22 February 2018
EMA/233126/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Repatha

International non-proprietary name: evolocumab

Procedure No. EMEA/H/C/003766/II/0017/G

Note

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

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List of abbreviations

ACC American College of Cardiology

ACE angiotensin converting enzyme

AHA American Heart Association

CANTAB Cambridge Neuropsychological Test Automated Battery

CRP C-reactive protein

CTTC Cholesterol Treatment Trialists Collaboration

evolocumab REPATHA, formerly known as AMG 145

FDA Food and Drug Administration

HR hazard ratio

IgG2 immunoglobulin G2

IVUS intravascular ultrasound

LDL-C low-density lipoprotein cholesterol

LDLR LDL receptor

NICE National Institute for Health Care Excellence

PAV percent atheroma volume

PCSK9 proprotein convertase subtilisin/kexin type 9

Q2W every 2 weeks

QM once monthly (every 4 weeks)

SC subcutaneous

SMQ Standard MedDRA Queries

SoC standard of care

SPA Special Protocol Assessment

SWMS68 Spatial Working Memory Strategy Index (6-8 Boxes)

TAV total atheroma volume

ULN upper limit of normal

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 25 May 2017 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
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
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None

Extension of Indication to include reduction of atherosclerotic cardiovascular disease risk in adults with high cardiovascular risk or adults with primary hypercholesterolaemia (heterozygous familial and

non-familial) or mixed dyslipidaemia, or adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia as an adjunct to diet based on the results from Study 20110118 (a category 3 PV activity in the Risk Management Plan, MEA 004); as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC were proposed to be updated. The Package Leaflet was proposed to be updated in accordance.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 5.1 of the SmPC to include important mechanistic information for healthcare professionals based on Study 20120153 (a category 3 PV activity, MEA 006).

Submission of an updated RMP version 2.0 in order to add two category 3 studies in the RMP (Study 20160250 and Study 20150338), as well as to update the milestones of five category 3 studies (20110110, 20110271, 20120138, 20130286, 20130295)

The requested group of variations proposed amendments to the Summary of Product Characteristics and 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/0101/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0101/2017 was not yet completed as some measures were deferred.

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.

Scientific advice

The CHMP Scientific Advice was received: EMEA/H/SA/2377/I/2012/II (EMA/CHMP/SAWP561197/2012).

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	Planned dates	Actual dates
Start of procedure:	17 June 2017	17 June 2017

Timetable	Planned dates	Actual dates
CHMP Rapporteur Assessment Report	11 August 2017	11 August 2017
CHMP Co-Rapporteur Assessment Report	11 August 2017	15 August 2017
PRAC Rapporteur Assessment Report	18 August 2017	18 August 2017
PRAC members comments	23 August 2017	23 August 2017
Updated PRAC Rapporteur Assessment Report	24 August 2017	n/a
PRAC Outcome	1 September 2017	1 September 2017
CHMP members comments	4 September 2017	4 September 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 September 2017	8 September 2017
1st Request for supplementary information (RfSI)	14 September 2017	14 September 2017
Submission	13 October 2017	12 October 2017
Start of procedure:	16 October 2017	16 October 2017
CHMP Rapporteur Assessment Report	14 November 2017	20 November 2017
PRAC Rapporteur Assessment Report	17 November 2017	17 November 2017
PRAC members comments	22 November 2017	22 November 2017
Updated PRAC Rapporteur Assessment Report	23 November 2017	23 November 2017
PRAC Outcome	30 November 2017	30 November 2017
CHMP members comments	04 December 2017	04 December 2017
Updated CHMP Rapporteur Assessment Report	7 December 2017	8 December 2017
2nd Request for supplementary information (RfSI)	14 December 2017	21 December 2017
Submission	23 January 2018	23 January 2018
Start of procedure:	24 January 2018	24 January 2018
PRAC Rapporteur Assessment Report	29 January 2018	26 January 2018
PRAC members comments	31 January 2018	31 January 2018
Updated PRAC Rapporteur Assessment Report	01 February 2018	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	07 February 2018	07 February 2018
PRAC Outcome	08 February 2018	08 February 2018
CHMP members comments	12 February 2018	12 February 2018
Updated CHMP Rapporteur Assessment Report	15 February 2018	16 February 2018
3rd Request for supplementary information (RSI)	22 February 2018	22 February 2018
Submission	27 February 2018	27 February 2018
Start of procedure:	28 February 2018	28 February 2018
CHMP Rapporteur Assessment Report	7 March 2018	7 March 2018
PRAC Rapporteur Assessment Report	7 March 2018	7 March 2018
PRAC/CHMP members comments	12 March 2018	12 March 2018

Timetable	Planned dates	Actual dates
Updated PRAC Rapporteur Assessment Report	15 March 2018	n/a
Updated CHMP Rapporteur Assessment Report	15 March 2018	15 March 2018
Opinion	22 March 2018	22 March 2018

2. Scientific discussion

2.1. Introduction

Evolocumab (REPATHA, formerly known as AMG 145) is a **fully human monoclonal immunoglobulin G2 (IgG2)** that binds specifically to proprotein convertase subtilisin/kexin type 9 (PCSK9), preventing its interaction with the low-density lipoprotein receptor (LDLR). The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and decreased circulating concentrations of low-density lipoprotein cholesterol (LDL-C).

Evolocumab was approved in the EU on 17 July 2015. **The initial approval of evolocumab** was based on the effects of evolocumab to lower LDL-C, a surrogate biomarker for cardiovascular risk reduction. At the time of the initial MA a statement was included in Section 4.1 of the EU SmPC that the effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined, as the outcome study: 20110118 was ongoing.

In **the current group of variations**, the Marketing Authorisation Holder (MAH) has submitted the results of Study 20110118 (n= 27564); a Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy in Patients with Clinically Evident Cardiovascular Disease, to extend the indication in adults with high cardiovascular risk, in fulfilment of post authorisation measure MEA 004.

Additionally, the MAH has submitted the results of study 20120153 (n= 968); A Double-blind, Randomized, Multi-center, Placebo-controlled, Parallel-group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization to provide Information about the effect of evolocumab on coronary atherosclerosis in fulfilment of post authorisation measure MEA 006.

The Risk Management Plan (version 2.0) has been updated with information about the following studies (20160250, 20150338, 20110110, 20110271, 20120138, 20130286, 20130295).

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

No environmental risk studies were included in this application. The applicant submitted a justification stating that evolocumab is considered to be a non-hazardous, biodegradable product. The environmental risk in terms of use and disposal was considered to be negligible and, therefore, did not require further testing as per the EU Enviromental Risk Assessment Guideline. Furthermore, the assessment performed does not indicate a requirement to take special precautions during the release to the environment that will result from use in patients or disposal of the product. As such, it is not considered necessary to include warnings or precautions within the product information in relation to environmental risks. The CHMP agreed with the conclusions of the Applicant.

2.2.2. Conclusion on the non-clinical aspects

No environmental risk studies were included in this application. A justification was provided specifying that this application does not lead to a significant increase in environmental exposure further to the use of evolocumab.

Considering the above, evolocumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the results of 2 studies, one large CV outcome study considered to be pivotal and one study measuring the effects of evolocumab on coronary atherosclerotic disease as measured by coronary intravascular ultrasound (IVUS).

Study 20110118 (also referred to as FOURIER) was a large, pivotal, global study designed to evaluate the impact of evolocumab on the risk of cardiovascular events and the benefit:risk of reducing LDL-C to levels not previously examined (i.e., < 25 to 40 mg/dL).

Study 20120153 (also referred to as GLAGOV) was a phase 3 study designed to determine the effects of evolocumab on coronary atherosclerotic disease as measured by coronary intravascular ultrasound (IVUS).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

2.4. Clinical efficacy

2.4.1. Main study

Study 20110118 (FOURIER): Evolocumab and Prevention of Major Adverse Cardiovascular Events

Methods

Study participants

Inclusion criteria

The study enrolled subjects with a **history of established cardiovascular disease** as determined by prior myocardial infarction, history of non-hemorrhagic stroke, or symptomatic peripheral arterial disease (intermittent claudication with ankle-brachial index < 0.85, or peripheral arterial revascularization procedure or amputation due to atherosclerotic disease) and ≥ 1 major risk factor or ≥ 2 minor risk

factors. Subjects were required to have LDL-C levels above desired levels despite statin treatment (LDL-C ≥ 70 mg/dL [1.8 mmol/L]) or non-high-density lipoprotein cholesterol ≥ 100 mg/dL [2.6 mmol/L]) on stable high- to moderate-intensity statin therapy at baseline).

Major risk factors were: diabetes (type 1 or type 2), age > 65 years, a qualifying myocardial infarction or stroke within 6 months of screening, current daily cigarette smoking, an additional prior MI or non-hemorrhagic stroke (excluding the qualifying diagnosis) or symptomatic PAD if enrolled with history of MI or non-hemorrhagic stroke.

Minor risk factors were: history of non-MI related coronary revascularization, residual coronary artery disease with > 40% stenosis in > 2 large vessels, HDL-C < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women, hsCRP > 2.0 mg/L, LDL-C ≥ 130 mg/dL (3.4 mmol/L) or non-HDL-C > 160 mg/dL (4.1 mmol/L), or metabolic syndrome as defined in the study protocol.

All subjects were required to take **at least atorvastatin 20 mg daily or equivalent**. Where locally approved, **atorvastatin 40 mg daily or equivalent**, was recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) who were not receiving at least atorvastatin 40 mg daily or equivalent, the investigator had to attest that higher dose statin therapy was not appropriate for that subject (e.g., dose not tolerated, dose not available in that country, other significant clinical concern). Subjects who entered screening and were not considered to be receiving optimal background lipid therapy were required to complete lipid therapy titration before the final screening visit. In amendment 4 (16 July 2013; 3150 patients enrolled) other statins than atorvastatin were also allowed as background therapy.

Exclusion criteria

Subjects could not be randomized within 4 weeks of their most recent MI or stroke. Other major exclusion criteria included, but were not limited to, New York Heart Failure Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30%; uncontrolled or recurrent ventricular tachycardia, systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg; untreated hyper- or hypothyroidism, estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m2, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN), creatine kinase (CK) > 5 x ULN; use of a cholesteryl ester transfer protein (CETP) inhibitor, mipomersen or lomitapide within 12 months prior to randomization; prior use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition treatment other than evolocumab or use of evolocumab < 12 weeks prior the final lipid screening.

Inclusion criteria reflect a population with established cardiovascular disease determined by prior myocardial infarction (MI), history of non-hemorrhagic stroke, or symptomatic peripheral arterial disease (PAD). According to the *2016 European guidelines on cardiovascular disease prevention in clinical practice* these patients can be classified as patients with a **very-high CV risk as they have documented CVD**. Of note, subjects could not be randomized within 4 weeks of their most recent CVD event (MI or stroke) i.e. patients are not administered Repatha during their acute CV event, but are allowed to stabilise first.

To enrich this population, **additional inclusion criteria were patients having ≥ 1 major risk factor or ≥ 2 minor risk factors i**n addition to the documented CVD. The impact of these individual risk factors (major and minor) to the overall CV risk may be different, while it may be difficult to further quantify the overall risk estimation of a patient adding these risk factors to the overall risk qualification. Although acceptable, this will not reclassify patient's risk in terms of guideline risk categories (already very high risk) and associated treatment recommendations, but may increase their CV risk as a continuous estimation, probably improving the possible demonstration of a treatment effect of the drug under investigation.

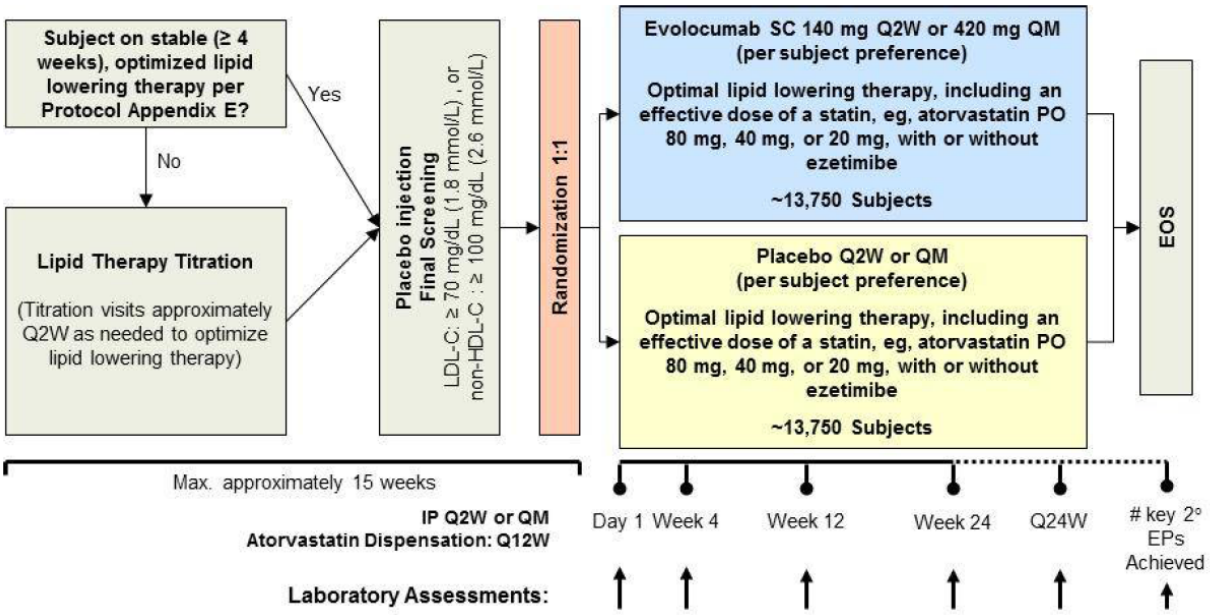
A particularly relevant **additional risk factor is the baseline LDL-C levels**. Subjects were required to have LDL-C levels above desired levels (LDL-C ≥ 70 mg/dL [1.8 mmol/L]) or non-HDL ≥ 100 mg/dL [2.6 mmol/L]) despite stable high- to moderate-intensity statin therapy at baseline. This is in line with clinical guidelines recommending drug intervention in very high risk patients with LDL-C levels of > 1.8 mmol/L to achieve target levels of < 1.8 mmol/L or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (*2016 European guidelines on cardiovascular disease prevention in clinical practice (p. 2331)).* Moreover, *2013 ACA/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults (p.10)* also supports such treatment strategy as specific LDL-C targets for initiation of therapy are not recommended (considering lack of evidence for specific targets). ''The lower the better'' was not specifically recommended in this guideline underscoring potential adverse effects and an unknown reduction in CV risk with new LLT therapy (on top of statins). Current study investigates this issue further. Non-statin therapy of ezetimibe already provided more evidence of moderate CV reduction associated with further LDL-C reduction in a selected population of ACS patients with inclusion criteria of LDL-C 1.3-2.6 mmol/L on top of simvastatin.

The use of **optimized moderate to high dose statin background therapy** was another eligibility criteria. Background statin therapy of at least atorvastatin 40 mg daily or equivalent (≥ 4 weeks on stable dose) was considered to represent high intensity statins use. Lower doses were only allowed in patients with LDL-C < 2.6 mmol/L, or > 2.6 mmol/L if well justified (eg, dose not tolerated, dose not available in that country, other significant clinical concern). Doses of at least 40 mg atorvastatin as inclusion criteria can be regarded as high intensity statin therapy for patients who will not likely demonstrate substantial additional LDL-C reduction when treated with even higher doses or a more potent statin.

Treatments

Subjects meeting eligibility criteria were randomized 1:1 to receive either double-blinded evolocumab or placebo. Randomization was stratified by final screening LDL-C (< 85 mg/dL [2.2 mmol/L] vs ≥ 85 mg/dL) and by geographical region (Europe, North America, Asia Pacific, and Latin America). Evolocumab (or matching placebo) was administered as either 140 mg every 2 weeks or 420 mg monthly. To reflect the expected use of evolocumab in clinical practice, subjects could initiate evolocumab and every 2 weeks or monthly and could switch between the 2 dosing regimens during the study based on personal preference.

Figure E1: General study design



Subjects were enrolled at 1242 clinical centers in 49 countries in the regions of Europe, North America, Asia Pacific, and Latin America.

Treatment

Evolocumab and placebo were investigational products in this study and were administered SC using a spring-based prefilled 1.0 mL autoinjector/pen (AI/pen). Evolocumab was administered at 1 of 2 dosing regimens:

- evolocumab 140 mg Q2W (1 prefilled AI/pen) or
- evolocumab 420 mg QM (3 prefilled AI/pens)

Placebo was administered at 1 of 2 dosing regimens:

- placebo SC Q2W (1 prefilled AI/pen) or
- placebo SC QM (3 prefilled AI/pens)

Prior to Protocol Amendment 4, subjects initiated their randomized investigational product treatment (evolocumab or placebo) on the Q2W dosing regimen; after the first 24 weeks of treatment, subjects had the opportunity every 3 months to switch between the Q2W and QM dosing regimens, based on preference and provided the appropriate supply of investigational product was available. Protocol amendment 4 allowed subjects to initiate investigational product at either the Q2W or QM dosing regimen, based on their preference.

Dose adjustments of IP (evolocumab or placebo) were not allowed in this study, other than switching dose schedules (Q2W or QM), as previously discussed. If, in the opinion of the investigator, a subject was unable to tolerate a specific dose, that subject discontinued IP but was instructed to continue to return for other study procedures and measurements until the end of the study.

The study was a multicentre international double-blinded placebo-controlled design, which was considered adequate to appropriately evaluate the effect of evolocumab Q2W or QM treatment on the risk of CV events. Initially, some uncertainties were identified in the prior-to-screening phase on the use of statins as the design was not well described. Subsequently, the applicant has made clear that 2665

subjects enrolled who had LDL-C > 2.6 mmol/L (> 100 mg/dL) were not receiving atorvastatin ≥ 40 mg daily or equivalent at randomization. The most common reason cited was a demonstrated intolerance to high-intensity statin therapy (38%), followed by subject at lipid goal (28%), subject refusal (11%), physician concern (9%), and dose not approved locally (0.3%). These reasons were balanced between treatment groups. A total of 3087 (11%) study subjects were titrated to a higher dose of statin during the lipid titration period prior to randomization. As a result, a total of 69.3% of study subjects were on high-intensity statin therapy at study baseline (at the end of the lipid therapy titration period). The subjects had to complete ≥ 2 weeks on this unchanged therapy before returning for the final screening visit and ≥ 4 weeks on this therapy before randomization, which allowed for stable dosing upon entering the study treatment phase of the study.

Of note, treatment effect was significant for both patients on high statin intensity and moderate statin intensity.

Objectives

Primary objective

The primary objective was to evaluate the effect of treatment with evolocumab, compared with placebo, on the risk for cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs first, in subjects with clinically evident cardiovascular disease.

Secondary objectives

Secondary objectives were to evaluate the effect of treatment with evolocumab, compared with placebo, in subjects with clinically evident cardiovascular disease on the risk for:

- cardiovascular death, myocardial infarction, or stroke
- cardiovascular death
- death by any cause
- myocardial infarction
- stroke
- coronary revascularization
- cardiovascular death or hospital admissions for worsening heart failure
- fatal or non-fatal ischemic stroke or transient ischemic attack (TIA)

Outcomes / endpoints

Primary endpoint

The primary endpoint was a composite of time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, and coronary revascularization, whichever occurred first.

Key secondary endpoint

The key secondary endpoint was a composite of time to cardiovascular death, myocardial infarction, and stroke, whichever occurred first.

Other secondary endpoints were:

- time to cardiovascular death
- time to death by any cause
- time to first myocardial infarction (fatal or non-fatal)
- time to first stroke
- time to first coronary revascularization
- time to cardiovascular death or first hospitalization for worsening heart failure, whichever occurs first
- time to ischemic fatal or non-fatal stroke or TIA, whichever occurs first

Exploratory endpoints

Exploratory endpoints in this study included: time to coronary death, total number of events from the components of the primary endpoint (myocardial infarction, hospitalization for unstable angina, stroke, coronary revascularization, and cardiovascular death), LDL-C response (LDL-C < 70 mg/dL [1.8 mmol/L]) at each scheduled assessment, change and percent change from baseline at each scheduled assessment in each of the following parameters: LDL-C, Total cholesterol, non-HDL-C, ApoB, Total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, Triglycerides, VLDL-C, HDL-C

Event adjudication

Events that occurred after randomization and up to the completed end-of-study visit and were potential endpoints (PEPs), ie, all cause death, myocardial infarction, stroke, revascularization, hospitalization for unstable angina, hospitalization for heart failure and transient ischemic attack (TIA), were to be reported as PEPs by the investigator. If a reported PEP was negatively adjudicated (did not meet the definitions of an endpoint), the event was reclassified as an adverse event or serious adverse event and was reported to regulatory agencies, as required. In addition, regular medical review by members of the Amgen study team of eCRFs was carried out to identify serious adverse events, lab parameters, and ECG findings (where applicable) that might indicate a PEP. When these cases where found, sites were queried to report the event as potential endpoints so they could be duly adjudicated by the CEC.

An independent CEC (TIMI) was established by Amgen to adjudicate all potential endpoint events, and facilitate review of aggregated analyses across the program. All potential endpoints were adjudicated using standardized definitions based on Clinical Data Interchange Standards Consortium definitions provided in “Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials and the Third Universal Definition of Myocardial Infarction” (Hicks et al, 2012). The CEC was blinded to treatment allocation and reviewed events according to prespecified criteria. All deaths and cardiovascular events contributing to the primary and all secondary efficacy endpoints were adjudicated by an independent external Clinical Events Committee (CEC), Thrombolysis in Myocardial Infarction (TIMI) Study Group (Boston, Massachusetts, USA).

In addition to the potential cardiovascular endpoints above, potential new onset diabetes events were adjudicated by the same CEC.

Sample size

The calculation for the sample size in Study 20110118 was based on the key secondary composite endpoint (3-component composite of cardiovascular death, myocardial infarction, or stroke) and assumed the following:

- A placebo event rate of approximately 2% per year (Baigent et al, 2011; Stone et al, 2011; SEARCH et al, 2010; Alberts et al, 2009; Wiviott et al, 2007; LaRosa et al, 2005; Pedersen et al, 2005; Cannon et al, 2004; de Lemos et al, 2004; MarketScan database; United Health Care database)
- A 26-month enrollment period, and
- A total 3% lost to follow-up rate over study duration of approximately 56 months.

The hazard ratio (HR) for the key secondary composite endpoint was assumed to be 0.8 based on the CTT Collaboration (2010) meta-analysis, which assessed the relationship between LDL-C reduction and cardiovascular events. This meta-analysis concluded that the relative risk decreases by 1% for every 1.8 mg/dL reduction in LDL-C. However, it was assumed that an attenuation of treatment effect would occur because of a 3-month treatment lag at the beginning of the study and a non-compliance rate of 10% per year during the course of the study. The overall type 1 error was controlled at a 0.05 significance level. After accounting for treatment lag and patient non-compliance with investigational product (IP), the attenuated HR was assumed to be approximately 0.85. Based on a 2-sided log-rank test for demonstrating the superiority of evolocumab over placebo, a total sample size of 27,500 subjects, with approximately 1630 subjects experiencing a key secondary endpoint event, was required to ensure approximately 90% power (Shih, 1995). Assuming an annualized event rate of approximately 4.5% and a HR of 0.8 for the primary composite endpoint, at the time of 1630 key secondary endpoint events observed among a total of 27,500 subjects, there would be approximately 3550 primary endpoint events observed which would ensure a power of 99.8% to demonstrate superiority of evolocumab over placebo in the primary composite endpoint.

Of note, the original sample size was 22,500 but was increased in protocol amendment 5 to account for a longer enrolment period (from 18 to 26 months) and a shorter study duration (from 58 to 56 months).

Randomisation

Assignment in a 1:1 ratio to the 2 treatment groups (evolocumab or placebo) was based on a computer-generated randomization schedule prepared by Amgen before the start of the study.

Randomization was stratified by the final screening LDL-C level (< 85 mg/dL [2.2 mmol/L] vs > 85 mg/dL) and by geographical region**,** defined as follows:

- Europe - all European countries, Israel
- North America - US and Canada
- Latin America
- Asia Pacific - all Asian countries, Australasia, and South Africa.

Once eligibility into the study was confirmed, a site representative made the randomization call to the Interactive Voice Response System / Interactive Web Response System (IVRS/IWRS) to obtain a unique randomization number for each subject.

The randomisation procedure was considered acceptable. Stratification factors were limited to screening LDL-C level and region, which was also acceptable.

Blinding (masking)

In order to maintain blinding, SC evolocumab and placebo were available for both the every 2 weeks (Q2W) or once monthly (QM) dosing schedules. Evolocumab and placebo were identical in appearance and the devices used for the administration of evolocumab and placebo for each dosing regimen were identical in appearance and use.

Furthermore, central laboratory results of the lipid panel were not reported to the investigator until unblinding of the clinical database. Throughout the study, the central laboratory compared LDL-C concentrations with the subject's prior assessed LDL-C without unblinding the study team, investigator, or site staff. A subject's treatment assignment was only unblinded when knowledge of the treatment was essential for the further management of the subject.

Blinding procedures applied were considered acceptable.

Statistical methods

The **full analysis set (FAS)**, which was defined as all randomized subjects analyzed according to their randomized treatment assignment, was used as the analysis set for the primary analysis of the primary and secondary efficacy endpoints.

