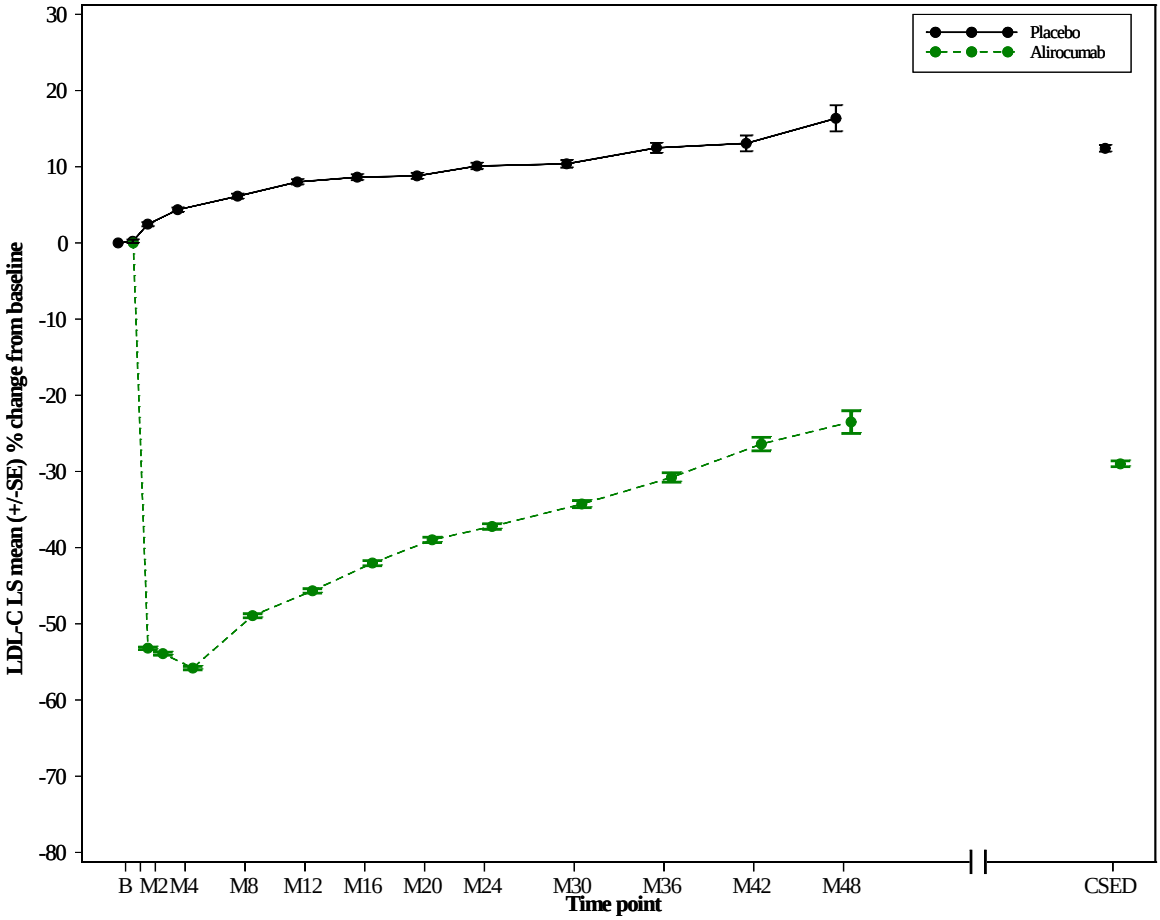
These 2 approaches to the analysis of the lipid parameters and more particularly for LDL-C provide different information relevant to the understanding of the effect of alirocumab in the context of this large CV outcomes study. The ITT approach evaluates the effect of alirocumab on a population of patients in whom the therapy is managed in accordance with the inclusion/exclusion criteria of the study and provides the best estimate of the LDL-C levels over the course of the study during the same period in which the effect on CV events and mortality was assessed. The on-treatment approach is relevant to the clinical question of efficacy as it evaluates the effects that can be expected in patients when the product is actually used.

Patients in the alirocumab group achieved a mean LDL-C value of 42.7 mg/dL (1.106 mmol/L) at Month 1 (mean baseline value: 92.4 mg/dL, 2.394 mmol/L), and mean LDL-C value was 66.4 mg/dL (1.721 mmol/L) at Month 48.

In the ITT analysis, a LS mean difference in percent change from baseline of -39.9% (95% CI: -44.6 to -35.2; nominal p<0.0001) was observed at Month 48. In the alirocumab group, mean percent change from baseline LDL-C reached a nadir of -55.8% at Month 4, rising to -45.7% at Month 12, and -23.5% at Month 48, and corresponding to differences versus placebo of -60.1%, -53.7%, and -39.9%, respectively. Evolution of LDL-C over time is illustrated in the figure below.

When comparing result from the on-treatment analysis, which excluded off-treatment LDL-C values for patients prematurely withdrawn from study treatment and those of the 730 patients switched to placebo due to 2 consecutive values <15 mg/dL (0.39 mmol/L), a LS mean difference of -54.7% (95% CI: -57.5 to -52.0; nominal p<0.0001) was noted at Month 48. Mean changes from baseline in LDL-C in the alirocumab group at Months 4, 12, and 48 were -58.3%, -52.8%, and -40.1%, respectively, corresponding to differences versus placebo of -62.7%, -59.0%, and -54.7%, respectively

Figure 4 - LDL-Cholesterol LS mean (+/- SE) percent change from baseline: Time profile - ITT analysis - ITT population - EFC11570



In the ITT analysis, a significant decrease in Apo B from baseline to Month 24 was observed in the alirocumab group (LS mean: -31.6%) compared to the placebo group (LS mean: +9.0%), with an LS mean difference for alirocumab versus placebo of -40.6% (95% CI: -41.7 to -39.5; nominal p<0.0001). The evolution over time for Apo B followed the same pattern as for LDL-C.

In the ITT analysis, a significant decrease in non-HDL-C from baseline to Month 48 was observed in the alirocumab group (LS mean: -18.6%) compared to the placebo group (+13.9%), with an LS mean difference of –32.5% (95% CI: -36.1 to -28.9; nominal p<0.0001). The evolution over time for non-HDL-C followed the same pattern as for LDL-C.

In the ITT analysis, a significant decrease in Lp(a) from baseline to Month 12 was observed in the alirocumab group (robust mean: -23.4%) compared with the placebo group (robust mean: -3.5%); with a robust mean difference for alirocumab versus placebo of –20.0% (95% CI: -20.9 to -19.0; nominal p<0.0001).

Ancillary analyses

Sensitivity analysis for the primary endpoint

Other analyses of the primary endpoint, including sensitivity analyses and supportive analyses that were performed provide additional information with regard to the consistency and robustness of the results observed in the study. Among these analyses, 2 analyses are of particular interest:

- A sensitivity analysis, the tipping-point analysis for incomplete follow-up for CV events: although in terms of patient-years, missing information represented only 0.9% leading to 99.1% ascertainment rate which is a very high rate, a tipping-point analysis was done to assess the robustness of the results relative to missing information on the primary endpoint.

  This tipping point analysis for MACE-plus was conducted using 2 different scenarios. In both scenarios, the tipping-point was reached for an imputed HR between 18 and 18.5, and between 11.5 and 12, for the 2 scenarios. It was concluded from these analyses that the results were robust to missing status on the primary endpoint since these tipping-points were highly implausible.

- A supportive analysis of the relationship between achieved LDL-C and risk of MACE-plus: this analysis that took into account baseline and all post-baseline LDL-C values did not assess the effect of alirocumab but rather assessed the association between LDL-C level (regardless of the way to achieve such levels including diet, physical activity, statins, other LMTs, or alirocumab) and MACE-plus risk.

Subgroup analyses

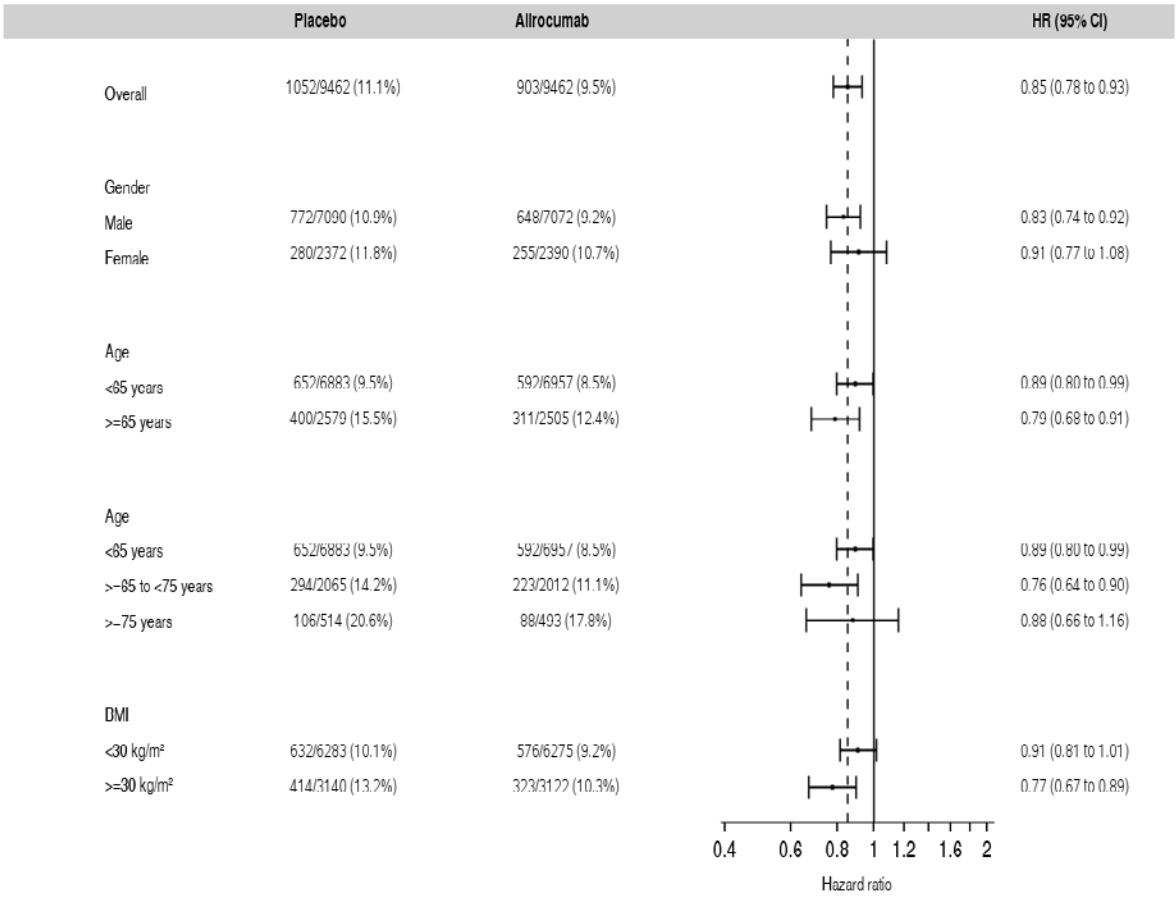
The relative risk reduction obtained with alirocumab compared to placebo was consistent (or higher) in patients with high CV risk according to baseline LDL-C ≥100 mg/dL as shown below according to main individual prognostic factors of MACE-plus (diabetes, BMI, time from ACS to randomization, baseline Lp[a] and CV risk scores [TIMI and abbreviated REACH scores]). Therefore, the 15% relative risk reduction with alirocumab led to a greater absolute risk reduction and greater benefit for the patients with higher baseline CV risks (ie, patients with diabetes, patients with BMI ≥30 kg/m², patients with baseline LDL-C ≥100 mg/dL, patients with baseline Lp[a] ≥50 mg/dL, and patients with high CV risk scores, and patients randomized shortly after the qualifying ACS event [<8 weeks, ≥8 weeks to <24 weeks]).

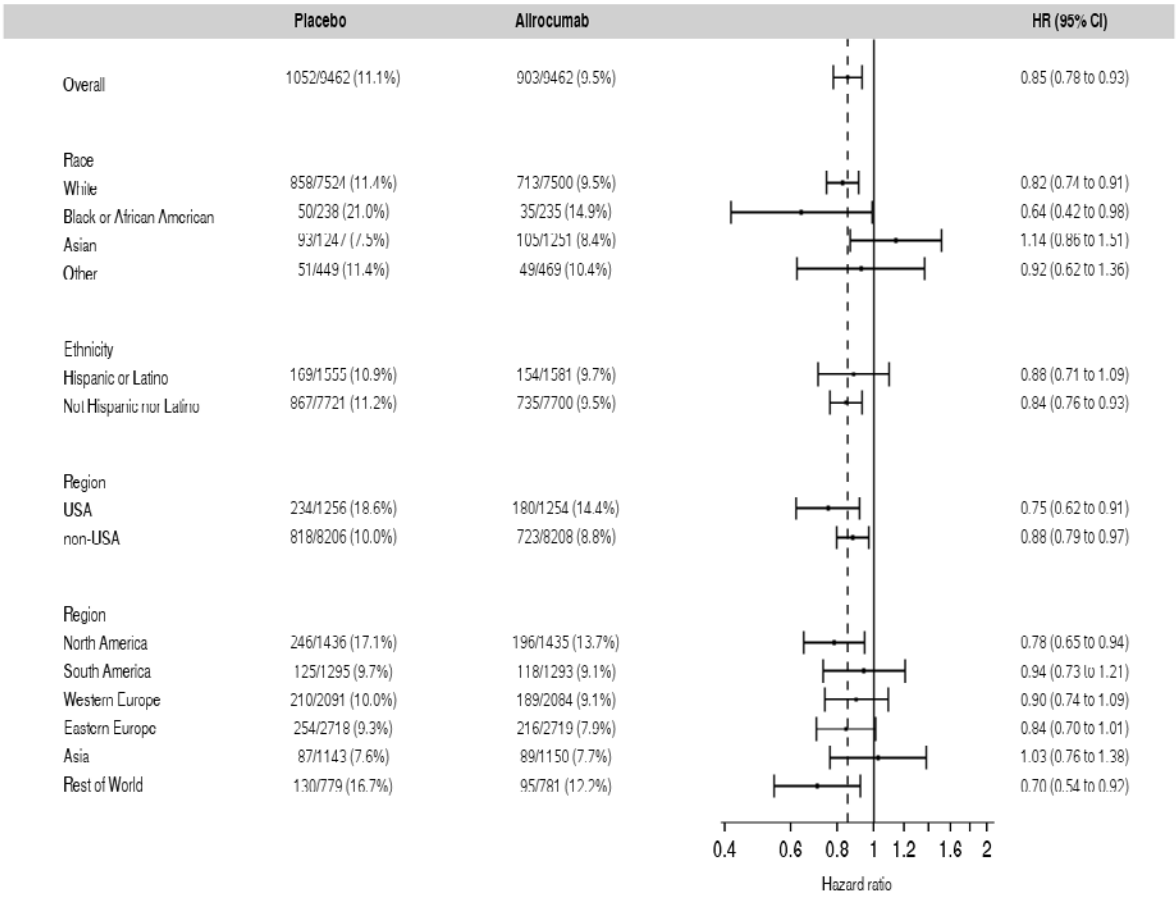
Table 14: Time to first occurrence of MACE-plus (primary endpoint) as per CEC according to risk scores and individual prognostic factors of CV events - ITT population - EFC11570

	Placebo n/N (%)	Alirocumab n/N (%)	Hazard ratio (95% CI)	Interaction p-value
BMI				0.0899
<30 kg/m²	632/6283 (10.1%)	576/6275 (9.2%)	0.91 (0.81 to 1.01)	
≥30 kg/m²	414/3140 (13.2%)	323/3122 (10.3%)	0.77 (0.67 to 0.89)	
Time from ACS event to randomization				0.7664
<8 weeks	322/2595 (12.4%)	279/2645 (10.5%)	0.85 (0.72 to 0.99)	
≥8 to <24 weeks	576/5078 (11.3%)	481/5035 (9.6%)	0.83 (0.74 to 0.94)	

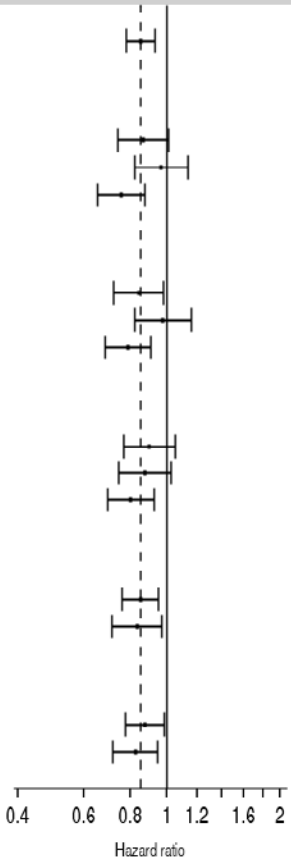
	Placebo n/N (%)	Alirocumab n/N (%)	Hazard ratio (95% CI)	Interaction p-value
≥24 weeks	154/1789 (8.6%)	143/1782 (8.0%)	0.91 (0.73 to 1.15)	
Diabetes mellitus status at baseline				0.9847
Diabetes	452/2751 (16.4%)	380/2693 (14.1%)	0.84 (0.74 to 0.97)	
Pre-Diabetes	380/4116 (9.2%)	331/4130 (8.0%)	0.86 (0.74 to 1.00)	
Normoglyceamic	220/2595 (8.5%)	192/2639 (7.3%)	0.85 (0.70 to 1.03)	
Baseline LDL-C				0.0891
<80 mg/dL / <2.07 mmol/L	341/3583 (9.5%)	296/3581 (8.3%)	0.86 (0.74 to 1.01)	
≥80 to <100 mg/dL / ≥2.07 to <2.59 mmol/L	291/3062 (9.5%)	283/3066 (9.2%)	0.96 (0.82 to 1.13)	
≥100 mg/dL / ≥2.59 mmol/L	420/2815 (14.9%)	324/2814 (11.5%)	0.76 (0.65 to 0.87)	
REACH score classification				0.8697
Reach risk score [-7 ; 0]	200/2886 (6.9%)	167/3011 (5.5%)	0.80 (0.65 to 0.98)	
Reach risk score [1 ; 3]	383/3895 (9.8%)	340/3828 (8.9%)	0.89 (0.77 to 1.03)	
Reach risk score [4 ; 9]	439/2604 (16.9%)	371/2555 (14.5%)	0.85 (0.74 to 0.97)	
Reach risk score [10 ; 19]	30/77 (39.0%)	25/68 (36.8%)	0.86 (0.51 to 1.47)	
TIMI score classification				0.5608
Low risk	298/4546 (6.6%)	249/4510 (5.5%)	0.84 (0.71 to 0.99)	
Intermediate risk	308/2754 (11.2%)	256/2816 (9.1%)	0.80 (0.68 to 0.94)	
High risk	446/2162 (20.6%)	398/2136 (18.6%)	0.89 (0.78 to 1.02)	

Note: Hazard ratio and p-value for treatment-by-subgroup factor interaction are based on Cox proportional hazard model including treatment, region, subgroup factor, and the treatment-by-subgroup interaction as covariates
The p-value is provided for descriptive purpose only

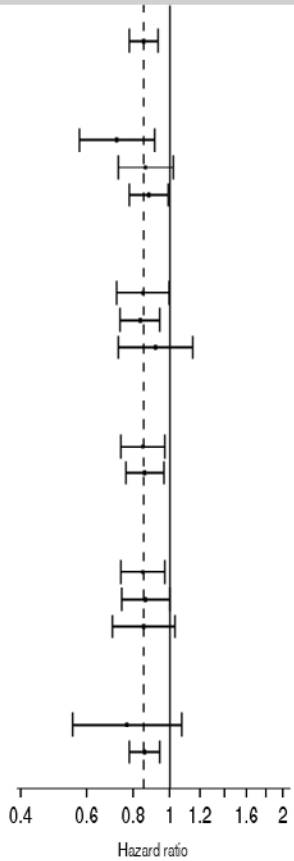

Placebo
Alirocumab
HR (95% CI)
Overall
1052/9462 (11.1%)
903/9462 (9.5%)
0.85 (0.78 to 0.93)
Gender
Male
772/7090 (10.9%)
648/7072 (9.2%)
0.83 (0.74 to 0.92)
Female
280/2372 (11.8%)
255/2390 (10.7%)
0.91 (0.77 to 1.08)
Age
<65 years
652/6883 (9.5%)
592/6957 (8.5%)
0.89 (0.80 to 0.99)
>=65 years
400/2579 (15.5%)
311/2505 (12.4%)
0.79 (0.68 to 0.91)
Age
<65 years
652/6883 (9.5%)
592/6957 (8.5%)
0.89 (0.80 to 0.99)
>=65 to <75 years
294/2065 (14.2%)
223/2012 (11.1%)
0.76 (0.64 to 0.90)
>=75 years
106/514 (20.6%)
88/493 (17.8%)
0.88 (0.66 to 1.16)
BMI
<30 kg/m²
632/6283 (10.1%)
576/6275 (9.2%)
0.91 (0.81 to 1.01)
>=30 kg/m²
414/3140 (13.2%)
323/3122 (10.3%)
0.77 (0.67 to 0.89)
0.4
0.6
0.8
1
1.2
1.6
2
Hazard ratio