Primary analyses of the primary and secondary efficacy endpoints included the events from the subject randomization date to the subject end-of-study date. For each event, the onset date adjudicated by the CEC was used as event onset date for time-to-event calculations. Vital status and potential endpoint status were monitored up until each subject's end-of-study visit. Unless prohibited by local law, every attempt was made to obtain vital status at the end of the study for all subjects, including those who withdrew consent.

In order to preserve the overall type 1 error rate at 0.05 in the final analysis of the primary and secondary composite endpoints, a multiplicity adjustment approach was applied. The primary composite endpoint was compared by the treatment groups at a significance level of 0.05. If the primary endpoint reached statistical significance at the 0.05 level, the key secondary composite endpoint was tested at a significance level of 0.05. If the key secondary composite endpoint reached statistical significance level of 0.05, then the endpoint of cardiovascular death was tested at a significance level of 0.05. If the endpoint of cardiovascular death reached statistical significance level of 0.05, the following testing was conducted in parallel under the weighted Bonferroni split:

- The endpoint of all-cause death was tested at a significance level of 0.04.
- Other remaining secondary endpoints were tested at an overall significance level of 0.01 applying the Hochberg method (Hochberg, 1988).

No multiplicity adjustment was used for exploratory or sensitivity analyses.

Endpoint	Analysis	Analysis Method(s)
Primary efficacy endpoint time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary	Primary Analyses	• Two survival functions were compared using a 2-sided log-rank test stratified by randomization stratification factors. • Kaplan-Meier curves were estimated by treatment group and displayed; Kaplan-Meier estimates and 95% CIs were calculated. • A hazard ratio (95% CI) was estimated from stratified Cox model, using the randomization stratification factors.

revascularization, whichever occurs first All adjudicated events were reported and analyzed	Sensitivity Analyses	• Analysis of the primary endpoint was repeated 1) using the start date of end-of-study visit period instead of the individual last potential endpoint collection date, 2) using the on-treatment analysis, 3) using last confirmed survival status date as defined in Appendix D of the SAP (Appendix 16.1.9 of Study 20110118), 4) stratifying the model from eCRF if the discrepancy in stratum assignment between IVRS and eCRF occurred in more than 5% of subjects, and 5) using per protocol set if more than 5% of subjects experienced an important protocol deviation. • Subgroup analyses were conducted to confirm consistency of the treatment effect. A Forest plot summarizing variability in hazard ratios across subgroups was generated. • Covariate analyses (one at a time) of the primary endpoint using Cox model was conducted. • Trend and consistency of treatment effect on the components of the primary endpoint was tested for heterogeneity using the Wei-Lin-Weissfeld method (Wei et al, 1989). • Proportional hazards assumption in the Cox model was assessed by: 1) visual inspection (Hosmer and Lemeshow, 1999); and 2) including randomized treatment group as a time dependent covariate in the model. • Sensitivity analyses will be conducted using all-cause death in place of CV death in the composite endpoint.
<u>Key secondary efficacy endpoint</u> time to cardiovascular death, myocardial infarction, or stroke, whichever occurs first	Primary Analyses	Same as for primary endpoint, where applicable.
	Sensitivity Analyses	Same as for primary endpoint, where applicable.

Endpoint	Analysis	Analysis Method(s)
Landmark analyses for the primary and key secondary efficacy endpoints	Ad-hoc Analyses (prespecified in the academic SAP from the TIMI Study Group [Sabatine et al, 2017; Supplementary Appendix]).	• The analysis was performed to explore the magnitude of the treatment effect in the period before and after a landmark time of 1 year. The time to the first event occurring in a given period was used in the analysis. For the year 0 to 1 period, subjects in the FAS were included and censored at the end of the period if their first event occurred after the end of the period or if they did not experience an event. For the period of year 1 onward, subjects in the FAS who were still alive and being followed at year 1 were included in the analysis, even if they experienced non-fatal events in the prior period. For each period, a hazard ratio and corresponding 95% CI was estimated from a stratified Cox model, stratified by the randomization stratification factors collected via IVRS. In addition, Kaplan-Meier curves by treatment were estimated and graphically displayed. Kaplan-Meier estimates and 95% CIs were calculated at year 1 (for the year 0 to 1 period) and years 2 and 3 (for the year 1 onwards period).
Other secondary efficacy endpoints time to cardiovascular death, death by any cause, first myocardial infarction (fatal or non-fatal), first stroke, first coronary revascularization, cardiovascular death or first hospitalization for worsening heart failure, (whichever occurs first), and time to ischemic fatal or non-fatal stroke or TIA (whichever occurs first)	Primary Analyses	Same as the primary analysis for the primary endpoint.
Exploratory endpoint time to coronary death	Primary Analyses	Same as the primary analysis of time to cardiovascular death.

The following baseline characteristics were used for covariate analyses:

- Stratification factors of the final screening LDL-C level (< 85 mg/dL [2.2 mmol/L] vs ≥ 85 mg/dL) and geographical region
- age at study enrollment (< 65 years, ≥ 65 years)
- sex
- race (White, non-white)
- prior MI: (No, < 1 year, 1 to < 2 years, ≥ 2 years)
- baseline PCSK9 level
- baseline LDL-C
- ezetimibe use at baseline (yes, no)

There was no planned interim analysis or stopping rule for efficacy or futility in this study.

The full analysis set was used for the primary and secondary analyses, which was considered acceptable. The primary endpoint was analysed using Kaplan-Meier and a Cox proportional hazards model, stratified for the factors used in randomisation. This was considered a standard method for a time to event endpoint and is acceptable. Sensitivity analyses included an analysis using start date of end-of-study visit period, using on-treatment analysis, using last confirmed survival date, using stratification with eCRF instead of IVRS data (in case of more than 5% discrepancy) and using the per protocol set (in case of more than 5% protocol deviations). These sensitivity analyses were acceptable. Furthermore, a sensitivity analysis was planned using all-cause death in place of CV death in the composite primary and key secondary endpoint. This was considered an important sensitivity analysis since an analysis of a composite endpoint including cardiovascular mortality 'censors' patients who die from non-CV causes, effectively making an assumption of continued treatment effect after death and hence provide treatment effects that are difficult to understand. The analysis of the key secondary and other secondary endpoints was the same as for the primary endpoint. Multiplicity in the testing of primary and secondary endpoints was handled by a hierarchical procedure, testing the primary endpoint, the key secondary endpoint and time to cardiovascular death and stopping when a test was not statistically significant. After that, the alpha was split using weighted Bonferroni, with 0.04 for time to all-cause death and 0.01 for all other secondary endpoints using a Hochberg procedure. This was considered to preserve the overall type I error rate and was acceptable.

Results

Participant flow

A total of 27,564 subjects (13,784 evolocumab group, 13,780 placebo group) were randomized with 27,525 (99.9%) subjects receiving IP (13,769 evolocumab, 13,756 placebo) and 27,353 subjects (99.2%) completing the study (13,691 evolocumab, 13,662 placebo). All 27,564 randomized subjects were included in the FAS for all primary and secondary efficacy endpoints. An end-of-study reason of death was reported by 3.1% of subjects completing the study (438 evolocumab, 419 placebo). Less than 1% of subjects discontinued the study due to either withdrawal of consent (88 evolocumab, 105 placebo) or lost to follow-up (5 evolocumab, 13 placebo). Of the 211 subjects who discontinued the study, vital status was available for 144 of the 193 subjects who withdrew consent; 67 subjects (49 subjects who withdrew consent and 18 subjects who were lost to follow-up) did not have vital status available at the end-of-study.

Mean (standard deviation [SD]) subject study exposure and follow-up was 26.1 (6.4) months and ranged from 0.03 months to 44.94 months. This was equivalent to 59,865 patient-years of follow-up; ascertainment of the primary endpoint was completed for 99.5% of potential patient-years of follow-up. Mean (SD) exposure to IP in the evolocumab group was 24.1 (8.2) months; 91.4% of subjects were exposed to IP for ≥ 12 months, 84.1% for ≥ 18 months, 53.7% for ≥ 24 months, and 4.5% for ≥ 36 months.

Table E1: Subject Disposition with Discontinuation Reason Study 20110118 (All Randomized Subjects)

	Placebo (N = 13780) n (%)	EvoMab (N = 13784) n (%)	Total (N = 27564) n (%)
Investigational product accounting			

	Placebo (N = 13780) n (%)	EvoMab (N = 13784) n (%)	Total (N = 27564) n (%)
Subjects who never received IP	24 (0.2)	15 (0.1)	39 (0.1)
Subjects who received IP	13756 (99.8)	13769 (99.9)	27525 (99.9)
Subjects who discontinued IP	1746 (12.7)	1682 (12.2)	3428 (12.4)
Adverse event	581 (4.2)	628 (4.6)	1209 (4.4)
Subject request	881 (6.4)	786 (5.7)	1667 (6.0)
Decision by Sponsor	37 (0.3)	22 (0.2)	59 (0.2)
Physician decision	47 (0.3)	34 (0.2)	81 (0.3)
Protocol specified criteria	11 (< 0.1)	14 (0.1)	25 (< 0.1)
Other	189 (1.4)	198 (1.4)	387 (1.4)
Study completion accounting			
Subjects who completed study	13662 (99.1)	13691 (99.3)	27353 (99.2)
Death	419 (3.0)	438 (3.2)	857 (3.1)
Subjects who discontinued study	118 (0.9)	93 (0.7)	211 (0.8)
Full consent withdrawn	105 (0.8)	88 (0.6)	193 (0.7)
Lost to follow-up	13 (< 0.1)	5 (< 0.1)	18 (< 0.1)

- EvoMab = Evolocumab (AMG 145); IP = investigational product; N = number of subjects randomized.

Number of subjects screened: 44664; First subject enrolled: 08 February 2013; Last subject completed study: 18 January 2017

A very small proportion of patient never received IP, which was reassuring. Further, a very large proportion (> 99.1%) completed the study. Within a mean follow-up period of 26 months, approximately 12.5% discontinued IP due to several reasons approximately similar across treatment arms. Adverse events and participant decision mostly contributed to this discontinuation though were followed for the remainder of the study.

Study Populations

The mean (SD) age of subjects was 62.5 (9.0) years, with 44.5% of subjects ≥ 65 years of age. Women accounted for 24.6% of subjects. The majority (85.1%) of subjects were white, 9.9% were Asian, and 2.4% were Black. A total of 62.9% of subjects were enrolled in European study centers; 16.6% at North American centers; 13.9% in Asia Pacific centers; and 6.6% in Latin American centers. Median (interquartile range [Q1, Q3]) baseline LDL-C was 2.37 [2.06, 2.81] mmol/L in the evolocumab group and 2.38 [2.06, 2.82] mmol/L in the placebo group (table E2).

Subjects enrolled in this study had established cardiovascular disease, and overall, 99.9% of subjects had a history of 1 or more cardiovascular events prior to entering the study. Eighty-one percent (81.1%) of subjects had a prior myocardial infarction, 19.4% had a prior stroke, and 13.2% had prior symptomatic peripheral artery disease (table E2).

60.2% of subjects were receiving high intensity statin therapy, 32.9% were receiving moderate-intensity statin therapy. By study baseline (at the end of the lipid therapy titration period), a total of 99.7% of subjects were on a high- (69.3%) or moderate-intensity (30.4%) statin therapy (table E3). Overall, 29.4% of subjects used atorvastatin 80 mg or equivalent, 38.8% used atorvastatin 40 mg or equivalent, and 25.8% used atorvastatin 20 mg or equivalent; the remaining subjects were on any statin plus ezetimibe or other statin (5.8%), other therapy (< 0.1%), or no therapy (< 0.1%). The use of other targeted medications at baseline included anti-platelet agents (92.6%), beta blockers (75.5%), angiotensin converting enzyme inhibitors (55.8%), or angiotensin receptor blockers (23.3%).

Table E2: Summary of Key Baseline Characteristics Study 20110118 (Full Analysis Set)

	Placebo (N = 13780)	EvoMab (N = 13784)	Total (N = 27564)

	Placebo (N = 13780)	EvoMab (N = 13784)	Total (N = 27564)
Sex - n (%)			
Male	10398 (75.5)	10397 (75.4)	20795 (75.4)
Female	3382 (24.5)	3387 (24.6)	6769 (24.6)
Age (years)			
Mean	62.5	62.5	62.5
SD	8.9	9.1	9.0
Age group - n (%)			
≥ 65 years	6093 (44.2)	6161 (44.7)	12254 (44.5)
≥ 75 years	1240 (9.0)	1286 (9.3)	2526 (9.2)
Qualifying cardiovascular event – n (%)			
Myocardial infarction	11206 (81.3)	11145 (80.9)	22351 (81.1)
≤ 12 months from qualifying MI to enrollment	2890 (21.0)	2821 (20.5)	5711 (20.7)
≤ 6 months from qualifying MI to enrollment	1811 (13.1)	1760 (12.8)	3571 (13.0)
≤ 3 months from qualifying MI to enrollment	778 (5.6)	782 (5.7)	1560 (5.7)
Non-hemorrhagic stroke	2651 (19.2)	2686 (19.5)	5337 (19.4)
≤ 12 months from qualifying stroke to enrollment	600 (4.4)	635 (4.6)	1235 (4.5)
≤ 6 months from qualifying stroke to enrollment	304 (2.2)	309 (2.2)	613 (2.2)
≤ 3 months from qualifying stroke to enrollment	110 (0.8)	108 (0.8)	218 (0.8)
Symptomatic PAD (intermittent claudication with ABI < 0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease)	1784 (12.9)	1858 (13.5)	3642 (13.2)
MI alone	9588 (69.6)	9525 (69.1)	19113 (69.3)
Non-hemorrhagic stroke alone	1671 (12.1)	1695 (12.3)	3366 (12.2)
Symptomatic peripheral arterial disease alone	748 (5.4)	757 (5.5)	1505 (5.5)
≥ 1 CV events	13773 (99.9)	13774 (99.9)	27547 (99.9)
2 CV events	1664 (12.1)	1679 (12.2)	3343 (12.1)
3 CV events	102 (0.7)	118 (0.9)	220 (0.8)
Months from qualifying MI to enrollment			
N	11191	11129	22320
Mean	64.985	65.369	65.177
SD	73.206	73.766	73.484
Median	39.491	40.575	40.033
Q1, Q3	11.269, 91.828	11.762, 89.265	11.532, 90.579
Months from qualifying stroke to enrollment			
N	2643	2674	5317
Mean	63.106	61.414	62.255
SD	69.251	67.372	68.311
Median	39.819	38.850	39.392
Q1, Q3	13.536, 88.082	12.780, 84.764	13.207, 86.374
Major risk factors			
Diabetes (type 1 or type 2)	5027 (36.5)	5054 (36.7)	10081 (36.6)
Age ≥ 65 years and ≤ 85 years	6092 (44.2)	6161 (44.7)	12253 (44.5)
MI or non-hemorrhagic stroke within 6 months of screening	2580 (18.7)	2548 (18.5)	5128 (18.6)
Additional prior MI or stroke (excluding the qualifying MI or stroke)	3675 (26.7)	3696 (26.8)	7371 (26.7)
Current daily cigarette smoking	3923 (28.5)	3854 (28.0)	7777 (28.2)
History of symptomatic PAD, if enrolled with history of MI or stroke	1036 (7.5)	1101 (8.0)	2137 (7.8)
Minor risk factors			
History of non-MI related coronary revascularization	3466 (25.2)	3488 (25.3)	6954 (25.2)
Residual coronary artery disease (≥ 40% stenosis in ≥ 2 large vessels)	2995 (21.7)	3012 (21.9)	6007 (21.8)
HDL-C < 40 mg/dL (male) or < 50 mg/dL (female)	5737 (41.6)	5770 (41.9)	11507 (41.7)
hsCRP > 2 mg/L	5770 (41.9)	5734 (41.6)	11504 (41.7)
LDL-C ≥ 130 mg/dL or non-HDL-C ≥ 160 mg/dL	2204 (16.0)	2209 (16.0)	4413 (16.0)
Metabolic syndrome	8125 (59.0)	8226 (59.7)	16351 (59.3)

	Placebo (N = 13780)	EvoMab (N = 13784)	Total (N = 27564)
Risk factors count			
≥ 1 major risk factors or ≥ 2 minor risk factors	13716 (99.5)	13738 (99.7)	27454 (99.6)
≥ 1 major and ≥ 2 minor risk factors	8080 (58.6)	8123 (58.9)	16203 (58.8)
≥ 1 major and < 2 minor risk factors	4755 (34.5)	4733 (34.3)	9488 (34.4)
0 major and ≥ 2 minor risk factors	881 (6.4)	882 (6.4)	1763 (6.4)
0 major risk factors and < 2 minor risk factors	64 (0.5)	46 (0.3)	110 (0.4)
LDL-C[a] (mg/dL)			
N	13779	13784	27563
Mean	97.6	97.8	97.7
SD	27.1	28.9	28.0
Median	92.0	91.5	91.5
Q1, Q3	79.5, 109.0	79.5, 108.5	79.5, 108.5
Min, Max	33, 604	23, 785	23, 785
LDL-Ca (mmol/L)			
N	13779	13784	27563
Mean	2.529	2.532	2.530
SD	0.703	0.748	0.726
Median	2.380	2.370	2.370
Q1, Q3	2.060, 2.820	2.060, 2.810	2.060, 2.810
Min, Max	0.85, 15.64	0.59, 20.32	0.59, 20.32

- ABI = ankle-brachial index; ACC/AHA = American College of Cardiology/American Heart Association;

CAD = coronary artery disease; CV = cardiovascular; EvoMab = evolocumab (AMG 145); HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein;

LDL-C = low-density lipoprotein cholesterol; max = maximum; MI = myocardial infarction;

min = minimum; N = number of subjects randomized; non-HDL-C = non-high-density lipoprotein cholesterol; PAD = peripheral artery disease;

PCSK9 = proprotein convertase subtilisin/kexin type 9;

Q1, Q3 = interquartile range; SD = standard deviation; VLDL-C = very low-density lipoprotein cholesterol.

- [a] When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C and calculated VLDL-C will be replaced with ultracentrifugation VLDL-C from the same blood sample, if available.

Table E3: Summary of Statin and Other Lipid-lowering Background Therapy and Statin Intensity at Baseline Study 20110118 (All Randomized Subjects)

	Placebo (N = 13780) n (%)	EvoMab (N = 13784) n (%)	Total (N = 27564) n (%)
Statin therapy intensity per ACC/AHA definition			
High intensity	9518 (69.1)	9585 (69.5)	19103 (69.3)
Moderate intensity	4229 (30.7)	4161 (30.2)	8390 (30.4)
Low intensity	25 (0.2)	27 (0.2)	52 (0.2)
Unknown	1 (<0.1)	4 (<0.1)	5 (<0.1)
None	7 (<0.1)	7 (<0.1)	14 (<0.1)
Background therapy category - n (%)			
Atorvastatin 20mg or equivalent	3567 (25.9)	3550 (25.8)	7117 (25.8)
Atorvastatin 40mg or equivalent	5343 (38.8)	5364 (38.9)	10707 (38.8)
Atorvastatin 80mg or equivalent	4060 (29.5)	4053 (29.4)	8113 (29.4)
Any statin + ezetimibe	711 (5.2)	725 (5.3)	1436 (5.2)
Other statin	92 (0.7)	85 (0.6)	177 (0.6)
Other therapy	4 (<0.1)	2 (<0.1)	6 (<0.1)
None	3 (<0.1)	5 (<0.1)	8 (<0.1)
Number of subjects reporting use of medications of interest[a]	13777 (100.0)	13779 (100.0)	27556 (100.0)
STATINS	13773 (99.9)	13777 (99.9)	27550 (99.9)
Atorvastatin	10884 (79.0)	10915 (79.2)	21799 (79.1)
Fluvastatin	7 (<0.1)	4 (<0.1)	11 (<0.1)
Lovastatin	3 (<0.1)	1 (<0.1)	4 (<0.1)
Pitavastatin	71 (0.5)	64 (0.5)	135 (0.5)
Pravastatin	24 (0.2)	18 (0.1)	42 (0.2)
Rosuvastatin	1796 (13.0)	1831 (13.3)	3627 (13.2)
Simvastatin	993 (7.2)	950 (6.9)	1943 (7.0)
FIBRATES	382 (2.8)	362 (2.6)	744 (2.7)
Fenofibrate	360 (2.6)	345 (2.5)	705 (2.6)
OTHER LIPID MODIFYING AGENTS	1095 (7.9)	1069 (7.8)	2164 (7.9)
Ezetimibe	714 (5.2)	726 (5.3)	1440 (5.2)
Omega-3 Fatty Acids	387 (2.8)	332 (2.4)	719 (2.6)

ACC/AHA = American College of Cardiology/American Heart Association; EvoMab = Evolocumab (AMG 145); N = number of subjects randomized.
Statins listed by only the statin component in the preferred term.
The preferred term of fish oil is combined under the preferred term of Omega-3 fatty acids.
Coded using WHODRUG version June 1, 2016.
[a] Because they were required per protocol, all statins are displayed. For other lipid-lowering medications of interest, only categories and medications used by ≥ 1.0% of subjects in any treatment group are summarized here

Randomisation was successful as can be expected from a study this size. Patients were relatively young with a mean age around 62.5, mostly white and male; there was limited representation of patients above 75 years (only 9.2%). There was adequate representation of EU, as 63% were included in European centres. Patients could be considered to be at very high risk with 80% with a history of MI, 19% with a history of non-haemorrhagic stroke. PAD contributed less to the risk classification with approximately 13%. A further increased risk was present for 99.5% of the patients due to an addition of ≥ 1 major risk factors or ≥ 2 minor risk factors. In particular, diabetes, age, additional MI or stroke, and cigarette smoking contributed to a further increased CV risk, while minor risk factors were also majorly present. Given this very high risk presentation of patients, the mean level of 2.5 mmol/L LDL-C at baseline fits in general well with practice guideline recommendations that these patients on average are eligible for (further) LLT treatment.

A large proportion of patients (69%) used a high intensity statin (mostly atorvastatin, some rosuvastatin) while 30% used a moderate intensity statin, with very little using low intensity or no statin, suggesting that most patients were treated according to current practice recommendations. A low percentage used additional ezetimibe (5%).

Outcomes and estimation

Evolocumab significantly reduced the risk of time to the first event of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization (primary composite endpoint) by 15% compared to placebo with a HR of 0.85 (95% CI 0.79, 0.92; p < 0.0001). A total of 2907 subjects (1344 [9.8%] evolocumab, 1563 [11.3%] placebo) experienced a positively-adjudicated event contributing to the primary composite endpoint; only the first event experienced by the subject contributed to the analysis. The majority of events (ie, defined as the first event) contributing to the analysis were myocardial infarction (752 events), coronary revascularization (743 events) and stroke (410 events) (table E4).

The treatment effect of evolocumab on the primary composite endpoint was driven by a reduction in the risk of myocardial infarction, stroke, and coronary revascularization; no effect was seen on cardiovascular death or hospitalization for unstable angina.

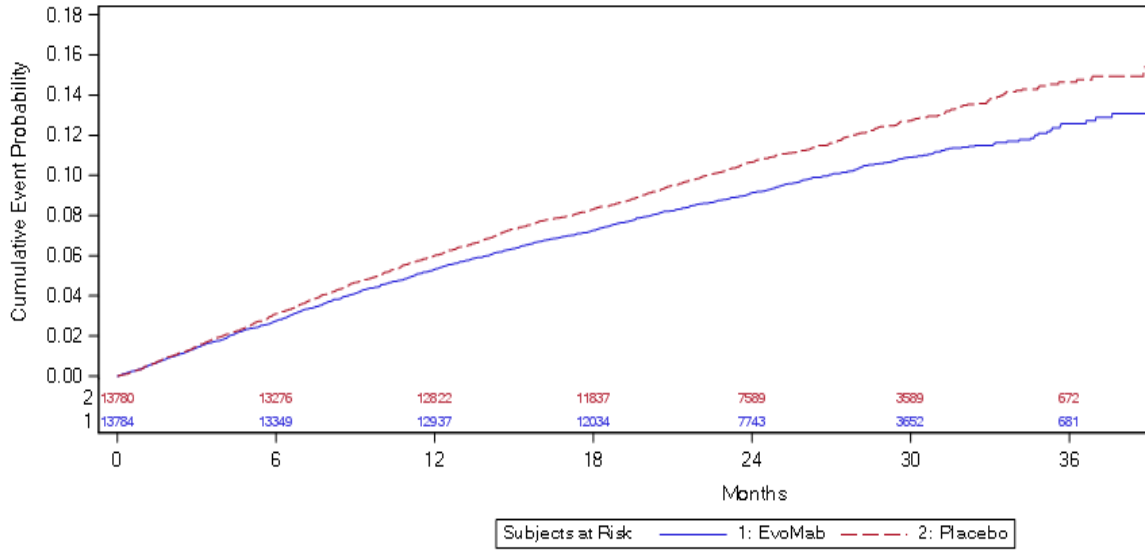
Table E4: Summary of First Component Events of Primary Endpoint Study 20110118 (Full Analysis Set)

	Placebo (N = 13780)	EvoMab (N = 13784)
Number of subjects with event - n (%)	1563 (11.34)	1344 (9.75)
First component event[a]		
Cardiovascular death	142	161
Myocardial infarction	423	329
Hospitalization for unstable angina	160	169
Coronary revascularization	394	349
Stroke	226	184
Multiple events occurred on the same day	218	152

EvoMab = Evolocumab (AMG 145); N = number of subjects randomized; %=(n/N)*100
Include the events occurring between the subject randomization date and the subject last confirmed survival status date, inclusive; The censoring date of the subjects without an event is the subject last non-fatal potential endpoints collection date
a Only the first event contributing to the primary endpoint is counted. If a subject has more than one event occurred on the same day and contribute to the primary endpoint, this subject is counted in the category of multiple events

The Kaplan-Meier (K-M) curve shows a treatment effect with evolocumab beginning at approximately 5 months with an absolute risk reduction relative to placebo that steadily increases over time.

Figure E2: Cumulative Incidence Estimates for Primary Endpoint (Cardiovascular Death, Myocardial Infarction, Hospitalization for Unstable Angina, Stroke, or Coronary Revascularization) Study 20110118 (Full Analysis Set).



A pre-specified sensitivity analysis showed that the proportional hazards assumption of the Cox model was not violated (p = 0.1672;). Additional pre-specified sensitivity analyses of the primary composite endpoint using the start date of the end-of-study visit period (SDEVP;), the per-protocol analysis set, the on-treatment analysis, and the last confirmed survival status date (LCSSD) were each consistent with the primary analysis of the primary composite endpoint (for all sensitivity analyses, HR = 0.85 [95% CI 0.79, 0.92]).

The absolute risk reduction (ARR) increased over time during the study and was 2.07 (95%CI 0.85-3.29) for the primary endpoint, and 2.02 (95%CI 0.96-3.08) for the key secondary endpoint after a mean of 36 months.

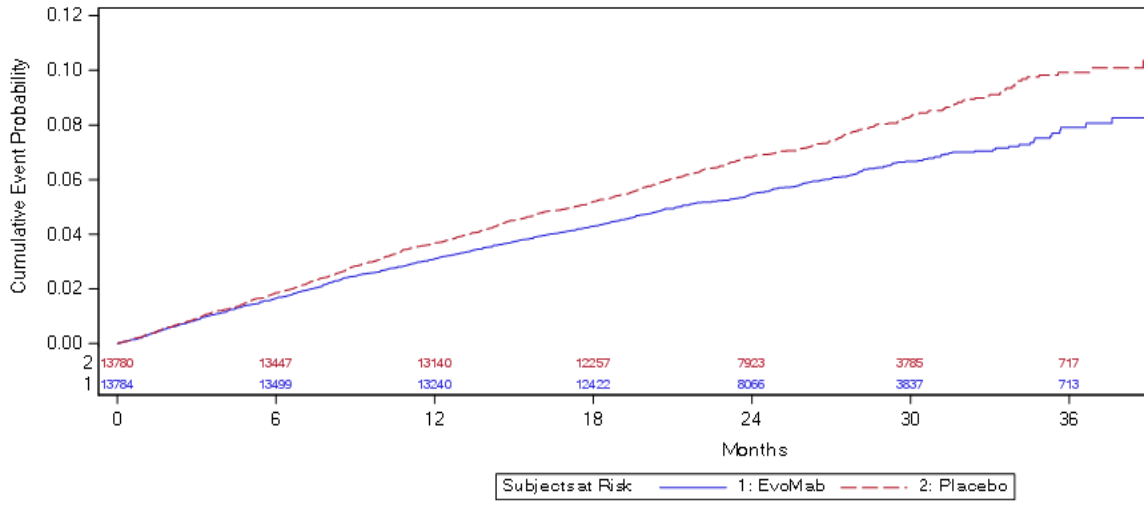
Key secondary endpoint

Cardiovascular death, myocardial infarction, and stroke

For the key secondary composite endpoint, evolocumab significantly reduced the risk of time to the first event of cardiovascular death, myocardial infarction, and stroke by 20% compared to placebo with a HR of 0.80 (95% CI 0.73, 0.88; p < 0.0001) (table E5). A total of 1829 subjects (816 [5.9%] evolocumab, 1013 [7.4%] placebo) experienced a positively-adjudicated cardiovascular event contributing to the key secondary composite endpoint; only the first event experienced by the subject contributed to the analysis. The majority of events contributing to the analysis (ie, defined as the first event) were myocardial infarction (1062 events) and stroke (425 events). The treatment effect of evolocumab on the key secondary composite endpoint was driven by a reduction in the risk of myocardial infarction and stroke.

Consistent with observations for the primary endpoint, the K-M curve shows a treatment effect with evolocumab beginning at approximately 5 months and an absolute risk reduction relative to placebo that steadily increases over time (figure E3).

Figure E3: Cumulative Incidence Estimates for Key Secondary Endpoint (Cardiovascular Death, Myocardial Infarction, or Stroke) Study 20110118 (Full Analysis Set)



Other (key) secondary endpoints

Table E5: Summary of Primary and Secondary Efficacy Endpoints Study 20110118 (Full Analysis Set)

	Placebo (N = 13780) n (%)	EvoMab (N = 13784) n (%)	Hazard Ratio (95% CI)	p-value
Primary endpoint	1563 (11.34)	1344 (9.75)	0.85 (0.79, 0.92)	< 0.0001
Key secondary endpoint	1013 (7.35)	816 (5.92)	0.80 (0.73, 0.88)	< 0.0001
Other secondary endpoints				
Time to cardiovascular death	240 (1.74)	251 (1.82)	1.05 (0.88, 1.25)	0.6188
Time to death by any cause	426 (3.09)	444 (3.22)	1.04 (0.91, 1.19)	0.5368
Time to first fatal or non-fatal myocardial infarction	639 (4.64)	468 (3.40)	0.73 (0.65, 0.82)	< 0.0001
Time to first fatal or non-fatal stroke	262 (1.90)	207 (1.50)	0.79 (0.66, 0.95)	0.0101
Time to first coronary revascularization	965 (7.00)	759 (5.51)	0.78 (0.71, 0.86)	< 0.0001
Time to cardiovascular death or first hospitalization for worsening heart failure	408 (2.96)	402 (2.92)	0.98 (0.86, 1.13)	0.8179
Time to ischemic fatal or non-fatal stroke or TIA	295 (2.14)	229 (1.66)	0.77 (0.65, 0.92)	0.0035
Time to hospitalization for unstable angina	239 (1.73)	236 (1.71)	0.99 (0.82, 1.18)	0.8889

P-values for the other secondary endpoints are nominal and not adjusted for multiplicity because no statistically significant reduction in the risk of cardiovascular death was observed.

Death adjudicated endpoints

Evolocumab had no observed effect on the overall risk of cardiovascular death (HR: 1.05, 95% CI: 0.88, 1.25; p = 0.6188) over the 26-month study duration. When the types of cardiovascular death were evaluated individually, the numerical incidence rates of death due to acute myocardial infarction and death due to stroke were slightly lower in the evolocumab group, consistent with the effect of evolocumab on fatal and non-fatal myocardial infarction and fatal and non-fatal stroke. Nevertheless, the majority of

cardiovascular deaths were due to sudden cardiac death, which were deaths that occurred unexpectedly, not following an acute myocardial infarction and included, among others, cases of unwitnessed death in a subject seen alive and clinically stable within the previous 24 hours. Evolocumab had no effect on sudden cardiac death, and thus, no effect on the overall risk of cardiovascular death.

Table E6: Summary of Adjudicated Cardiovascular Death Study 20110118 (Full Analysis Set).

	Placebo (N = 13780) n (%)	EvoMab (N = 13784) n (%)
Cardiovascular death	240 (1.74)	251 (1.82)
Sudden cardiac	143 (1.04)	151 (1.10)
Due to stroke	33 (0.24)	31 (0.22)
Due to heart failure	19 (0.14)	27 (0.20)
Due to an acute MI	30 (0.22)	25 (0.18)
Due to cardiovascular hemorrhage	3 (0.02)	7 (0.05)
Due to other cardiovascular causes	7 (0.05)	7 (0.05)
Due to cardiovascular procedures	5 (0.04)	3 (0.02)

The types and incidences of adjudicated non-cardiovascular deaths were also summarized and were similar between the evolocumab and placebo groups. No patterns were observed to suggest evolocumab increases the risk of mortality due to non-cardiovascular aetiologies.

Table E7: Summary of Adjudicated Non-cardiovascular Death Study 20110118 (Full Analysis Set)

	Placebo (N = 13780) n (%)	EvoMab (N = 13784) n (%)
Non-cardiovascular death	142 (1.03)	149 (1.08)
Malignancy	79 (0.57)	81 (0.59)
Infection; includes sepsis	30 (0.22)	28 (0.20)
Pulmonary	10 (0.07)	12 (0.09)
Trauma	9 (0.07)	7 (0.05)
Hepatobiliary	2 (0.01)	4 (0.03)
Suicide	3 (0.02)	4 (0.03)
Non-cardiovascular procedure or surgery	1 (0.01)	3 (0.02)
Pancreatic	1 (0.01)	3 (0.02)
Other non-cardiovascular	2 (0.01)	2 (0.01)
Renal	3 (0.02)	2 (0.01)
Gastrointestinal	0 (0.00)	1 (0.01)
Neurological	1 (0.01)	1 (0.01)
Non-cardiovascular hemorrhage	1 (0.01)	1 (0.01)

Exploratory endpoints

For completeness, a detailed accounting of cardiovascular events (including CV and non-CV deaths) that occurred in the study and contributed to the efficacy endpoints are provided below.

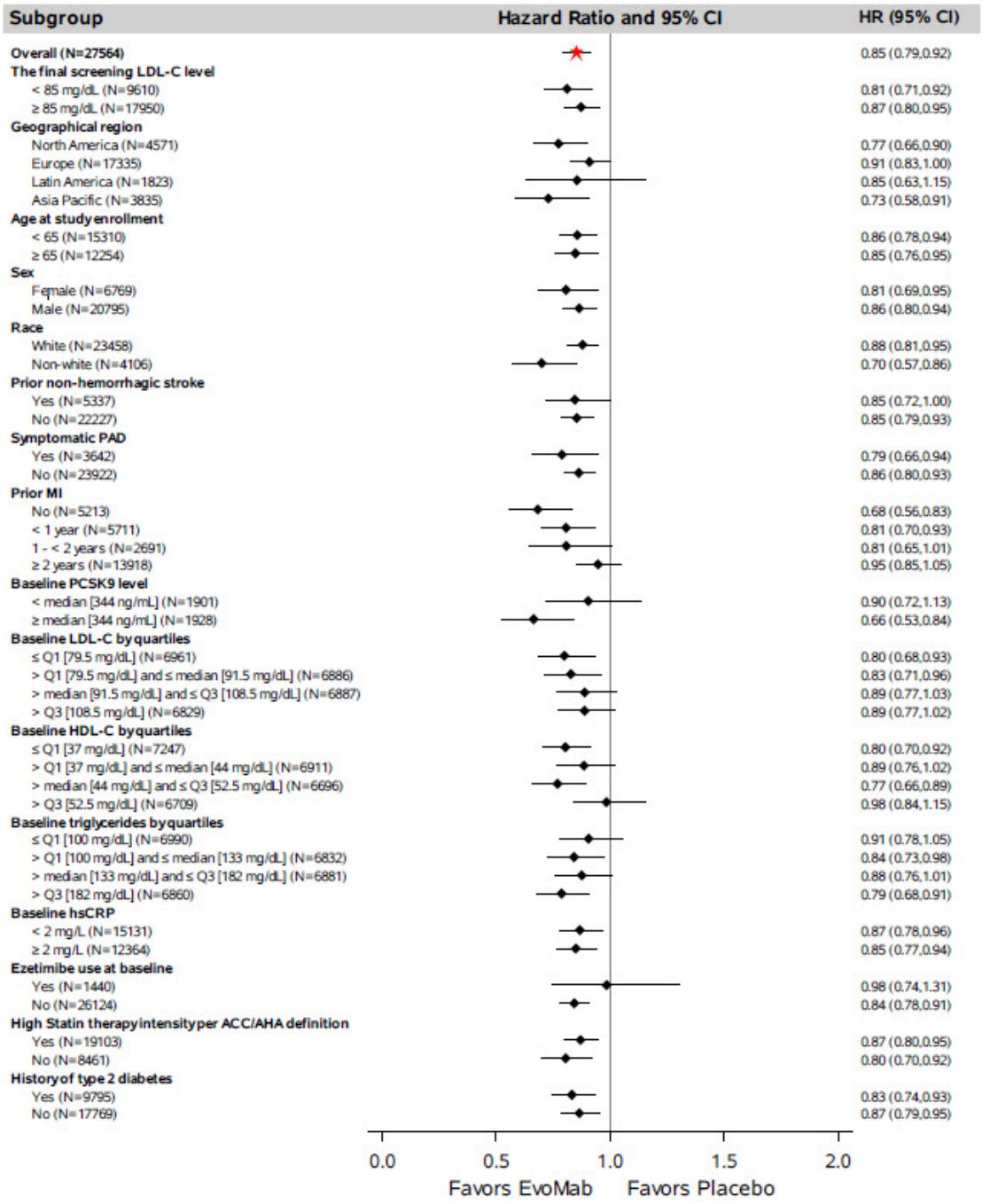
Table E8: Subject Incidence of Adjudicated Cardiovascular Events Study 20110118 (Full Analysis Set)

	Placebo (N = 13780) n (%)	EvoMab (N = 13784) n (%)
Number of subjects with any positively adjudicated cardiovascular event	1867 (13.55)	1640 (11.90)
Death	426 (3.09)	444 (3.22)
Cardiovascular	240 (1.74)	251 (1.82)
Coronary death	173 (1.26)	176 (1.28)
Non-cardiovascular	142 (1.03)	149 (1.08)
Undetermined	44 (0.32)	44 (0.32)
Myocardial infarction (fatal and non-fatal)	639 (4.64)	468 (3.40)
Fatal	27 (0.20)	23 (0.17)
Non-fatal	616 (4.47)	448 (3.25)
Hospitalization for unstable angina	239 (1.73)	236 (1.71)
Coronary revascularization	965 (7.00)	759 (5.51)
PCI	832 (6.04)	650 (4.72)
Related to MI or unstable angina event	486 (3.53)	342 (2.48)
Surgical	168 (1.22)	128 (0.93)
Related to MI or unstable angina event	52 (0.38)	55 (0.40)
Cerebrovascular event	330 (2.39)	264 (1.92)
Transient ischemic attack	76 (0.55)	61 (0.44)
Stroke (fatal and non-fatal)	262 (1.90)	207 (1.50)
Fatal	33 (0.24)	35 (0.25)
Ischemic	14 (0.10)	10 (0.07)
Ischemic with hemorrhagic conversion	4 (0.03)	4 (0.03)
Hemorrhagic stroke	10 (0.07)	15 (0.11)
Type undetermined	5 (0.04)	6 (0.04)
Non-fatal	231 (1.68)	176 (1.28)
Ischemic	191 (1.39)	142 (1.03)
Ischemic with hemorrhagic conversion	21 (0.15)	17 (0.12)
Hemorrhagic stroke	15 (0.11)	14 (0.10)
Type undetermined	9 (0.07)	7 (0.05)
Heart failure event	202 (1.47)	197 (1.43)
Heart failure hospitalization	201 (1.46)	194 (1.41)
Urgent heart failure visit	4 (0.03)	6 (0.04)

Subgroup analyses

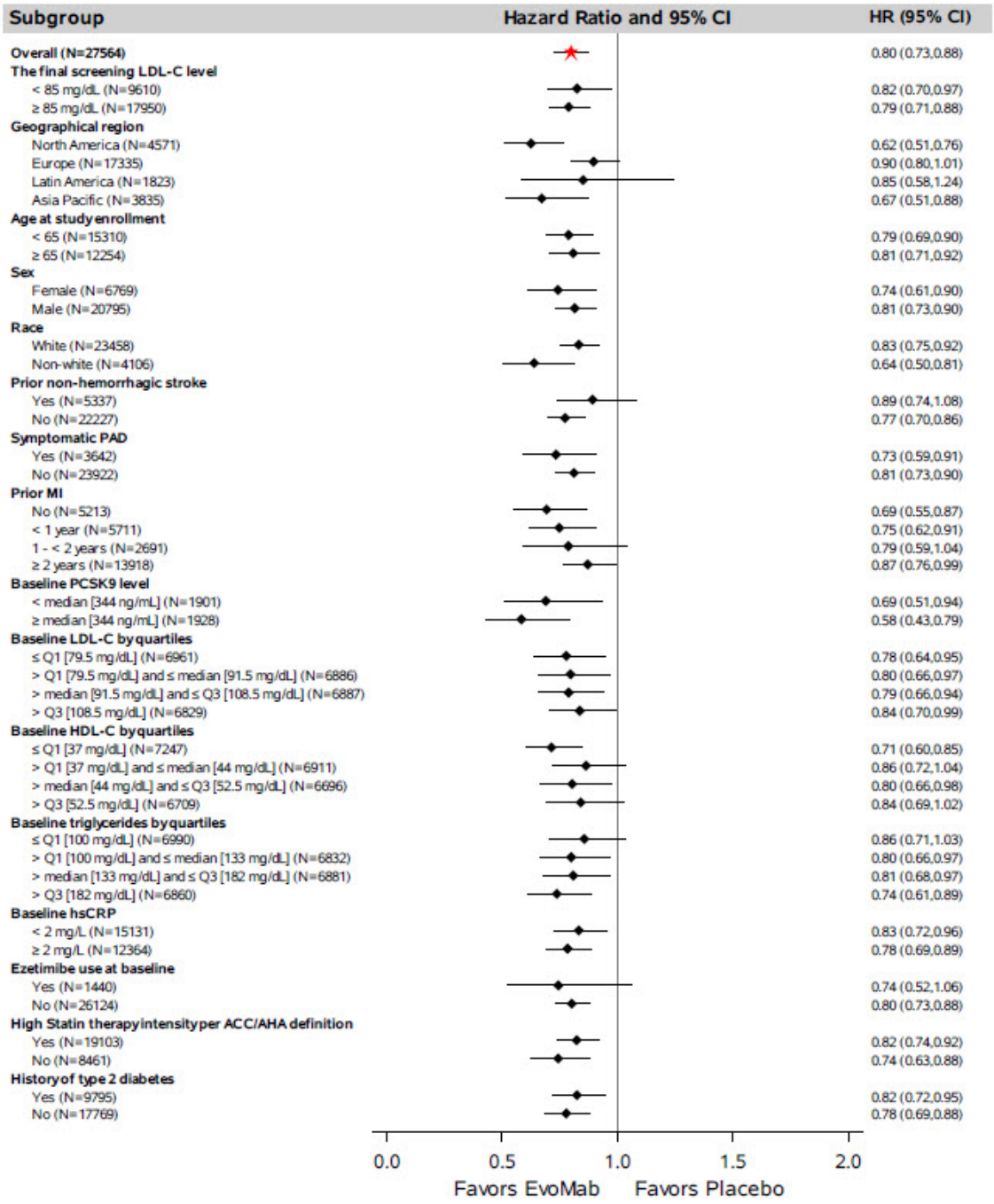
For the subgroup analyses in Study 20110118, the point estimates for the HRs (all < 1) were directionally consistent across all pre-specified subgroups, relative to placebo, for the primary composite endpoint of time to cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization.

Figure E4: Forest Plot of Hazard Ratio Estimates of Primary Composite Endpoint - Subgroup Analysis Study 20110118 (Full Analysis Set).



For the subgroup analyses, the point estimates for the HRs (all < 1) were directionally consistent across all prespecified subgroups, relative to placebo, for the key secondary composite endpoint of time to cardiovascular death, myocardial infarction, or stroke (figure 5). Significant treatment-by-subgroup interactions were found for race (p = 0.0363) and prior myocardial infarction (p = 0.0203) for the primary endpoint and for geographic region (p = 0.0117) and race (p = 0.0479) for the key secondary composite endpoint.

Figure E5: Forest Plot of Hazard Ratio Estimates of Key Secondary Endpoint - Subgroup Analysis Study 20110118 (Full Analysis Set).



Both the subgroup analyses on the primary endpoint and key secondary endpoint demonstrated a consistent beneficial effect. A significant p value for race in both endpoints and region in the key secondary endpoint was indicated. It was noticed that the treatment effect for Europe is less than other regions, in particular US. No reason for this observation could be found despite the applicant has made extensive effort to identify any possible reason for the observed lower treatment effect for Europe. It was confirmed that all regions demonstrated a trend towards a beneficial effect. Treatment effect for several of the risk parameters appeared to be counterintuitive and not consistently in agreement with this risk-effect relationship including e.g. LDL-C level, age, history of stroke, and diabetes. While, for

symptomatic PAD, prior MI, ezetimibe at baseline, and high intensity statin this is in line with what could be expected. Similarly, for PCSK9 levels the treatment effect was higher with higher levels of PCSK9. Of note, treatment effect in this selected PK analysis set was greater than for the overall population. Further, there seems to be potentially differential result for the primary endpoint in the race subgroup, but any clear reason could not be found. It is acknowledged that the study was not powered to demonstrate statistical treatment difference for subgroups of race. Reassuring is that for each race category a trend towards a beneficial effect could be demonstrated. The trend interaction p-value was significant (p=0.0363). The applicant has an extensive response discussing the factors that may potentially influenced the observed effect, but could not identify any clear factors that could reasonably explain the treatment difference between the White and non-White population. Some slight differences could be observed in baseline values pertaining to history of stroke, diabetes, betablocker and ACE/ARB use, high intensity statin use, and BMI, which could indicate a slightly higher risk profile for White patients compared to the non-White. However, this difference is counterintuitive to the observed slightly better effect on LDL-C observed and associated better effect on CV endpoints for the non-White population. Probably the interrelation between race and region may also obscure these observations. PK data could not clarify any difference in effect.

Both for the one third of patients on moderate and for the two third of patients on high dose statin therapy, the primary endpoint and key secondary endpoint was still significant in the advantage of evolocumab.

Ancillary analyses

Repeated Events

Adjudicated cardiovascular endpoint events of the types included in the primary composite efficacy endpoint were used to determine the treatment effect of evolocumab in reducing the risk for multiple events. A total of 4904 events occurred across both treatment groups and were included in the analysis. Overall, 1574 subjects experienced a single event, 960 experienced 2 events, and 373 subjects experienced ≥ 3 events. The mean number of events per subject was 0.159 in the evolocumab group and 0.197 in the placebo group. Results show that evolocumab reduced the risk for multiple events by 18%, with an event rate (95% CI) per patient-year of 0.080 (0.073, 0.088) in the evolocumab group and 0.098 (0.090, 0.107) in the placebo group.

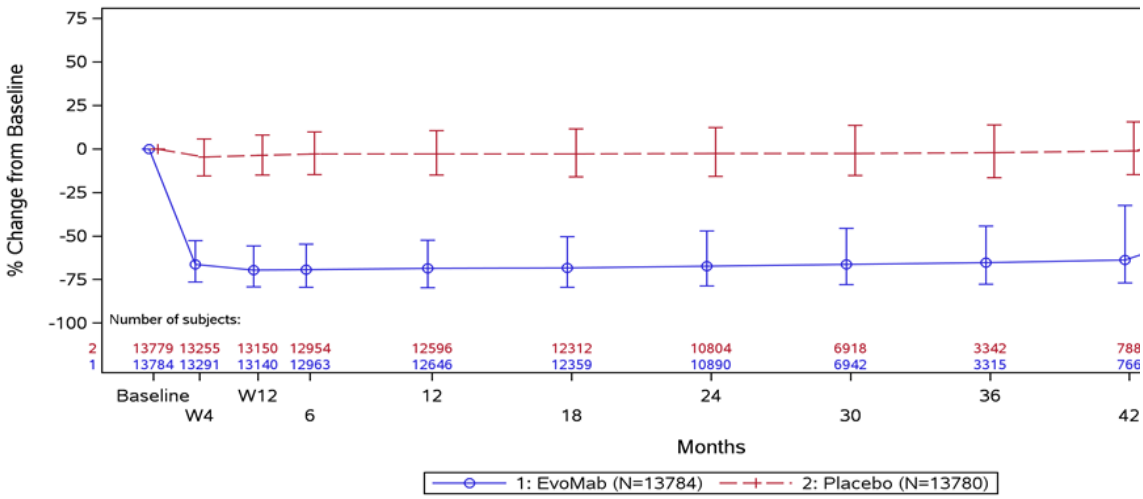
A comparable effect as for the primary endpoint for evolocumab could be demonstrated (18% reduction) when multiple events were considered.

LDL-C

The median (Q1, Q3) LDL-C at baseline was 91.5 (79.5, 108.5) mg/dL. Analysis of change and percent change in LDL-C demonstrated that evolocumab significantly reduced LDL-C, compared with placebo, at each post-baseline assessment (all p < 0.0001). Reductions in LDL-C to steady-state concentrations (trough levels) in the evolocumab group were observed by the first post-baseline assessment at week 4 and were maintained throughout the study, without attenuation of effect. Median (Q1, Q3) reductions in LDL-C ranged from 63.8% (32.3, 76.8) to 69.5% (55.7, 79.1) in the evolocumab group across study visits (excluding week 192, where N = 15), with corresponding median (Q1, Q3) achieved LDL-C concentrations ranging from 29.0 (1.0, 43.0) mg/dL to 35.0 (21.0, 64.0) mg/dL. Notably, achieved LDL-C concentrations for the lowest quartile of subjects in the evolocumab group were < 20 mg/dL. Mean (SE) reductions in LDL-C ranged from 48.1% (1.6%) to 63.4% (0.2%) in the evolocumab group, with corresponding mean (SE) achieved LDL-C concentrations ranging from 36.1 (0.3) mg/dL to 49.0 (1.6) mg/dL at the time points where LDL-C was assessed. In the placebo group, median (Q1, Q3) percent

change in LDL-C ranged from -4.6% (-15.4, 5.8) to -1.1% (-14.7, 15.6), with corresponding median (Q1, Q3) achieved LDL-C concentrations ranging from 87.0 (74.0, 104.0) mg/dL to 91.0 (75.5, 113.0) mg/dL at the time points where LDL-C was assessed. Mean (SE) change in LDL-C in the placebo group ranged from -4.6% (0.2%) to +5.4% (1.2%), with corresponding mean (SE) achieved LDL-C concentrations ranging from 91.9 (0.2) mg/dL to 99.8 (1.3) mg/dL at the time-points where LDL-C was assessed.