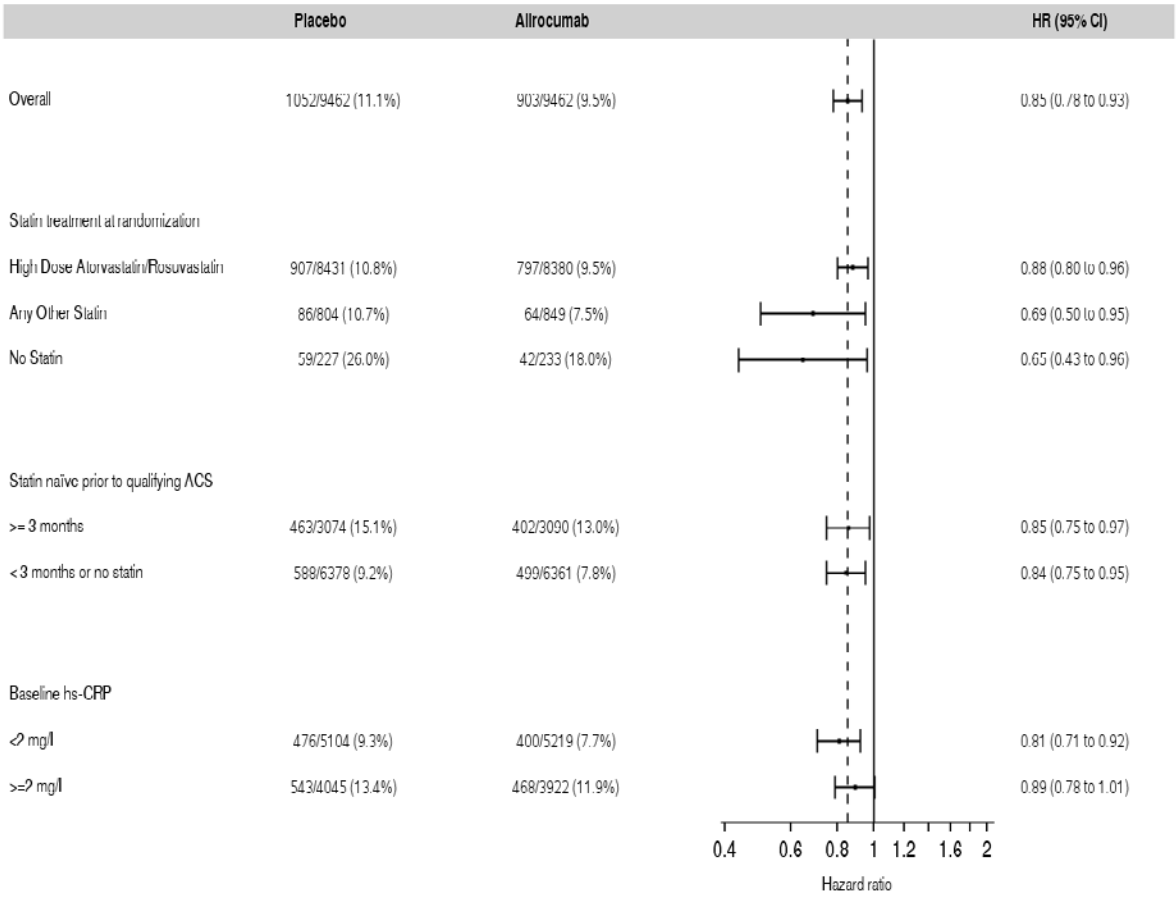

Placebo
Alirocumab
HR (95% CI)
Overall
1052/9462 (11.1%)
903/9462 (9.5%)
0.85 (0.78 to 0.93)
Race
White
858/7521 (11.4%)
713/7500 (9.5%)
0.82 (0.74 to 0.91)
Black or African American
50/238 (21.0%)
35/235 (14.9%)
0.64 (0.42 to 0.98)
Asian
93/1247 (7.5%)
105/1251 (8.4%)
1.14 (0.86 to 1.51)
Other
51/449 (11.4%)
49/469 (10.4%)
0.92 (0.62 to 1.36)
Ethnicity
Hispanic or Latino
169/1555 (10.9%)
154/1581 (9.7%)
0.88 (0.71 to 1.09)
Not Hispanic nor Latino
867/7721 (11.2%)
735/7700 (9.5%)
0.84 (0.76 to 0.93)
Region
USA
234/1256 (18.6%)
180/1254 (14.4%)
0.75 (0.62 to 0.91)
non-USA
818/8206 (10.0%)
723/8208 (8.8%)
0.88 (0.79 to 0.97)
Region
North America
246/1436 (17.1%)
196/1435 (13.7%)
0.78 (0.65 to 0.94)
South America
125/1295 (9.7%)
118/1293 (9.1%)
0.94 (0.73 to 1.21)
Western Europe
210/2091 (10.0%)
189/2084 (9.1%)
0.90 (0.74 to 1.09)
Eastern Europe
254/2718 (9.3%)
216/2719 (7.9%)
0.84 (0.70 to 1.01)
Asia
87/1143 (7.6%)
89/1150 (7.7%)
1.03 (0.76 to 1.38)
Rest of World
130/779 (16.7%)
95/781 (12.2%)
0.70 (0.54 to 0.92)
0.4
0.6
0.8
1
1.2
1.6
2
Hazard ratio

	Placebo	Alirocumab	HR (95% CI)
Overall	1052/9462 (11.1%)	903/9462 (9.5%)	0.85 (0.78 to 0.93)
Baseline LDL-C			
<80 mg/dL / <2.07 mmol/L	341/3583 (9.5%)	296/3581 (8.3%)	0.86 (0.74 to 1.01)
>=80 to <100 mg/dL / >=2.07 to <2.59 mmol/L	291/3062 (9.5%)	283/3066 (9.2%)	0.96 (0.82 to 1.13)
>=100 mg/dL / >=2.59 mmol/L	420/2815 (14.9%)	324/2814 (11.5%)	0.76 (0.65 to 0.87)
Baseline non-HDL-C			
<110 mg/dL / < 2.84 mmol/L	357/3928 (9.1%)	308/3999 (7.7%)	0.84 (0.72 to 0.98)
>=110 to <130 mg/dL / >=2.84 to <3.37 mmol/L	258/2535 (10.2%)	248/2471 (10.0%)	0.97 (0.82 to 1.16)
>=130 mg/dL / >=3.37 mmol/L	437/2997 (14.6%)	347/2991 (11.6%)	0.78 (0.68 to 0.90)
Baseline Apo B			
<75 mg/dL / <0.75 g/L	317/3643 (8.7%)	290/3687 (7.9%)	0.90 (0.76 to 1.05)
>=75 to <90 mg/dL / >=0.75 g/L to <0.9 g/L	312/2906 (10.7%)	281/2968 (9.5%)	0.87 (0.74 to 1.02)
>=90 mg/dL / >=0.9 g/L	423/2913 (14.5%)	332/2807 (11.8%)	0.80 (0.69 to 0.92)
Baseline Lp(a)			
<50 mg/dl / < 0.5 g/l	660/6345 (10.4%)	569/6389 (8.9%)	0.85 (0.76 to 0.95)
>=50 mg/dL / >= 0.5 g/L	355/2780 (12.8%)	295/2736 (10.8%)	0.83 (0.71 to 0.97)
Baseline fasting TG			
< 150 mg/dL / <1.7 mmol/L	580/5671 (10.2%)	522/5766 (9.1%)	0.87 (0.77 to 0.98)
>= 150 mg/dL / >=1.7 mmol/L	445/3587 (12.4%)	359/3498 (10.3%)	0.82 (0.72 to 0.94)



	Placebo	Alirocumab	HR (95% CI)
Overall	1052/9462 (11.1%)	903/9462 (9.5%)	0.85 (0.78 to 0.93)
Index ACS event			
UA	173/1614 (10.7%)	121/1568 (7.7%)	0.72 (0.57 to 0.91)
STEMI	289/3235 (8.9%)	257/3301 (7.8%)	0.86 (0.73 to 1.02)
NSTEMI	589/4601 (12.8%)	521/4574 (11.4%)	0.88 (0.78 to 0.99)
Time from ACS event to randomization			
<8 weeks	322/2595 (12.4%)	279/2645 (10.5%)	0.85 (0.72 to 0.99)
>=8 to <24 weeks	576/5078 (11.3%)	481/5035 (9.6%)	0.83 (0.74 to 0.94)
>=24 weeks	154/1789 (8.6%)	143/1782 (8.0%)	0.91 (0.73 to 1.15)
Diabetes mellitus at baseline			
Diabetes	452/2751 (16.4%)	380/2693 (14.1%)	0.84 (0.74 to 0.97)
Pre-Diabetes/Normoglycaemic	600/6711 (8.9%)	523/6769 (7.7%)	0.86 (0.76 to 0.96)
Diabetes mellitus status at baseline			
Diabetes	452/2751 (16.4%)	380/2693 (14.1%)	0.84 (0.74 to 0.97)
Pre-Diabetes	380/4116 (9.2%)	331/4130 (8.0%)	0.86 (0.74 to 1.00)
Normoglycaemic	220/2595 (8.5%)	192/2639 (7.3%)	0.85 (0.70 to 1.03)
Prior stroke			
Prior Stroke	77/305 (25.2%)	61/306 (19.9%)	0.77 (0.55 to 1.07)
No Prior Stroke	975/9157 (10.6%)	842/9156 (9.2%)	0.85 (0.78 to 0.94)




Placebo
Alirocumab
HR (95% CI)
Overall
1052/9462 (11.1%)
903/9462 (9.5%)
0.85 (0.78 to 0.93)
Statin treatment at randomization
High Dose Atorvastatin/Rosuvastatin
907/8431 (10.8%)
797/8380 (9.5%)
0.88 (0.80 to 0.96)
Any Other Statin
86/804 (10.7%)
64/849 (7.5%)
0.69 (0.50 to 0.95)
No Statin
59/227 (26.0%)
42/233 (18.0%)
0.65 (0.43 to 0.96)
Statin naïve prior to qualifying ACS
>= 3 months
463/3074 (15.1%)
402/3090 (13.0%)
0.85 (0.75 to 0.97)
< 3 months or no statin
588/6378 (9.2%)
499/6361 (7.8%)
0.84 (0.75 to 0.95)
Baseline hs-CRP
<2 mg/l
476/5104 (9.3%)
400/5219 (7.7%)
0.81 (0.71 to 0.92)
>=2 mg/l
543/4045 (13.4%)
468/3922 (11.9%)
0.89 (0.78 to 1.01)
0.4
0.6
0.8
1
1.2
1.6
2
Hazard ratio

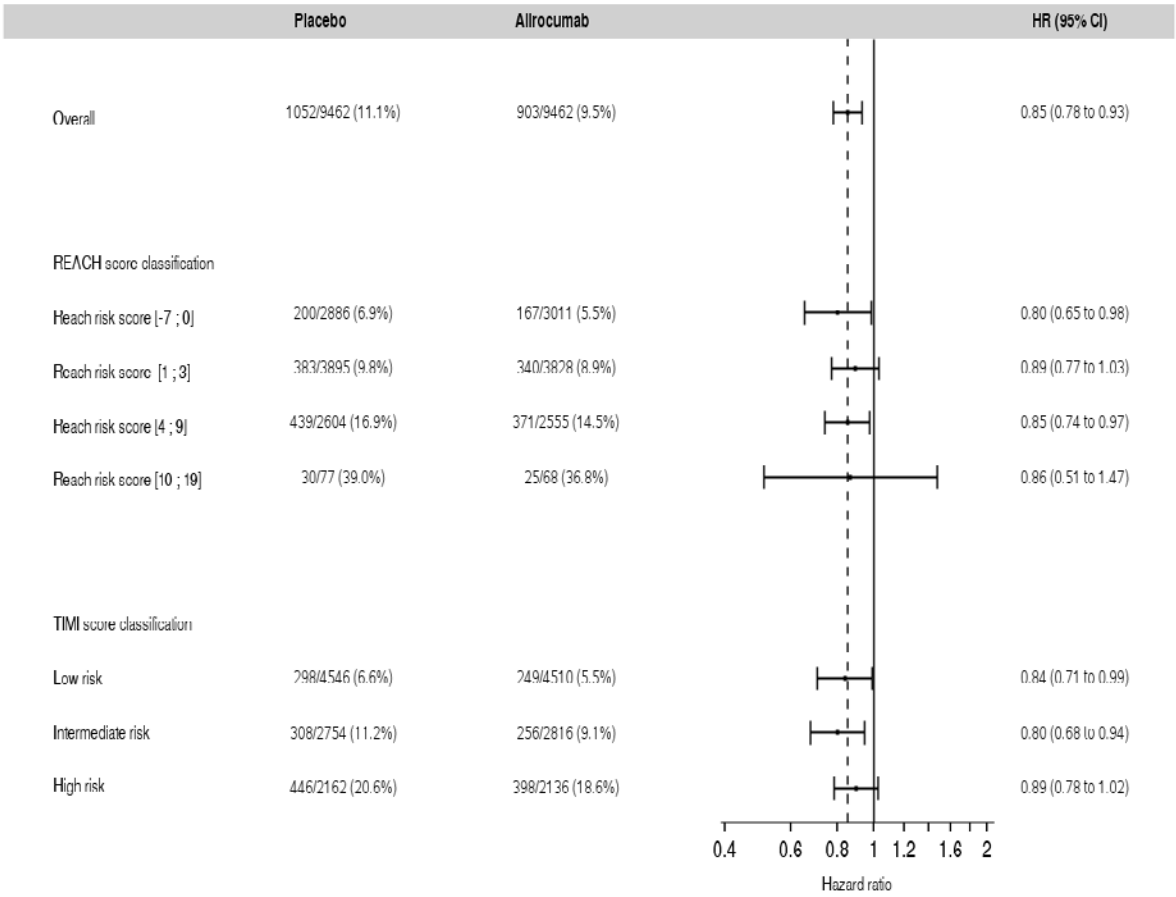


Figure 5: Time to first occurrence of MACE-plus (primary endpoint) as per CEC according to demographic characteristics - Forest plot (1/2) - ITT population – EFC11570

Subgroup of patients with baseline LDL-C ≥100 mg/dL

In the subgroup of patients with baseline LDL-C ≥100 mg/dL, the risk of MACE-plus was reduced by 24% as compared to placebo (HR: 0.76, 95% CI: 0.65 to 0.87). The greater treatment effect of alirocumab observed in this subgroup of patients can be explained by the higher absolute reduction in LDL-C versus placebo (-43.8 to -65.2 mg/dL during the course of the study) in those patients with higher LDL-C values at baseline (mean baseline LDL-C of 128.5 mg/dL) compared to patients with lower LDL-C values at baseline (from -27.2 to -44.1 mg/dL during the course of the study for patients with baseline LDL-C <80 mg/dL and from -37.4 to -54.2 mg/dL during the course of the study for patients with baseline LDL-C ≥80 and <100 mg/dL).

In addition, as expected based on the literature, patients in the placebo group with high baseline LDL-C (≥100 mg/dL) in the OUTCOMES study have a higher CV risk (event rate of 14.9%) compared to patients in the placebo group with lower baseline LDL-C (9.5%). This higher baseline CV risk led to a greater absolute reduction in MACE-plus in the alirocumab group compared to the placebo group (3.4% observed in the study).

In this particular subgroup, the Kaplan-Meier cumulative incidence curves for first occurrence of MACE-plus for the alirocumab and placebo groups began to diverge at about 6 months after randomization and continued to separate up to the end of the study.

Post-hoc analyses revealed that the magnitude of the treatment effect of alirocumab over placebo for all other efficacy endpoints was consistently greater than that seen in the overall population, supporting the greater benefit derived for this subgroup of patients. In particular, a notable benefit was seen for all death endpoints, with a reduction in the risk of CHD death of 28%, a reduction in the risk of CV death of 31%, and a reduction in the risk of all-cause death of 29% (see Table 15 below). This observation of a greater effect on different endpoints and notably on all-cause death and CV death in patients with baseline LDL-C ≥100 mg/dL is in line with a recent meta-analysis reported by Navarese et al. which showed a death benefit only in patients with baseline LDL-C ≥100 mg/dL.

Table 15 - Time to first occurrence of efficacy endpoints – ITT population - Patients with baseline LDL-C ≥100 mg/dL – EFC11570

Endpoint, n (%)	Placebo n/N (%)	Alirocumab n/N (%)	HR (95% CI)
MACE-plus	420/2815 (14.9%)	324/2814 (11.5%)	0.76 (0.65 to 0.87)
Non-fatal MI	290/2815 (10.3%)	231/2814 (8.2%)	0.79 (0.66 to 0.93)
Ischemic stroke	67/2815 (2.4%)	41/2814 (1.5%)	0.60 (0.41 to 0.89)
UA with hospitalization	23/2815 (0.8%)	11/2814 (0.4%)	0.48 (0.23 to 0.98)
CHD death	96/2815 (3.4%)	69/2814 (2.5%)	0.72 (0.53 to 0.98)
CV death	117/2815 (4.2%)	81/2814 (2.9%)	0.69 (0.52 to 0.92)
All-cause death	161/2815 (5.7%)	114/2814 (4.1%)	0.71 (0.56 to 0.90)

Extracted from 5.3.5.1 Study EFC11570 16-2-6-eff-response-data [16.2.6.1.4.4], [16.2.6.2.8.4], [16.2.6.2.9.4], [16.2.6.2.10.4], [16.2.6.2.5.4], [16.2.6.2.6.4], [16.2.6.2.7.4]
CHD = coronary heart disease; HR = hazard ratio; MACE-plus = composite endpoint of CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, or UA requiring hospitalization; MI = myocardial infarction; UA = unstable angina.

Patients with baseline LDL-C < 70mg/dL (1.81 mmol/L)

The table below presents the primary efficacy endpoint data by subgroup according to baseline low-density lipoprotein cholesterol (LDL-C) values (LDL-C < 70mg/dL or LDL-C ≥ 70 mg/dL). In patients with baseline LDL-C < 70mg/dL (whatever the LMT regimen during the run-in phase), the primary endpoint occurred in 8.6% patients in the alirocumab group and 9.6% patients in the placebo group, with a Hazard Ratio (HR) of 0.90 (95% CI: 0.73-1.11). The treatment effect was not significantly different in patients with baseline LDL-C <70 versus ≥70 mg/dL (interaction p value of 0.53).

Table 16 - Time to first occurrence of MACE-plus (primary endpoint) as per CEC according to LDL-C at baseline - ITT population

	Placebo n/N (%)	Alirocumab n/N (%)	Hazard ratio (95% CI)	Interaction p-value
Baseline LDL-C				0.5348
<70 mg/dL / <1.81 mmol/L	181/1881 (9.6%)	161/1870 (8.6%)	0.90 (0.73 to 1.11)	
≥70 mg/dL / ≥1.81 mmol/L	871/7579 (11.5%)	742/7591 (9.8%)	0.84 (0.76 to 0.92)	

Note: Hazard ratio and p-value for treatment-by-subgroup factor interaction are based on Cox proportional hazard model including treatment, region, subgroup factor, and the treatment-by-subgroup interaction as covariates
The p-value is provided for descriptive purpose only
PGM=PRODOPS/SAR236553/EFC11570/PUB_2018/REPORT/PGM/eff_sg_hr_cv4_i_t.sas
OUT=REPORT/OUTPUT/eff_sg_hr_cv4_peff_ldlgr4_i_t_i.rtf (02OCT2018 - 16:12)

Relationship between LDL-C reduction and CV risk reduction

Per the CTT Collaboration meta-analysis, that showed a 22% CV risk reduction per 1 mmol/L decrease in LDL-C, data from the OUTCOMES study showed consistent results with an estimated 25% MACE-plus reduction per 1 mmol/L decrease of LDL-C (HR: 0.75; 95% CI [0.72 to 0.78]). In another analysis in which the category of LDL-C ≥100 mg/dL was the referent group, compared to this category, the risk of MACE-plus was reduced by 70% (HR: 0.30; 95% CI: 0.15 to 0.58) when reaching LDL-C <20 mg/dL and by 53% (HR: 0.47; 95% CI: 0.41 to 0.53) when reaching LDL-C between 20 and 50 mg/dL. Therefore this analysis suggested that there is a further CV risk reduction when achieving LDL-C <20 mg/dL.

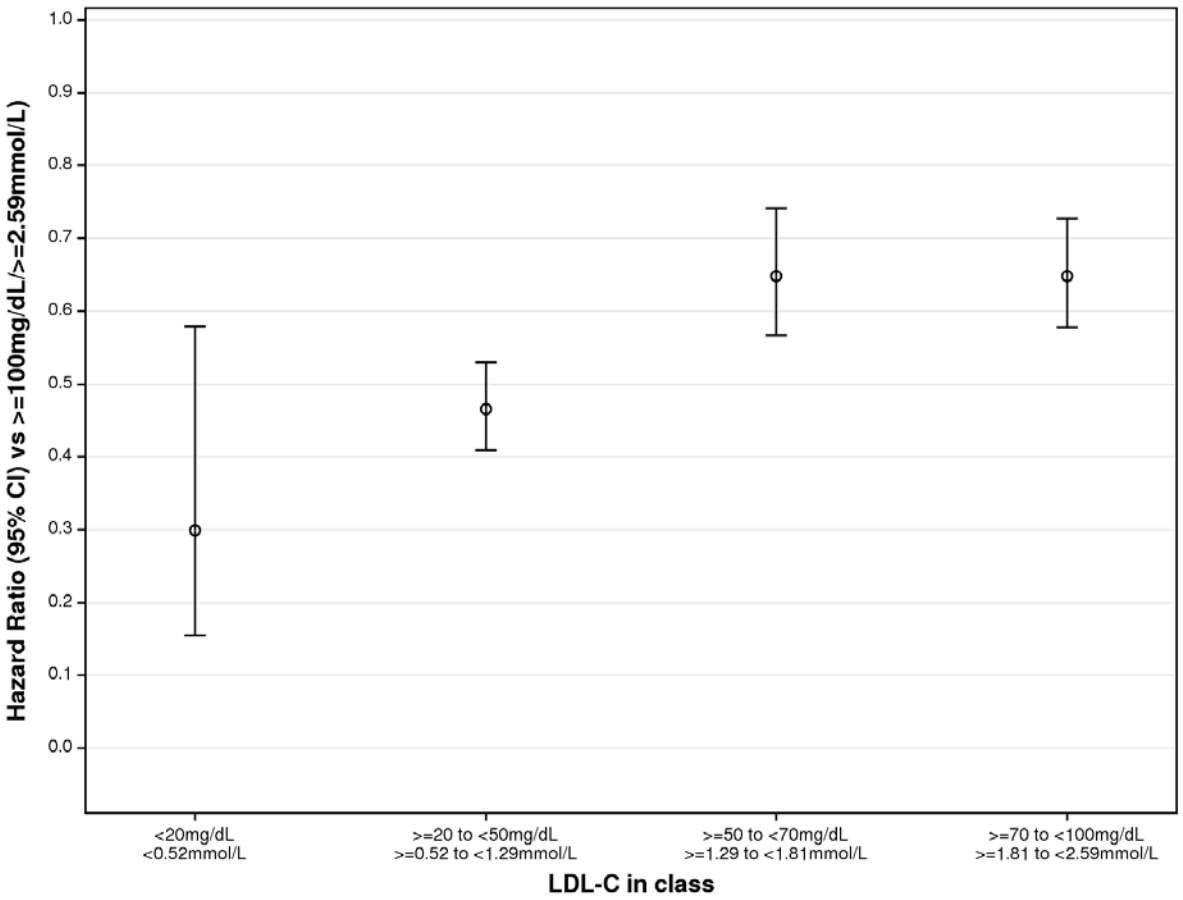


Figure 6: Relationship between MACE-plus events and LDL-C (in class) - Multivariate analysis adjusted on baseline characteristics - ITT population - EFC11570

Adjustment on: Gender, Age in categories, Diabetes status at baseline, Country, Time from ACS and BMI at baseline

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17: Summary of Efficacy for trial ODYSSEY (EFC11570)

Title: ODYSSEY Outcomes (EFC11570): 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				
Study identifier	EFC11570			
Design	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 months 2-16 weeks		
Hypothesis	Superiority			
Treatments groups	alirocumab	75 mg Q2W, uptitration after 2 months 150 Q2W if needed, <duration>, 9462		
	placebo	duration, 9462		
	group descriptor	Hazard ratio		
Endpoints and definitions	Primary endpoint	MACE-plus	CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, UA requiring hospitalisation	
	Secondary endpoint	Any CHD event	major CHD event, UA requiring hospitalization, ischemia-driven coronary revascularization procedure	
	Secondary endpoint	Major CHD event	CHD death, non-fatal MI	
	Secondary endpoint	Any CV event	non-fatal CHD event, any CV death, and non-fatal ischemic stroke	
	Secondary endpoint	Composite all cause mortality, no-fatal MI, non-fatal ischemic stroke		
	Secondary endpoint	CHD death		
	Secondary endpoint	CV death		
	Secondary endpoint	All-cause mortality		
Database lock	23 January 2018			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	alirocumab	placebo	HR (95%CI), p value
	Number of subject	9462	9462	18942
	Primary endpoint MACE-plus	903 (9.5%)	1052 (11.1%)	0.85 (0.78 to 0.93), p=0.0003
Notes				
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	alirocumab	placebo	HR (95%CI), p value
	Number of subject	9462	9462	18942

	Any CHD event	1199 (12.7%)	1349 (14.3%)	0.88 (0.81 to 0.95), p=0.0013
	Major CHD event	793 (8.4%)	899 (9.5%)	0.88 (0.80 to 0.96), p=0.0060
	Any CV event	1301 (13.7%)	1474 (15.6%)	0.87 (0.81 to 0.94), p=0.0003
	Composite all cause-mortality, no-fatal MI, non-fatal ischemic stroke	973 (10.3%)	1126 (11.9%)	0.86 (0.79 to 0.93), p=0.0003
	CHD death	205 (2.2%)	222 (2.3%)	0.92 (0.76 to 1.11), hierarchical testing violated
	CV death	240 (2.5%)	271 (2.9%)	0.88 (0.74 to 1.05), hierarchical testing violated
	Overall mortality	334 (3.5%)	392 (4.1%)	0.85 (0.73 to 0.98), hierarchical testing violated
	The secondary endpoints were performed according to a hierarchical testing			

Analysis performed across trials (pooled analyses and meta-analysis)

As described in the original dossier, the phase 3 program consisted of 10 studies with a double-blind treatment duration from 6 months to 24 months. This program was mainly focused on patients at very high or high CV risk and receiving a maximally tolerated dose of a potent statin, with or without other LMTs, representing ~80% of the total population. The majority of patients enrolled in these studies had CVD, including patients after ACS (at least 3 months). The definition of CV risk was based on US and EU guidelines in effect at the time of clinical development plan finalization. The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) 2011 guidelines and 2012 update were used to delineate very high and high CV risk. Overall, 5138 patients (97.0%) were at high/very high CV risk, including 70.6% (n=3518 patients) with ASCVD (including coronary artery, cerebrovascular, or peripheral artery disease) and 64.1% with a history of clinical CHD (encompassing prior MI, stroke, or PAD), and about 4% of patients with history of ACS of less than 12 months. Out of the 4219 patients randomized in the 6 studies using maximally tolerated dose of statin as a background therapy, 56.4% were treated with high intensity statin (ie, the same definition as for the OUTCOMES study: atorvastatin 40 mg or 80 mg, rosuvastatin 20 mg or 40 mg). In the context of this large phase 3 program, a comprehensive assessment of the benefit/risk balance with alirocumab included an assessment on the CV outcomes in order to get preliminary data prior to the results from the OUTCOMES study, even though patients enrolled in the OUTCOMES study were at higher risk. CV events were therefore adjudicated by the CEC in charge of the adjudication for the OUTCOMES study.

Although these studies were not designed or powered to provide positive CV outcomes evidence, based on the population enrolled, mainly patients at high risk with established CV disease, the duration of 18 to 24 months for 5 of the 10 studies, and the preliminary data demonstrating the strong LDL-C lowering effect with alirocumab, there was an expectation to obtain a beneficial trend for the reduction in CV events in favor of alirocumab versus the control groups (placebo and ezetimibe).

Results from the global pool of phase 3 studies demonstrated a lower rate of CV events positively adjudicated for MACE-plus in the alirocumab group versus placebo/ezetimibe group resulting in a risk reduction of 15% (HR: 0.85; 95% CI: 0.57 to 1.27).

Table 18 - Positively adjudicated cardiovascular TEAEs: MACE-plus - Summary table according to adjudication (Safety population) - Global pool of phase 3 studies at final analysis

Category of adjudication n(%)	Control (N=1792)	Alirocumab (N=3182)
Any patients with treatment emergent MACE-plus event n(%)	39 (2.2%)	65 (2.0%)
95% mid-p CI	1.6% to 2.9%	1.6% to 2.6%
Number of patients with an event per 100 patient year[a]	1.7	1.5
95% CI	1.2 to 2.3	1.1 to 1.9
Hazard ratio versus control (95% CI)[b]		0.85 (0.57 to 1.27)
CHD death (including undetermined cause)	10 (0.6%)	12 (0.4%)
Non-fatal MI	27 (1.5%)	37 (1.2%)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	3 (0.2%)	14 (0.4%)
Unstable angina requiring hospitalization	2 (0.1%)	2 (<0.1%)

Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)
Ezetimibe-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
n(%) = number and percentage of patients with at least one event

a Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period

b Calculated using a Cox model stratified on the study

Database updated for all studies

Efficacy of alirocumab on this broader ASCVD population was also shown in the largest phase 3 study, LONG TERM study, in which the efficacy and safety of alirocumab was evaluated for 18 months in 2341 patients with established CHD (70%) or a CHD risk equivalent (including 9.9% of patients with prior history of ischemic stroke, and 5.2% of patients with PAD) or with HeFH, and receiving maximally tolerated statin therapy. In this single study, the rate of MACE-plus was lower with alirocumab than with placebo (1.7% vs. 3.3%) with a relative risk reduction of 48% (HR of 0.52; 95% confidence interval (CI): 0.31 to 0.90); nominal p = 0.02).

The observations at the time of the phase 3 studies and LONG TERM study were very similar to the results observed in the OUTCOMES study despite the limitations described above and the fact that the population enrolled in the OUTCOMES study was at higher CV risk. The consistency in the results between the phase 3 program and the OUTCOMES study support the robustness of the results and the benefit of alirocumab in reducing MACE-plus in patients with CHD.

Clinical studies in special populations

Antibody response

Alirocumab was associated with a low level of immunogenicity.

Treatment-emergent ADA assay responses were observed in 504 (5.5%) patients in the alirocumab group and in 149 (1.6%) patients in the placebo group; however, the majority of these were low titer and transient responses. Persistent treatment-emergent ADA responses were observed in 0.7% and 0.4% of

patients in the alirocumab and placebo groups, respectively; the majority of these were also low titer responses. Only a few patients were positive for neutralizing antibodies (NAb) (43 [0.5%] patients in the alirocumab group and 6 (<0.1%) patients in the placebo group); most were positive only at a single occasion. Only 5 (<0.1%) patients in the alirocumab group and 1 patient in the placebo group had a positive NAb response on more than one occasion.

The percent change from baseline in LDL-C was explored according to the treatment-emergent ADA response (ie, persistent, transient, or indeterminate) and according to ADA titer. A substantial reduction of LDL-C was observed, regardless of the ADA status.

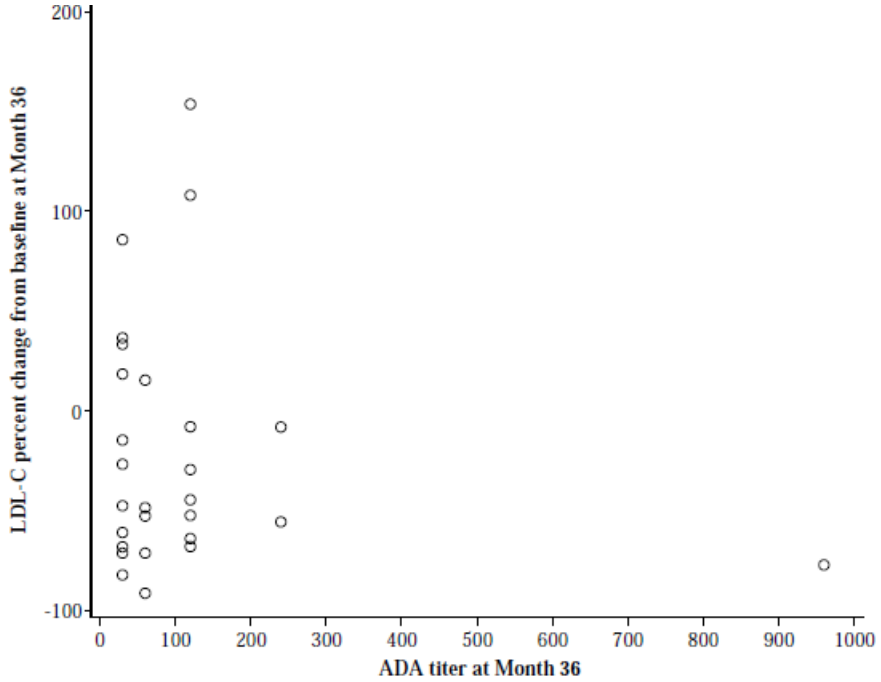


Figure 7: Percent change from baseline in LDL-C versus ADA titer at Month 36 during the treatment period

For each of the 43 patients in the alirocumab group with a NAb positive response, the ADA titers, the NAb positivity, and the LDL-C concentrations were plotted over time.

Anti-drug antibody responses, including NAb, did not appear to have a clinically meaningful impact on the efficacy of alirocumab.

2.3.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH submitted study EFC11570 ODYSSEY to investigate the effect of alirocumab on CV risk reduction. The study was a multicentre, international, randomized, double-blind, placebo-controlled, parallel-group study comparing the treatment of alirocumab 75 mg Q2W with possible uptitration to 150 mg Q2W after 2 months on top of optimal lipid lowering therapy versus background therapy (placebo arm). The primary objective is acceptable, except for the definition of the CV events, see further below. The secondary objectives are also relevant to provide further insight and support for the primary objective.

Patients should have been treated with optimal lipid lowering therapy before randomisation defined as intense statin therapy by atorvastatin 40 or 80 mg daily or rosuvastatin 20 or 40 mg daily, while other additional lipid lowering therapy was also allowed (except for fibrates). A documented intolerance to 2 or more statins and at least 2 weeks of non-statin LMT exposure prior to the screening visit can be acceptable to justify any absence of statin background therapy. This has previously been applied in the statin-intolerance studies during initial MAA.

A run-in phase of 2 to 16 weeks was used to identify those patients not on treatment goal with lipid lowering therapy and to initiate lipid lowering statin therapy for those not on high intensity statins. The use of a background therapy of moderate to high dose statin was an eligibility criterion to be applied during the run-in phase. Background statin therapy of at least atorvastatin 40 mg daily or at least rosuvastatin 20 mg (≥ 2 weeks on stable dose) was considered to represent high intensity statins use. Evaluation after 2 weeks of treatment is considered limited, and not in line with general dose recommendations for atorvastatin and rosuvastatin, although data suggest an optimal treatment effect was already achieved after 2 weeks of statin treatment.

Inclusion criteria (at randomisation) reflect a population with established cardiovascular disease determined by recent prior acute coronary syndrome (ACS) defined as patients hospitalised for an ACS event (STEMI, NSTEMI or UA (unstable angina)) 4 to 52 weeks prior to inclusion. According to the *2016 European guidelines on cardiovascular disease prevention in clinical practice (p. 2330)* these patients can be classified as patients with a very-high CV risk.

The risk classification based on LDL-C ≥70 mg/dL (≥1.81 mmol/L) is considered appropriate and in line with the ESC dyslipidaemia guideline 2016. However, apolipoprotein B (Apo B) ≥80 mg/dL (≥0.8 g/L), or non-high-density lipoprotein cholesterol (non-HDL-C) ≥100 mg/dL (≥2.59 mmol/L) are considered risk markers that can be used but this is especially of relevance when TG levels are high (ESC guideline). Specific treatment recommendations of patients with very high CV risk comply with the proposed LDL-C inclusion level (most important) and non-HDL-C inclusion level, however, any specific treatment level for Apo B is not given in the ESC guideline.

The exclusion criteria are generally acceptable to minimize interference with the main objectives of the study and allow optimal study adherence. Not allowing patient below the age of 40 years is not standard but could increase the CV risk profile.

After randomisation and initiation of treatment with 75 Q2W or placebo, patients could be uptitrated after 2 months of treatment from the 75 mg Q2W to 150 Q2W of alirocumab. This is considered acceptable as the optimal effect of the 75 mg Q2W should then be achieved, although a 3 months period was used in the studies in the initial dossier. The subsequent possibility of downtitration after this period is also acceptable, as this would appropriately reflect clinical practice. Further, the downtitration criteria and discontinuation criteria (substitution to placebo injection) when very low levels of LDL-C are observed (<25 mg/dL (0.65 mmol/L) or <15 mg/dL (0.39 mmol/L)) is considered appropriate.

The primary endpoint is a composite of time to coronary heart disease death, myocardial infarction, fatal and non-fatal stroke, and unstable angina requiring hospitalisation whichever came first. Unstable angina, in addition to the "harder" endpoints of MI, stroke and CHD death, is considered less robust in particular with respect to objective definitions and possible bias in relation to clinical decision-making. An important key secondary endpoint defined as cardiovascular death, myocardial infarction, and stroke, is considered of importance as this is the preferred endpoint according to the EMA guideline CV prevention [Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMEA/CHMP/EWP/311890/2007)]. It would have been preferred if this endpoint was higher in the hierarchical testing approach. Investigating CHD death is acceptable and has been accepted as composite of the primary endpoint in previous CV intervention studies, though there is current preference to

investigate overall mortality. Sufficient confidence regarding overall mortality and non-CV mortality is necessary in this case. Overall mortality is investigated as secondary endpoint, which is acceptable. Further evaluation of other single and components of cardiovascular events is acceptable as they could further support the key analyses and provide further knowledge of the treatment effect on cardiovascular prevention. Confirmation of the known LDL-C lowering effect is also of relevance.

Adjudication strategy by an independent CEC is considered standard procedure in large CV intervention trials and acceptable. Definitions according to the Food and Drug Administration (FDA)/Clinical Data Interchange Standards Consortium (CDISC) Standardized Definitions for End Point Events in Cardiovascular Trials, and on the Thygesen Universal Definition for the definition of MI, is acceptable.

The randomisation procedure is considered adequate. One stratification factor of country is acceptable. The blinding methods of the study are sufficiently described and acceptable.

Including several independent panels, especially for adjudication of efficacy events, is supported.

The study populations included an ITT population for all efficacy analyses and a safety population. Analysis of primary and secondary endpoints use Kaplan-Meier and Cox Proportional Hazard and ANCOVA as appropriate. The time to event analyses may have been influenced by informative censoring (e.g. non-CHD death in the primary analysis, or UA related treatment changes in the secondary endpoints). However, as time to MACE-plus with all-cause death is virtually the same as the primary endpoint and the prevalence of hospitalisation due to UA is relatively low compared to the harder endpoints in the primary composite, informative censoring is not considered to have had a major impact on the study results. The interim analysis plan and handling of multiplicity are considered acceptable.

Efficacy data

The study screened 35437 patients, with a number of 16513 patients who failed screening. Consequently, 18924 patients could be randomised and were almost all treated with study drug. A lower number of alirocumab treated patients completed the study treatment period compared to placebo (78% vs 84%), which can be explained by those patients that achieved very low levels of LDL-C (n=730; 7.7%). These patients rolled over to the placebo group in a blinded manner. A similar number of discontinuations due to AEs were observed (3.8% and 3.7%, respectively, for alirocumab vs placebo). Randomisation was successful as can be expected from a study this size.

The patients included were on average 58 years of age, primarily male, primarily of white origin and approximately half were treated in Europe. About 34% already had a history of CAD. They had a history of acute coronary syndrome (ACS) with a median time for ACS until randomisation of 3.6 months, resulting in a population at high risk for a CV event. These could be sub-categorised for 34.6% with STEMI, 48.6% with NSTEMI and 16.8% with UA. Several other risk factors also contributed to the increased CV risk of the patients including hypertension (64.7%), family history of CAD (35.8%), type 2 diabetes (24.4%) or other cardiovascular diseases (21.1%) including congestive heart failure, PAD and/or stroke. The number of patients over 75 years of age was limited (n=1007).

At the qualifying visit 99.5% had elevated lipid levels, mainly identified by LDL-C, with only 8% identified by Apo B (0.3% only on Apo B) and/or non-HDL-C (7.2% only on non-HDL-C). Of relevance, 19.8% (n=3715) of the patients had a LDL-C <70 mg/dL (<1.81 mmol/L) at baseline. According to the MAH, this proportion was higher than that observed at the qualifying visit (about 8%) and is likely explained by variability of LDL-C within individuals over short periods of time. As a result this means that 11.8% were not qualified to be included in the study at the qualification visit.

A substantial number of 88.8% of the patients received a high dose of statins at randomisation. Only 8.5% was on low to a moderate dose of statin and 2.4% was not on a statin. The most frequent reasons

for not taking statin were “Subject unable to tolerate 2 different statins” (n=304) and “Muscle symptoms and/or CPK increase while taking statin” (n=274). There appears some overlap between both categories; for 157 both reasons were given. Only one-third (32.6%) of patients who were randomized in the study were treated with statin for at least 3 months prior to the index ACS event, which may indicate that the others were not well treated before recruitment in the study, since dyslipidaemia prior to the run-in period was reported in 66.7% of the patients.

The largest proportion of patients were treated with the 75 mg Q2W dose, while 27.7% were uptitrated to the 150 mg Q2W dose and of these 8.5% was subsequently downtitrated. Of the alirocumab treated patients 7.7% switched to placebo between months 4-12 due to very low LDL-C levels.

The recruitment procedure can be considered acceptable. The applicant has sufficiently described the amendments made in the protocol and the statistical analysis plan during the study. This is acceptable. The ITT population included all patients who were randomised. For the safety population only 30 of the randomised patients were not included. Also, the population with anti-alirocumab antibody is mentioned.

A significant beneficial treatment effect of alirocumab versus placebo could be observed after a mean of 31 months of treatment on the composite primary endpoint (MACE-plus) of CHD death, non-fatal MI, fatal and non-fatal ischaemic stroke, or UA requiring hospitalisation with 149 less events that occurred in the alirocumab treated patients (903 [9.5%] vs 1052 [11.1%]) resulting in a 15% lower hazard ratio (HR of 0.85 (95% CI 0.78, 0.93; p = 0.0003)) with the effect diverging at approximately 8 months onward. This effect is mostly accountable to the benefit on non-fatal MI (83 less events), while other components contributing to the effect in order of frequency were CHD death, stroke and UA requiring hospitalisation. The sensitivity analyses using tipping point analysis using different scenarios provided reassurance that the primary analysis was not influenced by missing data. Significant reductions of 14%, 27%, and 39% were observed in the risk of non-fatal MI, ischaemic stroke, and UA requiring hospitalisation. The hierarchical testing of secondary composite endpoints showed a significantly consistent 12-14% reduction in composite of any CHD event (major CHD event, UA requiring hospitalization, ischemia-driven coronary revascularization procedure), any major CHD event (CHD death, non-fatal MI), any CV event (any non-fatal CHD event, any CV death, and non-fatal ischemic stroke), and CHMP guideline recommended composite endpoint of all-cause mortality, non-fatal MI, and non-fatal ischemic stroke. Reassuring is that also a reduction in CHD deaths and CV deaths were found, although these were not significantly reduced; the hierarchical testing was violated at the CHD deaths endpoint. Although the hierarchical testing was already violated, a significant reduction in all-cause death was found. No particular pattern could be observed for the type of non-CV-deaths.

The lipid lowering reduction was also evaluated and showed a substantial decrease of -55.8% at month 4 on LDL-C from a mean baseline level of 92.4 mg/dL (2.39 mmol/L). The effect diminished over time to a level of -39.9% at month 48. This was likely to treatment discontinuation and patients switching to placebo treatment because of very low levels of LDL-C. The on-treatment effect of LDL-C lowering was maintained throughout the study. Similar patterns were observed for ApoB and non-HDL-C.

A consistent beneficial effect for alirocumab on the primary endpoint was observed according to subgroups analysed except for the subgroup of Asia region and Asian race subgroups. Within subgroup types of BMI, age, baseline apoB, baseline Lp(a), and baseline fasting TG, an expected greater relative and absolute treatment effect according to higher baseline risk was found. For subgroups of time from ACS, diabetes, baseline LDL-C, REACH score, and TIMI score this was less clear with a greater absolute risk reduction but not corresponding relative risk reduction according to higher baseline risk. The baseline statin use showed consistent results with lowest absolute and relative effect for high dose statin use. The applicant provided some additional considerations on the subgroup of patients with baseline LDL-C ≥100 mg/dL, which as expected demonstrated a larger effect than the observed overall effect and obviously those with lower baseline LDL-C levels. A relatively low number of patients with anti-drug antibody (ADA)

response was observed (5.5.% vs 1.6%) for alirocumab vs placebo, respectively, with even lower rates for persistent ADA responses (0.7% vs 0.4%). No substantial diverging treatment effect was observed for these patients.

Additional analyses

A further analysis of the relation between LDL-C (categories) and CV risk reduction showed an effect of a 25% reduction per 1 mmol/L reduction in LDL-C on the primary endpoint in keeping with the CTT Collaboration meta-analysis demonstrating a 22% reduction per 1 mmol/L reduction in LDL-C, although these data are presented in relative terms without any presentation of placebo background risk. Considering this continuum in CV risk reduction with low achieved lipid levels, it is of interest to what extent the current study data challenge current guideline recommendations. In this respect, results for patients treated in the study not meeting current guideline recommendation for lipid treatment are of interest. In the subgroup of patients with lower baseline levels than the current recommended level for treatment of < 70 mg/dL (1.81 mmol/L) including 1870 alirocumab patients and 1881 placebo patients, 8.6% vs 9.6% experienced a primary MACE-plus event resulting in a HR of 0.90 (0.73 to 1.11), a beneficial effect only slightly less than the 0.84 (0.76 to 0.92) for the patients with LDL-C ≥70 mg/dL (with no significant p for interaction). These data thus may further challenge the current target driven clinical practice guideline recommendations and provides further support for the statement as included in the *EMA Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013, Rev. 3)* previously only associated with statin therapy of *"The relationship between LDL-C levels and CHD risk is present over a broad range of LDL levels. The dividing line between "normocholesterolaemia" and "hypercholesterolaemia" is arbitrary and in fact may be non-existent. Epidemiological data indicate a continuous increasing risk from very low to "normal" and high levels of LDL-C."*.

In addition to the results provided by the CV outcome study ODYSSEY OUTCOMES, an analysis across the trials of the original dossier including a broader range of CV risk population estimated a comparable CV reduction of 15% (HR: 0.85; 95% CI: 0.57 to 1.27), although the studies were not designed and powered to provide treatment effects of alirocumab on CV event reduction. Similar considerations apply to the previous LONG TERM study.

A relatively low number of patients with anti-drug antibody (ADA) response was observed (5.5% vs 1.6%) for alirocumab vs placebo, respectively, with even lower rates for persistent ADA responses (0.7% vs 0.4%). No substantial diverging effect on the treatment effect was observed for these patients.