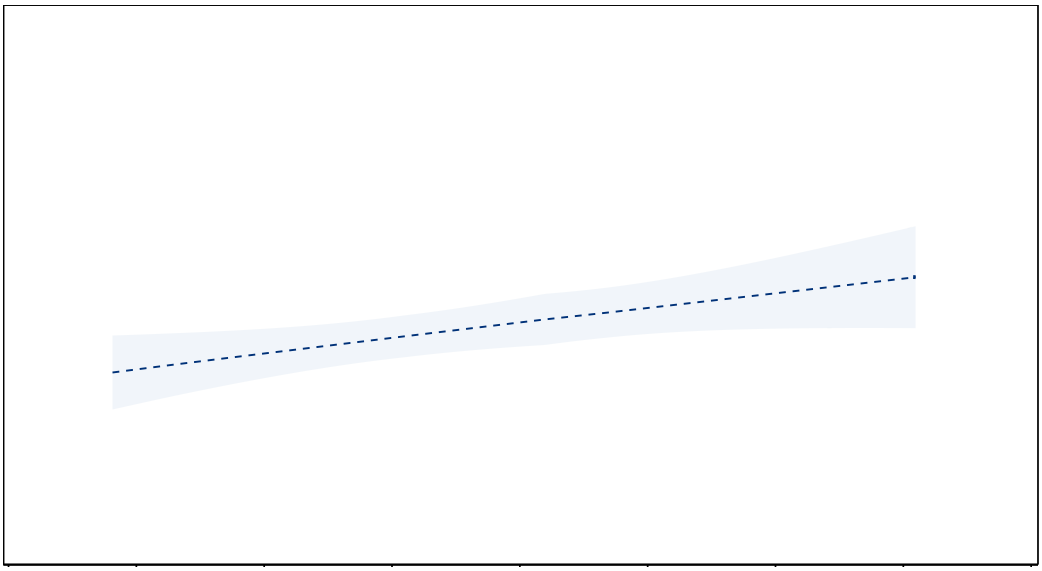
Figure E6: Median Percent Change From Baseline in LDL-C by Scheduled Visit and Treatment Group Study 20110118 (Full Analysis Set)



Post-baseline LDL-C vs cardiovascular risk

Additional analyses were conducted to determine if a relationship existed between post-baseline LDL-C concentrations and cardiovascular risk for the primary and key secondary composite endpoints, adjusting for covariates of age, sex, type 2 diabetes mellitus, prior history of myocardial infarction, prior history of stroke, baseline LDL-C, current smoking status and region. Using local regression of the adjusted event rate versus every 10th percent increment in achieved LDL-C, these analyses suggest a consistent relationship between achieved LDL-C and reduction in risk of cardiovascular events to LDL-C levels as low as 16.2 mg/dL (mean LDL-C in lowest decile); lower achieved LDL-C levels were associated with lower cardiovascular event rates. For the primary composite endpoint, adjusted event rates (95% CI) per 100 patient/years were 3.8 (3.1, 4.5) at mean postbaseline LDL-C concentrations ≤ 21.6 mg/dL (16.2 mg/dL mean LDL-C in lowest decile) and 5.0 (4.2, 5.8) at LDL-C concentrations ≥ 115.7 mg/dL (141.8 mg/dL mean LDL-C in highest decile). For the key secondary composite endpoint, adjusted event rates (95% CI) per 100 patient/years were 2.5 (1.9, 3.0) at mean post-baseline LDL-C concentrations ≤ 21.6 mg/dL (16.2 mg/dL mean LDL-C in lowest decile), to and 3.6 (2.8, 4.4), at LDL-C concentrations ≥ 115.7 mg/dL (141.8 mg/dL mean LDL-C in highest decile).

Figure E7: Adjusted Event Rate of Key Secondary Endpoint (Cardiovascular Death, Myocardial Infarction, or Stroke) by Average Postbaseline LDL-C up to the Key Secondary Endpoint Study 20110118 (Full Analysis Set).



Data on the LDL-C lowering effect were also provided, confirming the LDL-C lowering effect of evolocumab without attenuation during the duration of the study. The median level of 91.5 mg/dL (2.28 mmol/L) was reduced with approximately 48-63% to approximately 36-49 mg/dL (0.90 – 1.2 mmol/L) across the study.

Further, the data indicate a continuous relationship between the level in achieved LDL-C and adjusted CV event rates. Notably, at the lowest end, patients were still at risk of 2.5 events per 100/patient years without a clear cut-off.

Supportive study

Study 20120153 (GLAGOV): Evolocumab and Regression of Coronary Atherosclerotic Disease

Study 20120153 evaluated the effect of evolocumab upon coronary atherosclerotic disease burden as assessed by coronary IVUS in male and female subjects ≥ 18 years of age undergoing clinically-indicated coronary angiography.

Inclusion criteria

Eligible subjects were required to be on a stable, high- to moderate-intensity statin background therapy at randomization consisting of an effective statin dose, i.e., at least atorvastatin 20 mg daily or equivalent, and where locally approved, highly effective statin therapy (defined as at least atorvastatin 40 mg daily or equivalent) was recommended. For subjects with LDL-C > 100 mg/dL (2.6 mmol/L) and not

receiving at least atorvastatin 40 mg daily or equivalent, the investigator had to attest that the higher dose statin therapy was not appropriate for this subject. Subjects who were not on high to moderate-intensity statin therapy at screening, but were eligible, could enter the study following a lipid stabilization period of 2 to 4 weeks. During this period, the subject could either initiate or titrate statin therapy with a maximum of 1 up-titration step. Subjects were required to have LDL-C ≥ 80 mg/dL (2.07 mmol/L); however, subjects could have qualified with lower LDL-C levels ≥ 60 to < 80 mg/dL (1.55 to 2.07 mmol/L) if they also had at least 1 major or 3 minor cardiovascular risk factors. Subjects who met all entry criteria were randomized 1:1 to receive evolocumab 420 mg monthly SC or placebo monthly SC for 76 weeks. Randomization was stratified by region. Subjects underwent IVUS at baseline and at week 78.

Primary endpoint

The primary efficacy endpoint was the nominal change in percent atheroma volume (PAV) from baseline to week 78.

Secondary endpoints

Secondary efficacy endpoints were as follows and are listed in sequential order to reflect the multiplicity adjustment method:

Nominal change in TAV from baseline to week 78

Regression (any reduction from baseline) in PAV (yes, no)

Regression (any reduction from baseline) in TAV (yes, no).

Other endpoints included subject incidence of adjudicated events and routine safety parameters.

Analysis sets

The FAS included all randomized subjects who received at least 1 dose of IP and was used for all analyses except for IVUS-related efficacy endpoints. The IVUS analysis set (IAS) included subjects in the FAS with a baseline IVUS and an IVUS measurement conducted after week 52 (IVUS data collected after week 52 was considered clinically meaningful for the efficacy analysis). The IAS was used for the IVUS-related efficacy endpoints.

Analysis method

Change in PAV and TAV were analyzed using an analysis of covariance model, including terms for treatment group, stratification factor (region) and baseline PAV/TAV as covariates. Least square means and corresponding 95% CIs were calculated for each treatment (evolocumab and placebo) and for the difference between the treatment groups. The secondary efficacy endpoints of percentage of subjects demonstrating regression (any reduction from baseline) were analyzed using the Cochran-Mantel Haenszel test adjusted by the stratification factor. In order to preserve the family wise type 1 error rate at 0.05 for testing the primary and secondary endpoints, the primary analysis of primary endpoint was tested first. If the treatment effect from the primary analysis of the primary endpoint was significant at a significance level of 0.05, the hierarchical statistical testing of the secondary endpoints was tested with significance level of 0.05 in the sequential order listed above.

A key sensitivity analysis will be conducted using a multiple imputation procedure to impute the primary endpoint for those dosed subjects with missing endpoint data. The primary endpoint will also be analyzed for the completers population (adhered to the scheduled IP) using the same methodology as the primary analysis.

Results

Study disposition

A total of 1246 subjects were enrolled for the study and 970 subjects were randomized. Of the 970 subjects randomized, 968 (99.8%) subjects received at least 1 dose of IP and were included in the FAS. A total of 846 (87.2%) subjects (423 evolocumab, 423 placebo) had evaluable non-missing IVUS endpoint assessments at baseline and after week 52 and were included in the IAS. A total of 934 subjects (96.3%) completed the study (468 evolocumab, 466 placebo). Overall, 73 (7.5%) subjects discontinued IP (38 evolocumab, 35 placebo) during the study. Eighty-six (8.9%) subjects discontinued statin therapy (41 evolocumab, 45 placebo).

Baseline data

The mean (SD) age of subjects was 59.8 (9.2) years, with 31.9% of subjects ≥ 65 years of age. A total of 27.8% of subjects were women. The majority (93.8%) of subjects were white and 6% were of Hispanic/Latino ethnicity. A total of 68.5% of subjects were enrolled in study centers in Europe, 18.0% at centers in North America, and 10.3% from centers in Asia Pacific, which included 2.3% from Asia and 8.1% from Other Asia Pacific (Australasia and South Africa). Mean (SD) baseline LDL-C was 92.6 (27.5) mg/dL (2.397 [0.712] mmol/L) in the evolocumab group and 92.4 (26.9) mg/dL (2.394 [0.696] mmol/L) in the placebo group.

Nearly all (94.1%) subjects were National Cholesterol Education Program coronary heart disease high-risk (Grundy et al, 2004; National Cholesterol Education Program Adult Treatment Panel III, 2002). The incidence of major risk factors included 29.0% with myocardial infarction or hospitalization for unstable angina within the last 2 years and 20.9% with type 2 diabetes mellitus; a total of 83.0% of subjects entered the study with the minor risk factor of hypertension.

Overall, 92.1% of subjects had a history at baseline of disease within 1 or more coronary artery disease categories, including 85.4% coronary artery disease, 63.3% angina due to atherosclerotic coronary disease, 38.9% percutaneous coronary intervention, 35.1% myocardial infarction, and 0.6% coronary artery bypass graft. In addition, 10.8% of subjects had a history of cerebrovascular or peripheral arterial disease.

A total of 98.6% of subjects were on a statin at baseline (following the lipid stabilization period) with nearly all (98.3%) on high- (58.9%) or moderate- (39.4%) intensity statins. Overall, 17.3% of subjects used atorvastatin 80 mg or equivalent, 42.9% used atorvastatin 40 mg or equivalent, and 36.0% used atorvastatin 20 mg or equivalent; the remaining subjects were on any statin plus ezetimibe or other statin (2.5%), other therapy (0.7%), or no therapy (0.7 %).

Table E9: Baseline characteristics Study 20120153 (Full Analysis Set)

	Placebo QM (N = 484)	EvoMab 420 mg QM (N = 484)	Total (N = 968)
Sex - n (%)			
Male	350 (72.3)	349 (72.1)	699 (72.2)
Female	134 (27.7)	135 (27.9)	269 (27.8)
Age (years)			
n	484	484	968
Mean	59.8	59.8	59.8
SD	8.8	9.6	9.2
Median	60.0	60.0	60.0
Q1, Q3	54.0, 66.0	53.5, 67.0	54.0, 66.0
Min, Max	31, 83	30, 86	30, 86
Age group - n (%)			
≥ 65 years	145 (30.0)	164 (33.9)	309 (31.9)
≥ 75 years	21 (4.3)	32 (6.6)	53 (5.5)
Race - n (%)			
American Indian or Alaska Native	2 (0.4)	0 (0.0)	2 (0.2)
Asian	16 (3.3)	14 (2.9)	30 (3.1)
Black or African American	5 (1.0)	4 (0.8)	9 (0.9)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.2)	1 (0.1)
White	452 (93.4)	456 (94.2)	908 (93.8)
Multiple	6 (1.2)	7 (1.4)	13 (1.3)
Other	3 (0.6)	2 (0.4)	5 (0.5)
Ethnicity - n (%)			
Hispanic/Latino	24 (5.0)	34 (7.0)	58 (6.0)
Not Hispanic/Latino	460 (95.0)	450 (93.0)	910 (94.0)
Region - n (%)			
North America	88 (18.2)	86 (17.8)	174 (18.0)
Europe	331 (68.4)	332 (68.6)	663 (68.5)
Latin America	16 (3.3)	15 (3.1)	31 (3.2)
Asia Pacific[a]	49 (10.1)	51 (10.5)	100 (10.3)
Asia	12 (2.5)	10 (2.1)	22 (2.3)
Other[a]	37 (7.6)	41 (8.5)	78 (8.1)

Category Subcategory	Placebo QM (N = 484) n (%)	EvoMab 420 mg QM (N = 484) n (%)	Total (N = 968) n (%)
National cholesterol education program (NCEP) CHD risk categories			
High risk	459 (94.8)	452 (93.4)	911 (94.1)
Moderately high risk	11 (2.3)	10 (2.1)	21 (2.2)
Moderate risk	10 (2.1)	21 (4.3)	31 (3.2)
Lower risk	2 (0.4)	0 (0.0)	2 (0.2)
History of coronary artery disease diagnosis[a]	449 (92.8)	443 (91.5)	892 (92.1)
Coronary artery disease	418 (86.4)	409 (84.5)	827 (85.4)
Angina due to atherosclerotic coronary disease	303 (62.6)	310 (64.0)	613 (63.3)
Myocardial infarction	171 (35.3)	169 (34.9)	340 (35.1)
Coronary artery bypass graft	3 (0.6)	3 (0.6)	6 (0.6)
Percutaneous coronary intervention	188 (38.8)	189 (39.0)	377 (38.9)
Cerebrovascular or peripheral arterial disease by history	52 (10.7)	53 (11.0)	105 (10.8)
Transient ischemic attack	16 (3.3)	18 (3.7)	34 (3.5)
Stroke or cerebral infarction	11 (2.3)	9 (1.9)	20 (2.1)
Carotid or vertebral artery disease	28 (5.8)	29 (6.0)	57 (5.9)
Cardiovascular risk factors			
Major			
Peripheral arterial disease	9 (1.9)	12 (2.5)	21 (2.2)
Abdominal aortic aneurysm	4 (0.8)	3 (0.6)	7 (0.7)
Cerebrovascular disease	25 (5.2)	17 (3.5)	42 (4.3)
Myocardial infarction or Hospitalization for unstable angina within the last two years	144 (29.8)	137 (28.3)	281 (29.0)
Type 2 diabetes mellitus	104 (21.5)	98 (20.2)	202 (20.9)
Minor			
Current cigarette use	113 (23.3)	124 (25.6)	237 (24.5)
Hypertension	405 (83.7)	398 (82.2)	803 (83.0)
Low HDL-C	218 (45.0)	188 (38.8)	406 (41.9)
Family history of premature coronary heart disease	162 (33.5)	168 (34.7)	330 (34.1)
Age (men ≥ 50 year; women ≥ 55 years)	397 (82.0)	392 (81.0)	789 (81.5)
High sensitivity C-reactive protein ≥ 2 mg/L	197 (40.7)	197 (40.7)	394 (40.7)
Subjects with ≥ 3 minor risk factors	345 (71.3)	339 (70.0)	684 (70.7)

[a] Represents a historical diagnosis of coronary artery disease based on having at least 1 of the 5 conditions or procedures listed.

Primary results

Mean (SD) PAV at baseline was 36.4% (8.7%) in the evolocumab group and 37.2% (8.5%) in the placebo group. Mean (SD) TAV at baseline was 187.0 (81.8) mm^3 in the evolocumab group and 191.4 (85.7) mm^3 in the placebo group.

All primary and secondary efficacy endpoints met statistical significance and are summarized in the table E10. Evolocumab reduced PAV by 1.01% (0.64, 1.38) compared with placebo ($p < 0.0001$). Nominal change in PAV from baseline to week 78 (least squares mean [95% CI]) decreased by 0.96% (0.58, 1.33) in the evolocumab group and increased by 0.05% (-0.32, 0.42) in the placebo group.

Evolocumab reduced TAV by 4.89 mm^3 (2.53, 7.25) compared with placebo ($p < 0.0001$). Nominal change in TAV from baseline to week 78 (least squares mean [95% CI]) decreased by 5.80 mm^3 (3.41, 8.19) in the evolocumab group and by 0.91 mm^3 (−1.47, 3.29) in the placebo group.

Atherosclerosis regression, defined as any reduction in PAV was observed in 64.3% (95% CI: 59.6, 68.7) of evolocumab-treated subjects and 47.3% (95% CI: 42.6, 52.0) of placebo-treated subjects, and atherosclerosis regression defined as any reduction in TAV, was observed in 61.5% (95% CI: 56.7, 66.0) of evolocumab-treated subjects and 48.9% (95% CI: 44.2, 53.7) of placebo-treated subjects. Thus, atherosclerosis regression, as measured by PAV, was achieved by 17.0% (95% CI: 10.3, 23.5) more subjects in the evolocumab group compared with the placebo group ($p < 0.0001$), and atherosclerosis regression, as measured by TAV, was achieved by 12.5% (95% CI: 5.8, 19.1) more subjects in the evolocumab group, compared with the placebo group ($p = 0.0002$).

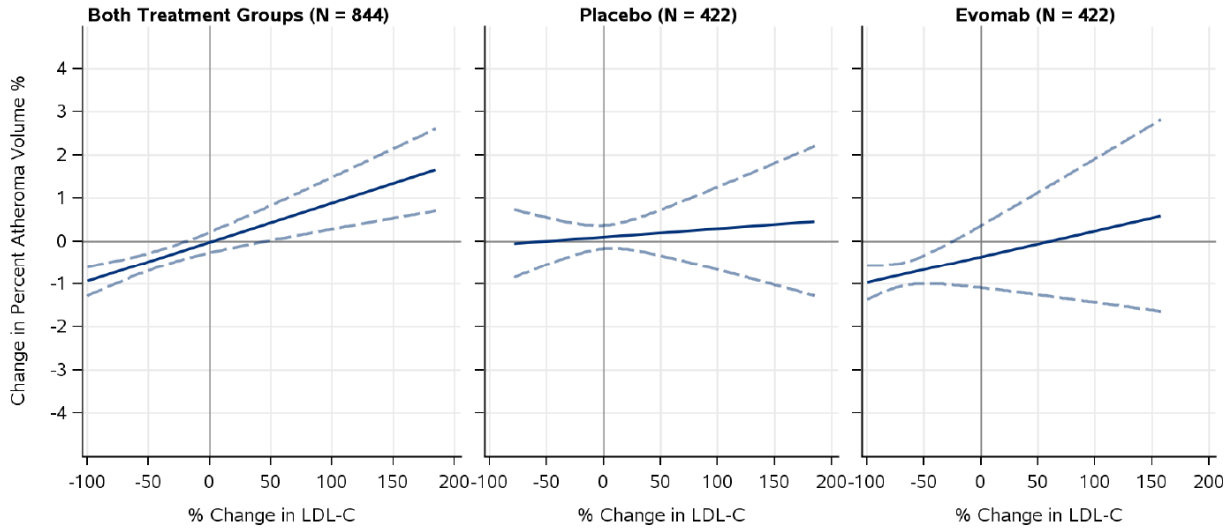
Table E10: Summary of Efficacy Results Study 20120153 (IVUS Analysis Set)

Endpoint	Summary type	Placebo QM (N = 423)	Evolocumab 420 mg QM (N = 423)	Treatment Difference (Evolocumab – Placebo)	P-value
Change in PAV (%)	LSM (95% CI)	0.05 (-0.32, 0.42)	-0.96 (-1.33, -0.58)	-1.01 (-1.38, -0.64)	< 0.0001
	Median (95% CI)	0.13 (-0.10, 0.38)	-0.96 (-1.22, -0.66)	-1.09 (-1.46, -0.72)	< 0.0001
Change in TAV (mm^3)	LSM (95% CI)	-0.91 (-3.29, 1.47)	-5.80 (-8.19, -3.41)	-4.89 (-7.25, -2.53)	< 0.0001
	Median (95% CI)	0.38 (-1.28, 2.22)	-3.57 (-4.51, -1.70)	-3.96 (-6.18, -1.73)	< 0.0001
Regression in PAV	n (%) (95% CI)	200 (47.3) (42.6, 52.0)	272 (64.3) (59.6, 68.7)	17.0 (10.3, 23.5)	< 0.0001
Regression in TAV	n (%) (95% CI)	207 (48.9) (44.2, 53.7)	260 (61.5) (56.7, 66.0)	12.5 (5.8, 19.1)	0.0002

- CI = confidence interval; IVUS = intravascular ultrasound; LSM = least squares mean;

N = Number of subjects in the IVUS analysis set; QM = monthly; PAV = percent atheroma volume; TAV = total atheroma volume.

Figure E8: Comparison of Percent Reduction in LDL-C and Nominal Change in Percent Atheroma Volume from Baseline to Week 78 - Study 20120153 (IVUS Analysis Set)



Results of subgroup analyses were consistent with the results in the overall subject population for the primary endpoint.

Reductions in LDL-C at week 12 were maintained through end-of-study (week 78). Mean (SD) LDL-C decreased by 61.6% (27.0%) from baseline at week 76 (end of dosing interval [ie, trough]) in the evolocumab group; mean (SD) LDL-C concentrations at this time point was 35.9 (27.9) mg/dL. Mean LDL-C in the placebo group remained generally unchanged throughout the study.

Results according to baseline LDL-C level

Ad-hoc analyses of change in PAV were conducted in subgroups using a dichotomous LDL-C cutoff (< 70 mg/dL and ≥ 70 mg/dL at baseline) to assess whether treatment effects were observed in subjects entering the study who had baseline LDL-C levels below the most stringent treatment target in global guidelines. Subjects with lower LDL-C at baseline (< 70 mg/dL) who received evolocumab saw numerically greater reductions in PAV, compared with placebo, than subjects with higher baseline LDL-C (≥ 70 mg/dL). The results suggest incremental benefit on atherosclerotic plaque burden even at baseline LDL-C levels below 70 mg/dL.

Table E11: Efficacy Results in Baseline LDL-C Subgroups < or ≥ 70 mg/dL at Week 78 Study 20120153 (IVUS Analysis Set)

Subgroup	Endpoint	Summary type	Placebo QM	Evolocumab 420 mg QM	Treatment Difference (Evolocumab – Placebo)
Baseline LDL-C < 70 mg/dL			N = 75	N = 69	
	Change in PAV (%)	LSM (95% CI)	-0.35 (-1.12, 0.41)	-1.97 (-2.82, -1.12)	-1.62 (-2.49, -0.74)
		Median (95% CI)	0.17 (-0.65, 0.44)	-1.75 (-2.15, -1.14)	-1.93 (-2.65, -1.20)
	Regression in PAV	n (%) (95% CI)	48.0 (36.7, 59.3)	81.2 (71.9, 90.4)	33.2 (17.7, 46.4)
	LDL-C (mg/dL)[a]	Mean (SE)	71.0 (2.5)	17.7 (1.6)	-53.3 (2.9)
Baseline LDL-C ≥ 70 mg/dL			N = 348	N = 354	
	Change in PAV (%)	LSM (95% CI)	0.13 (-0.29, 0.56)	-0.76 (-1.18, -0.34)	-0.90 (-1.30, -0.49)
		Median (95% CI)	0.13 (-0.15, 0.39)	-0.79 (-1.02, -0.39)	-0.92 (-1.33, -0.52)
	Regression in PAV	n (%) (95% CI)	47.1 (41.9, 52.4)	61.0 (55.9, 66.1)	13.9 (6.5, 21.1)
	LDL-C (mg/dL)[a]	Mean (SE)	94.0 (1.6)	30.0 (1.4)	-64.0 (2.2)

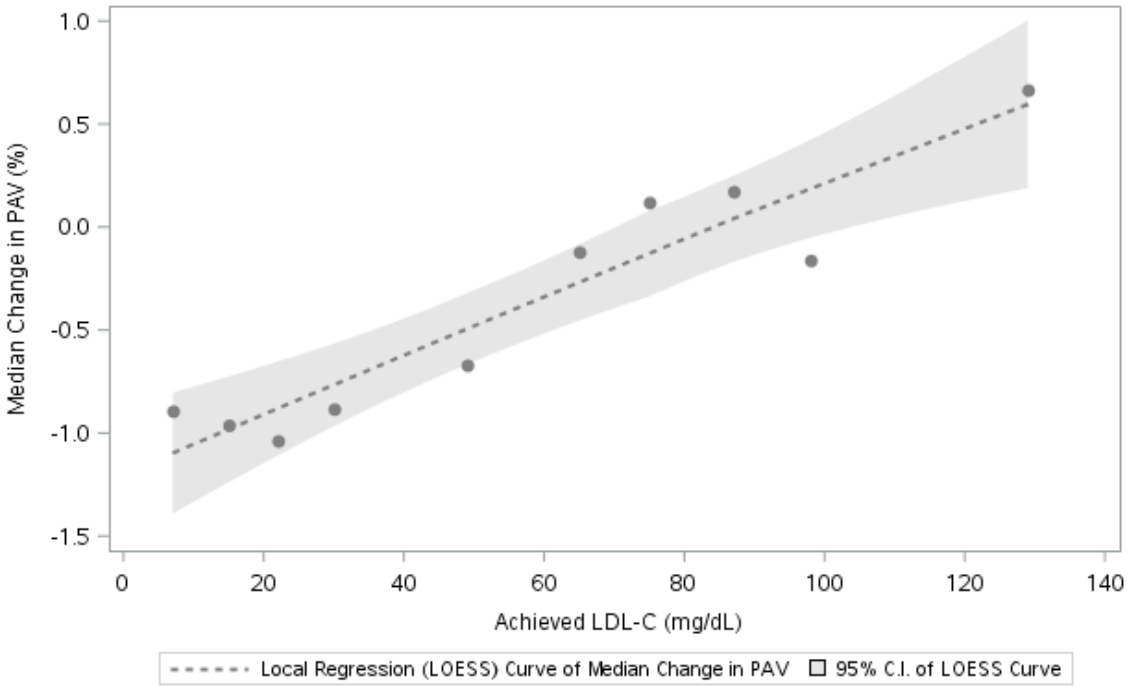
- CI = confidence interval; IVUS = intravascular ultrasound; LDL-C = low-density lipoprotein cholesterol; LSM = least squares mean; PAV = percent atheroma volume; QM = monthly; SE = standard error.
- [a] LDL-C for this analysis represents the latest LDL-C value available within the same analysis window as the follow-up IVUS assessment.
-

Relationship LDL-C level and change in PAV

To examine the relationship between LDL-C level and change in PAV, an ad-hoc local regression was conducted using methodology that did not impose a linear relationship between the response and explanatory variables. This analysis showed a continuous relationship between achieved LDL-C and change in PAV, with evidence of regression at LDL-C levels beginning between 80 mg/dL and 90 mg/dL

and continuing to LDL-C levels as low as 7 mg/dL (the lowest achieved LDL-C in this study); lower achieved LDL-C levels were associated with greater reductions in PAV. This relationship was observed across the spectrum of post-baseline LDL-C levels, and no lower LDL-C threshold for this relationship was identified.