2.3.4. Conclusions on the clinical efficacy

The MAH submitted the results for the large outcome study ODYSSEY OUTCOMES, a multicentre, international, randomized, double-blind, placebo-controlled, parallel-group study including patients with recent acute coronary syndrome, with additionally some other CV risk factors, demonstrating a significant effect on a composite endpoint of time to coronary heart disease death, myocardial infarction, fatal and non-fatal stroke, and unstable angina requiring hospitalisation when treated with alirocumab 75 mg Q2W with possible uptitration to 150 mg Q2W after 2 months on top of optimal lipid lowering therapy versus background therapy (placebo arm). This was generally supported with a consistent effect across several secondary endpoints, although the hierarchical testing was lost for CHD death, CV death and overall mortality. Also a consistent effect was generally observed across subgroups including patients already at very low LDL-C levels who can currently not be identified based on the current approved indication.

2.4. Clinical safety

Introduction

The pre-specified statistical analysis plan considered 3 tiers of AEs.

- Tier 1 represents TEAEs for which hypotheses and a comprehensive analytical approach were prospectively defined.
- Tier 2 represents common TEAEs (not pre-specified) and thus TEAEs for which the prior probability is low that these represent adverse reactions. The approach to Tier 2 was based on the use of statistical tests to screen TEAEs which are then assessed clinically.
- Tier 3 represents infrequent TEAEs which are assessed clinically. The final output is represented in a series of conclusions that identify ADRs to inform product labelling and future pharmacovigilance activities.

Data Monitoring Committee

A data monitoring committee (DMC) composed of members who were independent from the Sponsor and the study Investigators, was implemented in order to monitor patient safety by conducting formal reviews of accumulated safety data that were unblinded. During their periodic reviews of safety data throughout the study, the CV DMC also analyzed the aggregate safety data for patients who achieved LDL-C <25 mg/dL (0.65 mmol/L) and more particularly, reviewed AEs potentially associated with LDL-C <25 mg/dL (0.65 mmol/L).

An external physician, independent from the Sponsor and the Investigator sites (called the “Independent Physician”), was in charge of monitoring the safety of patients with low LDL-C through the review of the unblinded safety data of patients with 2 consecutive LDL-C <25 mg/dL (0.65 mmol/L) and more particularly, AEs predefined as potentially associated with LDL-C <25 mg/dL (0.65 mmol/L). One of the objectives of this review, done throughout the study, was to allow the CV DMC to get further information in addition to the aggregate safety data for these patients at the time of their periodic reviews.

Neurocognitive Expert Panel

An independent Neurocognitive Expert Panel (NCEP) composed of 3 clinicians with experience in the management/assessment of patients with neurocognitive impairment was implemented to review in a blinded fashion and on an ongoing basis, all neurocognitive AEs reported during the study. As planned the NCEP prepared an interim assessment based on the blinded review of all neurocognitive AEs before database lock. This assessment provides their expert opinion on the likeliness that in the study, patients' cognitive function had been altered or not independent of confounding factors. Then once the database was locked a final report was issued based on the knowledge of the treatment assigned for each patient and provides their conclusion on a potential neurocognitive signal associated with the administration of alirocumab.

Diabetes Expert Panel

An Independent Diabetes Expert Panel (DEP) composed of 3 clinicians with experience in the management/assessment of patients with diabetes, was implemented during the course of the trial, to review in a blinded fashion, potential cases of diabetes only identified as “diabetes” through the use of anti-diabetic medication reported before, at baseline or after baseline.

In addition, 2 other committees were implemented in the study, a Steering Committee that was in charge to provide the Sponsor with scientific and strategic direction for the study and had the overall

responsibility for its execution, and a Clinical Events Committee responsible for defining, validating, and classifying, in a blinded fashion, all suspected CV events that were to be reported.

Patient exposure

In the safety population, the median duration of treatment exposure was 30.90 months for the alirocumab group and 31.80 months for the placebo group. In the alirocumab group a total of 8071 (87%) patients were exposed for ≥12 months, 7248 (78%) patients for ≥24 months, 3105 (33%) for ≥36 months, and 555 (6%) for ≥48 months.

The cumulative exposure to alirocumab (23 061.8 patient-years) was slightly lower as compared to that of placebo (24 234.4 patient-years) due to 730 (7.7%) patients in the alirocumab group who were switched to placebo due to 2 consecutive LDL-C <15 mg/dL (<0.39 mmol/L).

Of the 9451 patients randomized and treated in the alirocumab group, 2615 (27.7%) had their dose up-titrated to 150 mg. Of these 2615 patients, 805 (8.5% of the total number of patients) had their dose subsequently down-titrated to 75 mg. A total of 730 (7.7%) patients randomized and treated in the alirocumab group were switched to placebo, most of them between 4 to 12 months after initiation of treatment with alirocumab. In the alirocumab group, cumulative exposures to alirocumab 75 mg and 150 mg were 17 948.4 and 5113.5 patient-years, respectively.

Table 19: Exposure to investigational medicinal product - Safety population

	Placebo (N=9443)	**Alirocumab (N=9451)**
IMP injection exposure (patient-years)	24234.4	23061.8
Duration of IMP injection exposure (months)		
Number	9273	9297
Mean (SD)	31.36 (12.00)	29.77 (12.98)
Median	31.80	30.90
Min : Max	0.5 : 60.5	0.5 : 61.0
Duration of IMP injection exposure by category [n(%)]		
Number	9273	9297
<2 months	200 (2.2%)	220 (2.4%)
≥2 months to <6 months	292 (3.1%)	510 (5.5%)
≥6 months to <12 months	368 (4.0%)	496 (5.3%)
≥12 months to <24 months	671 (7.2%)	823 (8.9%)
≥24 months to <36 months	4403 (47.5%)	4143 (44.6%)
≥36 months to <48 months	2714 (29.3%)	2550 (27.4%)
≥48 months to <60 months	624 (6.7%)	554 (6.0%)
≥60 months	1 (<0.1%)	1 (<0.1%)
Number of IMP injections		
Number	9273	9297
Mean (SD)	66.0 (25.9)	62.7 (27.8)
Median	67.0	65.0
Min : Max	1 : 128	1 : 133

	Placebo (N=9443)	Alirocumab (N=9451)
Number of IMP injections by categories [n (%)]		
Number	9273	9297
<4	182	205
≥4 to <13	329	551
≥13 to <26	411	550
≥26 to <39	472	567
≥39 to <52	392	366
≥52 to <65	2371	2272
≥65 to <78	1957	1862
≥78 to <104	2624	2437
≥104 to <120	521	472
≥120	14	15

Adverse events

The TEAE period was defined as the time from the first dose of double-blind IMP injection up to the day of the last dose of double-blind IMP injection +70 days (10 weeks) as concentrations of alirocumab could generally be measured until 10 weeks after the discontinuation of double-blind IMP injection. For patients with last contact date within 70 days after the last dose of IMP, the TEAE period was up to the last contact date.

The percentages of patients who experienced TEAEs, treatment-emergent serious adverse event (SAE), and TEAEs leading to treatment discontinuation were comparable between treatment groups (see Table 20 below).

Table 20 - Overview of adverse event profile: Treatment-emergent adverse events - Safety population - EFC11570

n(%)	Placebo (N=9443)	Alirocumab (N=9451)
Patients with any TEAE	7282 (77.1%)	7165 (75.8%)
Patients with any treatment emergent SAE	2350 (24.9%)	2202 (23.3%)
Patients with any TEAE leading to death	222 (2.4%)	181 (1.9%)
Patients with any TEAE leading to permanent treatment discontinuation	324 (3.4%)	343 (3.6%)
TEAE leading to alirocumab discontinuation	NA	339 (3.6%)
TEAE leading to placebo discontinuation[a]	324 (3.4%)	4 (<0.1%)

n(%) = number and percentage of patients with at least one TEAE

a For alirocumab group, it corresponds to patients who were were initially treated with alirocumab but then switched to placebo due to 2 consecutive LDL-C values <15 mg/dL and who subsequently discontinued treatment due to AE with onset after switching but during the TEAE period

The AEs profile according to uptitration status was comparable.

Table 21: Overview of adverse event profile: Treatment emergent adverse events according to up-titration status - Safety population - Patients with at least 1 inj. post up-titration time point IVRS/IWRS transaction in alirocumab group

n(%)	Not up-titrated in alirocumab group (N=6561)	Up-titrated in alirocumab group (N=2615)
Patients with any TEAE	4673 (71.2%)	1793 (68.6%)
Patients with any treatment emergent SAE	1359 (20.7%)	574 (22.0%)
Patients with any TEAE leading to death	111 (1.7%)	48 (1.8%)
Patients with any TEAE leading to permanent treatment discontinuation	184 (2.8%)	80 (3.1%)
TEAE leading to alirocumab discontinuation	180 (2.7%)	80 (3.1%)
TEAE leading to placebo discontinuation[a]	4 (<0.1%)	0

The most frequently reported TEAEs at the system organ class (SOC) level (≥10% of patients in either treatment group) are presented in Table 22. Overall, no meaningful treatment group differences were observed at the SOC level.

Table 22 - Number (%) of patients with TEAEs that occurred with SOC >=10% in any treatment group by decreasing order in the alirocumab group - Safety population - EFC11570

Primary System Organ Class n(%)	Placebo (N=9443)	Alirocumab (N=9451)
Infections and infestations	2811 (29.8%)	2829 (29.9%)
Musculoskeletal and connective tissue disorders	2385 (25.3%)	2406 (25.5%)
General disorders and administration site conditions	1945 (20.6%)	2016 (21.3%)
Gastrointestinal disorders	1896 (20.1%)	1826 (19.3%)
Injury, poisoning and procedural complications	1591 (16.8%)	1539 (16.3%)
Nervous system disorders	1601 (17.0%)	1483 (15.7%)
Respiratory, thoracic and mediastinal disorders	1457 (15.4%)	1375 (14.5%)
Investigations	1370 (14.5%)	1285 (13.6%)
Cardiac disorders	1403 (14.9%)	1262 (13.4%)
Metabolism and nutrition disorders	1322 (14.0%)	1199 (12.7%)
Vascular disorders	1266 (13.4%)	1167 (12.3%)

Only rows with frequency of at least 10% in at least one column are shown
MedDRA 20.1 . n(%) = number and percentage of patients with at least one TEAE.

The only TEAE (preferred term [PT] level) with an incidence of ≥2% in the alirocumab group and a ≥0.5% difference compared with the placebo group was injection site reaction (3.8% vs 2.1%).

The following TEAEs (PT level) with an incidence of ≥2% in the placebo group and a ≥0.5% difference compared with the alirocumab group in order of decreasing frequency were: angina pectoris (4.5% versus 5.0% in the alirocumab and placebo groups, respectively), accidental overdose (3.7% versus 4.4%), dizziness (3.6% versus 4.1%), and anxiety (1.7% versus 2.4%).

The Tier 2 analysis of TEAEs ("common TEAEs") was conducted on TEAEs for which there were at least 6 patients with an event overall in the safety population. TEAEs (PT or high level term [HLT]) identified as requiring further consideration by the Tier 2 analysis were those events reported in more than 1% of patients in either treatment group for which the lower bound of the 95% CI for the HR for alirocumab versus placebo was greater than 1. The only Tier 2 TEAE that met the criteria above was injection site reactions (HLT or PT); this TEAE was also an AESI. None of the other Tier 2 TEAEs meeting the criteria above were assessed as safety signals.

Adverse events of special interest

The frequencies for adverse events of special interest are in Table 23 provided below. Also, these adverse events are discussed in more detail below.

Table 23 - Adverse events of special interest and other potentially significant AEs (Tier 1 events) - Safety population - EFC11570

Event	Placebo (N=9443)	Alirocumab (N=9451)	Hazard ratio versus placebo (95% CI)[a]
Adverse events of special interest:			
Local injection site reaction, n(%)	203 (2.1%)	360 (3.8%)	1.82 (1.54 to 2.17)
Allergic events, n(%)	736 (7.8%)	748 (7.9%)	1.05 (0.95 to 1.17)
Neurologic events, n(%)	420 (4.4%)	375 (4.0%)	0.92 (0.80 to 1.06)
Neurocognitive disorders, n(%)	167 (1.8%)	143 (1.5%)	0.89 (0.71 to 1.11)
Other potentially significant AEs:			
Hepatic disorders, n(%)	534 (5.7%)	500 (5.3%)	0.97 (0.85 to 1.09)
Diabetes mellitus (DM) or diabetic complication, n(%)	924 (9.8%)	820 (8.7%)	0.92 (0.84 to 1.01)
Diabetes mellitus or diabetic complications: pts with DM at baseline, n/N (%)	583/2747 (21.2%)	506/2688 (18.8%)	0.92 (0.81 to 1.03)
New onset diabetes: pts without DM at baseline, n/N (%)	676/6696 (10.1%)	648/6763 (9.6%)	1.00 (0.89 to 1.11)
Cataracts, n(%)	134 (1.4%)	120 (1.3%)	0.93 (0.73 to 1.20)

a Calculated using a Cox model
n(%) = number and percentage of patients with at least one event.
CI: confidence interval
Extracted from 5.3.5.1 Study EFC11570 [Section 11.3.4.1] and [Table 42] to [Table 45], [Table 47] to [Table 51].

Allergic events

The incidence of general allergic TEAEs (based on a company MedDRA query (CMQ) for PTs potentially related to allergic events) was similar between alirocumab and placebo groups (7.9% versus 7.8%, respectively; 3.3 events versus 3.1 events per 100 patient-years, respectively; HR: 1.05; 95% CI: 0.95 to 1.17).

The most frequently reported general allergic TEAEs (PTs reported in at least 0.5% of patients in any treatment group) were rash (1.2% in the alirocumab group versus 1.1% in the placebo group), pruritus (0.8% versus 0.7%), asthma (0.6% each), eczema (0.5% versus 0.6%), and conjunctivitis (0.4% versus 0.5%). Among the patients who experienced general allergic TEAEs, the majority reported mild events in intensity (61.1% and 61.3% in the alirocumab or placebo groups, respectively) or moderate events in intensity (33.0% and 32.5%, respectively). No difference was identified in the outcome of general allergic TEAEs between the alirocumab and placebo groups with a majority of patients having recovered from the general allergic TEAE (79.4% in the alirocumab group and 74.6% in the placebo group, respectively).

Based on the above CMQ, serious general allergic TEAEs were reported by 0.8% of patients in the alirocumab group and 0.9% of patients in the placebo group. General allergic TEAEs with a fatal outcome were reported in 8 patients (<0.1%) in the alirocumab group and 9 patients (<0.1%) in the placebo group. In most of the patients (7 and 8 in the alirocumab and placebo groups, respectively) death was due to respiratory failure in the context of serious concomitant disease and unlikely to be allergic in nature. The remaining patient in the alirocumab group had a medical history of asthma and died from an

asthma crisis without a triggering factor. The remaining patient in the placebo group patient died from "choked on food".

General allergic TEAEs led to treatment discontinuation in 0.4% of patients in both groups. In the alirocumab group, general allergic TEAEs leading to permanent treatment discontinuation were mainly reported as: rash, dermatitis allergic, hypersensitivity, and urticaria. In the placebo group, TEAE leading to permanent treatment discontinuation were most often reported as dermatitis allergic, hypersensitivity, and acute respiratory failure.

Local injection site reactions

The incidence of local injection site reactions (according to the AE category as per e-CRF) was higher in the alirocumab group compared to the placebo group (3.8% versus 2.1%, respectively; 1.6 events versus 0.8 events per 100 patient-years; HR: 1.82; 95% CI: 1.54 to 2.17). Most local injection site reactions occurred before Month 12 in both treatment groups.

Most patients who experienced a local injection site reaction TEAE had a single episode (70.8% of patients in the alirocumab group and 80.8% in the placebo group). The majority of events were mild or moderate in intensity. Local injection site reaction TEAEs with a severe intensity were reported in 1.1% and 0.5% of patients who reported local injection site reactions in the alirocumab and placebo groups, respectively.

Most local injection site reaction TEAEs were transient (median duration of 6 and 8 days in the alirocumab and placebo groups, respectively) and almost all patients recovered.

The most frequent symptoms associated with local injection site reactions (by decreasing order in the alirocumab group) were erythema/redness (2.1% of patients in the alirocumab group versus 0.7% in the placebo group), swelling (1.5% versus 0.7%), pain (1.5% versus 0.8%), tenderness (1.3% versus 0.6%), and itching (1.3% versus 0.4%).

Serious local injection site reactions were reported in 3 (<0.1%) patients in the alirocumab group and none in the placebo group. All recovered. Local injection site reactions led to permanent treatment discontinuation in 0.3% of patients in the alirocumab and <0.1% of patients in the placebo group.

A higher proportion of the ADA-positive patients experienced injection site reactions compared with ADA-negative patients (7.5% of ADA positive patients versus 3.6% of ADA-negative patients).

Hemolytic anaemia

Although confirmed hemolytic anemia was an AESI, it was reported in less than 6 patients overall and, accordingly, was evaluated as a Tier 3 event.

Confirmed hemolytic anemia was reported in 3 patients in the alirocumab group and in 1 patient of the placebo group. None of the 3 cases of hemolytic anemia reported in the alirocumab group were considered related.

None of the patients with hemolytic anemia had concomitant low LDL-C (<25 mg/dL).

Neurologic events

Overall, the percentages of patients who reported neurologic events of interest during the TEAE period were similar between alirocumab and placebo groups (4.0% versus 4.4%, respectively, 1.6 events versus 1.7 events per 100 patient-years, HR: 0.92; 95% CI: 0.80 to 1.06).

Among patients who experienced neurologic events, the majority reported mild (62.1% and 62.9% in the alirocumab or placebo groups, respectively) or moderate events (34.4% and 33.8%, respectively). Only a small proportion of patients with neurologic TEAEs reported a severe event (3.5% and 3.3%, respectively).

The most frequently reported neurologic events (PTs reported in at least 0.5% of patients in any treatment group) were hypoesthesia (alirocumab: 1.0% versus placebo: 0.9%), paresthesia (0.9% versus 1.1%), and muscular weakness (0.5% versus 0.4%).

Serious neurologic TEAEs were reported in 0.3% of patients in the alirocumab group and 0.4% of patients in the placebo group. No fatal case was reported. Few patients (<0.1% of patients in each group) discontinued study treatment due to a neurologic TEAE.

Neurocognitive events

Based on the CMQ defined by the Sponsor, the incidence of neurocognitive events was similar between alirocumab and placebo groups (1.5% versus 1.8%, respectively; 0.6 events versus 0.7 events per 100 patient-years, HR: 0.89; 95% CI: 0.71 to 1.11).

On the basis of the grouping of terms recommended by the FDA, neurocognitive events were reported in similar incidences: 1.4% of patients in the alirocumab and 1.6% of patients in the placebo group, respectively; 0.6 event per 100 patient-years in each treatment group; HR: 0.92; 95% CI: 0.73 to 1.17).

Among patients who experienced neurocognitive TEAEs, the majority reported events mild in intensity and few were reported as severe in intensity (5.6% in the alirocumab group and 4.8% in the placebo group). No difference was identified in the outcome of neurocognitive TEAEs between the alirocumab and placebo groups, and approximately half of the patients in both treatment groups recovered from these events.

Confusional state (PT) was detected as an event reported in a higher number of patients in the alirocumab group (0.2%) as compared to the placebo group (<0.1%) in the Tier 2 analysis. During their blinded review of these cases, the independent NCEP panel found an alternative cause in all but one event of confusional state, reported in the alirocumab group indicating the lack of evidence for a potential signal of confusional state associated with alirocumab.

Serious neurocognitive TEAEs were reported in 0.2% of patients in both groups. One (<0.1%) patient in the alirocumab group and 3 (<0.1%) patients in the placebo group had a neurocognitive TEAE leading to death. Review of individual cases identified pre-existing medical history explaining the cause of death. A total of 0.1% and 0.2% of patients in the alirocumab and placebo groups, respectively, permanently discontinued study treatment due to a neurocognitive TEAE.

Hepatic disorders

The incidence of hepatic disorder TEAEs was similar between the alirocumab group and the placebo group (5.3% versus 5.7%, 2.2 events per 100 patient-years in both groups; HR: 0.97; 95% CI: 0.85 to 1.09).

The most frequently reported TEAEs in the hepatic disorders standardized MedDRA query (PTs reported in at least 0.5% of patients in any treatment group) were alanine aminotransferase increased (1.4% in the alirocumab group versus 1.8% in the placebo group), hepatic steatosis (0.8% versus 1.0%), gamma-glutamyltransferase increased (0.7% versus 0.7%), and potential drug-induced liver injury (0.6% versus 0.4%).

Drug-induced liver injury was the PT used to encode any verbatim term that attributed a drug as the cause of the elevation of liver enzymes, regardless of the magnitude of the elevation and whatever the drug (eg, IMP or statin). In all patients with TEAEs coded to the PT drug-induced liver injury assessed by the Investigators as possibly related to the IMP in the alirocumab group, alternative causes, most often statin therapy, were identified. The imbalance in the incidence of TEAEs coded to the PT drug-induced liver injury should be reviewed in combination with the other events pertaining to the hepatic disorders standardized MedDRA query and to changes in liver enzymes (potentially clinically significant abnormality) that showed no difference between alirocumab and the placebo.

Potential Hy's law cases were reported at low and similar incidences in the alirocumab and the placebo group (0.2% each). Alternative causes of potential Hy's law, other than statin therapy, were identified in all but 1 patient in the alirocumab group in whom the potential Hy's law was detected at the end of study visit and no follow-up was reported.

Serious hepatic disorder TEAEs were reported in 0.6% of patients in both treatment groups. There were 3 and 4 fatal cases reported in the alirocumab and placebo groups, respectively (<0.1% for both). Hepatic disorder TEAEs led to permanent treatment discontinuation in 0.4% and 0.3% of patients in the alirocumab and placebo groups, respectively.

Diabetes mellitus

Diabetes mellitus or diabetic complications in patients regardless of their diabetes status at baseline

The incidence of diabetes mellitus or diabetic complication TEAEs in patients regardless of their diabetes status at baseline was similar between the alirocumab and placebo groups (8.7% versus 9.8%, respectively; 3.6 versus 3.9 events per 100 patient-years, respectively; HR: 0.92; 95% CI: 0.84 to 1.01).

Diabetes mellitus or diabetic complications TEAEs in patients with diabetes at baseline

In patients with diabetes at baseline, the incidence of diabetes mellitus or diabetic complication TEAEs was similar between alirocumab and placebo groups (18.8% versus 21.2%; 8.9 versus 9.7 events per 100 patient-years; HR: 0.92; 95% CI: 0.81 to 1.03).

Analysis of the cumulative incidences of diabetes mellitus or diabetic complication TEAEs over time showed similar trend between the alirocumab and the placebo groups.

New onset of diabetes mellitus in patients with no diabetes at baseline

New onset of diabetes analysis combined information from TEAEs, antidiabetic medications with a confirmed diagnosis per the external diabetes experts and laboratory parameters (HbA_{1c} and fasting glucose).

In patients with no diabetes at baseline (including normoglycemic patients and pre-diabetes patients at baseline), the incidence of new onset of diabetes (NOD) during the TEAE period was similar between alirocumab and placebo groups (9.6% versus 10.1%, respectively; 4.0 events per 100 patient-years in both treatment groups; HR: 1.00; 95% CI: 0.89 to 1.11).