Figure E9: Median Change in PAV by Every 10th Percentile of Achieved LDL-C Study 20120153



IVUS = intravascular ultrasound; LDL-C = low-density lipoprotein cholesterol; PAV = percent atheroma volume.

Note: Locations of the scatter dots on the x-axis represent the 5th, 15th, and every subsequent tenth percentile through 95, of the last LDL-C value within the same analysis window as the follow-up IVUS assessment.

GLAGOV study was conducted to demonstrate reduction in atherosclerotic disease burden by assessing the atheroma volume in the coronary vessels after 78 weeks of treatment with evolocumab on top of high- (58.9%) or moderate- (39.4%) intensity statins. This was assessed by using the IVUS method. The primary analysis of nominal change in PAV was analysed using ANCOVA, using all FAS patients with a baseline and week 52 IVUS measurement. As sensitivity analysis the primary analysis was repeated in the FAS using multiple imputation for missing IVUS data. This was considered acceptable. The patients included were 60 years old, mainly white and male, and mainly included in Europe, with 85% having coronary artery disease and 35% a history of MI. The population represents a patient population being at high CV risk with mainly a documented history of CHD, although with substantially less documented history of MI or stroke as include in the main outcome study. Yet, mean levels of LDL-C at baseline were at the lower end of 2.4 mmol/L, thus eligible for LLT treatment in agreement with the clinical practice guidelines (*2016 ESC/EAS Guidelines for the management of dyslipidaemias*).

The data could be considered supportive for demonstration of reduction of coronary atherosclerotic burden as PAV was significantly reduced from baseline to week 78 for patients treated with evolocumab compared to a background therapy of statins. Although the effect could be considered moderate as PAV only decreased by 0.96% (0.58, 1.33) in the evolocumab group and increased by 0.05% (-0.32, 0.42) in the placebo group. Of note, baseline levels of PAV were different in both treatment groups, yet this was higher for placebo. Other endpoints of TAV, atherosclerotic regression (defined as any reduction in PAV),

were supportive for the primary endpoint. Also, patients at lower baseline levels demonstrated a treatment effect for evolocumab on PAV reduction. Moreover, a relationship between change in PAV and achieved LDL-C level could be demonstrated.

2.4.2. Discussion on clinical efficacy

To evaluate the effect of evolocumab Q2W or QM treatment on the risk of CV events, a multicentre international double-blinded placebo-controlled pivotal cardiovascular outcome study has been performed.

Inclusion criteria consisted of patients with **established CV disease** by prior myocardial infarction (MI), history of non-hemorrhagic stroke, or symptomatic peripheral arterial disease (PAD). In accordance to practical guidelines (e.g. *ESC CV prevention, 2013 ACA/AHA treatment of blood cholesterol*) these patients can be classified as having a very-high CV risk eligible for LDL-C treatment. More specifically, subjects were required to have **LDL-C levels above desired levels (LDL-C ≥ 70 mg/dL [1.8 mmol/L])** or non-HDL ≥ 100 mg/dL [2.6 mmol/L]) despite stable high- to moderate-intensity statin therapy at baseline. This study could provide more evidence whether ''the lower the better'' theory holds for lipid lowering therapies beyond current evidence of statin therapy, and non-statin therapy (e.g. recent results of the outcome study with ezetimibe). The use of **optimized high dose statin background therapy** was defined as at least atorvastatin 40 mg daily or equivalent (≥ 4 weeks on stable dose). Lower doses were only allowed in patients with LDL-C < 2.6 mmol/L, or > 2.6 mmol/L if well justified (e.g., dose not tolerated, dose not available in that country, other significant clinical concern).

To enrich this population, additional inclusion criteria were present of **patients having ≥ 1 major risk factor or ≥ 2 minor risk factors in addition** to the documented CVD. This will not reclassify patient's risk in terms of guideline risk categories (already very high risk) and associated treatment recommendations, but may increase their CV risk as a continuous estimation, probably to improve the possible demonstration of a treatment effect of the drug under investigation. Of note, subjects could not be randomized within 4 weeks of their most recent CVD event (MI or stroke) allowing for a wide time frame of latest documented CVD event.

This resulted in inclusion of a relatively young patient population (n=27564) with a mean age around 62.5, mostly white and male; with limited representation of patients above 75 years (only 9.2%), but an **adequate representation of EU patients (63%)**. Patients could be considered to be at very high risk with 80% with a history of MI, 19% with a history of non-haemorrhagic stroke. PAD contributed less to the risk classification with approximately 13%. A further increased risk was present for 99.5% of the patients due to an addition of ≥ 1 major risk factors or ≥ 2 minor risk factors. In particular, diabetes, age, additional MI or stroke, and cigarette smoking contributed to a further increased CV risk, while minor risk factors were also majorly present. Given this representation of very high risk patients, the mean level of 2.5 mmol/L of LDL-C at baseline was generally in line with clinical practice guideline recommendations indicating that **these patients on average are eligible for further LLT treatment**. A large proportion of patients **(69%) used a high intensity statin** (mostly atorvastatin, some rosuvastatin) while 30% used a moderate intensity statin, with very little using low intensity or no statin, suggesting that most patients were treated according to current practice recommendations. A low percentage used additional ezetimibe (5%).

The primary endpoint is a composite of time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, and coronary revascularization, whichever occurred first. **Investigating CV 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. In this case, sufficient confidence regarding overall mortality and non-CV mortality is necessary

(EMA/CHMP/SAWP/620990/2012). The primary endpoint has included **hospitalization for unstable angina and coronary revascularization in the primary endpoint in addition to the "harder" endpoints** of MI, stroke and CV death. These **former events are considered less robust** in particular with respect to objective definitions and possible bias in relation to clinical decision making. It is reassuring that the **key secondary endpoint** has been defined as time to cardiovascular death, myocardial infarction, and stroke, which is the preferred endpoint according to the *EMA Guideline on the evaluation of medicinal product for cardiovascular disease prevention (EMEA/CHMP/EWP/311890/2007)* and that event driven study end will be determined by this key secondary endpoint, and not by the primary endpoint. Further evaluation of single components and other components of possible cardiovascular events is acceptable as they could further support the key analyses and provide further knowledge of the treatment effect on cardiovascular prevention, although they are part of hierarchical testing and could become exploratory when one of the hierarchical tests is not met. Events are adjudicated by an independent CEC as commonly seen in large CV intervention trials.

By **reduction of 48-63% in LDL-C** with a median level of 2.28 mmol/L LDL-C at baseline to approximately 0.90 – 1.2 mmol/L during the study, a beneficial treatment effect of evolocumab versus placebo can be observed after 5 months. The median duration of follow-up was 26 months. For the composite primary endpoint of MI, stroke, CV death, hospitalization for unstable angina, or coronary revascularization, **219 less events that occurred in the evolocumab treated patients (1344 [9.8%] vs 1563 [11.3%]) resulting in 15% lower hazard ratio (HR of 0.85 (95% CI 0.79, 0.92; p < 0.0001))**. This effect is mostly accountable to the benefit on the atherosclerotic effect on MI (94 less events out of 752 events), stroke (42 less out of 410 events) and coronary revascularization (45 less out of 743 events). This result can be considered robust as pre-specified sensitivity analyses did not alter this finding including **a sensitivity analysis using all-cause mortality in place of cardiovascular mortality**. Approximately 12.5% discontinued treatment, and a very large proportion (> 99.1%) completed the study. There appears a lag-time of approximately 5 months before the KM curve starts to separate throughout the period of the study showing the benefit of evolocumab treatment. The **key secondary endpoint of MI, stroke and CV death provided similar observation** as for the primary endpoint with a HR of 0.80 (95% CI 0.73, 0.88; p < 0.0001) and diverging KM lines over time. A comparable effect as for the primary endpoint for evolocumab could be demonstrated (18% reduction) when multiple events were considered.

Despite these beneficial effects, **evolocumab could not reduce CV death and overall death**; first events of CV death were 161 vs 142 events; crude HR of 1.14), overall CV death events 251 vs 240; HR 1.05 (0.88, 1.25) and mortality events (444 vs 426 events; HR 1.04 (0.91, 1.19). These observations create uncertainty on the effect of evolocumab treatment on CV risk reduction. First, these events were found to be slightly higher, although not-significant, thus any chance finding cannot be excluded. Also, it cannot be excluded that study duration may have been too short to observe any beneficial (or detrimental) effect of evolocumab treatment. Further, when looking more in detail into CV death events, these were mostly attributed to sudden cardiac death. For non-CV death, no specific pattern could be observed to clarify any difference in effect.

The primary endpoint and key secondary endpoint demonstrated a consistent beneficial effect across a wide range of subgroups. However, the treatment effect for Europe is less than other regions, in particular US. No reason for this observation could be identified. The current treatment effects for several of the risk parameters appear to be counterintuitive and not consistently in agreement with this risk-effect relationship including e.g. LDL-C level, age, history of stroke, and diabetes. While, for symptomatic PAD, prior MI, ezetimibe at baseline, and high intensity statin this is in line with what can be expected. Similarly, for PCSK9 levels **the treatment effect is higher with higher levels of PCSK9**. Of note, treatment effect in this selected PK analysis set is greater than for the overall population. The

absolute risk reduction was approximately 2% for the entire study period for the primary endpoint. And, data indicate **a continuous relationship between the level of achieved LDL-C and adjusted CV event rates**. Notably, at the lowest end, patients were still at risk of 2.5 events per 100/patient years without a clear cut-off.

Supportive data for demonstration of reduction of coronary atherosclerotic burden come from the **GLAGOV study** in 968 patients of 60 years old, mainly white, male, mainly included in Europe, with 85% having coronary artery disease and 35% a history of MI, and a LDL-C baseline level of 2.4 mmol/L, who were treated with **evolocumab for 78 weeks on top of high- (58.9%) or moderate- (39.4%) intensity statins**. PAV (percent atheroma volume) was significantly reduced, although **the effect could be considered moderate** as PAV only decreased by 0.96% (0.58, 1.33) in the evolocumab group and increased by 0.05% (-0.32, 0.42) in the placebo group. Of note, baseline levels of PAV was different in both treatment group, yet this was higher for placebo, thus any advantage for evolocumab is not expected. Other endpoints of TAV, atherosclerotic regression (defined as any reduction in PAV), were supportive for the primary endpoint. Also, patients at lower baseline levels demonstrated a treatment effect for evolocumab on PAV reduction. Moreover, a relationship between change in PAV and achieved LDL-C level could be demonstrated.

2.4.3. Conclusions on the clinical efficacy

In the **FOURIER study** evolocumab demonstrated a **significant reduction** on the composite primary endpoint of time to CV death, MI, hospitalization for unstable angina, stroke, and coronary revascularization, whichever occurred first after a mean of 26 months of treatment with the beneficial effect starting at approximately 5 months of treatment and primarily **driven by MI and stroke and coronary revascularization**. A **sensitivity analysis using all-cause mortality** in place of cardiovascular mortality showed similar results. The primary and key secondary endpoints demonstrated a **consistent beneficial effect across a wide range of subgroups**. Despite that included patients were in need for lowering LDL-C levels according to their very high cardiovascular risk and as recommended in the European clinical practice guideline (e.g. *2016 ESC/EAS Guideline on cardiovascular disease prevention in clinical practice),* the effect could be considered moderate with a **15% reduction of the primary endpoint** and a **2% absolute risk reduction**. No effect on CV death and overall mortality could be demonstrated, however, this has been the case with other lipid lowering therapies as well (e.g. ezetimibe, atorvastatin). Slightly non-significant **increased hazard ratios for CV death** (251 vs 240; HR 1.05 (0.88, 1.25) and **overall mortality** (444 vs 426 events; HR 1.04 (0.91, 1.19) were observed.

These results were further supported by **GLAGOV imaging study** demonstrating a moderate effect on percent atheroma volume after 78 weeks (-0.96% (0.58, 1.33) for evolocumab vs 0.05% (-0.32, 0.42)) for placebo representing a **reduction of coronary atherosclerotic burden**.

The FOURIER study supports treating to LDL-C levels ''*as low as possible''.* There is no indication of a J-shaped curve, while there seems to be no lower limit of LDL-C at which potential benefit disappears.

2.5. Clinical safety

Introduction

The safety database was assessed using the following data:

- The primary focus of this Summary of Clinical Safety (SCS) is the results from Study 20110118 (FOURIER).
- In addition, safety data are presented from Study 20120153 (GLAGOV) which evaluated the effects of 18 months of evolocumab compared with placebo on coronary atherosclerotic disease burden as assessed by intravascular ultrasound (IVUS) in subjects with coronary artery disease on high- to moderate-intensity statin therapy.
- A subset of Study 20110118 subjects enrolled in Study 20130385 (EBBINGHAUS) (n=1204), a phase 3, double-blind, placebo-controlled, multicenter study to evaluate the effect of evolocumab on cognitive function using a validated Cambridge Neuropsychological Test Automated Battery (CANTAB) assessment.

Patient exposure

A total of 24 385 subjects were exposed to any dose of evolocumab representing 49 755 patient-years of exposure. In the phase 3 cardiovascular outcomes study (Study 20110118 [FOURIER] and its open-label extension, Study 20130295), 16 234 subjects were exposed to 140 mg Q2W and 420 mg once monthly (QM) evolocumab representing 31 583 patient-years of exposure. In the phase 3 atherosclerosis imaging study (Study 20120153 [GLAGOV] and its open-label extension, Study 20140128), 864 subjects were exposed to 420 mg QM evolocumab representing 1604 patient-years of exposure. As of 17 January 2017, an estimated 61 600 subjects have been exposed to evolocumab in the postmarking setting.

Table S1: Estimated Cumulative Subject Exposure in Evolocumab Clinical Trials

	EvoMab-treated Subjects
Overall	
Number of Subjects	24385
Total pt-year exposure	49755.4
Number of Subjects	
≥ 1 year	19472
≥ 2 years	13836
≥ 3 years	3929
≥ 4 years	893
≥ 5 years	409
≥ 6 years	0
Phase 1	
Number of Subjects	728
Total pt-year exposure	150.9
Phase 2 and 3 Lipid-lowering Studies	
Homozygous Familial Hypercholesterolemia Studies	
Number of Subjects	109
Total pt-year exposure	328.4
Number of Subjects	
≥ 1 year	99
≥ 2 years	90
≥ 3 years	71
≥ 4 years	9
≥ 5 years	0
Severe Familial Hypercholesterolemia Studies	
Number of Subjects	194
Total pt-year exposure	519.9
Number of Subjects	
≥ 1 year	192
≥ 2 years	181
≥ 3 years	15
≥ 4 years	3
≥ 5 years	0
Other Hyperlipidemia and Mixed Dyslipidemia Studies	
Number of Subjects	6256
Total pt-year exposure	15569.5
Number of Subjects	
≥ 1 year	4935
≥ 2 years	4282
≥ 3 years	2591
≥ 4 years	881
≥ 5 years	409
≥ 6 years	0

	EvoMab-treated Subjects
Phase 3 Cardiovascular Outcomes Study	
Number of Subjects	16234
Total pt-year exposure	31582.8
Number of Subjects	
≥ 1 year	13546
≥ 2 years	8897
≥ 3 years	1162
≥ 4 years	0
Phase 3 Atherosclerosis Imaging Study	
Number of Subjects	864
Total pt-year exposure	1604.1
Number of Subjects	
≥ 1 year	700
≥ 2 years[a]	386
≥ 3 years[a]	90
≥ 4 years[a]	0

- Phase 1 studies include: 20080397, 20080398, 20110121, 20120133, 20120136, 20110168, 20120341, 20150111, 20150353, 20140213
- Homozygous familial hypercholesterolemia includes subjects from studies 20110233 and 20110271.
- Severe familial hypercholesterolemia includes subjects from study 20110271 without homozygous familial hypercholesterolemia.
- Other Hyperlipidemia and Mixed Dyslipidemia studies include: Phase 2- 20090158, 20090159, 20101154, 20101155, 20110110, 20110231; Phase 3 - 20110109, 20110114, 20110115, 20110116, 20110117, 20120138, 20120348, 20120356, and 20120122, 20120332 part B and C, 20130194, 20140316
- Phase 3 Atherosclerosis Imaging Study includes subjects from study 20120153 and 20140128.
- Phase 3 Cardiovascular Outcomes Study includes subjects from studies 20110118 and 20130295.
- Ongoing studies (data cutoff date) include: 20110110 (17JAN2017), 20120138 (17JAN2017), 20110271 (17JAN2017), 20140128 (17JAN2017),
- 20140316 (17JAN2017), 20130295 (17JAN2017), 20150353 (22JAN2017)
- EvoMab = Evolocumab (AMG 145); pt-year = patient years, where years are calculated as the sum of period durations for the treatment group across subjects divided by 365.25.
- [a] Exposure beyond the 1.5 years duration of Study 20120153 are from Study 20140128, an open-label extension study for Study 20120153.

Study 20110118 (FOURIER)

A total of 27 525 subjects (SAS) were randomized and received at least 1 dose of investigational product (evolocumab or placebo) in Study 20110118. All of these subjects were included in the safety analysis set and exposure was balanced between treatment groups. Median (Q1, Q3) study exposure (length of follow-up) was 26.0 (21.8, 30.4) months and ranged from 0.03 months to 44.94 months. Overall mean (SD) exposure to investigational product was 24.1 (8.2) months; 25 166 (91.4%) subjects were exposed to investigational product for ≥ 12 months, 23 158 (84.1%) subjects for ≥ 18 months, 14 775 (53.7%) subjects for ≥ 24 months, and 1226 (4.5%) subjects for ≥ 36 months.

Table S2: Summary of Exposure Study 20110118 (Safety Analysis Set - Actual Treatment Group)

	Placebo (N = 13756)	EvoMab (N = 13769)	Total (N = 27525)
Duration of IP exposure (months)[a]			
N	13756	13769	27525
Mean	24.107	24.161	24.134
SD	8.261	8.152	8.206
Median	24.723	24.805	24.772
Q1, Q3	19.384, 30.160	19.483, 30.127	19.417, 30.160
Min, Max	0.03, 43.04	0.07, 41.46	0.03, 43.04
IP exposure categorization - n(%)			
≥ 12 months	12549 (91.2)	12617 (91.6)	25166 (91.4)
≥ 18 months	11527 (83.8)	11631 (84.5)	23158 (84.1)
≥ 24 months	7343 (53.4)	7432 (54.0)	14775 (53.7)
≥ 36 months	633 (4.6)	593 (4.3)	1226 (4.5)
Duration of study exposure (months)[b]			
n	13756	13769	27525
Mean	26.094	26.093	26.094
SD	6.394	6.332	6.363
Median	26.021	25.988	26.021
Q1, Q3	21.749, 30.456	21.749, 30.423	21.749, 30.423
Min, Max	0.03, 43.17	0.07, 44.94	0.03, 44.94
Study exposure categorization - n(%)			
≥ 12 months	13517 (98.3)	13546 (98.4)	27063 (98.3)
≥ 18 months	12761 (92.8)	12814 (93.1)	25575 (92.9)
≥ 24 months	8361 (60.8)	8392 (60.9)	16753 (60.9)
≥ 36 months	781 (5.7)	761 (5.5)	1542 (5.6)

- EOS = end of study; EvoMab = Evolocumab (AMG 145); IP = investigational product; N = number of subjects randomized and dosed; Q2W = every 2 weeks; QM = once monthly.
- [a] Q2W subjects: IP exposure (months) = [min(Last IP Dose Date + 14 days, EOS Date) - First IP Dose Date + 1]/ 365.25 * 12; QM subjects: IP exposure (months) = [min(Last IP Dose Date + 28 days, EOS Date) - First IP Dose Date + 1]/ 365.25 * 12.
- [b] Study exposure (months) = (EOS Date - subject randomization date + 1)/ 365.25 * 12.

Study 20120153 (GLAGOV)

A total of 968 subjects (484 evolocumab, 484 placebo) received at least 1 dose of investigational product. Median (Q1, Q3) exposure to investigational product was 18.4 months (18.4, 18.5) in each treatment group.

A considerable number of 24 385 subjects have been exposed to evolocumab representing 49 755 patient-years of exposure. Moreover, it has been estimated that 61 600 subjects have been exposed to evolocumab in the postmarketing setting. Evaluation of the most recent PSUR (data lock 1 January 2017) did not reveal any new safety issues. In the current submission, safety data on the exposure in the pivotal study (FOURIER), a total of 27525 subjects, and 968 included in the GLAGOV study will be discussed, in addition to post-marketing data. The safety data of the pivotal study substantially builds up on the currently available controlled safety data, although exposure was limited to a median of 26 months in the pivotal study and 78 weeks in the GLAGOV study.

Adverse events

Evolocumab was well-tolerated and no new safety concerns were identified in the studies included in this submission or during long-term treatment. The safety profile of evolocumab was consistent in subjects with low (< 25 mg/dL and < 40 mg/dL) post-baseline LDL-C; specifically, the incidence of muscle events, hepatic events, neurocognitive events, demyelination or peripheral neuropathy events, and the incidence of positively-adjudicated new onset of diabetes mellitus (NODM) was comparable between evolocumab and placebo groups.

The incidence of treatment emergent adverse events including adverse events leading to discontinuation of investigational product and serious adverse events was balanced between the evolocumab and placebo groups.

Table S3: Summary of Subject Incidence of Treatment Emergent Adverse Events Study 20110118 (Safety Analysis Set - Actual Treatment Group)

	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
All treatment emergent adverse events	10644 (77.4)	10664 (77.4)
Grade ≥ 2	9179 (66.7)	9219 (67.0)
Grade ≥ 3	4669 (33.9)	4646 (33.7)
Grade ≥ 4	606 (4.4)	543 (3.9)
Serious adverse events	3404 (24.7)	3410 (24.8)
Leading to discontinuation of investigational product	573 (4.2)	608 (4.4)
Serious	254 (1.8)	267 (1.9)

The incidence of these adverse events was generally similar between the evolocumab and placebo groups. The most common (≥ 5% of subjects) adverse events in either treatment group (evolocumab, placebo) were diabetes mellitus (8.8%, 8.2%), hypertension (8.0%, 8.7%), nasopharyngitis (7.8%, 7.4%), and upper respiratory tract infection (5.1%, 4.8%).

Table S4: Treatment Emergent Adverse Events by Preferred Term in Descending Order of Frequency Preferred Terms Reported by ≥ 1% of Subjects in Any Treatment Group Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Preferred Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
Number of subjects reporting treatment emergent adverse events	10644 (77.4)	10664 (77.4)
Diabetes mellitus	1130 (8.2)	1207 (8.8)
Hypertension	1190 (8.7)	1108 (8.0)
Nasopharyngitis	1021 (7.4)	1068 (7.8)
Upper respiratory tract infection	655 (4.8)	698 (5.1)
Back pain	651 (4.7)	673 (4.9)
Arthralgia	589 (4.3)	605 (4.4)
Urinary tract infection	558 (4.1)	584 (4.2)
Bronchitis	561 (4.1)	573 (4.2)
Myalgia	527 (3.8)	555 (4.0)
Dizziness	435 (3.2)	474 (3.4)
Angina pectoris	536 (3.9)	472 (3.4)
Influenza	419 (3.0)	472 (3.4)
Diarrhoea	430 (3.1)	469 (3.4)
Headache	508 (3.7)	440 (3.2)
Cough	468 (3.4)	436 (3.2)
Pain in extremity	451 (3.3)	428 (3.1)
Pneumonia	322 (2.3)	336 (2.4)
Atrial fibrillation	323 (2.3)	335 (2.4)
Fatigue	336 (2.4)	325 (2.4)
Muscle spasms	296 (2.2)	316 (2.3)
Osteoarthritis	334 (2.4)	309 (2.2)
Dyspnoea	311 (2.3)	303 (2.2)
Non-cardiac chest pain	360 (2.6)	299 (2.2)
Oedema peripheral	298 (2.2)	278 (2.0)
Musculoskeletal pain	282 (2.1)	273 (2.0)
Anaemia	282 (2.1)	269 (2.0)
Angina unstable	324 (2.4)	268 (1.9)
Depression	259 (1.9)	264 (1.9)
Chest pain	255 (1.9)	247 (1.8)
Type 2 diabetes mellitus	219 (1.6)	246 (1.8)
Nausea	235 (1.7)	233 (1.7)
Hyperuricaemia	188 (1.4)	224 (1.6)
Gout	193 (1.4)	219 (1.6)
Lower respiratory tract infection	193 (1.4)	216 (1.6)
Cataract	220 (1.6)	210 (1.5)
Sinusitis	192 (1.4)	201 (1.5)
Contusion	209 (1.5)	200 (1.5)
Hyperglycaemia	205 (1.5)	188 (1.4)
Abdominal pain	194 (1.4)	185 (1.3)
Fall	185 (1.3)	184 (1.3)
Rash	172 (1.3)	182 (1.3)
Abdominal pain upper	152 (1.1)	180 (1.3)

Preferred Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
Blood creatine phosphokinase increased	154 (1.1)	177 (1.3)
Hypotension	180 (1.3)	177 (1.3)
Gastrooesophageal reflux disease	143 (1.0)	174 (1.3)
Vertigo	176 (1.3)	169 (1.2)
Chronic obstructive pulmonary disease	195 (1.4)	168 (1.2)
Syncope	178 (1.3)	162 (1.2)
Benign prostatic hyperplasia	161 (1.2)	157 (1.1)
Constipation	198 (1.4)	157 (1.1)
Palpitations	124 (0.9)	157 (1.1)
Insomnia	141 (1.0)	156 (1.1)
Musculoskeletal chest pain	155 (1.1)	156 (1.1)
Peripheral arterial occlusive disease	129 (0.9)	156 (1.1)
Dyspepsia	156 (1.1)	154 (1.1)
Haematuria	157 (1.1)	150 (1.1)
Gastroenteritis	144 (1.0)	148 (1.1)
Asthenia	139 (1.0)	135 (1.0)
Vomiting	145 (1.1)	128 (0.9)
Sciatica	144 (1.0)	103 (0.7)

Treatment related adverse events

Overall, 1341 (9.7%) subjects in the evolocumab group and 1240 (9.0%) subjects in the placebo group experienced at least 1 treatment-related adverse event. Most treatment-related adverse events were grade 1 or 2. Grade ≥ 3 treatment-related adverse events were reported in 1.4% of subjects in each group; grade ≥ 4 treatment-related adverse events were reported in 0.1% of subjects in the evolocumab group and 0.2% of subjects in the placebo group. The most common treatment-related adverse events in both groups combined (evolocumab, placebo) were myalgia (0.9%, 0.8%), diabetes mellitus (0.5%, 0.4%), diarrhea (0.4% in each group), and fatigue (0.4% in each group).

Table S5: Treatment-emergent Adverse Events Related to Investigational Product and Reported for ≥ 0.1% of Subjects in Any Treatment Group Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Preferred Term	Placebo (N = 13756)	EvoMab (N = 13769)
Number of subjects reporting a treatment-related treatment-emergent adverse event	1240 (9.0)	1341 (9.7)
Myalgia	111 (0.8)	123 (0.9)
Diabetes mellitus [a]	60 (0.4)	66 (0.5)
Diarrhoea	58 (0.4)	56 (0.4)
Fatigue	61 (0.4)	53 (0.4)
Headache	42 (0.3)	47 (0.3)
Arthralgia	38 (0.3)	46 (0.3)
Injection site pain	29 (0.2)	46 (0.3)
Muscle spasms	42 (0.3)	43 (0.3)
Dizziness	28 (0.2)	39 (0.3)
Nausea	51 (0.4)	35 (0.3)
Blood creatine phosphokinase increased	30 (0.2)	31 (0.2)
Pruritus	28 (0.2)	30 (0.2)
Pain in extremity	29 (0.2)	29 (0.2)
Hepatic enzyme increased	11 (< 0.1)	27 (0.2)
Alanine aminotransferase increased	36 (0.3)	24 (0.2)
Rash	27 (0.2)	23 (0.2)
Nasopharyngitis	17 (0.1)	21 (0.2)
Rhinorrhoea	27 (0.2)	20 (0.1)
Injection site erythema	12 (< 0.1)	20 (0.1)
Hypertension	23 (0.2)	19 (0.1)
Muscular weakness	10 (< 0.1)	19 (0.1)
Back pain	14 (0.1)	18 (0.1)
Injection site reaction	10 (< 0.1)	18 (0.1)
Cough	12 (< 0.1)	17 (0.1)
Malaise	6 (< 0.1)	16 (0.1)
Memory impairment	13 (< 0.1)	15 (0.1)
Upper respiratory tract infection	6 (< 0.1)	15 (0.1)
Asthenia	27 (0.2)	14 (0.1)
Abdominal pain	17 (0.1)	11 (< 0.1)
Aspartate aminotransferase increased	18 (0.1)	10 (< 0.1)
Injection site bruising	18 (0.1)	10 (< 0.1)
Hyperglycaemia	14 (0.1)	10 (< 0.1)
Type 2 diabetes mellitus	17 (0.1)	8 (< 0.1)

- EvoMab = Evolocumab (AMG 145); MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects randomized and dosed.
- Data are presented as number (%) of subjects. Coded using MedDRA version 19.1.
- [a] Reference to adverse events of diabetes mellitus refers to investigator-reported events that were coded to the preferred term diabetes mellitus and may represent a new diagnosis of diabetes mellitus or a worsening/exacerbation of a pre-existing condition.

Adverse events according to achieved LDL-C subgroup

Analysis of adverse events by lowest achieved post-baseline LDL-C showed no increased incidence of adverse events in subjects who achieved low LDL-C with evolocumab. The overall subject incidence of treatment emergent adverse events was 68.4% and 73.2% in evolocumab-treated subjects who achieved LDL-C values < 25 mg/dL and < 40 mg/dL, respectively, compared with 73.6% and 77.7% in evolocumab-treated subjects and placebo-treated subjects with LDL-C ≥ 40 mg/dL, respectively. The most common adverse events (≥ 5% of subjects) in any LDL-C group were diabetes mellitus, nasopharyngitis, hypertension, and back pain. While the types of adverse events were similar across all post-baseline LDL-C groups, the subject incidence of individual preferred terms was generally similar or lower in evolocumab-treated subjects who achieved LDL-C < 25 mg/dL and < 40 mg/dL than in evolocumab-treated subjects or placebo-treated subjects with LDL-C ≥ 40 mg/dL.

Table S6: Treatment Emergent Adverse Events Occurring in ≥ 1% of Subjects in LDL-C < 25 mg/dL Group by Preferred Term in Descending Order of Frequency Lowest Postbaseline LDL-C Achieved Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Preferred Term	Placebo ≥ 40 mg/dL (N = 13334) n (%)	EvoMab < 25 mg/dL (N = 9518) n (%)	< 40 mg/dL (N = 12039) n (%)	≥ 40 mg/dL (N = 1582) n (%)
Number of subjects reporting treatment emergent adverse events	10355 (77.7)	6512 (68.4)	8812 (73.2)	1164 (73.6)
Diabetes mellitus	1085 (8.1)	678 (7.1)	929 (7.7)	147 (9.3)
Nasopharyngitis	998 (7.5)	599 (6.3)	808 (6.7)	90 (5.7)
Hypertension	1153 (8.6)	570 (6.0)	801 (6.7)	144 (9.1)
Upper respiratory tract infection	647 (4.9)	410 (4.3)	545 (4.5)	65 (4.1)
Back pain	634 (4.8)	352 (3.7)	505 (4.2)	81 (5.1)
Bronchitis	543 (4.1)	330 (3.5)	455 (3.8)	59 (3.7)
Urinary tract infection	548 (4.1)	322 (3.4)	447 (3.7)	66 (4.2)
Arthralgia	580 (4.3)	294 (3.1)	442 (3.7)	73 (4.6)
Angina pectoris	524 (3.9)	260 (2.7)	370 (3.1)	39 (2.5)
Myalgia	514 (3.9)	256 (2.7)	385 (3.2)	65 (4.1)
Influenza	409 (3.1)	252 (2.6)	366 (3.0)	33 (2.1)
Cough	461 (3.5)	245 (2.6)	335 (2.8)	42 (2.7)
Dizziness	423 (3.2)	237 (2.5)	342 (2.8)	50 (3.2)
Pain in extremity	445 (3.3)	229 (2.4)	317 (2.6)	44 (2.8)
Diarrhoea	426 (3.2)	224 (2.4)	318 (2.6)	51 (3.2)
Headache	495 (3.7)	192 (2.0)	280 (2.3)	73 (4.6)
Pneumonia	315 (2.4)	191 (2.0)	265 (2.2)	38 (2.4)
Atrial fibrillation	315 (2.4)	190 (2.0)	278 (2.3)	27 (1.7)
Osteoarthritis	328 (2.5)	184 (1.9)	262 (2.2)	22 (1.4)
Dyspnoea	307 (2.3)	160 (1.7)	220 (1.8)	37 (2.3)
Fatigue	332 (2.5)	155 (1.6)	229 (1.9)	31 (2.0)
Non-cardiac chest pain	358 (2.7)	149 (1.6)	229 (1.9)	38 (2.4)
Anaemia	268 (2.0)	148 (1.6)	216 (1.8)	27 (1.7)
Muscle spasms	289 (2.2)	146 (1.5)	223 (1.9)	30 (1.9)
Chest pain	251 (1.9)	144 (1.5)	197 (1.6)	21 (1.3)
Type 2 diabetes mellitus	214 (1.6)	143 (1.5)	203 (1.7)	18 (1.1)
Musculoskeletal pain	280 (2.1)	139 (1.5)	207 (1.7)	28 (1.8)
Lower respiratory tract infection	190 (1.4)	139 (1.5)	181 (1.5)	15 (0.9)
Cataract	215 (1.6)	135 (1.4)	172 (1.4)	17 (1.1)
Gout	190 (1.4)	133 (1.4)	172 (1.4)	22 (1.4)
Oedema peripheral	294 (2.2)	132 (1.4)	208 (1.7)	30 (1.9)

Preferred Term	Placebo ≥ 40 mg/dL (N = 13334) n (%)	EvoMab < 25 mg/dL (N = 9518) n (%)	< 40 mg/dL (N = 12039) n (%)	≥ 40 mg/dL (N = 1582) n (%)
Angina unstable	317 (2.4)	131 (1.4)	190 (1.6)	45 (2.8)
Depression	250 (1.9)	127 (1.3)	198 (1.6)	38 (2.4)
Hyperuricaemia	177 (1.3)	125 (1.3)	178 (1.5)	21 (1.3)
Blood creatine phosphokinase increased	149 (1.1)	108 (1.1)	146 (1.2)	13 (0.8)
Contusion	207 (1.6)	108 (1.1)	141 (1.2)	21 (1.3)
Chronic obstructive pulmonary disease	193 (1.4)	105 (1.1)	134 (1.1)	23 (1.5)
Hyperglycaemia	192 (1.4)	100 (1.1)	138 (1.1)	36 (2.3)
Rash	169 (1.3)	100 (1.1)	133 (1.1)	14 (0.9)
Abdominal pain	194 (1.5)	98 (1.0)	132 (1.1)	22 (1.4)
Gastrooesophageal reflux disease	140 (1.0)	97 (1.0)	144 (1.2)	20 (1.3)
Fall	182 (1.4)	95 (1.0)	144 (1.2)	19 (1.2)
Vertigo	174 (1.3)	92 (1.0)	136 (1.1)	17 (1.1)
Benign prostatic hyperplasia	160 (1.2)	92 (1.0)	133 (1.1)	10 (0.6)
Nausea	229 (1.7)	91 (1.0)	144 (1.2)	36 (2.3)

Study 20120153 (GLAGOV)

The incidence, type and severity of treatment emergent adverse events, serious adverse events, adverse events leading to investigational product discontinuation, and fatal adverse events were comparable between the evolocumab and placebo groups.

In Study 20120153, the most common (≥ 5% of evolocumab-treated subjects) treatment emergent adverse events (evolocumab, placebo) were angina pectoris (7.4%, 8.9%), myalgia (7.0%, 5.8%), chest pain (7.0%, 5.4%), hypertension (6.0%, 7.6%), and non-cardiac chest pain (5.8%, 3.7%). Nearly all adverse events of myalgia were considered non serious, CTCAE grade 1 or 2 in severity and rarely led to discontinuation of study therapy. All adverse events of chest pain except 1 were non serious and all were grade 1 or 2 in severity; none of these events were considered related to investigational product by the investigator. Most adverse events of non-cardiac chest pain in both groups were grade 1 or 2 and non serious with no action taken with regard to investigational product; slightly more events of non-cardiac chest pain in the evolocumab group, compared with placebo, were serious and grade 3. One event of non-cardiac chest pain (placebo group) was grade 4 and serious.

In summary, the incidence of **adverse events was generally similar** between evolocumab and placebo (77.4%), with severity of adverse events also found to be similar (serious adverse events 24.8% vs 24.7%). Diabetes mellitus (8.8%, 8.2%), hypertension (8.0%, 8.7%), nasopharyngitis (7.8%, 7.4%), upper respiratory tract infection (5.1%, 4.8%), and back pain (4.9%, 4.7%) were the most commonly reported adverse events with approximately similar frequency (except diabetes) between treatment arm and placebo. In the original submitted dossier nasopharyngitis, upper respiratory tract infection and back pain were also the most frequently reported, although generally with a lower incidence (2.5%-5.9%).

Consistent with the original submitted dossier, **the incidence of adverse events for patients achieving very low levels of LDL-C was not different** from patients with higher LDL-C levels. The overall subject incidence of treatment emergent adverse events was 68.4% and 73.2% in evolocumab-treated subjects who achieved LDL-C values < 25 mg/dL and < 40 mg/dL, respectively, compared with 73.6% and 77.7% in evolocumab-treated subjects and placebo-treated subjects with LDL-C ≥ 40 mg/dL, respectively.

The incidence profile of adverse events in het GLAGOV study was slightly different with angina pectoris (7.4%, 8.9%), myalgia (7.0%, 5.8%), chest pain (7.0%, 5.4%), hypertension (6.0%, 7.6%), and non-cardiac chest pain (5.8%, 3.7%) reported as most commonly reported adverse events, with slightly different incidence for evolocumab versus placebo. These were not reported to be related to study medication.

Other significant events of special interest

Neurocognitive adverse events

Overall, the incidence of potential neurocognitive (evolocumab, placebo) adverse events (217 [1.6%], 202 [1.5%]) in Study 20110118 was balanced between groups. The incidence of the treatment emergent adverse events with the preferred term of amnesia was numerically higher in the evolocumab group compared with placebo (51 [0.4%], 33 [0.2%], respectively), however the incidence of adverse events in the HLT of memory loss (excluding dementia), which includes the events with preferred terms of memory impairment, amnesia, transient global amnesia, amnestic disorder and retrograde amnesia was generally balanced between groups (133 [1%] evolocumab, 118 [0.9%] placebo), as was the incidence of events within the HLGT of mental impairment disorders (176 [1.3%] evolocumab subjects, 175 [1.3%] placebo subjects). Events of amnesia were generally non-serious, grade 1 or 2 in severity, and did not lead to discontinuation of investigational product.

The majority of potential neurocognitive adverse events were non-serious and CTCAE grade 1 or grade 2 (72 [0.5%] evolocumab subjects, 68 [0.5%] placebo subjects) in severity. Grade ≥ 3 adverse events occurred in 16 (0.1%) subjects in the evolocumab group and 18 (0.1%) subjects in the placebo group; grade ≥ 4 adverse events occurred in 1 (<0.1%) subject and 2 (<0.1%) subjects in the evolocumab and placebo groups, respectively. Overall, no pattern related to time to onset or action taken with investigational product was identified. Grade ≥ 4 events were all serious, with 2 events of confusional state (1 evolocumab, 1 placebo) and 1 event of retrograde amnesia (placebo); investigational product was continued in these subjects and the events resolved.

Table S7: Incidence of Potential Neurocognitive Treatment Emergent Adverse Events by High Level Group Term Study 20110118 (Safety Analysis Set - Actual Treatment Group)

High Level Group Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
Number of subjects reporting potential neurocognitive adverse events	202 (1.5)	217 (1.6)
Mental impairment disorders	175 (1.3)	176 (1.3)
Deliria (incl confusion)	22 (0.2)	34 (0.2)
Disturbances in thinking and perception	10 (<0.1)	8 (<0.1)
Cognitive and attention disorders and disturbances	2 (<0.1)	4 (<0.1)
Dementia and amnestic conditions	0 (0.0)	1 (<0.1)

A total of 22 subjects (10 [<0.1%] evolocumab subjects, 12 [<0.1%] placebo subjects) had a potential neurocognitive adverse event that was reported as serious by the investigator. The incidence and types of serious adverse events was balanced between treatment groups. A total of 29 subjects (20 [0.1%] evolocumab subjects, 9 [< 0.1%] placebo subjects) had a neurocognitive adverse event leading to

discontinuation of investigational product. The majority of events leading to discontinuation were non serious and CTCAE grade 1 or grade 2 in severity in both treatment groups.

In the analysis of potential neurocognitive adverse events by lowest post-baseline LDL-C, all high level group terms had a similar or lower incidence in evolocumab subjects who achieved LDL-C < 25 mg/dL or < 40 mg/dL than in evolocumab or placebo subjects with LDL-C ≥ 40 mg/dL, indicating there was no increased risk for these events with low LDL-C levels in subjects treated with evolocumab.

Table S8: Incidence of Potential Neurocognitive Treatment Emergent Adverse Events by Lowest Postbaseline LDL-C Achieved by High Level Group Term Study 20110118 (Safety Analysis Set - Actual Treatment Group)

	Placebo	EvoMab		
High Level Group Term	⩾ 40 mg/dL (N = 13334) n (%)	< 25 mg/dL (N = 9518) n (%)	< 40 mg/dL (N = 12039) n (%)	⩾ 40 mg/dL (N = 1582) n (%)
Number of subjects reporting potential neurocognitive adverse events	198 (1.5)	132 (1.4)	170 (1.4)	17 (1.1)
Mental impairment disorders	171 (1.3)	113 (1.2)	141 (1.2)	13 (0.8)
Deliria (incl confusion)	22 (0.2)	14 (0.1)	25 (0.2)	2 (0.1)
Disturbances in thinking and perception	9 (<0.1)	4 (<0.1)	4 (<0.1)	1 (<0.1)
Cognitive and attention disorders and disturbances	2 (<0.1)	2 (<0.1)	2 (<0.1)	1 (<0.1)
Dementia and amnestic conditions	0 (0.0)	1 (<0.1)	1 (<0.1)	0 (0.0)

Cognitive evaluation of CANTAB assessment (Cambridge Neuropsychological Test Automated Battery)

Subjects in this sub-study, including a subset of Study 20110118 subjects enrolled in Study 20130385 (EBBINGHAUS), were tested for executive function; working memory, memory and psychomotor speed; and global cognitive function to achieve the primary, secondary and exploratory study objectives. Assessments were performed with the Cambridge Neuropsychological Test Automated Battery (CANTAB®), a language-independent battery of computerized tests that is used to assess neuropsychological function (Sahakian et al, 1988; Sahakian et al, 1993; Morris et al, 1988). The individual tests for this study were chosen because they assess the cognitive domains of psychomotor speed/attention, episodic memory and working memory/executive function and have shown to be sensitive to drug induced impairment or improvement in performance (Jäkälä et al, 1999; Attwood et al, 2007; Rusted and Warburton, 1988; Greig et al, 2005; Harmer et al, 2001; Elliott et al, 1997). The primary hypothesis of Study 2013085 was that, in subjects receiving optimized statin therapy in combination with evolocumab, the mean change from baseline over time in executive function, as assessed by the Spatial Working Memory (SWM) strategy index of executive function would be non-inferior to that of subjects receiving statin therapy in combination with placebo.

Overall baseline demographics and characteristics in Study 20130385 were representative of the Study 20110118 population. The mean (SD) age of subjects in Study 20130385 was 62.7 (8.7) years and 43.9% and 9.4% of subjects were ≥ 65 and ≥ 75 years of age, respectively. A total of 28.2% of subjects were female. The majority (92.4%) of subjects were white and 1.7% were of Hispanic ethnicity.

Cerebrovascular disease (CVD) history was reported in 26.2% of subjects (evolocumab 25.6%, placebo 26.9%) participating in Study 20130385, with 19.9% reporting prior stroke (evolocumab 18.9%, placebo 20.9%). For subjects in Study 20130385, prior strokes within 5 years of enrollment into Study 20110118 were reported in 11.4% of subjects (evolocumab 11.6%, placebo 11.2%). All subjects in Study

20130385, were on a statin at baseline (following the lipid stabilization period) with 70.8% on high- and 29.2% on moderate-intensity statins. Baseline CANTAB assessments were balanced between treatment groups.

Assessment by CANTAB SWM strategy index of executive function showed that evolocumab had no clinically meaningful effect on executive function. The mean (SD) SWMS68 raw score at baseline was 17.8 (3.5) and 17.8 (3.4) in the evolocumab and placebo groups, respectively. Small changes from baseline were observed in both treatment groups during the study; mean raw scores at each visit ranged from 17.5 to 17.7 in the evolocumab group and 17.4 to 17.7 in the placebo group. Table S8 summarizes the results of the primary and secondary endpoints, in both Z and raw scores, where higher Z scores or lower raw scores indicated better performance. Z score represents the standardized measure of how far an individual subject deviates from the study cohort average at baseline.

Analysis of the primary endpoint demonstrated that evolocumab was non-inferior to placebo for change from baseline over time executive function, as assessed by CANTAB SWM strategy index of executive function. The treatment difference (95% CI) was 0.0072 (-0.0664, 0.0808). Because the upper bound of the 95% CI was less than 0.1889 (the non-inferiority margin; 20% of the observed common standard deviation) the criteria for non-inferiority were met. Least squares mean (95% CI) values for the change from baseline in SWMS68 Z scores were 0.1134 (0.0449, 0.1820) and 0.1206 (0.0535, 0.1877) for the evolocumab and placebo group, respectively, where higher values indicated better performance. The mean change from baseline in SWMS68 scores was similar over time between the evolocumab and the placebo group.

No clinically meaningful effect of evolocumab on other cognitive domains (working memory, memory function, and psychomotor speed; all secondary endpoints) was observed. Small changes from baseline were observed in both treatment groups during the study for the secondary endpoints, change from baseline over time in SWMBE48 and in PALTEA, and these changes were similar over time in the placebo- and evolocumab-treated groups for these cognitive domains (working memory, and memory function).

The change from baseline over time in Reaction Time Index Median Five-Choice Reaction Time (RTIMDFRT) was slightly higher for the evolocumab group compared with the placebo group; this difference is not considered clinically relevant. The mean (SD) RTIMDFRT raw score at baseline was 356.74 (65.01) and 355.10 (77.60) msec in the evolocumab and placebo groups, respectively. Small changes from baseline were observed in both treatment groups during the study; mean raw scores at each visit ranged from 357.48 to 363.30 msec in the evolocumab group and 353.61 to 357.94 msec in the placebo group. Least squares mean change from baseline (95% CI) in RTIMDFRT raw scores were 4.12 (-0.86, 9.10) msec and -1.09 (-5.98, 3.79) msec for the evolocumab and placebo group, respectively, where lower values indicated better performance. Confidence intervals for the change overlapped indicating no statistical difference. The analysis of change from baseline in RTIMDFRT Z scores was similar to the raw score analysis.