The incidence of NOD in the patients with prediabetes was 13.8% versus 15.0% in the alirocumab and placebo groups, respectively (HR: 0.97; 95% CI: 0.86 to 1.09). As expected, the incidence of NOD during the TEAE period in normoglycemic patients was much lower (3.0% in the alirocumab group and 2.4% in the placebo group; HR: 1.28; 95% CI: 0.92 to 1.79).

Cataract

The incidence of cataract TEAEs was similar between alirocumab and placebo groups (1.3% and 1.4%, respectively, 0.5 events per 100 patient-years in each treatment group; HR: 0.93; 95% CI: 0.73 to 1.20).

Other adverse events

Musculoskeletal and connective tissue disorders

Adverse events in the musculoskeletal and connective tissue disorders SOC were reported with similar incidences in both groups: 2406 (25.5%) patients in the alirocumab group and 2385 (25.3%) patients in the placebo group. Serious AEs in this SOC were reported in 205 (2.2%) patients in the alirocumab group and in 209 (2.2%) patients in the placebo group.

The most frequently reported TEAEs (PT ≥1.0%) were myalgia (alirocumab: 5.6% versus placebo: 5.3%), back pain (4.3% versus 4.2%), arthralgia (3.9% versus 3.7%), pain in extremity (3.1% versus 3.2%), muscle spasms (2.3% versus 2.1%), osteoarthritis (2.2% in both groups), musculoskeletal pain (1.9% versus 2.3%) and musculoskeletal chest pain (1.1% versus 1.4%).

Renal adverse events

Adverse events in the renal and urinary disorders SOC were reported in 668 (7.1%) patients in the alirocumab group and in 696 (7.4%) patients in the placebo group. Serious AEs in the renal and urinary disorders SOC were reported in 144 (1.5%) patients in the alirocumab group and in 165 (1.7%) patients in the placebo group.

The most frequently reported AEs (PT ≥1.0%) were acute kidney injury (1.1% in the alirocumab group versus 1.5% in the placebo group), chronic kidney disease (1.0% in both groups) and nephrolithiasis (0.8% versus 1.1%, respectively).

Adverse events in patients treated with alirocumab with 2 consecutive LDL-C < 25 mg/dL (0.65 mmol/L) and LDL-C < 15 mg/dL (0.39 mmol/L)

In the overall population, as described above, analyses by treatment group showed no differences between alirocumab and placebo groups for neurologic events, neurocognitive events, NOD, or cataract TEAEs. These data do not indicate a direct effect of alirocumab on these events. The evaluation of the potential relationship of achieving low LDL-C levels with occurrence of certain AEs is presented below.

All analyses related to low LDL-C should be interpreted with caution given the major limitation of the comparison between post-randomization subgroups. To attempt to reduce the bias introduced by this limitation, adjustment on prognostic factors for each event was done in the second step analysis. The list of prognostic factors was determined based on literature review and expert discussion for validation. However, bias due to unmeasured or unknown factors cannot be adjusted.

No signal was identified in the screening approach that was judged to require further analysis in the second step. Therefore, the second step analysis focused only on the prespecified events (neurological events, neurocognitive events, NOD, and cataract) adjusted on prognostic factors of each event. For all these events, analyses were performed on 3 observation periods:

- The low LDL-C period per SAP applied for patients with 2 consecutive low LDL-C (<25 mg/dL and <15 mg/dL) using the period starting from the date of the first low LDL-C up to the last alirocumab 150 mg injection +70 days if patient was on 150 mg or up to the last alirocumab injection +70 days if patient was on 75 mg. For patients without 2 consecutive LDL-C values <25 mg/dL (or 15 mg/dL), the analysis period was the TEAE period. For NOD, as discussed further below, this prespecified approach introduced a strong bias due to the fact that the vast majority of NODs were detected by laboratory parameters (HbA_{1c} and fasting glucose) that were infrequently assessed during the study.
- The TEAE period from the first injection to the last alirocumab injection +70 days for both patients with or without 2 consecutive low LDL-C values.
- The extended TEAE period: from the first injection to the last IMP injection (alirocumab or placebo in case of switch) +70 days for both patients with or without 2 consecutive low LDL-C values to allow a longer follow-up for patients switched to placebo due to 2 consecutive LDL-C <15 mg/dL (0.39 mmol/L).

Overall, there were comparable frequencies for AEs, serious AEs, AEs leading to death and AEs leading to permanent treatment discontinuation in patients who achieved two consecutive LDL-C levels <25mg/dL (or <15 mg/dL, respectively), compared to the subgroup of alirocumab-treated patients who did not.

Table 24 - Overview of adverse event profile: Treatment emergent adverse events during low LDL-C period according to LDL-C level (25 mg/dL, 0.65 mmol/L) - Safety population

	Alirocumab LDL-C ≥ 25 mg/dL, 0.65 mmol/L (N=5146)		Alirocumab 2 LDL-C <25 mg/dL, 0.65 mmol/L (N=4305)	
n	n	Rate per 100 patient year[a]	n	Rate per 100 patient year[a]
Patients with any TEAE	3935	79.4	2655	72.0
Patients with any treatment emergent SAE	1256	11.4	671	10.3
Patients with any TEAE leading to death	121	0.9	49	0.7
Patients with any TEAE leading to permanent treatment discontinuation	264	2.1	72	1.0

n = number of patients with at least one TEAE

Alirocumab 2 LDL-C <25 mg/dL group: Only TEAEs that occurred, worsened or became serious the day or after the first of the 2 consecutive (spaced out by at least 21 days) LDL-C <25mg/dL are considered. The analysis period ends at the last injection of 150 mg + 70 days for patients down-titrated from 150 mg to 75 mg in this group.

Alirocumab LDL-C ≥25 mg/dL group: alirocumab patients without 2 consecutive LDL-C <25 mg/dL.

[a] Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of analysis period.

PGM=PRODOPS/SAR236553/EFC11570/PUB_2018/REPORT/PGM/ae_overview_ldl_s_t.sas
OUT=REPORT/OUTPUT/ae_overview_ldl252_s_t_i.rtf (08OCT2018 - 18:26)

Table 25 - Overview of adverse event profile: Treatment emergent adverse events during low LDL-C period according to LDL-C level (15 mg/dL, 0.39 mmol/L) - Safety population

	Alirocumab LDL-C ≥ 15 mg/dL, 0.39 mmol/L (N=8669)		Alirocumab 2 LDL-C <15 mg/dL, 0.39 mmol/L (N=782)	
n	n	Rate per 100 patient year[a]	n	Rate per 100 patient year[a]
Patients with any TEAE	6700	76.6	341	87.9
Patients with any treatment emergent SAE	2099	10.9	67	12.4
Patients with any TEAE leading to death	175	0.8	4	0.7

n	Alirocumab LDL-C ≥ 15 mg/dL, 0.39 mmol/L (N=8669)		Alirocumab 2 LDL-C <15 mg/dL, 0.39 mmol/L (N=782)	
	n	Rate per 100 patient year[a]	n	Rate per 100 patient year[a]
Patients with any TEAE leading to permanent treatment discontinuation	334	1.5	9	1.6

n = number of patients with at least one TEAE

Alirocumab 2 LDL-C <15 mg/dL group: Only TEAEs that occurred, worsened or became serious the day or after the first of the 2 consecutive (spaced out by at least 21 days) LDL-C <15mg/dL are considered. The analysis period ends at the last injection of 150 mg + 70 days for patients down-titrated from 150 mg to 75 mg in this group.

Alirocumab LDL-C ≥15 mg/dL group: alirocumab patients without 2 consecutive LDL-C <15 mg/dL.

[a] Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of analysis period.

PGM=PRODOPS/SAR236553/EFC11570/PUB_2018/REPORT/PGM/ae_overview_ldl_s_t.sas OUT=REPORT/OUTPUT/ae_overview_ldl152_s_t_i.rtf (08OCT2018 - 18:26)

Neurologic events

The adjusted analyses on the different observation periods were consistent and did not show any difference in the rate of neurologic events between alirocumab-treated patients with 2 consecutive LDL-C <25 mg/dL (0.65 mmol/L) (or <15 mg/dL [0.39 mmol/L]) and alirocumab-treated patients without these low LDL-C levels.

Table 26: Second step: Number (%) of patients with neurologic TEAE(s) and hazard ratio according to LDL-C level (25 and 15 mg/dL, 0.65 and 0.39 mmol/L) adjusted on prognostic factors – Safety population - Alirocumab treated patients

n events (rate per 100 patient year) Hazard ratio (95% CI)	Alirocumab LDL-C ≥25mg/dL (N=5146)	Alirocumab 2 LDL-C <25mg/dL (N=4305)	Alirocumab LDL-C ≥15mg/dL (N=8669)	Alirocumab 2 LDL-C <15mg/dL (N=782)
Low LDL-C period	215 (1.7)	102 (1.4)	352 (1.6)	14 (2.5)
		0.73 (0.57 to 0.92)		1.01 (0.59 to 1.74)
TEAE period	215 (1.7)	160 (1.5)	352 (1.6)	23 (2.0)
		0.87 (0.70 to 1.06)		1.07 (0.70 to 1.64)
Extended TEAE period	215 (1.7)	173 (1.5)	353 (1.6)	35 (1.7)
		0.87 (0.71 to 1.06)		1.06 (0.75 to 1.51)

Extracted from 16-2-7-ae-data [16.2.7.9.3.1] to [16.2.7.9.3.6]

Low LDL-C period: from the date of the first low LDL-C up to the last alirocumab 150 mg injection (if low LDL-C value occurred while the patient was on alirocumab 150 mg) or up to the last alirocumab injection (if low LDL-C value occurred while the patient was on alirocumab 75 mg) + 70 days

TEAE period: from first injection to last alirocumab injection + 70 days

Extended TEAE period: from first injection to last injection (alirocumab or placebo) + 70 days

Neurocognitive events

The adjusted analyses on the different observation periods did not show consistent differences in the rate of neurocognitive events between alirocumab-treated patients with 2 consecutive LDL-C <25 mg/dL (0.65 mmol/L) and alirocumab-treated patients without these low LDL-C values. Very few events were reported in the patients with 2 consecutive LDL-C values <15 mg/dL (0.39 mmol/L), resulting in variations of the estimated HR (some higher than 1; some lower than 1) among different analysis periods. Moreover, consistent with there being few events, there were wide CIs around these HRs.

Table 27: Second step: Number (%) of patients with neuro-cognitive disorders TEAE(s) and hazard ratio according to LDL-C level (25 and 15 mg/dL, 0.65 and 0.39 mmol/L) adjusted on prognostic factors - Safety population - Alirocumab treated patients

n events (rate per 100 patient year) Hazard ratio (95% CI)	Alirocumab LDL-C ≥25mg/dL (N=5146)	Alirocumab 2 LDL-C <25mg/dL (N=4305)	Alirocumab LDL-C ≥15mg/dL (N=8669)	Alirocumab 2 LDL-C <15mg/dL (N=782)
Low LDL-C period	79 (0.6)	51 (0.7) 1.13 (0.79 to 1.63)	137 (0.6)	6 (1.0) 1.69 (0.73 to 3.92)
TEAE period	79 (0.6)	64 (0.6) 0.98 (0.71 to 1.37)	137 (0.6)	6 (0.5) 0.91 (0.40 to 2.07)
Extended TEAE period	80 (0.6)	66 (0.6) 0.94 (0.67 to 1.30)	138 (0.6)	8 (0.4) 0.70 (0.34 to 1.43)

Extracted from 16-2-7-ae-data [16.2.7.9.5.1] to [16.2.7.9.5.6]
Low LDL-C period: from the date of the first low LDL-C up to the last alirocumab 150 mg injection (if low LDL-C value occurred while the patient was on alirocumab 150 mg) or up to the last alirocumab injection (if low LDL-C value occurred while the patient was on alirocumab 75 mg) + 70 days
TEAE period: from first injection to last alirocumab injection + 70 days
Extended TEAE period: from first injection to last injection (alirocumab or placebo) + 70 days

Table 28: Second step: Number (%) of patients with neuro-cognitive disorders (FDA grouping) TEAE(s) and hazard ratio according to LDL-C level (25 and 15 mg/dL, 0.65 and 0.39 mmol/L) adjusted on prognostic factors - Safety population - Alirocumab treated patients

n events (rate per 100 patient year) Hazard ratio (95% CI)	Alirocumab LDL-C ≥25mg/dL (N=5146)	Alirocumab 2 LDL-C <25mg/dL (N=4305)	Alirocumab LDL-C ≥15mg/dL (N=8669)	Alirocumab 2 LDL-C <15mg/dL (N=782)
Low LDL-C period	76 (0.6)	45 (0.6) 1.03 (0.71 to 1.51)	126 (0.6)	6 (1.0) 1.95 (0.84 to 4.55)
TEAE period	76 (0.6)	56 (0.5) 0.89 (0.63 to 1.26)	126 (0.6)	6 (0.5) 1.02 (0.45 to 2.32)
Extended TEAE period	77 (0.6)	57 (0.5) 0.83 (0.59 to 1.17)	127 (0.6)	7 (0.3) 0.67 (0.31 to 1.44)

Extracted from 16-2-7-ae-data [16.2.7.9.7.1] to [16.2.7.9.7.6]
Low LDL-C period: from the date of the first low LDL-C up to the last alirocumab 150 mg injection (if low LDL-C value occurred while the patient was on alirocumab 150 mg) or up to the last alirocumab injection (if low LDL-C value occurred while the patient was on alirocumab 75 mg) + 70 days
TEAE period: from first injection to last alirocumab injection + 70 days
Extended TEAE period: from first injection to last injection (alirocumab or placebo) + 70 days

New onset diabetes

Two step approaches were applied for the prespecified events, including NOD.

The prespecified first step - second screening approach analysis that compared alirocumab versus placebo according to categories based on baseline LDL-C showed no differences between the 2 treatment groups across the 5 categories, with HR point estimates close to 1. In particular a HR<1 was observed in the 2 lowest categories, ie, baseline LDL-C <70 mg/dL and baseline LDL-C ≥70 to <90 mg/dL. In the lowest category of baseline LDL-C <70 mg/dL, the incidence of NOD was 12.6% in the placebo group as compared to 9.6% in the alirocumab group.

Contrary to neurological, neurocognitive, and cataract events that were detected through AE reporting, NODs were detected from AEs, laboratory parameters (HbA_{1c} and fasting glucose), and initiation of antidiabetic medications. After results became available, it was observed that the vast majority of NODs were detected through laboratory parameters, and more particularly HbA_{1c}.
In most cases, even when diabetes was reported as AE, the onset date was concomitant to the measurement of laboratory parameters. Measurements of HbA_{1c} and fasting glucose were yearly assessments with the first measurement performed at Month 12.

Therefore, the low LDL-C period as per the SAP was associated with a decrease of the time period where the patients were at risk of an event and with an increase of the rate in patient-years. Because of this major bias, the calculated incidence of NOD in patients with 2 consecutive LDL-C values <15 mg/dL (0.39 mmol/L) as compared with patients without such levels was considered unreliable.

Over the TEAE and extended TEAE periods, the calculated incidence of NOD in patients with 2 consecutive LDL-C <25 mg/dL (0.65 mmol/L), as compared with patients without such levels showed estimated HRs slightly above 1. Higher HRs were observed in patients with 2 consecutive LDL-C <15 mg/dL (0.39 mmol/L). It should be noted that this analysis has the limitation of any comparison of post-randomization subgroups. Despite adjustment on prognostic factors for NOD, remaining confounders cannot be ruled out.

Table 29: Second step: Number (%) of patients with new onset of diabetes and hazard ratio according to LDL-C level (25 and 15 mg/dL, 0.65 and 0.39 mmol/L) adjusted on prognostic factors - Safety population - Alirocumab treated patients

n events (rate per 100 patient year) Hazard ratio (95% CI)	Alirocumab LDL-C ≥25mg/dL (N=3739)	Alirocumab 2 LDL-C <25mg/dL (N=3024)	Alirocumab LDL-C ≥15mg/dL (N=6238)	Alirocumab 2 LDL-C <15mg/dL (N=525)
TEAE period	324 (3.6)	324 (4.5) 1.22 (1.03 to 1.44)	606 (3.9)	42 (5.6) 1.52 (1.10 to 2.10)
Extended TEAE period	330 (3.6)	368 (4.6) 1.22 (1.04 to 1.44)	619 (3.9)	79 (5.9) 1.46 (1.14 to 1.87)

Extracted from 16-2-7-ae-data [16.2.7.9.9.1] to [16.2.7.9.9.4]
TEAE period: from first injection to last alirocumab injection + 70 days
Extended TEAE period: from first injection to last injection (alirocumab or placebo) + 70 days

To further explore any relationship between NOD and low LDL-C, 2 post-hoc analyses were conducted:

- A post-hoc propensity matching analysis. This analysis was done to assess the risk of developing NOD in alirocumab patients who achieved 2 consecutive LDL-C <15 mg/dL compared to placebo patients matched to these alirocumab patients based on baseline characteristics that predict a predisposition to achieving 2 consecutive LDL-C <15 mg/dL. This analysis intended to identify placebo-treated patients that likely would have achieved low LDL-C levels if they were exposed to alirocumab (matching done between 3 non-diabetic placebo patients and 1 non-diabetic alirocumab patient).

  The comparison was adjusted on between-group baseline differences in prognostic factors of NOD. The analysis showed a HR of 1.09 (0.83 to 1.42). This analysis has also the limitations inherent to the limited number of baseline factors that were used to match with the placebo patients. Despite the adjustment on prognostic factors for NOD, remaining confounders cannot be ruled out.

Table 30: New onset of diabetes during the extended TEAE period according to LDL-C level - Safety population - Patients with no diabetes at baseline - Comparison of patients with 2 consecutive LDL-C <15 mg/dL to propensity-matched placebo patients

	Alirocumab 2 LDL-C <15mg/dL n/N(%)	Matched Placebo n/N(%)	HR (95% CI)
New onset of diabetes	79 / 525 (15.0)	204 / 1575 (13.0)	1.09 (0.83 to 1.42)

Analysis period (extended emergence period) is defined as the period from date of first injection date until the last injection date (including blinded placebo injections) + 70 days.
Adjusted hazard ratios and 95% CI are determined from a multivariate Cox model including the covariate for treatment arm and prognostic factors of the event analyzed.
Prognostic factors: Age, BMI at baseline, HbA1c at baseline, CRP at baseline, LDL-C at baseline, Fasting Glucose (<100 mg/dL, >=100 mg/dL), Baseline HDL-C (<40mg/dL, >=40 mg/dL), Baseline TG (<150 mg/dL, >=150mg/dL) statin naive, statin intensity at randomization, race, ethnicity and medical history of hypertension.
New onset of diabetes is defined using specific TEAE terms, antidiabetic initiation with a confirmed diagnosis per the external diabetes experts and HbA1c/fasting glucose values
Matched placebo corresponds to the 3 patients in Placebo arm with no diabete at baseline matching with each alirocumab patients with at least 2 consecutive LDL-C values <15 mg/dL according to region, Lp(a) at baseline and LDL-C at baseline

- A post-hoc analysis of NOD similar to the analysis published in the FOURIER study. In this analysis, adjusted on prognostic factors for NOD, no differences across the 5 groups based on LDL-C levels at Month 1 were observed. In particular, similar results were observed for the subgroup of patients with achieved LDL-C <20 mg/dL compared to the subgroup of patients with achieved LDL-C ≥100 mg/dL at Month 1 used as the reference subgroup (HR: 1.04, 95% CI: 0.80 to 1.34). In addition to the limitation of comparing post-randomization subgroups, this analysis might be less sensitive than the analyses described above due to the categorization of patients based on a single value and the use of a higher threshold (20 mg/dL instead of 15 mg/dL); however, it has been performed to have a better comparison to the published data from another PCSK9 inhibitor.

Table 31: New onset of diabetes during the extended TEAE period by achieved LDL-C at 1 month after randomization - Safety population - Patients with no diabetes at baseline and with an available on-treatment LDL-C at 1 month

	LDL-C at 1 month				
	<20 mg/dL / <0.52 mmol/L N=1006	≥20 to <50 mg/dL / ≥0.52 to <1.29 mmol/L N=3812	≥50 to <70 mg/dL / ≥1.29 to <1.81 mmol/L N=2190	≥70 to <100 mg/dL / ≥1.81 to <2.59 mmol/L N=3753	≥100 mg/dL / ≥2.59 mmol/L N=2016
NOD [n(%)]	113 (11.2%)	363 (9.5%)	226 (10.3%)	400 (10.7%)	197 (9.8%)
[HR (95%CI)]	1.04 (0.80 to 1.34)	0.91 (0.75 to 1.10)	0.94 (0.76 to 1.15)	1.03 (0.86 to 1.24)	ref

Adjusted hazard ratios and 95% CI are determined from a multivariate Cox model including the on-treatment LDL-C achieved at Month 1 (<20, [20 to 50[, [50 to 70[, [70, to 100[, =>100 mg/dL) and prognostic factors of the NOD.
Prognostic factors: Age, BMI at baseline, HbA1c at baseline, CRP at baseline, LDL-C at baseline, Fasting Glucose (<100 mg/dL, >=100 mg/dL), Baseline HDL-C (<40mg/dL, >=40 mg/dL), Baseline TG (<150 mg/dL, >=150mg/dL) statin naive, statin intensity at randomization, race, ethnicity and medical history of hypertension.
New onset of diabetes is defined using specific AE terms on the extended TEAE period, antidiabetic initiation with a confirmed diagnosis per the external diabetes experts and HbA1c/fasting glucose values
Extended TEAE period is from first IP to last IP (active or not) + 70 days

Cataract

In the alirocumab group, the number of cataracts per 100 patient-years in patients with 2 consecutive LDL-C values <25 mg/dL (0.65 mmol/L) was higher than those who did not have 2 consecutive LDL-C values <25 mg/dL. In patients with 2 consecutive LDL-C values <15 mg/dL (0.39 mmol/L), very few cataracts were reported, resulting in variations of the estimated HR, however consistently above 1, across the different analysis periods with wide CIs. These analyses could also still be biased by the comparison of post-randomization subgroups since the prognostic factors of cataract were not all accounted for in the analysis as some were not collected in the database (eg, funduscopic evidence of large Drusen, iris color, sunlight exposure, or waist circumference).