Table S9: Summary of Results of Primary and Secondary Endpoints Study 20130385 (Cognitive Function Primary Analysis Set)

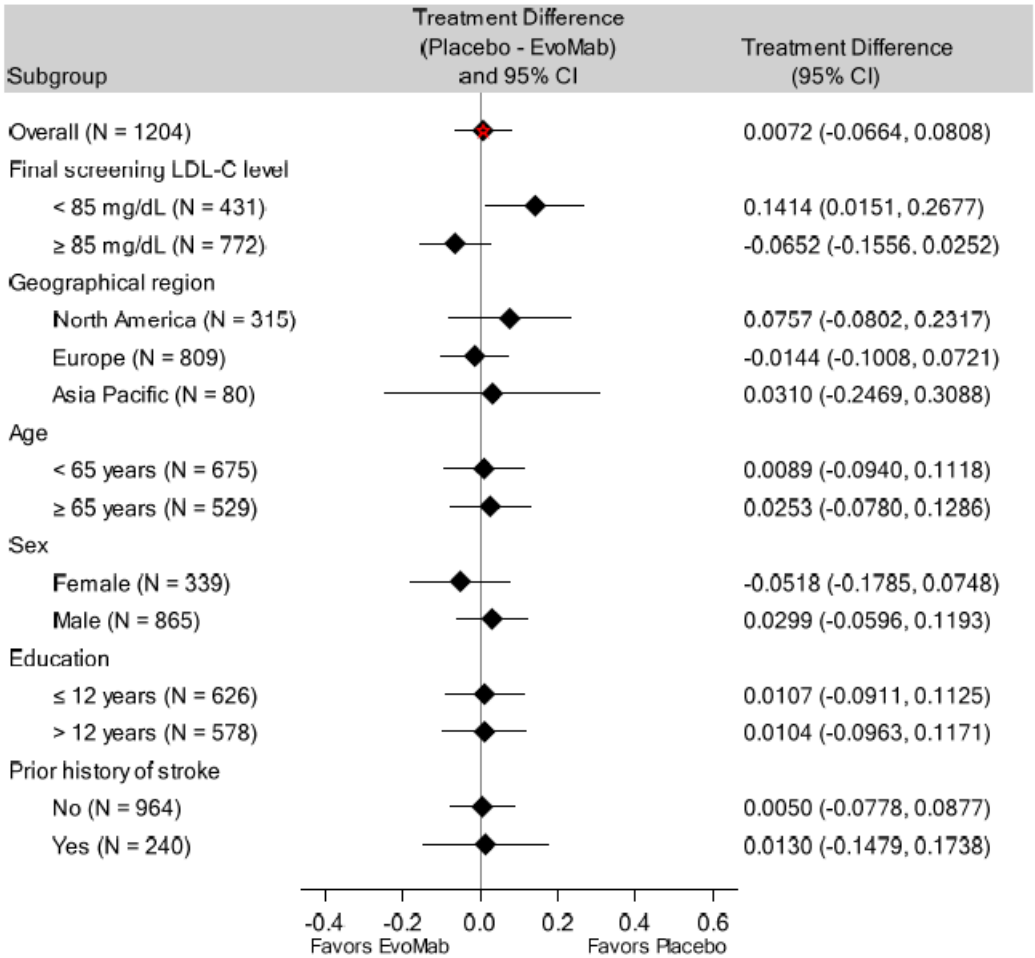
Change from baseline in CANTAB assessment over the observation period	Least squares mean estimate (95% CI) Placebo (N = 618)[a]	Least squares mean estimate (95% CI) Evolocumab (N = 586)[a]	Treatment difference estimate (95% CI) (Placebo - EvoMab)[a]	Non-Inferiority Margin[b]

Change from baseline in CANTAB assessment over the observation period	Least squares mean estimate (95% CI) Placebo (N = 618)[a]	Least squares mean estimate (95% CI) Evolocumab (N = 586)[a]	Treatment difference estimate (95% CI) (Placebo - EvoMab)[a]	Non-Inferiority Margin[b]
Z Scores				
Spatial Working Memory Strategy Index (6-8 Boxes) (SWMS68)	0.1206 (0.0535, 0.1877)	0.1134 (0.0449, 0.1820)	0.0072 (-0.0664, 0.0808)	0.1889[c]
Spatial Working Memory Between-Errors Score (4-8 Boxes) (SWMBE48)	0.1024 (0.0373, 0.1675)	0.0691 (0.0026, 0.1355)	0.0333 (-0.0378, 0.1045)	N/A
Paired Associates Learning Total Errors Adjusted (PALTEA)	0.1098 (0.0511, 0.1686)	0.0873 (0.0273, 0.1472)	0.0226 (-0.0422, 0.0873)	N/A
Reaction Time Index Median Five-Choice Reaction Time (RTIMDFRT)	0.0153 (-0.0529, 0.0834)	-0.0575 (-0.1270, 0.0121)	0.0727 (-0.0022, 0.1477)	N/A
Raw Scores				
Spatial Working Memory Strategy Index (6-8 Boxes) (SWMS68)	-0.41 (-0.64, -0.18)	-0.39 (-0.62, -0.15)	-0.02 (-0.28, 0.23)	-0.65[c]
Spatial Working Memory Between-Errors Score (4-8 Boxes) (SWMBE48)	-1.08 (-1.76, -0.39)	-0.73 (-1.43, -0.03)	-0.35 (-1.10, 0.40)	N/A
Paired Associates Learning Total Errors Adjusted (PALTEA)	-2.06 (-3.16, -0.96)	-1.64 (-2.76, -0.51)	-0.42 (-1.64, 0.79)	N/A
Reaction Time Index Median Five-Choice Reaction Time (RTIMDFRT) (milliseconds)	-1.09 (-5.98, 3.79)	4.12 (-0.86, 9.10)	-5.21 (-10.58, 0.16)	N/A

- EvoMab = Evolocumab (AMG 145); IVRS = Interactive Voice Response System; SWM = spatial working memory; CANTAB = Cambridge Neuropsychological Test Automated Battery; N = number of subjects in the cognitive function primary analysis set;
- [a] Based on the repeated measures mixed-effect linear model which includes stratification factors (from IVRS), age, education level, baseline SWM strategy index of executive function (Z or raw score), treatment group, scheduled visit and the interaction of treatment with scheduled visit as covariates. A higher Z score or a lower raw score reflects better performance.
- [b] The non-inferiority margin is 20% of the observed standard deviation which is estimated from observations in the placebo group by a repeated measures mixed-effect linear model including scheduled visit as a covariate.
- [c] For Z scores refer to the upper bound of the 95% CI, and for raw scores refer to the lower bound of the confidence interval for the non-inferiority criteria.

An analysis of the treatment differences in change from baseline in SWMS68 Z score and raw score was conducted for subgroups. For all subgroups, 95% CIs overlapped with the 95% CI for the treatment difference in the overall population, indicating consistency of results across subgroups.

Figure S1: Forest Plot of Change from Baseline in CANTAB Spatial Working Memory (SWM) Strategy of Index of Executive Function in Z Score – Subgroup Analysis Study 20130385 (Cognitive Function Primary Analysis Set)



Based on a numerical difference in the pre-specified < 85 mg/dL and ≥ 85 mg/dL subgroups, an additional ad-hoc subgroup analysis by baseline LDL-C in quartiles was conducted to further investigate whether there was any relationship between baseline LDL-C levels and the primary endpoint (figure S2). This analysis showed that there was no directional relationship between baseline LDL-C and the primary endpoint, either for the between-group treatment difference, or the scores in the individual placebo and evolocumab treatment arms considered separately. No pattern was observed in corresponding analyses of the other three cognitive domains. In addition, observed results in subjects with on-treatment LDL-C values lower than 25 mg/dL were comparable to the overall population observed.

Figure S2: Forest Plot of Change From Baseline in CANTAB Spatial Working Memory (SWM) Strategy Index of Executive Function in Raw Score - Subgroup Analysis by Final Screening LDL-C Quartiles Study 20130385 (Cognitive Function Primary Analysis Set)

- N = number of subjects in the cognitive function primary analysis set; EvoMab = Evolocumab (AMG 145); Subgroup is data-derived; IVRS = Interactive Voice Response System; SWM = spatial working memory; CANTAB = Cambridge Neuropsychological Test Automated Battery; LDL-C = low density lipoprotein cholesterol.
- A lower raw score reflects better performance.
- If a subject experienced a stroke during the study, the cognitive function assessments post the stroke are excluded from the analysis.
- Least square mean and treatment difference are estimated from the repeated measures mixed-effect linear model within each subgroup which includes stratification factors (from IVRS), age, education level, baseline SWM strategy index of executive function (raw score), treatment group, scheduled visit and the interaction of treatment with scheduled visit as covariates. When one of the stratification factors is the subgroup of interest, only the model will use the data-derived subgroup of interest and the other randomization stratification factor from IVRS.

SWMS68 for subjects with any post-baseline LDL-C value < 25 mg/dL and < 40 mg/dL compared with subjects with no post-baseline LDL-C values < 25 mg/dL and < 40 mg/dL were evaluated over time in the CFFAS group; the results in Z score are presented in table S9. SWM68 scores over time were comparable across various post-baseline LDL-C groups, in both the evolocumab and the placebo group. Results in raw score showed similar trends.

Table S10: Summary of CANTAB Spatial Working Memory (SWM) Strategy of Index of Executive Function in Z Score by Scheduled Visit Lowest Post-baseline LDL-C Achieved Study 20130385 (Cognitive Function Full Analysis Set)

	Placebo	EvoMab		
	⩾ 40 mg/dL (N = 969)	< 25 mg/dL (N = 661)	< 40 mg/dL (N = 865)	⩾ 40 mg/dL (N = 115)

	Placebo	EvoMab		
	⩾ 40 mg/dL (N = 969)	< 25 mg/dL (N = 661)	< 40 mg/dL (N = 865)	⩾ 40 mg/dL (N = 115)
Baseline				
n	967	133	222	115
Mean	-0.0287	-0.0593	0.0369	0.0540
SE	0.0316	0.0820	0.0696	0.0932
Median	-0.0549	-0.0549	-0.0549	-0.0549
Q1, Q3	-0.6375, 0.5276	-0.6375, 0.2363	-0.6375, 0.5276	-0.6375, 0.5276
Week 24				
n	893	449	703	101
Mean	0.0442	0.0365	0.0275	0.0345
SE	0.0330	0.0464	0.0376	0.0996
Median	-0.0549	-0.0549	-0.0549	-0.0549
Q1, Q3	-0.6375, 0.5276	-0.6375, 0.5276	-0.6375, 0.5276	-0.6375, 0.5276
Week 48				
n	894	525	767	99
Mean	0.0431	0.0965	0.1091	0.1304
SE	0.0332	0.0461	0.0385	0.1029
Median	-0.0549	-0.0549	-0.0549	0.2363
Q1, Q3	-0.6375, 0.5276	-0.6375, 0.5276	-0.6375, 0.5276	-0.6375, 0.8189
Week 96				
n	864	580	771	92
Mean	0.1008	0.1118	0.1139	0.1065
SD	1.0239	1.0304	1.0378	1.0598
SE	0.0348	0.0428	0.0374	0.1105
Median	-0.0549	-0.0549	-0.0549	-0.0549
Q1, Q3	-0.6375, 0.5276	-0.6375, 0.5276	-0.6375, 0.5276	-0.6375, 0.6732
Min, Max	-1.803, 4.023	-1.803, 2.567	-1.803, 4.023	-2.094, 2.567

- CANTAB = Cambridge Neuropsychological Test Automated Battery; N = number of subjects enrolled with lowest post-baseline LDL-C < 25, < 40, ≥ 25, or ≥ 40 mg/dL achieved on and before 30 days after the last dose of investigational product date; EvoMab = Evolocumab (AMG 145); LDL-C = low density lipoprotein cholesterol Data include CANTAB measurements after the first postbaseline low LDL-C achieved or all CANTAB measurements if no low LDL-C. Baseline measurements used in calculating change from baseline may be before the first postbaseline low LDL-C achieved. A higher Z score reflects better performance

Potential Demyelination Events and Peripheral Neuropathy Events

Overall, the incidence of potential demyelination (evolocumab, placebo) adverse events (102 [0.7%], 143 [1.0%]) in Study 20110118 was low in both groups and occurred in a higher proportion of placebo subjects than evolocumab subjects.

The incidence of potential demyelination adverse events by high level term was also low and generally similar between groups; events (evolocumab, placebo) under the high level terms of peripheral neuropathies not elsewhere classifiable (NEC; 53 [0.4%], 71 [0.5%]) and sensory abnormalities NEC (34 [0.2%], 57 [0.4%]) were the most commonly reported and, in each case, occurred in a higher proportion of placebo subjects than evolocumab subjects.

The majority of adverse events were CTCAE grade 1 or grade 2 in severity. Grade 3 adverse events occurred in 15 (0.1%) subjects in the evolocumab group and 23 (0.2%) subjects in the placebo group. Grade 4 events occurred in no subjects in the evolocumab group and in 1 (< 0.1%) subject in the placebo group. There were no fatal events. Overall, 4 (< 0.1%) subjects in the evolocumab group and 2 (< 0.1%) subjects in the placebo group discontinued investigational product due to potential demyelination events.

The incidence of serious potential demyelination adverse events was low in both groups and occurred in a higher proportion of placebo (16 [0.1%]) subjects than evolocumab (11 [< 0.1%]) subjects. There

were 4 serious events of Guillain-Barré syndrome (1 evolocumab, 3 placebo) and 1 serious event of acute demyelinating polyneuropathy (1 evolocumab); in 2 of the 5 cases (1 evolocumab, 1 placebo) risk factors were reported.

There were 6 events of multiple sclerosis acute and progressive (4 evolocumab, 2 placebo). Of these, 4 subjects had a history of multiple sclerosis, and in 2 subjects (1 evolocumab, 1 placebo), multiple sclerosis was a new diagnosis. All events were non serious, considered unrelated to investigational product, and none led to discontinuation of investigational product.

In the analysis of potential demyelination events and peripheral neuropathy events by post-baseline LDL-C, no increased risk of these events in subjects with low LDL-C levels was observed. The incidence of all events was similar or lower in evolocumab-treated subjects with LDL-C < 25 mg/dL (0.6%) or < 40 mg/dL (0.7%) than in evolocumab or placebo (0.7% and 1.1%, respectively) subjects with LDL-C ≥ 40 mg/dL.

Table S11: Treatment Emergent Adverse Events Occurring in > 1 Subject by High Level Term Using Demyelination Events (Broad SMQ) and Peripheral Neuropathy SMQ (Narrow) Study 20110118 (Safety Analysis Set - Actual Treatment Group)

High Level Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
All treatment emergent adverse events	143 (1.0)	102 (0.7)
Peripheral neuropathies NEC	71 (0.5)	53 (0.4)
Sensory abnormalities NEC	57 (0.4)	34 (0.2)
Trigeminal disorders	7 (<0.1)	6 (<0.1)
Multiple sclerosis acute and progressive	2 (<0.1)	4 (<0.1)
Plasma cell neoplasms NEC	0 (0.0)	3 (<0.1)
Acute polyneuropathies	3 (<0.1)	1 (<0.1)
Spinal cord and nerve root disorders NEC	2 (<0.1)	1 (<0.1)
Chronic polyneuropathies	1 (<0.1)	1 (<0.1)
Optic nerve disorders NEC	1 (<0.1)	1 (<0.1)

Table S12: Incidence of Potential Demyelination Events and Peripheral Neuropathy Treatment Emergent Adverse Events by Lowest Postbaseline LDL-C Achieved by High Level Group Term ≥ 2 Subjects any Treatment Group Study 20110118 (Safety Analysis Set - Actual Treatment Group)

	Placebo	EvoMab		
High Level Term	⩾ 40 mg/dL (N = 13334) n (%)	< 25 mg/dL (N = 9518) n (%)	< 40 mg/dL (N = 12039) n (%)	⩾ 40 mg/dL (N = 1582) n (%)
Number of subjects reporting adverse events	142 (1.1)	56 (0.6)	83 (0.7)	11 (0.7)
Peripheral neuropathies	70 (0.5)	28 (0.3)	42 (0.3)	6 (0.4)
Sensory abnormalities NEC	57 (0.4)	18 (0.2)	27 (0.2)	4 (0.3)
Trigeminal disorders	7 (<0.1)	5 (<0.1)	5 (<0.1)	1 (<0.1)
Multiple sclerosis acute and progressive	2 (<0.1)	2 (<0.1)	4 (<0.1)	0 (0.0)
Plasma cell neoplasms	0 (0.0)	2 (<0.1)	3 (<0.1)	0 (0.0)
Acute polyneuropathies	3 (<0.1)	1 (<0.1)	1 (<0.1)	0 (0.0)

	Placebo	EvoMab		
High Level Term	⩾ 40 mg/dL (N = 13334) n (%)	< 25 mg/dL (N = 9518) n (%)	< 40 mg/dL (N = 12039) n (%)	⩾ 40 mg/dL (N = 1582) n (%)
Spinal cord and nerve root disorders	2 (<0.1)	1 (<0.1)	1 (<0.1)	0 (0.0)

Injection site reactions

Injection site reactions including pain, erythema, and bruising are adverse drug reactions with evolocumab. There were no new safety findings related to injection site reactions in Study 20110118. Analysis of potential injection site reactions showed a higher overall incidence of these events in the evolocumab group than in the placebo group using both narrow (1.9% evolocumab, 1.5% placebo) and broad (2.0% evolocumab, 1.5%, placebo) search strategies. The incidences of individual injection site reaction adverse event preferred term was generally similar between the evolocumab and placebo groups and there was no difference greater than 0.1% between groups. Adverse events within the narrow search strategy for potential injection site reactions that occurred in > 0.1% of subjects in either treatment group are summarized in table S12.

The majority of injection site reaction events were CTCAE grade 1 for both evolocumab and placebo (238 [89.1%] evolocumab subjects, 189 [91.3%] placebo subjects); the most common grade 1 events were injection site pain and injection site bruising. CTCAE grade 2 events were the majority of the remaining events (27 [10.1%] evolocumab subjects, 17 [8.2%] placebo subjects) and the most common grade 2 event was injection site pain. Grade ≥ 3 adverse events occurred in 2 (< 0.1%) subjects receiving evolocumab (injection site erythema and injection site reaction) and in 1 (< 0.1%) subject receiving placebo (injection site pain); all 3 events were nonserious and investigational product was discontinued. There were no grade ≥ 4 events and no serious events (table S13). Injection site reaction events led to discontinuation of investigational product in 14 (0.1%) evolocumab subjects and 9 (< 0.1%) placebo subjects; the most common event leading to discontinuation was injection site pain.

There were 2 subjects with positive anti-drug antibody (ADA) tests who reported an injection site reaction during the study. The first subject had a positive ADA recorded at baseline; 5 months later the subject reported grade 1 injection related reaction and 2 weeks after that tested negative for ADA. The second subject had negative ADA at baseline and had an injection site reaction reported twice (grade 1 injection site bruising followed by grade 2 injection site reaction 3 months later) while on study; positive ADA were recorded 2 months after the last injection site reaction. Evolocumab was continued in both subjects and neither subject reported a subsequent injection site reaction during the remainder of the study.

Table S13: Treatment Emergent Adverse Events That Occurred in > 0.1% of Subjects in Any Treatment Group by Preferred Term Using Narrow Search Strategy for Potential Injection Site Reaction Events Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Preferred Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
All treatment emergent adverse events	207 (1.5)	267 (1.9)
Injection site pain	56 (0.4)	66 (0.5)
Injection site bruising	48 (0.3)	48 (0.3)
Injection site haematoma	28 (0.2)	36 (0.3)
Injection site erythema	17 (0.1)	26 (0.2)
Injection site haemorrhage	19 (0.1)	21 (0.2)

Table S14: Summary of Subject Incidence of Treatment Emergent Adverse Events Using Narrow Search Strategy for Potential Injection Site Reaction Events Study 20110118 (Safety Analysis Set - Actual Treatment Group)

	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
All treatment emergent adverse events	207 (1.5)	267 (1.9)
Grade ≥ 2	18 (0.1)	29 (0.2)
Grade ≥ 3	1 (<0.1)	2 (<0.1)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	9 (<0.1)	14 (0.1)
Serious	0 (0.0)	0 (0.0)
Device related adverse events	132 (1.0)	156 (1.1)
Grade ≥ 2	9 (<0.1)	16 (0.1)
Grade ≥ 3	1 (<0.1)	1 (<0.1)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious	0 (0.0)	0 (0.0)

Study 20120153 (GLAGOV)

In Study 20120153, evaluation using an Amgen MedDRA query for injection site reaction terms showed that subjects in the evolocumab group had a slightly higher incidence of injections site reaction events compared with the placebo group. Using narrow search strategies, 14 (2.9%) subjects in the evolocumab group and 9 (1.9%) subjects in the placebo group had an injection site reaction event. Using broad search strategies, 18 (3.7%) subjects in the evolocumab group and 12 (2.5%) subjects in the placebo group had an injection site reaction event.

Muscle adverse events

In Study 20110118, no imbalance was noted in the musculoskeletal and connective tissue disorder SOC (3350 [24.3%] evolocumab, 3354 [24.4%] placebo). No musculoskeletal and connective tissue disorder events occurred in > 5% of subjects. The most common (≥ 3% of subjects) events were back pain (673 [4.9%] evolocumab and 651 [4.7%] placebo), arthralgia (605 [4.4%] evolocumab and 589 [4.3%]

placebo), myalgia (555 [4.0%] evolocumab and 527 [3.8%] placebo) and pain in extremity (428 [3.1%] evolocumab and 451 [3.3%] placebo).

In addition, potential muscle events were evaluated using both the narrow (< 0.1% evolocumab, 0.1% placebo) and broad (10.0% evolocumab, 9.8% placebo) rhabdomyolysis/myopathy SMQ search strategies. No adverse events within the narrow search strategy for potential muscle events occurred in > 0.1% of subjects in either treatment group. Within the broad search strategy, adverse event incidence by high level term was balanced across treatment groups.

Within the narrow search strategy, the type and severity of adverse events was balanced between treatment groups. CTCAE grade 1 or grade 2 adverse events were reported in 6 (< 0.1%) evolocumab subjects and 8 (< 0.1%) placebo subjects. Events that were ≥ grade 3 were reported in 7 (< 0.1%) subjects in each treatment group and grade 4 events (all rhabdomyolysis) were reported in 2 (< 0.1%) subjects in each treatment group. Serious adverse events were reported in 6 (< 0.1%) evolocumab subjects and 7 (< 0.1) placebo subjects. There were no fatal adverse events. Events within the narrow search strategy leading to discontinuation of investigational product were also balanced between groups (3 [< 0.1%] evolocumab, 3 [< 0.1%] placebo).

Of the 13 serious events, 11 were rhabdomyolysis (5 evolocumab, 6 placebo) and 2 were myopathy (both evolocumab). There was no pattern in the time to onset of the rhabdomyolysis events and all events resolved. All except 1 of the serious rhabdomyolysis events were considered unrelated to investigational product and were attributed to other agents (eg, statin, fibrate, chemotherapy) or were complications of other events (fall, CVA). The related event (evolocumab group) was also considered related to statin and occurred in a subject who had started weight lifting 2 weeks prior to the event onset. The 2 myopathy events were attributed to other agents (statin, chemotherapy, steroids) and were considered unrelated to evolocumab.

There were also no imbalances between groups in potential muscle events using the broad search strategy based on achieved post-baseline LDL-C levels; the incidence of all events was similar or lower for subjects in the evolocumab LDL-C < 25 mg/dL (7.4%) or < 40 mg/dL (8.6%) groups than for subjects in the evolocumab or placebo groups with LDL-C ≥ 40 mg/dL (10.1% and 9.9%, respectively. There were too few events using the narrow search strategy to evaluate potential muscle events based on achieved post-baseline LDL-C levels.

Table S15: Treatment Emergent Adverse Events Using Narrow Search Strategy for Potential Muscle Events Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Preferred Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
All treatment emergent adverse events	15 (0.1)	13 (<0.1)
Rhabdomyolysis	11 (<0.1)	8 (<0.1)
Myopathy	3 (<0.1)	4 (<0.1)
Myoglobin blood increased	1 (<0.1)	1 (<0.1)

Study 20120153 (GLAGOV)

In Study 20120153, muscle adverse events were similar between the evolocumab and placebo treatment groups. Using narrow search strategies, no subject had a muscle adverse event. Using broad search

strategies, 66 (13.6%) subjects in the evolocumab group and 61 (12.6%) subjects in the placebo group had a muscle adverse event.

Myalgia was 1 of the most frequently reported adverse events in both treatment groups and was reported in 7.0% subjects in the evolocumab group and 5.8% subjects in the placebo group. Events of myalgia were generally nonserious, grade 1 or 2 in severity and rarely led to discontinuation of study therapy. Six subjects (3 evolocumab, 3 placebo) reported grade 3 myalgia. In 2 evolocumab subjects the events were serious; 1 serious myalgia event occurred in the setting of hypoparathyroidism and hypocalcemia and the other serious myalgia event occurred in a subject with history of chronic joint pain and statin-induced myalgia.

Hepatic adverse events

In Study 20110118, the incidence of adverse events in the hepatobiliary disorder SOC was similar between treatment groups (296 [2.1%] evolocumab, 256 [1.9%] placebo). No hepatobiliary disorder SOC events occurred in ≥ 1% of subjects. Cholelithiasis was the single event that occurred in ≥ 0.5% subjects (77 [0.6%] evolocumab and 72 [0.5%] placebo).

In addition, transaminase elevations and potential hepatic disorder events were evaluated using the drug related hepatic disorders - comprehensive search SMQ. In both the narrow SMQ (evolocumab 3.0% and placebo 2.7%) and broad SMQ (evolocumab 3.1% and placebo 2.8%) adverse events were similar between treatment groups. Adverse event incidence by high level term was balanced across treatment groups.

The majority of events within the narrow SMQ were nonserious and CTCAE grade 1 or grade 2 in severity. Events that were grade ≥ 3 were reported in 81 (0.6%) subjects in the evolocumab group and 77 (0.6%) subjects in the placebo group. Grade 4 events were reported in 16 subjects (13 [<0.1%] evolocumab, 3 [<0.1%] placebo). The majority of CTCAE grade 3 and 4 events were reports of liver function test abnormalities.

Overall, serious adverse events from the narrow SMQ were reported in 130 subjects (72 [0.5%] evolocumab, 58 [0.4%] placebo). Six subjects reported serious grade 4 events of hepatic failures (3 evolocumab, 1 placebo), hepatorenal syndrome (1 evolocumab), and hepatic cirrhosis (1 evolocumab). Alternative etiologies (heart failure, chronic alcoholism, bacterial peritonitis, acute pancreatitis) were provided for the 4 hepatic failure events, the hepatorenal syndrome occurred immediately following surgery for colon cancer, and the hepatic cirrhosis event was reported as decompensated postviral (hepatitis C) liver cirrhosis in a subject previously diagnosed with non-Hodgkin's lymphoma. None of these events was considered related to investigational product. There were 8 serious adverse events (6 evolocumab and 2 placebo) with a fatal outcome, all of which had alternative etiologies; 4 were grade 4 events and were described above: hepatic failure (2 evolocumab), hepatic cirrhosis (1 evolocumab), and hepatorenal syndrome (1 evolocumab). The other fatal events occurring in evolocumab subjects were grade 3 hepatic failure in the setting of renal failure and urosepsis (1 subject) and grade 2 suspected drug-induced liver injury (DILI) with an alternative etiology of chronic alcoholism and heart failure (1 subject). Two fatal hepatocellular carcinoma events occurred in placebo subjects.