Table 32: Second step: Number (%) of patients with cataract TEAE(s) and hazard ratio according to LDL-C level (25 and 15 mg/dL, 0.65 and 0.39 mmol/L) adjusted on prognostic factors – Safety population - Alirocumab treated patients

n events (rate per 100 patient year) Hazard ratio (95% CI)	Alirocumab LDL-C ≥25mg/dL (N=5146)	Alirocumab 2 LDL-C <25mg/dL (N=4305)	Alirocumab LDL-C ≥15mg/dL (N=8669)	Alirocumab 2 LDL-C <15mg/dL (N=782)
Low LDL-C period	56 (0.4)	44 (0.6) 1.25 (0.84 to 1.87)	113 (0.5)	5 (0.9) 1.60 (0.63 to 4.03)
TEAE period	56 (0.4)	64 (0.6) 1.32 (0.93 to 1.90)	113 (0.5)	7 (0.6) 1.15 (0.53 to 2.48)
Extended TEAE period	56 (0.4)	71 (0.6) 1.34 (0.94 to 1.90)	114 (0.5)	13 (0.6) 1.18 (0.66 to 2.09)

Extracted from 16-2-7-ae-data [16.2.7.9.12.1] to [16.2.7.9.12.6]
Low LDL-C period: from the date of the first low LDL-C up to the last alirocumab 150 mg injection (if low LDL-C value occurred while the patient was on alirocumab 150 mg) or up to the last alirocumab injection (if low LDL-C value occurred while the patient was on alirocumab 75 mg) + 70 days
TEAE period: from first injection to last alirocumab injection + 70 days
Extended TEAE period: from first injection to last injection (alirocumab or placebo) + 70 days

Adverse drug reactions

To identify ADRs from the alirocumab clinical data, a tier-based approach was utilized similar to that used for the original dossier. For Tier 1 TEAEs, hypotheses and a comprehensive analytical approach were prospectively defined. For Tier 2, common TEAEs (not prespecified) were evaluated. These are TEAEs for which the prior probability was low that an individual term would represent an adverse reaction. The approach to these common TEAEs is based on the use of statistical tests to screen TEAEs which were then assessed clinically. Tier 3 corresponds to infrequent TEAEs for which descriptive analyses only were performed.

In the original submission, the following ADRs were identified for alirocumab: injection site reactions, hypersensitivity, hypersensitivity vasculitis, upper respiratory tract signs and symptoms, pruritus, urticaria, and eczema nummular.

In the OUTCOMES study, the only TEAE identified as an ADR was injection site reactions reported at a slightly higher rate with alirocumab as compared to placebo (3.8% versus 2.1%). This ADR was previously identified in the original submission.

For general allergic TEAEs (based on a CMQ for PTs potentially related to allergic events), no event (at PT level) was detected as a potential signal with alirocumab as compared to the placebo through the Tier 2 analysis. The rare and sometimes serious allergic events identified as ADRs in the original submission, were reported at similar incidence in the alirocumab and placebo groups in the OUTCOMES study: pruritus (alirocumab group: 0.8%; versus placebo group: 0.7%), urticaria (0.4% versus 0.3%), eczema

nummular (<0.1% in both groups), hypersensitivity (0.2% in both groups) and hypersensitivity vasculitis (0 versus < 0.1%). In summary, the analysis of TEAEs pertaining to the general allergic TEAEs grouping has not revealed any new safety signal in the OUTCOMES study.

Analysis of neurologic events overall (AESI) or at event level (PT) did not reveal any difference between the treatment groups that would indicate that one of these neurologic events is an ADR.

Neurocognitive TEAEs were reported at comparable rates in the alirocumab and the placebo groups. Confusional state (PT) was an event detected through the Tier 2 analysis, however based on the findings of the independent NCEP during their blinded review, this event is not considered as ADR.

Hepatic disorder TEAEs were reported at comparable rates in the alirocumab and the placebo groups. TEAEs coded to the PT drug-induced liver injury (PT) and gallbladder polyp (PT) were detected through the Tier 2 analysis but the clinical conclusion based on the review of the cases was that there was no clinically meaningful difference between the treatment groups. The analysis of the events pertaining to the hepatic disorders SMQ and the results of liver enzymes including PCSA analyses, do not indicate that the administration of alirocumab could be associated with a signal on hepatic disorders. Thus, no hepatic disorder is considered as ADR.

Diabetes mellitus or diabetic complications in patients with diabetes at baseline were reported at comparable rates in the alirocumab and the placebo groups. Review of all TEAEs at PT level did not reveal any differences between treatment groups.

NOD were reported at comparable rates in the alirocumab and the placebo groups. Additionally, the changes over time in mean HbA_{1c} and fasting glucose were similar in the alirocumab and the placebo groups, overall. Analysis according to diabetes status at baseline showed no meaningful changes in mean HbA_{1c} (%) and mean fasting glucose, in patients with no diabetes at baseline (normoglycemic or with pre-diabetes at baseline).

Cataract conditions (HLT) were reported in comparable number of patients in the alirocumab and the placebo groups.

In summary, no new ADRs other than those already known were identified in the OUTCOMES study.

Overdose with the IMP

Overall, 3.3% of patients in the alirocumab group versus 4.0% of patients in the placebo group were reported to have had an overdose with the IMP.

Overdoses with the IMP (alirocumab or placebo) were asymptomatic and accidental in the majority of patients. Two patients in the alirocumab and in the placebo groups each reported symptomatic overdose. In the 2 patients in the alirocumab group who reported symptomatic overdose, one reported injection site reaction, and the other one reported a nonserious, moderate muscular weakness concomitant with the overdose but which was assessed as not related to the IMP by the Investigator. Five patients in the alirocumab and 8 patients in the placebo group reported intentional overdose with the IMP.

Pregnancy

No pregnancies were reported in female participants. Pregnancies in partner's participant were reported for 6 patients (<0.1%) in the alirocumab group versus 2 patients (<0.1%) in the placebo group. In the 7 cases all pregnancies ended in normal delivery of healthy newborns (information provided by the partner). In the remaining case no further information was provided and it concerns the placebo group patient.

Serious adverse event / deaths / other significant events

Serious adverse events

The percentages of patients who experienced a treatment-emergent SAE were similar between alirocumab and placebo groups (23.3% versus 24.9%).

There were no clinically meaningful differences between treatment groups for any individual SOC or PT. The most frequently reported treatment-emergent SAEs (PT), ie, that occurred in ≥0.5% of patients in either the alirocumab or placebo groups are presented in Table 33.

Table 33 - Number (%) of patients with treatment emergent SAE(s) that occurred with PT >= 0.5% in any treatment group by decreasing order in the alirocumab group - Safety population - EFC11570

Preferred Term n(%)	Placebo (N=9443)	Alirocumab (N=9451)
Non-cardiac chest pain	222 (2.4%)	219 (2.3%)
Angina pectoris	133 (1.4%)	113 (1.2%)
Pneumonia	108 (1.1%)	96 (1.0%)
Atrial fibrillation	98 (1.0%)	82 (0.9%)
Syncope	73 (0.8%)	67 (0.7%)
Acute kidney injury	62 (0.7%)	57 (0.6%)
Osteoarthritis	46 (0.5%)	50 (0.5%)
Chronic obstructive pulmonary disease	51 (0.5%)	38 (0.4%)

Only rows with frequency of at least 0.5% in at least one column are shown
MedDRA 20.1 . n(%) = number and percentage of patients with at least one SAE.

Deaths

Any death that occurred from randomization until CSED was not considered as AE but as an efficacy endpoint, and had to be submitted to the CEC for adjudication. However, when the cause of death could not be determined, the Investigator was also to report “Sudden Death” or “Undetermined cause of death” as an SAE.

Overall 334 deaths (3.5%) in the alirocumab group and 392 (4.2%) deaths in the placebo group were reported during the course of the study until the CSED (**oup and** 1 in the placebo group).

Table 34). For both components of all-cause death, CV death, and non-CV death, a lower frequency was observed in the alirocumab group (2.3% and 1.0%, respectively) as compared with the placebo group (2.6% and 1.3%, respectively).

During the TEAE period, a total of 233 (2.5%) patients died in the alirocumab group and 273 (2.9%) patients in the placebo group. For the non-CV deaths, no differences were observed between alirocumab and placebo groups (0.6% in both groups).

Deaths that occurred after the CSED and up to the clinical database lock were not adjudicated per protocol. A total of 13 (0.1%) deaths in the alirocumab group and 6 (<0.1%) deaths in the placebo group were reported after the CSED; among them 10 occurred during the TEAE period (5 [<0.1%] in each group) and 9 post-treatment (8 in the alirocumab group and 1 in the placebo group).

Table 34 - Number (%) of patients who died by study period - Safety population - EFC11570

	Placebo (N=9443)	Alirocumab (N=9451)
Death until CSED	392 (4.2%)	334 (3.5%)
Death during the TEAE period	273 (2.9%)	233 (2.5%)
Death post-treatment	119 (1.3%)	101 (1.1%)
Death post CSED	6 (<0.1%)	13 (0.1%)
Death during the TEAE period	5 (<0.1%)	5 (<0.1%)
Death post-treatment	1 (<0.1%)	8 (<0.1%)

CSED: common study end date

Laboratory findings

No relevant abnormalities were identified on review of all laboratory assessments.

HbA1c

Analysis according to diabetes status at baseline showed that in patients with no diabetes at baseline, no meaningful changes from baseline in mean HbA1c were observed during the treatment period in either treatment group: the mean increase in HbA1c from baseline at Month 36 was +0.20% and +0.19%, in the alirocumab and the placebo groups, respectively, for patients normoglycemic at baseline, and +0.09% and +0.14%, in the 2 groups, respectively, for patients with pre-diabetes at baseline. In patients with diabetes at baseline, mean HbA1c tended to increase over time; however, with a similar magnitude in both treatment groups at +0.34% and +0.36%, in the alirocumab and the placebo groups respectively, at Month 36.

Renal function parameters

No treatment group differences were observed in the number of patients with PCSAs for renal function parameters during the TEAE period regardless of baseline status.

Table 35: Renal function - Number of patients with abnormalities (PCSA) during the TEAE period - Safety population

Laboratory parameter PCSA criteria n/N1 (%)	Placebo (N=9443)	Alirocumab (N=9451)
Creatinine		
≥ 150 µmol/L (Adults)	370/8867 (4.2%)	325/8536 (3.8%)
≥ 30% change from baseline	813/8863 (9.2%)	701/8534 (8.2%)
≥ 100% change from baseline	117/8863 (1.3%)	100/8534 (1.2%)
eGFR		
≥ 60 - < 90 mL/min/1.73m^2 (mild decrease in GFR)	5642/8837 (63.8%)	5321/8508 (62.5%)
≥ 30 - < 60 mL/min/1.73m^2 (moderate decrease in GFR)	1725/8837 (19.5%)	1723/8508 (20.3%)
≥ 15 - < 30 mL/min/1.73m^2 (severe decrease in GFR)	115/8837 (1.3%)	96/8508 (1.1%)
< 15 mL/min/1.73m^2 (end stage renal disease)	18/8837 (0.2%)	16/8508 (0.2%)
Blood urea nitrogen		
≥ 17 mmol/L	119/8837 (1.3%)	83/8506 (1.0%)
Urate		
< 120 µmol/L	12/8824 (0.1%)	13/8492 (0.2%)
> 408 µmol/L or > ULN (if ULN ≥ 408 µmol/L)	1395/8824 (15.8%)	1369/8492 (16.1%)

The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period.
For PCSA including condition based only on change from baseline, the denominator is restricted on patients having (not missing) baseline and a post-baseline values during the TEAE period
PCSA classification is performed on the worst value

Liver enzymes

Increases in ALT meeting these pre-specified criteria were reported in the TEAE period for 221 (2.4%) patients in the alirocumab group compared with 234 (2.5%) patients in the placebo group. No treatment group differences were observed in the number of patients with PCSAs of liver function parameters at any time during the TEAE period, in particular ALT values >3 ULN were reported in 2.3% of patients in the alirocumab group and 2.4% of patients in the placebo group; ALT values >10 ULN were reported in 0.3% of patients in the alirocumab group and 0.2% in the placebo group. Combination of ALT>3 ULN with total bilirubin >2 ULN (potential Hy's law case) was observed in 16 (0.2%) patients in the alirocumab group and 21 (0.2%) patients in the placebo group. In the 16 patients with potential Hy's law cases in the alirocumab group, an alternative etiology was not identified in one patient. This case was reported at the end-of-treatment visit but follow-up was not obtained (Patient No. 011570-070-007-002). Similarly, in the 21 patients with potential Hy's law case in the placebo group, alternative etiologies were identified in all but 3 patients (Patients 011570-356-057-024; 011570-616-008-042 and 011570-703-006-050).

Table 36: Liver function - Number of patients with abnormalities (PCSA) during the TEAE period - Safety population

Laboratory parameter PCSA criteria n/N1 (%)	Placebo (N=9443)	Alirocumab (N=9451)
Alanine aminotransferase		
> 3 ULN	228/9341 (2.4%)	212/9369 (2.3%)
> 5 ULN	86/9341 (0.9%)	89/9369 (0.9%)
> 10 ULN	20/9341 (0.2%)	31/9369 (0.3%)
> 20 ULN	9/9341 (<0.1%)	9/9369 (<0.1%)
Aspartate aminotransferase		
> 3 ULN	166/9338 (1.8%)	160/9367 (1.7%)
> 5 ULN	61/9338 (0.7%)	65/9367 (0.7%)
> 10 ULN	20/9338 (0.2%)	27/9367 (0.3%)
> 20 ULN	8/9338 (<0.1%)	9/9367 (<0.1%)
Alkaline phosphatase		
> 1.5 ULN	208/9342 (2.2%)	184/9369 (2.0%)
Total bilirubin		
> 1.5 ULN	213/9341 (2.3%)	188/9368 (2.0%)
> 2 ULN	78/9341 (0.8%)	61/9368 (0.7%)
Alanine aminotransferase and total bilirubin		
ALT > 3 ULN and BILI > 2 ULN	21/9340 (0.2%)	16/9368 (0.2%)
Direct bilirubin and bilirubin		
BILDIR > 35 % BILI and BILI > 1.5 ULN	26/1099 (2.4%)	15/1026 (1.5%)

CK levels

Creatine kinase values >3 ULN were observed in 5.0% of patients in the alirocumab group versus 5.1% of patients in the placebo group, and values >10 ULN were observed in 0.5% of patients in each treatment group.

Vital signs

No meaningful changes in vital signs (DBP, SBP, HR and weight) were observed over time in any treatment group (see Table 37 below).

Table 37: Number of patients with abnormalities during the TEAE period - Safety population

Vital Signs parameter PCSA criteria n/N1 (%)	Placebo (N=9443)	Alirocumab (N=9451)
Systolic blood pressure		
≤ 95 mmHg and decrease from baseline ≥ 20 mmHg	310/9365 (3.3%)	321/9376 (3.4%)
≥ 160 mmHg and increase from baseline ≥ 20 mmHg	1325/9365 (14.1%)	1320/9376 (14.1%)
Diastolic blood pressure		
≤ 45 mmHg and decrease from baseline ≥ 10 mmHg	52/9365 (0.6%)	43/9376 (0.5%)
≥ 110 mmHg and increase from baseline ≥ 10 mmHg	198/9365 (2.1%)	188/9376 (2.0%)
Heart rate		
≤ 50 bpm and decrease from baseline ≥ 20 bpm	130/9365 (1.4%)	127/9376 (1.4%)
≥ 120 bpm and increase from baseline ≥ 20 bpm	26/9365 (0.3%)	24/9376 (0.3%)
Weight		
≥ 5% decrease from baseline	2328/9167 (25.4%)	2118/9184 (23.1%)
≥5% increase from baseline	3913/9167 (42.7%)	3716/9184 (40.5%)

Safety in special populations

Adverse events in patients with ADA response

Treatment-emergent positive ADA assay responses were observed in 5.5% of patients in the alirocumab group and in 1.6% of patients in the placebo group. Most of the treatment-emergent ADA responses were classified as very low titer, transient responses, with only 0.7% and 0.4% of the patients experiencing persistent responses in the alirocumab group and the placebo group, respectively; the majority of these were also low titer responses. The incidence of NAb was very low, 0.5% in the alirocumab group and <0.1% in the placebo group, and mostly transient.

In the alirocumab group, 78.6% of treatment-emergent ADA-positive patients and 76.2% of ADA-negative patients had at least 1 TEAE during the study. The safety profile in the ADA-positive patients was generally similar to that observed in the ADA-negative patients, with the exception of local injection site reaction with a higher frequency in the ADA-positive patients (7.5%) than in the ADA-negative patients (3.6%). Among the patients with a persistent ADA response, 10.4% had local injection site reactions.

As identified in the original submission, the ADA positive response was not associated with any special pattern of TEAEs, except an increased rate of injection site reactions.

Safety according to age

Significant ($p<0.10$) interactions were measured between the treatment groups and age for local injection site reaction. A lower incidence of events in older patients was detected compared to youngest patients. There is no mechanism to explain this interaction. Within the limitations of a small sample size in the older age groups, in particular for very old patients, no age-related safety concern emerged across these 4 age groups.

Table 38 - Overview of treatment-emergent adverse events by age - Safety population - EFC11570

MedDRA Terms	Age <65 years		Age ≥65 to <75 years		Age ≥75 to <85 years		Age ≥85 years	
	Placebo (N=6869)	Alirocumab (N=6952)	Placebo (N=2061)	Alirocumab (N=2007)	Placebo (N=493)	Alirocumab (N=470)	Placebo (N=20)	Alirocumab (N=22)
Total TEAEs	5240 (76.3%)	5191 (74.7%)	1603 (77.8%)	1583 (78.9%)	421 (85.4%)	372 (79.1%)	18 (90.0%)	19 (86.4%)
Total treatment-emergent SAEs	1569 (22.8%)	1499 (21.6%)	587 (28.5%)	540 (26.9%)	186 (37.7%)	155 (33.0%)	8 (40.0%)	8 (36.4%)
Fatal	115 (1.7%)	102 (1.5%)	69 (3.3%)	51 (2.5%)	32 (6.5%)	24 (5.1%)	3 (15.0%)	2 (9.1%)
Hospitalization/prolong existing hospitalization	1398 (20.4%)	1332 (19.2%)	529 (25.7%)	474 (23.6%)	160 (32.5%)	136 (28.9%)	7 (35.0%)	8 (36.4%)
Life-threatening	85 (1.2%)	78 (1.1%)	41 (2.0%)	28 (1.4%)	10 (2.0%)	11 (2.3%)	0	0
Disability/incapacity	28 (0.4%)	26 (0.4%)	17 (0.8%)	9 (0.4%)	2 (0.4%)	6 (1.3%)	0	0
Other (medically significant)	344 (5.0%)	318 (4.6%)	146 (7.1%)	131 (6.5%)	44 (8.9%)	27 (5.7%)	3 (15.0%)	1 (4.5%)
AE leading to drop-out	196 (2.9%)	222 (3.2%)	92 (4.5%)	99 (4.9%)	36 (7.3%)	22 (4.7%)	0	0
Psychiatric disorders (SOC)	809 (11.8%)	787 (11.3%)	209 (10.1%)	193 (9.6%)	66 (13.4%)	40 (8.5%)	1 (5.0%)	3 (13.6%)
Nervous system disorders (SOC)	1451 (21.1%)	1402 (20.2%)	501 (24.3%)	470 (23.4%)	144 (29.2%)	116 (24.7%)	8 (40.0%)	5 (22.7%)
Accidents and injuries: Injury, poisoning and procedural complications (SOC)	1389 (20.2%)	1424 (20.5%)	437 (21.2%)	440 (21.9%)	124 (25.2%)	108 (23.0%)	8 (40.0%)	6 (27.3%)
Cardiac disorders (SOC)	1712 (24.9%)	1605 (23.1%)	610 (29.6%)	552 (27.5%)	184 (37.3%)	152 (32.3%)	8 (40.0%)	10 (45.5%)
Vascular disorders (SOC)	1918 (27.9%)	1852 (26.6%)	686 (33.3%)	626 (31.2%)	192 (38.9%)	175 (37.2%)	9 (45.0%)	10 (45.5%)
Cerebrovascular disorders (SMQ)	97 (1.4%)	66 (0.9%)	45 (2.2%)	28 (1.4%)	11 (2.2%)	8 (1.7%)	1 (5.0%)	1 (4.5%)
Infections and infestations (SOC)	1972 (28.7%)	2023 (29.1%)	670 (32.5%)	655 (32.6%)	191 (38.7%)	175 (37.2%)	11 (55.0%)	8 (36.4%)
Anticholinergic syndrome (SMQ)	479 (7.0%)	441 (6.3%)	191 (9.3%)	151(7.5%)	53 (10.8%)	53 (11.3%)	3 (15.0%)	2 (9.1%)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	4084 (59.5%)	4072 (58.6%)	1336 (64.8%)	1256 (62.6%)	353 (71.6%)	309 (65.7%)	17 (85.0%)	18 (81.8%)

Extracted from 2.7.4 Summary of Clinical Safety Appendix [1.4.1.2.1 to 1.4.1.2.5]

Table 39 - Overview of adverse event profile: Treatment emergent adverse events according to eGFR at baseline - Safety population

	≥15 to <30 (severe decrease in GFR)		≥30 to <60 (moderate decrease in GFR)		≥60 to <90 (mild decrease in GFR)		≥90 (normal)	
n(%)	Placebo (N=26)	Alirocumab (N=39)	Placebo (N=1232)	Alirocumab (N=1238)	Placebo (N=5747)	Alirocumab (N=5804)	Placebo (N=2433)	Alirocumab (N=2366)
Patients with any TEAE	22 (84.6%)	36 (92.3%)	992 (80.5%)	977 (78.9%)	4438 (77.2%)	4392 (75.7%)	1825 (75.0%)	1758 (74.3%)
Patients with any treatment emergent SAE	13 (50.0%)	17 (43.6%)	401 (32.5%)	384 (31.0%)	1385 (24.1%)	1292 (22.3%)	551 (22.6%)	507 (21.4%)
Patients with any TEAE leading to death	3 (11.5%)	3 (7.7%)	67 (5.4%)	51 (4.1%)	104 (1.8%)	92 (1.6%)	48 (2.0%)	34 (1.4%)
Patients with any TEAE leading to permanent treatment discontinuation	4 (15.4%)	3 (7.7%)	57 (4.6%)	59 (4.8%)	189 (3.3%)	206 (3.5%)	74 (3.0%)	75 (3.2%)

n(%) = number and percentage of patients with at least one TEAE

[a] Patient can be counted in more than one category

PGM=PRODOPS/SAR236553/EFC11570/PUB_2018/REPORT/PGM/ae_overview_subgrp_s_t.sas
OUT=REPORT/OUTPUT/ae_overview_subgrp_gfr1_s_t_i.rtf (28SEP2018 - 15:04)

For renal impairment a slightly higher incidence of AEs was observed, however, this was independent of treatment allocation. Very limited patients with GFR < 30 ml/min/1.73 m² were included (n=65).

Discontinuation due to adverse events

The percentages of patients with TEAEs leading to permanent treatment discontinuation were similar between the alirocumab and placebo groups (3.6% versus 3.4%).

The most frequently reported TEAEs (PTs) leading to permanent treatment discontinuation that occurred in ≥0.2% of patients in either the alirocumab or placebo groups, respectively, were (by decreasing order in the alirocumab group): myalgia reported at the same incidence in both treatment groups (0.2%) and injection site reactions (0.2% in the alirocumab group versus <0.1% in the placebo group).

Post marketing experience

Cumulatively, from 01-Jul-2015 to 30-Sep-2017, the worldwide sales represented 116.72 million mg of alirocumab (whatever the form) over this 27-month-period. Assuming a mean daily dose of 5.4 mg per day (World Health Organisation Defined Daily Dose), the number of patient days is estimated to be of 21.61 million (number of milligrams divided by 5.4), and the number of patient-years to be of 59 216 cumulatively (number of patient-day divided by 365).

Based on the information collected and analyzed during the post-marketing period through 30-Sep-2017, the Sponsor added influenza-like illness to its Company Core Data Sheet as having been reported with post-marketing use and is updating its labeling worldwide accordingly.

2.4.1. Discussion on clinical safety

In this long term cardiovascular outcome study patients were treated for a mean period of 31 months with alirocumab (background lipid lowering therapy) including 8071 (87%) patients exposed for ≥12 months, 7248 (78%) patients for ≥24 months, 3105 (33%) for ≥36 months, and 555 (6%) for ≥48 months. This is substantially longer than the treatment periods obtained in the original MAA. A slightly higher cumulative exposure in the placebo group was seen which could be clarified by the fact that some patients (n=730; 7.7%) from the alirocumab were switched to placebo due to very low LDL-C levels as per protocol. A proportion of 27.7% of the patients (2615) were uptitrated to the 150 mg, and of these patients 805 (8.5%) patients were subsequently downtitrated. In the presentation of the adverse events, generally, no distinction between both doses in presentation has been made. As in the original dossier no different pattern in AEs has been observed between both doses.

Although AEs were commonly reported, these were approximately similar between the alirocumab and placebo group (75.8% vs 77.1%). Also the serious AEs were reported in a similar frequency (23.3% vs 24.9%). The drug was generally well tolerated as the percentage of patients who discontinued due to AEs was relatively low and occurred in a comparable frequency in both groups (3.6% versus 3.4%).

The most common AE reported more for alirocumab than placebo (≥0.5% difference) was injection site reaction (3.8% vs 2.1%), which occurred mostly within the first year of treatment. These were mostly mild to moderate, transient (6-8 days), and occurred mostly as a single episode (70% vs 80%). Most reported were erythema/redness (2.1% vs 0.7%), swelling (1.5% vs 0.7%), pain (1.5% vs 0.8%), tenderness (1.3% vs 0.6%), and itching (1.3% vs 0.4%). Only 3 patients treated with alirocumab reported serious local injection site reactions, which all recovered. Only 0.3% vs <0.1% discontinued due to local injection site reactions. The slightly higher frequency of AEs reported for ADA positive patients (78.6% vs 76.2%) was mainly attributed to the higher frequency of local injection site reactions (7.5% vs 3.6%), and may suggest that these events can be partly explained by an immunological response. Any other pattern could not be observed between ADA positive and ADA negative patients. In the current dossier, injection site reactions were also the only identified adverse drug reaction (ADR) (3.8% vs 2.1%). This ADR was already known from the original dossier. The additional ADRs already identified in

the original dossier were hypersensitivity, hypersensitivity vasculitis, upper respiratory tract signs and symptoms, pruritus, urticaria, and eczema nummular. These could not be identified in the current study.

No clear signs of any effect of alirocumab on musculoskeletal and connective tissue disorders were observed. No difference was observed for musculoskeletal and connective tissue disorders (25.4% vs 25.3%). Some of these event were slightly more reported for alirocumab while others were slightly lower: myalgia (5.6% vs 5.3%), back pain (4.3% vs 4.2%), arthralgia (3.9% vs 3.7%), pain in extremity (3.1% vs 3.2%), muscle spasms (2.3% vs 2.1%), osteoarthritis (2.2% in both groups), musculoskeletal pain (1.9% vs 2.3%) and musculoskeletal chest pain (1.1% vs 1.4%). Further, no differences were observed in patients with increased CK levels according to treatment group (>3 ULN: 5.0% vs 5.1%; >10 ULN: 0.5% vs 0.5%).

Special attention has also been given to certain other adverse events. Further, the safety profile for those patients achieving very low LDL-C levels have been examined. The data for the <15 mg/dL subgroup is limited including 782 patients and thus any conclusions for this subgroup should be drawn with caution, while the data for the <25mg/dL subgroup including 4305 patients appears more substantial. In general, no relevant differences in AE frequencies were observed for these very low levels of LDL-C subgroups compared to higher LDL-C levels.

Neurologic events were infrequently reported and more in the placebo group (4.0% vs 4.4%). These were only severe in 3.5% vs 3.3% of the cases. Hypoesthesia (1.0% vs 0.9%), paresthesia (0.9% vs 1.1%), and muscular weakness (0.5% vs 0.4%) were mostly reported. Further, no substantial difference was found for patients achieving very low levels of LDL-C vs higher achieved LDL-C levels (slightly lower in the < 25 mg/dL subgroup vs ≥ 25 mg/dL group; slightly higher in the < 15 mg/dL subgroup vs ≥ 15 mg/dL group) ranging from 1.4-2.5%.

Specific attention has also been given to neurocognitive events, which were evaluated by an independent NCEP panel. This was specifically done since these events have previously been associated with very low LDL-C levels, although the initial dossier did not give any sign of such an association, but definite conclusions were difficult to draw due to the low frequencies. Currently, these events were found in a low frequency and no difference between treatment groups was found (1.5% vs 1.8%). Only 5.6% vs 4.8% of these events were evaluated as severe. Confusional state was more reported for alirocumab (0.2% vs < 0.1%) but not considered treatment related. One (<0.1%) patient in the alirocumab group and 3 (<0.1%) patients in the placebo group had a neurocognitive AE leading to death of which pre-existing medical history could explain the cause of death. Neurocognitive events were also very limited reported (0.4-1.0%) in the very low LDL-C groups (LDL-C < 25 mg/dL) and showed comparable frequencies to the LDL-C ≥ 25 mg/dL group, making any definite conclusions difficult.

Diabetes was assessed by an independent diabetes panel. Treatment with alirocumab did not give any clear sign of increased diabetes risk. New onset diabetes in patients without diabetes at baseline, overall diabetes cases, and diabetes in patients with diabetes at baseline all reported similar incidences as to placebo; 9.6% vs 10.1%, 8.7% vs 9.8%, 18.8% vs 21.2%, respectively. No meaningful differences were observed for change from baseline in mean HbA1c with +0.09% and +0.14% change for patients normoglycemic at baseline for alirocumab vs placebo, strengthening this observation. Diabetes risk was also assessed in the very low LDL-C achieved subgroup. New onset diabetes was detected through several ways including AEs, laboratory parameters (HbA_{1c} and fasting glucose), and initiation of antidiabetic medications. New onset diabetes was observed at slightly higher frequency (4.5% vs 3.6% in the < 25 and ≥ 25 mg/dL subgroup; 5.6% vs 3.9% in the < 15 and ≥ 25 mg/dL subgroup) although the patient numbers in the <15 mg/dL subgroup were limited. A propensity matching comparison found a HR of 1.09 (0.83 to 1.42). A further analysis (similar to the FOURIER study) according to achieved LDL-C subgroup (5 groups) did not show a substantial higher risk in the < 20 mg/dL (<0.52 mmol/L) subgroup vs the ≥100 mg/dL (≥2.59 mmol/L) subgroup (11.2% vs 9.8%) and a lack of a clear trend across the 5

subgroups. Therefore, any higher incidence of new onset diabetes with very low LDL-C levels by alirocumab treatment remains inconclusive.

Ophthalmological events were more frequently reported with alirocumab during the initial dossier though remained inconclusive due to the low numbers. In particular, cataract was considered a potential risk in very low LDL-C levels based on very limited data. In the current dossier, the frequency of cataract was low and similar between both treatment groups (1.3%vs 1.4%). In very low LDL-C levels few AEs of cataract were reported (0.4% - 0.9%) which were, however, all consistently slightly higher for the lower LDL-C subgroups. Further data will likely be available from the ODYSSEY PASS observational study. Until then cataract should at least remain included as potential risk in the RMP.

For allergic reactions, a similar frequency was found (7.9% vs 7.8%), with rash, pruritus, asthma, eczema and conjuctivitus being the most observed AEs with the majority being mild (61%) to moderate (33%) and most recovered (79% vs 74%). Hemolytic anaemia was reported to be very rare (3 vs 1 patients), and none considered to be related to alirocumab treatment.

There was no sign of any hepatic disorders with alirocumab as AEs were similarly reported (5.3% vs 5.7%) with most frequently reported AEs being alanine aminotransferase increased (1.4% vs 1.8%), hepatic steatosis (0.8% vs 1.0%), gamma-glutamyltransferase increased (0.7% vs 0.7%), and potential drug-induced liver injury (0.6% vs 0.4%). Potential Hy's law cases were similar (0.2%) and serious hepatic disorder AEs were reported in 0.6% of patients in both treatment groups. Differences in liver enzyme abnormalities were also not meaningful. Increases in ALT according to pre-specified criteria (elevations of ALT ≥3 x ULN (if baseline ALT <ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ULN) for reporting an AE) were 221 (2.4%) vs 234 (2.5%); ALT values >3 ULN was 2.3% vs 2.4%; ALT values >10 ULN was 0.3% vs 0.2%; and combination of ALT>3 ULN with total bilirubin >2 ULN (potential Hy's law case) was 16 (0.2%) vs 21 (0.2%) patients in the placebo group.

Adverse events in the renal and urinary disorders SOC did not report any imbalance (668 (7.1%) vs 696 (7.4%)). This was supported by an absence of differences for renal function abnormalities. Patients with more than 30% change in eGFR not being different (8.2% vs 9.2%). Also no differences were observed for renal function abnormalities with patients with more than 30% change in eGFR not being different (8.2% vs 9.2%). Also no differences were observed for eGFR levels (62.5% vs 63.8% eGFR 60-90, 20.3% vs 19.5% eGFR 30-60, 1.1% vs 1.3% eGFR 15-30 mL/min/1.73m^2) or abnormal urate levels (16.1% vs 15.8%).

Serious adverse events were reported at comparable frequency (23.3% vs 24.9%) confirming previous findings in the initial MAA. The most frequently reported serious AEs were non-cardiac chest pain, angina pectoris, pneumonia, atrial fibrillation, syncope, acute kidney injury, osteoaethritis, and chronic obstructive pulmonary disease, all at comparable frequencies. A lower frequency of deaths was reported with alirocumab (3.5% vs 4.2%), also including deaths which could not be determined by the CEC for efficacy.

No meaningful differences were observed in vital signs including blood pressure, heart rate and weight.

Specific data according to age categories of <65 years, 65-75 years, 75-85 years, and >85 shows a slightly higher incidence of AEs ≥ 75 years of age, however, numbers are small and do not allow for any conclusions. For renal impairment a slightly higher incidence of AEs was observed, however, this was independent of treatment assignment. Very limited patients with GFR < 30 ml/min/1.73 m² were included (n=65).

Any data on gonadal steroid hormones and gonadotropins were only very limited, but did not show relevant alterations.

2.4.2. Conclusions on clinical safety

With the presentation of safety data of the current outcome trial, the controlled safety data for alirocumab have been extensively increased. Safety data were generally in line with those observed in the original dossier. The results provide some more reassurance on some of the safety issues typically known to be associated with lipid lowering drugs, including musculoskeletal adverse events, diabetes and hepatic safety. While other safety issues including some aspects on the safety in very low LDL-C levels remain inconclusive. Results show a possible higher frequency of cataract in very low LDL-C levels, therefore, this remains as potential risk in the RMP.

2.4.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Risk management plan

The MAH submitted an updated RMP version 4.0 with this application and thereafter RMP versions 4.1 and 4.2.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.2 is acceptable. PRAC endorsed PRAC Rapporteur assessment report.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.2 with the following content:

Safety concerns

Summary of the safety concerns

Important identified risks	Immunogenicity Systemic hypersensitivity reactions
Important potential risk	Cataract (in context of very low LDL-C[a]) Neurocognitive disorders
Missing information	Use in children and adolescents Use in pregnant and lactating women Use in patients with severe hepatic impairment Long-term use (>5 years) Clinical impact of very low LDL-C[a] for extended period of time Influence of alirocumab on gonadal steroid hormones and gonadotropins (in men and women)

a ie, less than 25 mg/dL (0.65 mmol/L)
LDL-C: Low Density Lipoprotein-Cholesterol.

Pharmacovigilance plan

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 8 - Ongoing and planned required additional pharmacovigilance activities (by the competent authority) (category 3)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
R727-CL-1532: A trial with a dedicated prospective assessment of neurocognitive function Ongoing	Evaluate neurocognitive function with use of PRALUENT after 96 weeks of treatment versus placebo. Evaluate the effect of PRALUENT in comparison with placebo on lipoproteins. Evaluate the safety and tolerability of PRALUENT.	Neurocognitive disorders	Final protocol submission to EMA Report submission to EMA	22-Apr-2016 Q2 2021
R727-CL-1609: Long Term Safety Study (Neurocognitive Function Open-Label Extension) Planned	Evaluate long-term safety of PRALUENT Evaluate effect of PRALUENT on LDL-C Evaluate effect of PRALUENT on other lipid parameters	Safety in long-term use (>5 years) Clinical impact of very low LDL-C for extended period of time, including New Onset Diabetes and Cataract (AESI) Circulating gonadal steroid hormones and gonadotropins levels measured in both men and women	Final protocol submission Report submission to EMA	03-Jun-2016 Q4 2024
ALIROC07997: A PASS in patients infected with HIV Ongoing	Monitor muscle events, and liver function and creatine kinase abnormalities in HIV patients treated with alirocumab by quantifying the incidences of these safety outcomes using existing healthcare databases	Safety data in patients infected with HIV	Final protocol submission to EMA Yearly interim report submission to EMA	16-Aug-2016 Dec-2017 to Dec-2020 with first interim report submitted

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Final report submission to EMA	on 20-Dec-2017 Q2 2022
OBS14697: Drug utilization survey Planned	Evaluate the effectiveness of the PRALUENT (brand name of alirocumab) dosing recommendations for the 3 dosage regimens approved to date, ie, 75 mg once every two weeks, 150 mg once every two weeks, and 300 mg once every 4 weeks (monthly) to avoid very low LDL-C levels.	Clinical impact of very low LDL-C for extended period of time	Final protocol submission to EMA Yearly interim report submission to EMA Final report submission to EMA	21-Apr-2016 Q3 2019 and Q3 2020 Q3 2021
Pediatric Phase 2 Dose finding study: DFI14223 Ongoing	Evaluate the effect of alirocumab administered every 2 weeks or every 4 weeks on LDL-C levels after 8 weeks of treatment in heterozygous familial hypercholesterolemia. Evaluate the safety and tolerability of alirocumab.	Safety of patients with LDL-C <50 mg/dL Growth and gonadal hormones Neurocognitive events Neurological events Allergic drug reactions, local injection site reactions.	Final report submission to EMA	Q3 2019
Pediatric Phase 3 study: EFC14643 Planned	Evaluate the efficacy of alirocumab versus placebo after 24 weeks of double-blind treatment on LDL-C and other lipid parameters, and safety in patients with heterozygous familial hypercholesterolemia 8 to 17 years of age on top of optimal Statin and other lipid modifying therapy. Evaluate the efficacy, safety and tolerability of alirocumab	Safety of patients with LDL-C <50 mg/dL Growth and gonadal hormones Neurocognitive events Neurological events Allergic drug reactions, local injection site reactions.	Final report submission to EMA	Q2 2024
Pediatric Phase 3 study: EFC14660	Evaluate the efficacy of alirocumab on LDL-C levels at Week 12 up to 48 weeks of treatment in children with	Safety of patients with LDL-C <50 mg/dL	Final report submission to EMA	Q1 2022

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Planned	homozygous familial hypercholesterolemia 8 to 17 years of age on top of background treatments. Evaluate the safety and tolerability of alirocumab up to 48 weeks of treatment.	Growth and gonadal hormones Neurocognitive events Neurological events Allergic drug reactions, local injection site reactions.		

EMA: European Medicines Agency; AESI: Adverse Event of Special Interest; HIV: Human Immunodeficiency Virus, LDL-C: Low Density Lipoprotein-Cholesterol; PASS: Post-Authorization Safety Study; Q: Quarter.

Risk minimisation measures

V.3. SUMMARY OF RISK MINIMIZATION MEASURES

Safety concern	Risk minimization measures
Important identified risks	
Immunogenicity	**Routine risk minimization measures:** Labelled in section 4.8 of the SmPC. Prescription only medicine **Additional risk minimization measures:** None
Systemic hypersensitivity reactions	**Routine risk minimization measures** Labelled in sections 4.4, and 4.8 of the SmPC. Labelled in sections 2 and 4 of PL. Prescription only medicine **Additional risk minimization measures:** None

Important potential risk	
Cataract (in context of very low LDL-C[a])	**Routine risk minimization measures** Prescription only medicine **Additional risk minimization measures:** None
Neurocognitive disorders	**Routine risk minimization measures** Prescription only medicine **Additional risk minimization measures:** None
Missing information	
Use in children and adolescents	**Routine risk minimization measures** Labelled in section 4.2 of SmPC. Labelled in section 2 of PL. Prescription only medicine **Additional risk minimization measures:** None
Use in pregnant and lactating women	**Routine risk minimization measures** Labelled in section 4.6 of SmPC. Labelled in section 2 of PL. Prescription only medicine **Additional risk minimization measures:** None

Use in patients with severe hepatic impairment	**Routine risk minimization measures** Labelled in sections 4.2 and 4.4 of SmPC. Labelled in section 2 of PL. Prescription only medicine **Additional risk minimization measures:** None
Long-term use (>5 years)	**Routine risk minimization measures** Prescription only medicine **Additional risk minimization measures:** None
Clinical impact of very low LDL-C[a] for extended period of time	**Routine risk minimization measures** Labelled in section 4.2 and 4.8 of SmPC. Prescription only medicine **Additional risk minimization measures:** None
Influence of alirocumab on gonadal steroid hormones and gonadotropins (in men and women)	**Routine risk minimization measures** Prescription only medicine **Additional risk minimization measures:** None

a ie, less than 25 mg/dL (0.65 mmol/L)
LDL-C: Low Density Lipoprotein-Cholesterol; PASS: Post Authorization Safety

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The wording of the indication in section 4.1 of the SmPC has been updated as follows (New text in bold, removed text strikethrough):

"Primary hypercholesterolaemia and mixed dyslipidaemia

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

~~The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.~~

Established atherosclerotic cardiovascular disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- **in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,**
- **alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.**

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1."

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The change is not related to a change in legal status or to a new presentation, and no particular critical safety issues have been identified with Praluent. Therefore, as per the "Guideline on the readability of the labelling and package leaflet of medicinal products for human use", a new consultation with target patient groups for the package leaflet is not considered mandatory nor necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Alirocumab is a fully human monoclonal immunoglobulin G2 directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9), which inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. LDLR is the primary receptor that clears circulating LDL, therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.

In the initial submission, alirocumab has demonstrated a substantial and consistent reduction in LDL-C and other lipid parameters alone and on top of existing lipid lowering therapy (LLT) options including statins and ezetimibe in several groups of patients with hypercholesterolaemia and mixed dyslipidaemia. Alirocumab has demonstrated an acceptable safety profile. Based on these observations the following indication was approved at the time of the initial marketing authorisation of Praluent:

Hypercholesterolaemia and mixed dyslipidaemia

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LD -C goals with the maximum tolerated dose of a statin or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contra-indicated.*

The effect of Praluent on cardiovascular morbidity and mortality has not yet been determined.

In the current variation, the following indication was proposed by the MAH mainly based on the submitted results of the **ODYSSEY OUTCOMES** study (n=18924 patients), a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of CV events in patients with established CV disease (CVD) and who have experienced an ACS event within 4 to 52 weeks prior to randomization.

Based on this study the applicant proposed the following (additional) indication:

Prevention of Cardiovascular Events in Established Atherosclerotic Cardiovascular Disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce the risk of major adverse cardiovascular events (coronary heart disease death, myocardial infarction, stroke, unstable angina requiring hospitalization) and all-cause mortality by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- *in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*

However, this proposed additional indication has been subject to further discussion and modification during the procedure, see below.

3.1.1. Disease or condition

Cardiovascular disease comprises a group of diseases that include both vessels in the heart and other arterial blood vessels, thereby including coronary heart disease (CHD), coronary artery disease (CAD), and ACS, among several other conditions. All these are characterized by atherosclerosis and can be asymptomatic, with the exception of ACS, which encompasses unstable angina (UA) and myocardial infarction (MI). Patients with recent ACS are a subset of the patients with CVD who are characterized by a high risk for suffering recurrent coronary events in the near term. Registry data indicate CV mortality as high as 13% at 5 years, with more than 4 out of 5 deaths occurring after initial discharge from hospital, supported by a rate of recurrent events being higher in the first months after hospitalisation. Despite a higher CV risk for patients shortly after ACS, beyond one year the risk wanes progressively to that of the general population of patients with established CVD. Moreover, the origin of CV events in all CVD conditions is driven by a similar physiopathology. With respect to the OUTCOMES study, patients were enrolled within a year of an ACS event. Thus, during the course of the study, these patients progressively evolved to a more chronic status. Moreover, the design of the OUTCOMES study can be viewed as a prognostic enrichment strategy as patients with recent ACS have a greater likelihood of having MACE compared with the “more chronic” patient population with established CVD.

Epidemiological and pharmacological intervention trials have demonstrated a strong and direct linear relationship between LDL-C levels and CV events; for example, the Cholesterol Treatment Trialist (CTT) Collaboration meta-analysis that examined 26 large statin CV event trials encompassing approximately 170 000 patients demonstrated that a 22% reduction in major CV events could be ascribed to every 1 mmol/L (38.6 mg/dL) reduction in LDL-C, even in patients with baseline LDL-C levels <2 mmol/L [77 mg/dL]). In practice, many high CV risk patients are not treated with optimized regimens of statins and, even if they are, cannot achieve optimal LDL-C levels of 30 mg/dL to 50 mg/dL (0.78 mmol/L to 1.29 mmol/L) with most available oral lipid-lowering drugs, leaving a substantial residual risk for patients. An unmet need remains, and therefore, additional pharmacological therapies for the prevention of CVD may be necessary, particularly for high-risk patients with ACS.

Recent data from the FOURIER CV outcome study conducted with evolocumab (Repatha) have provided additional support to the concept that lower LDL-C values obtained via PCSK9 inhibition are associated with reduction in risk of CV events beyond that achievable with standard oral lipid-lowering treatment alone. This benefit was demonstrated in a secondary prevention scenario in patients with established arteriosclerotic cardiovascular disease (ASCVD).

3.1.2. Available therapies and unmet medical need

There are 3 categories of lipid-lowering drugs that are registered for the prevention of CV risk including statins (HMG CoA reductase inhibitors), ezetimibe (inhibitor of the intestinal absorption of cholesterol and related plant sterols), and evolocumab (a PCSK9 inhibitor).

Statins are among the most studied drugs in CVD prevention and considered as the gold-standard for CV risk prevention in clinical guidelines. Although clinical guidelines clearly support the use of statins as treatment initiation with a LDL-C target <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 mmol/L and 3.5 mmol/L (70 mg/dL and 135 mg/dL) in patients at very high-risk, a need exists for additional therapies for LDL-C lowering and CVD prevention, because some patients who are already receiving a maximum tolerated dose of a statin still have a residual CVD risk due to high baseline LDL-C or limitations in statin tolerability. It is well known that some patients suffer from statin side effects (eg, myalgia) that limit their ability to take a statin or a high enough dose of statin to reach their LDL-C goal. Statin-intolerant patients are at higher risk of not achieving target LDL-C levels appropriate to their level of CV risk given that non-statin therapies, other than PCSK9 inhibitors, typically provide only about a 15-20% reduction in LDL-C.

Ezetimibe is also registered in several countries to reduce the risk of CV events in adult patients with CHD and a history of ACS when added to ongoing statin therapy or initiated concomitantly with a statin. In clinical guidelines ezetimibe is recommended to be used as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose or in patients intolerant to statins or with contraindications to these drugs, although the absolute benefit from adding ezetimibe may be limited.

For the reduction of CV risk, evolocumab is indicated to reduce the cardiovascular risk in patients with “established atherosclerotic cardiovascular disease (myocardial infarction, stroke, or peripheral arterial disease) . . .”. This indication is based on the results of the CV outcomes trial conducted with evolocumab, the FOURIER study. This study was a double-blind, randomized (1:1 ratio), placebo-controlled, event-driven study involving 27564 patients with established cardiovascular disease and with LDL-C ≥70 mg/dL and/or non-HDL-C ≥100 mg/dL despite high-or moderate-intensity statin therapy, with a median follow-up duration of 26 months. Established cardiovascular events was defined as a history of myocardial infarction, non-haemorrhagic stroke, or symptomatic peripheral artery disease, as well as additional CV risk factors, which appears somewhat wider than the patients included in the ODYSSEY OUTCOME study. Evolocumab significantly reduced the risk for the primary composite endpoint (time to first occurrence of

CV death, MI, stroke, hospitalization for UA, or coronary revascularization; HR 0.85; 95%CI: 0.79 to 0.92; p<0.001), with an absolute risk reduction of approximately 2% within this time frame.

3.1.3. Main clinical study

3.1.3.1. Favourable effects

In the **ODYSSEY OUTCOMES** study (n=18924 patients) alirocumab demonstrated a **significant reduction** on the composite primary endpoint of time to CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, or UA requiring hospitalisation, whichever occurred first (903 [9.5%] vs 1052 [11.1%]; HR of 0.85 (95% CI 0.78, 0.93; p < 0.0001)) after a mean of 31 months of treatment with the beneficial effect starting at approximately 8 months of treatment and primarily **driven by MI** (83 less events). This translated in an absolute risk reduction of approximately 1.6% for the entire study period for the primary endpoint. Included were **patients at very high CV risk** identified by documented ACS event within 4 to 52 weeks (median 3.6 months) prior to randomisation, and an elevated LDL-C level in need for LLT according to practice guidelines. About 34% had a previous documented CAD, 21% had another CVD (CHF, PAD or cerebrovascular disease) and/or additional CV risk factors (hypertension, family history of CAD, diabetes). The observed treatment effect was a result of an observed LDL-C reduction of 40-56% from a starting median level of 2.39 mmol/L in LDL-C in patients primarily **treated with high intensity statin** background therapy (89%). Alirocumab also reduced Apo B, non-HDL-C, fasting TGs, and Lp(a) and increased HDL-C – as also shown in earlier studies.

The primary endpoint demonstrated a **consistent beneficial effect** across a wide range of subgroups, except for the Asian population. A consistent effect was seen for a subgroup with already low levels of LDL-C at baseline (<1.81 mmol/L). Further, a continuous relationship between the level of achieved LDL-C and adjusted CV event rates could be demonstrated.

Hierarchical testing of **secondary composite endpoints** of any CHD event (major CHD event, UA requiring hospitalization, ischaemia-driven coronary revascularization procedure), any major CHD event (CHD death, non-fatal MI), any CV event (any non-fatal CHD event, any CV death, and non-fatal ischemic stroke), and CHMP guideline recommended composite endpoint of all-cause mortality, non-fatal MI, and non-fatal ischemic stroke showed consistent beneficial effects until the statistical testing was violated at the level of the CHD deaths endpoint.

3.1.3.2. Uncertainties and limitations about favourable effects

A trend of reduction in **CHD deaths and CV deaths** was observed. Further a nominally statistically significant reduction in **all-cause death** was demonstrated, however, the hierarchical testing was already violated for analysing of this endpoint. No particular pattern could be observed for the type of non-CV deaths.

The inclusion of **unstable angina requiring hospitalisation** in the primary endpoint is considered less robust in particular with respect to objective definitions and may introduce bias in relation to clinical decision making. However, UA contributed the least to the primary endpoint in comparison to the other components, and the effect was consistent with the primary analysis for those (combined) endpoints excluding UA.

There was a limited representation of **patients above 75 years** (1007 patients, 5.3%).

3.1.3.3. Unfavourable effects

The **overall exposure** data from clinical studies has **substantially increased** from 3340 patients in the initial dossier to an additional 18924 subjects treated in the pivotal study (OUTCOME). Further, it has

been estimated that the alirocumab exposure has reached 59216 patient years in the postmarking setting at time of writing this report.

Consistent with the initial submission, alirocumab generally displays a **safety profile similar to that of the placebo group** with 75.8% vs 77.1% for alirocumab and placebo reported adverse events. Comparable to the initial dossier, the most common adverse event was injection site reaction (3.8% vs 2.1%) for alirocumab and placebo, respectively, and this was the only **drug related adverse event** identified. **Serious adverse events** between alirocumab and placebo were also similar (23.3% vs 24.9%). Most frequently reported serious adverse events were found in the group of ischaemic coronary artery disorders (non-cardiac chest pain (2.3% vs 2.4%), angina pectoris (1.2% vs 1.4%)). The safety profile according to **dose level** was comparable.

Slightly more patients treated with alirocumab **discontinued** (21.9% vs 15.8%) mainly due to blinded roll-over to placebo in case of very low LDL-C levels (7.7%). Alirocumab was generally well tolerated with low number of discontinuations **due to adverse events** (3.6% vs 3.4%). This included myalgia (0.2%, 0.2%), and injection site reactions (0.2% vs <0.1%), respectively.

The incidence of **local injection site reactions** was slightly higher in the alirocumab group (3.8% versus 2.1% in the control group) mostly during the first year of treatment. However, the adverse events were of mild to moderate intensity and transient and barely resulted in discontinuations (0.2% vs <0.1%). The differences in injection site reactions may partly be explained by immunological responses due to the presence of **anti-alirocumab antibodies.** Anti-alirocumab antibodies were infrequent but more frequent in the alirocumab group (5.5%) compared with the control group (1.6%). The slightly higher frequency of AEs reported for ADA positive patients (78.6% vs 76.2%) was mainly attributed to the higher frequency of local injection site reactions (7.5% vs 3.6%). Apart from the issues discussed with injection site reactions, no other clinically relevant adverse events differences were detected. The incidence in neutralizing antibodies was low with 43 patients (0.5%) in the alirocumab group versus 6 patients (<0.1%) in the control group.

Alirocumab treatment was not associated with any apparent **musculoskeletal related AEs**, adverse events known to be associated with existing lipid modifying therapy. The incidences of these AEs was comparable (25.4% vs 25.3%) although some small differences in individual AEs appeared, e.g. myalgia (5.6% vs 5.3%), back pain (4.3% vs 4.2%), arthralgia (3.9% vs 3.7%), muscle spasms (2.3% vs 2.1%), musculoskeletal pain (1.9% vs 2.3%) and musculoskeletal chest pain (1.1% vs 1.4%). Yet, no differences were observed in patients with increased CK levels according to treatment group (>3 ULN: 5.0% vs 5.1%; >10 ULN: 0.5% vs 0.5%).

The frequency of **neurocognitive adverse events** as assessed by an independent panel was low and comparable between treatment groups (1.5% vs 1.8%). These AEs were also very limited reported (0.4-1.0%) in the very low LDL-C groups (LDL-C < 25 mg/dL) and showed comparable frequencies to the LDL-C ≥ 25 mg/dL group, although the limited numbers make any definite conclusions difficult.

A similar incidence of new onset of **diabetes mellitus** (NODM) was observed for alirocumab 9.6% vs 10.1%, while change from baseline in HbA1c values were also comparable (+0.09% and +0.14%). Very low levels also did not provide a clear sign for an increased risk for diabetes. New onset diabetes was observed at slightly higher frequency (4.5% vs 3.6% in the < 25 and ≥ 25 mg/dL subgroup; 5.6% vs 3.9% in the < 15 and ≥ 15 mg/dL subgroup). However, a propensity matching comparison found a HR of 1.09 (0.83 to 1.42). Also, a further analysis (similar to the FOURIER study) according to achieved LDL-C subgroup (5 groups) did not show a substantial higher risk in the < 20 mg/dL (<0.52 mmol/L) subgroup vs the ≥100 mg/dL (≥2.59 mmol/L) subgroup (11.2% vs 9.8%) and a lack of a clear trend across the 5 subgroups.

No clear effect on **hepatic disorders** of alirocumab was observed (5.3% vs 5.7%). Differences in liver enzyme abnormalities were also not meaningful. Increases in ALT according to pre-specified criteria were 221 (2.4%) vs 234 (2.5%); ALT values >3 ULN was 2.3% vs 2.4%; ALT values >10 ULN was 0.3% vs 0.2%; and combination of ALT>3 ULN with total bilirubin >2 ULN (potential Hy's law case) was 16 (0.2%) vs 21 (0.2%).

No clear effect on **renal disorders** was observed (7.1% vs 7.4%). Also, there were no differences in renal function abnormalities or other renal markers.

For **other adverse events of special interest** including allergic reactions (7.9% vs 7.8%), haemolytic anaemia (3 vs 1) and neurologic events (4.0% vs 4.4%) no meaningful differences were observed.

No meaningful differences were observed in vital signs including **blood pressure**, heart rate and weight.

3.1.3.4. Uncertainties and limitations about unfavourable effects

Exposure in the pivotal study was **limited to a median of 31 months**; this may be too short to exclude long term effects. An open-label extension study is being performed to further address long term safety longer than 5 years of treatment, the clinical impact of very low LDL-C levels for extended period of time, neurocognitive disorders, and gonadal steroid hormones and gonadotropins, to be finalised in 2024.

In the current dossier, the frequency of **cataract** was low and similar between both treatment groups (1.3%vs 1.4%). In very low LDL-C levels few AEs of cataract were reported (0.4% - 0.9%) which were, however, all consistently slightly higher for the lower LDL-C subgroups. Therefore, cataract is maintained as a potential risk in the RMP.

Relative limited safety data is available for patients **> 75 years of age** (n=1007; 5.3%), although this can be considered sufficient in absolute terms. A slightly higher incidence of AEs was observed for ≥ 75 years of age, however, numbers are small and do not allow for any conclusions.

A slightly higher incidence of AEs were observed in patients with **renal impairment**, but this was not related to treatment assignment. Very limited numbers of patients with severe renal impairment were included (n=65). Additional safety data on patients with **liver insufficiency** are lacking as these were not specifically screened for at inclusion.

Any data on **gonadal steroid hormones and gonadotropins** were very limited, but did not show any relevant alterations.

3.1.3.5. Effects Table

Table 40: Effects Table for Praluent – cardiovascular risk reduction indication - sept 2018

Effect	Short description	Unit	Alirocumab	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
		N	**9462**	**9462**		
Primary endpoint	**CHD death, non-fatal MI, fatal and non-fatal ischaemic stroke, or UA requiring hospitalisation**	%	9.5% (n=903)	11.1% (n=1052)	SoE: HR 0.85 (0.78 to 0.93), p=0.0003; consistent effect in subgroups	

Effect	Short description	Unit	Alirocumab	Control	Uncertainties / Strength of evidence	References
Secondary endpoint	**All cause mortality, non fatal MI, non fatal ischemic stroke**	%	10.3% (n=973)	11.9% (n=1126)	SoE: HR 0.86 (0.79 to 0.93), p=0.0003 ; significant as 4th step in hierarchical testing after any CHD, major CHD, any CV event *See notes below	
Unfavourable Effects						
Patients who discontinued study treatment		%	21.9% (7.7% blinded roll-over to placebo due to very low LDL-C)	15.8%	Protocol defined required roll-over to placebo that was independent of any adverse effects	
Patients discontinued due to AE		%	3.6%	3.4%	Unc: No clear pattern - myalgia (0.2%, 0.2%), and injection site reactions (0.2% vs <0.1%)	
Injection site reactions		%	3.8%	2.1%	SoE: other AEs, musculoskeletal related AEs, neurocognitive adverse events, diabetes mellitus, hepatic disorders, renal disorders were comparable in frequencies	
Anti-alirocumab antibodies			5.5%	1.6%	SoE: slightly higher frequency of AEs in ADA positives (78.6% vs 76.2%) mainly due to local injection site reactions (7.5% vs 3.6%)	

Abbreviations: CHD = coronary heart disease, MI = myocardial infarction, UA = unstable angina, AE = adverse event, ADA = antidrug antibody, HR = hazard ratio, CV = cardiovascular,

Notes: Within the hierarchical testing of secondary endpoints only the secondary endpoint of all-cause mortality, non-fatal MI, non-fatal ischemic stroke is mentioned as this is the EMA guideline recommended endpoint.

3.2. Benefit-risk assessment and discussion

3.2.1. Importance of favourable and unfavourable effects

In the initial MAA, alirocumab was approved mainly based on a demonstration of a substantial and consistent reduction in LDL-C and other lipid parameters alone and on top of existing lipid lowering therapy (LLT) options including statins and ezetimibe in several groups of patients with hypercholesterolaemia and mixed dyslipidaemia.

In the current dossier, alirocumab has demonstrated a beneficial effect of reducing cardiovascular events primarily on MI in a selected patient group with very high cardiovascular risk primarily as identified by a recent ACS (acute coronary syndrome 4 to 52 weeks before randomisation). The effect observed for ischaemic events of MI can be considered clinically relevant, especially since this is supported by a trend towards a beneficial effect on cardiovascular death and overall mortality. In particular, a continuous

relation between the achieved LDL-C levels and adjusted CV event rates was observed, with no apparent lower limit of LDL-C at which the potential benefit disappears.

Regarding safety, alirocumab displayed an acceptable safety profile with a comparable incidence of adverse events to that of the placebo group (statin and other lipid lowering therapy), with limited patients discontinuing treatment or showing serious adverse events. In addition, alirocumab treatment did not cause any major effects on known safety problems associated with existing lipid lowering therapies such as liver disorders, renal disorders, diabetes and musculoskeletal disorders, or generally any effects in those reaching very low LDL-C levels.

For a lifelong treatment, a follow-up period of 31 months can be considered limited. Longer term data is being generated (see risk management plan section) intended to be finalised by 2024, although these data are open-label and not controlled.

3.2.2. Balance of benefits and risks

The applicant has conducted an outcome study to address and confirm the cardiovascular safety and efficacy of alirocumab in a patient population largely identified on their CV risk profile (very high CV risk primarily based on recent ACS). In agreement with clinical practice guidelines (e.g. *2016 ESC/EAS Guideline on cardiovascular disease prevention in clinical practice)* the included patients had elevated LDL-C despite treatment with statins and other lipid lowering therapy, but were still in need for further treatment due to their very high cardiovascular risk primarily defined by their recent cardiovascular event, amongst some other additional CV risk characteristics. Despite the need for further lowering LDL-C levels according to their very high cardiovascular risk profile*,* the effect could be considered moderate with a 15% reduction of the primary endpoint and an approximate 1.6% absolute risk reduction achieved over 31 months of treatment. Yet, the effect was consistent, primarily achieved by reduction in ischaemic events of MI, and supported by a trend towards a beneficial effect in CV death and overall mortality. Importantly, the effect was consistent among subgroups with generally a more beneficial effect with higher baseline risk.

The ODYSSEY OUTCOMES study supports treating of LDL-C to ‘’*as low as possible’’* levels, which has been subject to discussion in recent years (e.g. in *2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults*). An additional analysis demonstrated that there is no indication of a J-shaped curve, while there seems to be no lower limit of LDL-C at which potential CV benefit disappears. Further, a consistent treatment effect is also observed across the entire range of initial baseline LDL-C level. For instance, a consistent effect including a (trend towards a) beneficial effect was observed in the lowest subgroup of patients with LDL-C levels of < 70 mg/dL at baseline. Moreover, patients who had an LDL-C <70 mg/dL [1.81 mmol/L] at baseline (20% [n = 3751]) also demonstrated a beneficial effect being only slightly less than for the overall population. This further supports the statement as included in the *EMA Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013, Rev. 3)* of *“The relationship between LDL-C levels and CHD risk is present over a broad range of LDL levels. The dividing line between "normocholesterolaemia" and "hypercholesterolaemia" is arbitrary and in fact may be non-existent. Epidemiological data indicate a continuous increasing risk from very low to “normal” and high levels of LDL-C.”*

Although the data did not indicate a higher incidence of adverse events with very low LDL-C levels compared to higher achieved levels of LDL-C, the 31 month treatment period could still be considered relatively short to reveal certain consequences of lifelong very low LDL-C levels or other alirocumab effects. It remains important to follow this up closely for a longer period of time as addressed in the open-label follow-up study described in the RMP. In the past, with statins, concerns were raised of assumed increased risk when cholesterol would be lowered too much, including an increased risk for

cancer, haemorrhagic stroke, non-cardiovascular death, neurocognitive abnormalities and alterations in steroid production. The current dossier has specifically addressed several of these safety aspects, but these concerns remain unconfirmed, which can be considered reassuring. However, an inconclusive signal remains present for cataract, which therefore remains included in the RMP. For other safety aspects, including adverse events specifically known to be associated with existing lipid lowering therapy, including muscle related events, hepatic events, renal events, and diabetes, these have been further monitored within the current study as well, and did not give rise to specific concerns. Further, adverse events of hypersensitivity and immunological events have been followed-up without any clear safety signs with alirocumab treatment. Overall, any new safety issues not already included within current SmPC could not be identified.

3.2.3. Additional considerations on the benefit-risk balance

In addition to the current indication for alirocumab of primary hypercholesterolaemia and mixed dyslipidaemia, the applicant initially proposed the following indication to be added:

Prevention of cardiovascular events in established atherosclerotic cardiovascular disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce the risk of major adverse cardiovascular events (coronary heart disease death, myocardial infarction, stroke, unstable angina requiring hospitalization) and all-cause mortality by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,

- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

The proposed added indication comprises a patient population largely identified based on their (very high) CV risk profile. In agreement with clinical practice guidelines (e.g. *2016 ESC/EAS Guideline on cardiovascular disease prevention in clinical practice)* the included patients had elevated LDL-C despite treatment with statins and other lipid lowering therapy, but were still in need for further treatment due to their very high cardiovascular risk (see further discussion in section 3.2.2.).

However, some issues in relation to the proposed indication were identified and were further considered during the procedure. These related to the following:

- Including a separate underlined statement of *"prevention of cardiovascular disease''* was not accepted, as it might have implied that alirocumab could also be indicated for primary prevention which is not the case. Further, the term primary prevention at large ("*detecting a disease in its earliest stages, before symptoms appear, and intervening to slow or stop its progression")*, is not applicable to the selected patient population of the ODYSSEY OUTCOMES study.

- Mortality was proposed to be mentioned in the indication: *to reduce the risk of … all-cause mortality*. However, although a significant effect on mortality was noticed, the overall significance of the result on mortality was obtained when the hierarchical testing was already violated. Moreover, separate endpoints should generally not be included within the indication (guideline on Summary of Product Characteristics 2009). Therefore, explicit inclusion of a mortality benefit in the indication was not acceptable. A reduction of all-cause mortality was observed with only nominal, statistical significance only when taking into account the predefined, failed hierarchical

testing procedure, (HR 0.85, 95% CI: 0.73, 0.98). The findings are presented in section 5.1 of the SmPC.

- The statement of *to reduce the risk of major adverse cardiovascular events (coronary heart disease death, myocardial infarction, stroke, unstable angina requiring hospitalization)* was not considered entirely appropriate as the indication should be consistent with SmPC guideline recommendations (A guideline on Summary of Product Characteristics 2009) indicating that study endpoints should generally not be included in the indication.
- Finally, it was questioned whether the cardiovascular benefit as demonstrated in the selected very high cardiovascular risk patient population from the ODYSSEY OUTCOMES study, which is a-priori characterized by the presence of a recent ACS, could be extrapolated to the cardiovascular risk population at large. This was considered applicable by CHMP based on the reasoning provided below.

The ODYSSEY OUTCOMES study included patients with a recent ACS event in the last 1-12 months. This is representative for a population with established cardiovascular disease and could be considered as having very high CV risk, in line with learned society clinical practice guidelines e.g. ESC CV risk prevention guideline. In accordance with these practice guidelines, classifying patients with a comparable very high cardiovascular risk based on established atherosclerotic cardiovascular disease is generally not limited to one vascular area and thus includes also patients with other compromised vascular domains like stable CAD, stroke and PAD. It was considered being evident that similar CV risk reduction management is applicable for these patients. Moreover, the OUTCOMES study data confirm that, based on the same underlying disease, the effect observed with alirocumab in reducing the risk of CV events over the course of several years post-ACS can be translated to a broader population with established ASCVD following a continuous spectrum. More specifically, patients were administered alirocumab during their acute CV event, but only after stabilization. Although patients were enrolled within a year of an ACS event, patients entered the chronic phase of ASCVD during the course of the study, as they were followed for three years after an ACS event. The analyses of CV events in the OUTCOMES study according to the time period showed that the benefit with alirocumab was consistent over time, also in a stage that patients were clearly considered to have stable ASCVD, beyond 1 year. Furthermore, two pre-specified analyses in the pool of phase 3 studies and in the phase 3 LONG TERM study, both of which mostly included patients with established atherosclerotic cardiovascular disease, but not acute ACS, showed a positive effect on CV risk.

Of note, patients with established atherosclerotic cardiovascular disease and statin-intolerance or for whom a statin is contra-indicated could also be treated based on this indication. Although, such data have not been provided or evaluated, this would be acceptable based on extrapolation from LDL-C lowering data from the initial submission.

Based on these considerations, the applicant amended the indication during the procedure to the following finally accepted proposal:

Established atherosclerotic cardiovascular disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- *in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

3.3. Conclusions

The overall B/R of the proposed new indication for Praluent is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of adults with established atherosclerotic cardiovascular disease to reduce the risk of major adverse cardiovascular events by lowering LDL-C levels, as an adjunct to correction of other risk factors, in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. The final study report of Study EFC11570 was provided in support of the application; a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an acute coronary syndrome. As a consequence, sections, 4.1, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is being updated accordingly. In addition, an updated RMP version 4.2 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Additional market protection

In accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004, the Marketing authorisation holder applied for an additional one year marketing protection period in the framework of this application. Following the CHMP's initial assessment the applicant subsequently withdrew their request.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Praluent-H-C-3882-II-42’.