In total, there were 6 reports of suspected DILI (4 [< 0.1%] evolocumab, 2 [< 0.1%] placebo) per investigators. None of these evolocumab subjects had AST or ALT > 5 x ULN or total bilirubin > 2 x ULN at any study laboratory assessment. Three of these events were nonserious (1 evolocumab, 2 placebo). The evolocumab subject had suspected DILI reported 6 days after the first dose of evolocumab which occurred coincident with an event of benign prostatic hypertrophy and urine retention requiring urinary catheter placement. Investigational product and statin were withheld per protocol and liver function tests

normalized, however per subject decision investigational product and statin were not restarted. The 2 suspected DILI events in the placebo group occurred in the setting of acute gangrenous perforated appendix and alcohol poisoning. The remaining 3 suspected DILI events occurred in evolocumab subjects and were considered serious. One fatal event noted alcohol use and ischemic liver due to heart failure as possible contributing factors; and 1 event occurred in the setting of rhabdomyolysis and the events were attributed to a drug interaction between atorvastatin and amiodarone and considered unrelated to evolocumab; evolocumab and statin were discontinued and the events resolved. The third event occurred in a subject who reported being hospitalized with fever and nausea and diagnosed with drug-induced hepatitis/ suspected DILI; liver enzymes from study center visits were normal and no laboratory data or other medical records were made available to the investigator to support the diagnosis. Evolocumab and statin were withdrawn per protocol.

In the analysis of transaminase elevations and potential hepatic disorders by post-baseline LDL-C levels, there was no increase in the incidence of adverse events in evolocumab subjects who achieved LDL-C < 25 mg/dL or < 40 mg/dL than in evolocumab or placebo subjects with LDL-C ≥ 40 mg/dL.

Table S16: Transaminase Elevations and Potential Hepatic Disorders Adverse Events by High Level Term Occurring in ≥ 0.1% Subjects Using Narrow Search Strategy for Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Category High Level Term	Placebo (N = 13756) Subjects with at least 1 event n (%)	EvoMab (N = 13769) Subjects with at least 1 event n (%)
All treatment emergent adverse events for Transaminase Elevations and Potential Hepatic Disorders Narrow SMQ	370 (2.7)	407 (3.0)
Liver function analyses	242 (1.8)	265 (1.9)
Hepatocellular damage and hepatitis NEC	68 (0.5)	74 (0.5)
Hepatic and hepatobiliary disorders NEC	15 (0.1)	19 (0.1)
Coagulation and bleeding analyses	14 (0.1)	16 (0.1)

Study 20120153 (GLAGOV)

In Study 20120153, evaluation using SMQs for hepatic terms showed that hepatic adverse events were similar between the evolocumab and placebo treatment groups. Using narrow search strategies, 12 (2.5%) subjects in the evolocumab group and 10 (2.1%) subjects in the placebo group had a hepatic adverse event. Using broad search strategies, 13 (2.7%) subjects in the evolocumab group and 11 (2.3%) subjects in the placebo group had a hepatic adverse event.

Diabetes

In Study 20110118, potential events of new onset of diabetes mellitus (NODM) in subjects not known to have pre-existing diabetes mellitus at baseline were adjudicated by the CEC and were identified using potential hyperglycemic events of elevated FBG, elevated HbA1c, new adverse event related to hyperglycemia, or initiation of a new medication for hyperglycemia.

Baseline and demographic characteristics of subjects with NODM were generally similar to those without NODM; as expected, mean (SD) FBG levels in subjects with positively adjudicated NODM (103.8 [12.3]

mg/dL evolocumab; 104.5 [15.1] mg/dL placebo) were higher at baseline than subjects without NODM (96.7 [10.7] mg/dL evolocumab; 96.7 [11.1] mg/dL placebo) across both treatment groups.

The overall incidence of NODM was comparable in the evolocumab and placebo groups, 8.1% and 7.7%, respectively. As expected, review of subgroup analyses of NODM among subjects with baseline normoglycemia [FBG < 100 mg/dL], impaired fasting glucose [FBG 100 to < 126 mg/dL], or metabolic syndrome showed that incidence rates (evolocumab, placebo) of NODM in both treatment groups were lower for subjects with normoglycemia at baseline (4.8%, 4.4%) than for subjects with either metabolic syndrome (11.6%, 11.3%) or impaired fasting glucose (13.3%, 12.8%) at baseline.

The incidence of NODM was not increased in subjects with low post-baseline LDL-C. The incidence of NODM for evolocumab subjects who achieved lowest post-baseline LDL-C levels of < 25 mg/dL (4.8%) or < 40 mg/dL (4.6%) were lower than either evolocumab subjects (8.2%) or placebo (7.6%) subjects with LDL-C ≥ 40 mg/dL (table S16).

No safety concern was identified from the evaluation of FBG and HbA1c in the studies included in this submission.

Table S17: Summary of Subject Incidence of Adjudicated Positive Postbaseline New Onset Diabetes Lowest Postbaseline LDL-C Achieved Study 20110118 (Safety Analysis Set - Actual Treatment Group)

	Placebo	EvoMab		
	≥ 40 mg/dL (N = 13334) n (%)	< 25 mg/dL (N = 9518) n (%)	< 40 mg/dL (N = 12039) n (%)	≥ 40 mg/dL (N = 1582) n (%)
Subjects without type I or II diabetes at baseline[a] - N[o]	8113	5719	7332	914
New onset diabetes	619 (7.6)	276 (4.8)	334 (4.6)	75 (8.2)

In the assessment of events of special interest in the current dossier, specific attention has been given to **neurocognitive abnormalities**, as very low levels of LDL-C have been associated with increased risk of neurocognitive abnormalities, although this was not observed in the initial submitted dossier. The incidence of **neurocognitieve adverse events was generally similar** between treatment arms (1.6% vs 1.5 %, evolocumab vs placebo). Amnesia was numerically higher in the evolocumab group compared with placebo (51 [0.4%], 33 [0.2%], however, when reported in the grouped term memory loss (memory impairment, amnesia, transient global amnesia, amnestic disorder and retrograde amnesia), incidence was only slightly higher (133 [1%] evolocumab, 118 [0.9%] placebo). Of particular interest, for patients achieving very low LDL-C levels, the incidence of these adverse events was approximately similar to placebo (1.1% - 1.5%).

Additionally, specific attention has been given to possible neuropsychological effects when treated with evolocumab **by testing a representative subset of the pivotal study through cognitive evaluation of CANTAB assessment (EBBINGHAUS study)**. No difference in effect on the cognitive domain of executive function could be observed, as analysed according to a non-inferiority analysis. Furthermore, no clear difference according to subgroups could be observed. Also, for other cognitive domains (working memory, memory function, and psychomotor speed; all secondary endpoints) no difference was found. Also, **no difference in effect on the cognitive domain of executive function could be observed for subgroups with very low level of LDL-C**. The change from baseline over time in Reaction Time Index Median Five-Choice Reaction Time (RTIMDFRT) was slightly higher for the

evolocumab group compared with the placebo group; this difference was not considered clinically relevant. The primary objective of the EBBINGHAUS study is to exclude a negative effect on cognitive function as compared to standard of care. The CANTAB is an accepted assessment scale for evaluation of cognitive function and is often used in the context of evaluation of potential cognitive effects of medicine use. However, in this case it was questioned whether the study duration of 96 weeks is sufficient to pick up changes considering that cognitive dysfunction due to (possible) amyloid accumulation develops slowly. Moreover the majority of subjects included probably had no or unknown cognitive dysfunction as this was not an in/exclusion criterion. Considering this **no definite conclusions on the potential impact of evolocumab on cognitive function can be drawn** based on the EBBINGHAUS study.

No effect on the incidence of potential demyelination adverse events could be observed as this was slightly higher for placebo than for evolocumab (102 [0.7%], 143 [1.0%]). Also, these events was similar or lower in evolocumab-treated subjects with LDL-C < 25 mg/dL (0.6%) or < 40 mg/dL (0.7%) than in evolocumab or placebo (0.7% and 1.1%, respectively). Serious events were higher for placebo (16 [0.1%]) than evolocumab (11 [< 0.1%]) and not considered related to study drug.

As expected**, injection site reaction occurred at a higher overall incidence in the evolocumab group** than in the placebo group using both narrow (1.9% evolocumab, 1.5% placebo) and broad (2.0% evolocumab, 1.5%, placebo) search strategies and generally non-serious. There were 2 subjects with positive anti-drug antibody (ADA) tests who reported an injection site reaction during the study, without any consequence for treatment continuation. Device related events occurred slightly more for evolocumab (156, 1.1% vs 132, 1.0%) mainly classified as non-serious. The GLAGOV study provided similar findings.

For **musculoskeletal and connective tissue disorders, no difference could be observed** (3350 [24.3%] evolocumab, 3354 [24.4%] placebo). The most common of these events, as also known from the original submitted dossier, were **back pain** (673 [4.9%] evolocumab and 651 [4.7%] placebo), arthralgia (605 [4.4%] evolocumab and 589 [4.3%] placebo), myalgia (555 [4.0%] evolocumab and 527 [3.8%] placebo) and pain in extremity (428 [3.1%] evolocumab and 451 [3.3%] placebo). Overall, there were 19 events of rhabdomyolysis. Of the 13 serious events, 11 were rhabdomyolysis (5 evolocumab, 6 placebo) and 2 were myopathy (both evolocumab). One of the serious rhabdomyolysis events was considered related, but was also considered related to statin and occurred in a subject who had started weight lifting 2 weeks prior to the event onset. The 2 myopathy events were attributed to other agents (statin, chemotherapy, steroids) and were considered unrelated to evolocumab.

Hepatic disorders were slightly more reported for evolocumab than placebo ((296 [2.1%] evolocumab, 256 [1.9%] placebo). Also, slightly more serious hepatic events occurred (72 [0.5%] vs 58 [0.4%]). Six subjects reported serious grade 4 events of hepatic failures (3 evolocumab, 1 placebo), hepatorenal syndrome (1 evolocumab), and hepatic cirrhosis (1 evolocumab), all not considered related to study drug. Eight serious events had a fatal outcome, but could be explained by an alternative etiology. There were 6 reports of suspected DILI (4 [< 0.1%] evolocumab, 2 [< 0.1%] placebo) without any elevation in liver enzymes of AST or ALT > 5 x ULN or total bilirubin > 2 x ULN. Of the 3 serious events in evolocumab, one fatal event noted alcohol use and ischemic liver due to heart failure as possible contributing factors; and 1 event occurred in the setting of rhabdomyolysis and the events were attributed to a drug interaction between atorvastatin and amiodarone and considered unrelated to evolocumab; evolocumab and statin were discontinued and the events resolved. The third event occurred in a subject who reported being hospitalized with fever and nausea and diagnosed with drug-induced hepatitis/ suspected DILI; liver enzymes from study centre visits were normal and no laboratory data or other medical records were made available to the investigator to support the diagnosis. Evolocumab and statin were withdrawn per protocol.

The overall incidence of **new onset of diabetes mellitus (NODM)** was slightly higher for evolocumab 8.1% vs placebo 7.7%. NODM in both treatment groups were lower for subjects with normoglycemia at baseline (4.8%, 4.4%) than for subjects with either metabolic syndrome (11.6%, 11.3%) or impaired fasting glucose (13.3%, 12.8%) at baseline. However NODM was lower in the overall clinical program for evolocumab compared with the control treatment. Considering that DM reporting was lower in the overall program and differences in percentages in reporting in the FOURIER study were < 1% difference it is acceptable not to include diabetes mellitus as AE in section 4.8 of the SmPC.

Serious adverse event / deaths

Serious adverse events that occurred in ≥ 1.0% of subjects by high level term in either treatment group are summarized in table S17 and those occurring in ≥ 0.5% of subjects by preferred term in either treatment group are summarized in table S18. The overall incidence of serious adverse events was similar between the evolocumab (24.8%) and placebo (24.7%) groups. There were no notable differences in the types or incidence of serious adverse events between the evolocumab and placebo groups by SOC and HLT. Serious adverse events (evolocumab, placebo) under the high level terms of ischaemic coronary artery disorder (3.6%, 4.0%); peripheral vasoconstriction, necrosis and vascular insufficiency (1.5%, 1.3%); and lower respiratory tract and lung infections (1.3%, 1.5%) were the most commonly reported. The most common serious adverse events by preferred term occurring in ≥ 1.0% of subjects (evolocumab, placebo) in either treatment group were unstable angina (1.7%, 2.0%), angina pectoris (1.5%, 1.6%), pneumonia (1.1% in each group), atrial fibrillation (0.9%, 1.0%), and non-cardiac chest pain (0.8% 1.0%). Cardiovascular events, e.g, non-cardiac chest pain and unstable angina, may include events initially reported as potential endpoints which were negatively adjudicated by the CEC.

Table S18: Treatment Emergent Serious Adverse Events Occurring in ≥ 1.0% of Subjects in Either Treatment Group by High Level Term Study 20110118 (Safety Analysis Set - Actual Treatment Group)

High Level Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
Number of subjects reporting treatment emergent adverse events	3404 (24.7)	3410 (24.8)
Ischaemic coronary artery disorders	549 (4.0)	502 (3.6)
Peripheral vasoconstriction, necrosis and vascular insufficiency	180 (1.3)	204 (1.5)
Lower respiratory tract and lung infections	207 (1.5)	180 (1.3)
Heart failures NEC	158 (1.1)	174 (1.3)
Supraventricular arrhythmias	180 (1.3)	171 (1.2)
Pain and discomfort NEC	179 (1.3)	152 (1.1)

- EvoMab = Evolocumab (AMG 145); MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects randomized and dosed; NEC = not elsewhere classifiable

Table S19: Treatment Emergent Serious Adverse Events Occurring in ≥ 0.5% of Subjects in Either Treatment Group by Preferred Term Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Preferred Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
Number of subjects reporting treatment emergent adverse events	3404 (24.7)	3410 (24.8)
Angina unstable	278 (2.0)	233 (1.7)
Angina pectoris	221 (1.6)	208 (1.5)
Pneumonia	152 (1.1)	147 (1.1)
Atrial fibrillation	132 (1.0)	119 (0.9)
Non-cardiac chest pain	133 (1.0)	109 (0.8)
Osteoarthritis	100 (0.7)	91 (0.7)
Peripheral arterial occlusive disease	82 (0.6)	94 (0.7)
Cardiac failure	66 (0.5)	66 (0.5)
Syncope	56 (0.4)	63 (0.5)
Acute kidney injury	64 (0.5)	64 (0.5)
Chronic obstructive pulmonary disease	64 (0.5)	64 (0.5)

- EvoMab = Evolocumab (AMG 145); MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects randomized and dosed

Table S20: Treatment Emergent Serious Adverse Events Occurring in > 0.1% of Subjects in LDL-C < 25 mg/dL Group by Preferred Term in Descending Order of Frequency – Lowest Postbaseline LDL-C Achieved Study 20110118 (Safety Analysis Set - Actual Treatment Group)

	Placebo	EvoMab		
Preferred Term	≥ 40 mg/dL (N = 13334) n (%)	< 25 mg/dL (N = 9518) n (%)	< 40 mg/dL (N = 12039) n (%)	≥ 40 mg/dL (N = 1582) n (%)
Number of subjects reporting treatment emergent adverse events	3313 (24.8)	1967 (20.7)	2766 (23.0)	375 (23.7)
Angina pectoris	213 (1.6)	119 (1.3)	169 (1.4)	15 (0.9)
Angina unstable	273 (2.0)	115 (1.2)	171 (1.4)	36 (2.3)
Pneumonia	146 (1.1)	74 (0.8)	110 (0.9)	23 (1.5)
Atrial fibrillation	129 (1.0)	70 (0.7)	99 (0.8)	11 (0.7)
Non-cardiac chest pain	132 (1.0)	56 (0.6)	88 (0.7)	12 (0.8)
Osteoarthritis	97 (0.7)	55 (0.6)	81 (0.7)	4 (0.3)
Peripheral arterial occlusive disease	80 (0.6)	44 (0.5)	73 (0.6)	11 (0.7)
Cardiac failure	63 (0.5)	36 (0.4)	53 (0.4)	10 (0.6)
Acute kidney injury	64 (0.5)	35 (0.4)	47 (0.4)	7 (0.4)
Chronic obstructive pulmonary disease	63 (0.5)	34 (0.4)	50 (0.4)	9 (0.6)
Syncope	54 (0.4)	34 (0.4)	50 (0.4)	5 (0.3)
Diabetes mellitus	55 (0.4)	33 (0.3)	45 (0.4)	9 (0.6)
Cardiac failure chronic	45 (0.3)	31 (0.3)	44 (0.4)	3 (0.2)
Urinary tract infection	37 (0.3)	30 (0.3)	36 (0.3)	4 (0.3)
Musculoskeletal chest pain	36 (0.3)	29 (0.3)	37 (0.3)	4 (0.3)
Chest pain	48 (0.4)	25 (0.3)	38 (0.3)	2 (0.1)
Hypertension	38 (0.3)	25 (0.3)	37 (0.3)	9 (0.6)
Coronary artery disease	46 (0.3)	24 (0.3)	29 (0.2)	1 (<0.1)
Prostate cancer	38 (0.3)	23 (0.2)	35 (0.3)	4 (0.3)
Carotid artery stenosis	38 (0.3)	22 (0.2)	34 (0.3)	1 (<0.1)
Anaemia	25 (0.2)	22 (0.2)	24 (0.2)	1 (<0.1)
Cellulitis	27 (0.2)	21 (0.2)	32 (0.3)	3 (0.2)
Cardiac failure congestive	35 (0.3)	20 (0.2)	33 (0.3)	10 (0.6)
Inguinal hernia	21 (0.2)	20 (0.2)	29 (0.2)	2 (0.1)
Cholecystitis acute	30 (0.2)	19 (0.2)	30 (0.2)	2 (0.1)
Gastrointestinal haemorrhage	16 (0.1)	19 (0.2)	25 (0.2)	0 (0.0)
Transient ischaemic attack	36 (0.3)	18 (0.2)	32 (0.3)	3 (0.2)
Benign prostatic hyperplasia	26 (0.2)	18 (0.2)	26 (0.2)	3 (0.2)
Back pain	28 (0.2)	17 (0.2)	25 (0.2)	5 (0.3)
Ventricular tachycardia	27 (0.2)	17 (0.2)	21 (0.2)	2 (0.1)
Intermittent claudication	22 (0.2)	16 (0.2)	26 (0.2)	4 (0.3)
Myocardial infarction	30 (0.2)	16 (0.2)	24 (0.2)	6 (0.4)
Dyspnoea	18 (0.1)	16 (0.2)	23 (0.2)	2 (0.1)
Peripheral artery stenosis	32 (0.2)	16 (0.2)	21 (0.2)	2 (0.1)
Peripheral ischaemia	38 (0.3)	15 (0.2)	26 (0.2)	7 (0.4)
Atrial flutter	17 (0.1)	15 (0.2)	25 (0.2)	0 (0.0)
Cholelithiasis	22 (0.2)	15 (0.2)	18 (0.1)	3 (0.2)
Femur fracture	6 (<0.1)	15 (0.2)	16 (0.1)	2 (0.1)

In Study 20110118, the overall incidence of adverse events reported in the system organ class of neoplasms benign, malignant and unspecified (incl cysts and polyps) was low and balanced between groups (evolocumab 622 [4.5%], placebo 621 [4.5%]). The overall incidence of potential malignancies,

using the narrow SMQ search for malignant or unspecified tumors, was also balanced between groups (463 [3.4%] evolocumab, 450 [3.3%] placebo)

Study 20120153 (GLAGOV)

In Study 20120153, treatment emergent serious adverse events were reported for 135 (27.9%) subjects in the evolocumab group and 142 (29.3%) subjects in the placebo group. The 3 most commonly reported serious adverse events by preferred term in the evolocumab group (evolocumab, placebo) were angina pectoris (3.5%, 2.3%), non-cardiac chest pain (2.3%, 1.2%) and unstable angina (1.7%, 1.4%). A total of 14 (2.9%) subjects in the evolocumab group and 21 (4.3%) subjects in the placebo group had treatment emergent serious adverse events that were CTCAE grade 4 in severity; 1 grade 4 serious adverse event (stroke [cerebrovascular accident] in a placebo subject) was considered related to investigational product.

In summary, no difference was found in the incidence of serious adverse events between evolocumab and placebo. Most frequently reported serious adverse events were found in ischemic coronary artery disorders and most were unstable angina (1.7%, 2.0%), angina pectoris (1.5%, 1.6%), pneumonia (1.1% in each group), atrial fibrillation (0.9%, 1.0%), and non-cardiac chest pain (0.8% 1.0%), which were not different in frequency between both treatment groups. For patients with very low LDL-C, serious adverse events pattern was not different from placebo. No difference in the incidence of cancer was observed. In the GLAGOV study, the most serious adverse events were also reported in the cardiovascular system. The most frequent serious adverse events were angina pectoris (3.5%, 2.3%), non-cardiac chest pain (2.3%, 1.2%) and unstable angina (1.7%, 1.4%) and slightly reported more for evolocumab.

Deaths

Deaths by any cause were adjudicated by a CEC efficacy endpoints in Study 20110118 and have been reported in the efficacy section.

Study 20120153 (GLAGOV)

In Study 20120153, fatal treatment emergent adverse events occurred in 3 (0.6%) subjects in the evolocumab group and 2 (0.4%) subjects in the placebo group. These included 1 event of sudden death, 1 event of hepatic neoplasm, and 1 event of lung carcinoma cell type unspecified stage 3 in the evolocumab group, and 1 event of lung adenocarcinoma and 1 event of sudden death in the placebo group. In addition, 3 deaths occurred outside of the treatment phase of the study. One subject had a fatal adverse event of myocardial infarction during the lipid stabilization period, before starting investigational product. Two subjects in the placebo group had fatal adverse events (bladder cancer and cardiac arrest) after EOS.

None of the deaths were considered related to investigational product by the investigator

Adverse events leading to discontinuation of study treatment

Overall, the incidence of adverse events leading to discontinuation of investigational product was low and similar between the evolocumab (4.4%) and placebo (4.2%) treatment groups. Adverse events leading to discontinuation in ≥ 0.1% of subjects in either treatment group (evolocumab, placebo) were myalgia (37 [0.3%] subjects; 46 [0.3%] subjects), fatigue (12 [< 0.1%] subjects; 23 [0.2%] subjects), and arthralgia (14 [0.1%] subjects; 13 [< 0.1%] subjects).

The incidence of CTCAE grade 4 adverse events leading to discontinuation of investigational product was similar between treatment groups (0.6% evolocumab subjects, 0.6% placebo subjects); no pattern was observed in the types of grade 4 events that led to discontinuation. The incidence of serious adverse

events leading to discontinuation of investigational product was also similar between groups (1.9% evolocumab, 1.8% placebo).

Table S21: Treatment Emergent Adverse Events Leading to Discontinuation of Investigational Product Occurring in ≥ 10 Subjects Overall by Preferred Term in Descending Order of Frequency Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Preferred Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
Number of subjects reporting treatment emergent adverse events	573 (4.2)	608 (4.4)
Myalgia	46 (0.3)	37 (0.3)
Arthralgia	13 (<0.1)	14 (0.1)
Headache	8 (<0.1)	13 (<0.1)
Hepatic enzyme increased	4 (<0.1)	13 (<0.1)
Asthenia	12 (<0.1)	12 (<0.1)
Fatigue	23 (0.2)	12 (<0.1)
Dizziness	11 (<0.1)	10 (<0.1)
Memory impairment	2 (<0.1)	10 (<0.1)
Pain in extremity	8 (<0.1)	10 (<0.1)
Alanine aminotransferase increased	7 (<0.1)	9 (<0.1)
Rash	10 (<0.1)	9 (<0.1)
Hypersensitivity	4 (<0.1)	8 (<0.1)
Injection site pain	4 (<0.1)	8 (<0.1)
Muscular weakness	4 (<0.1)	7 (<0.1)
Nausea	9 (<0.1)	7 (<0.1)
Pneumonia	8 (<0.1)	7 (<0.1)
Back pain	7 (<0.1)	6 (<0.1)
Diarrhoea	7 (<0.1)	6 (<0.1)
Lung neoplasm malignant	10 (<0.1)	6 (<0.1)
Muscle spasms	10 (<0.1)	6 (<0.1)
Abdominal pain	7 (<0.1)	5 (<0.1)
Myocardial infarction	7 (<0.1)	5 (<0.1)
Acute kidney injury	7 (<0.1)	3 (<0.1)
Pruritus	9 (<0.1)	3 (<0.1)
Osteoarthritis	9 (<0.1)	2 (<0.1)

EvoMab = Evolocumab (AMG 145); MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects randomized and dosed

Study 20120153 (GLAGOV)

In Study 20120153, treatment emergent adverse events leading to discontinuation of investigational product occurred in 3.3% subjects in the evolocumab group and 2.3% subjects in the placebo group; no notable differences in the types of events were observed between treatment groups. The most frequent adverse event leading to discontinuation of investigational product (evolocumab, placebo) was myalgia (0.2%, 0.6%); all other events occurred in ≤ 2 subjects in the study.

Nearly all adverse events leading to discontinuation of investigational product were CTCAE grade 1, 2 or 3. One event of hepatic neoplasm in a subject in the evolocumab group and 1 event of unstable angina

in the placebo group were CTCAE grade 4; neither event was considered related to investigational product by the investigator.

In summary, adverse events leading to discontinuation was a minor part of all discontinuations (12.4%) and approximately similar between evolocumab treatment and placebo (4.4% vs 4.2%, respectively). As can be expected, discontinuation was twice more than during the initially submitted studies, apparently not directly related to initiation of therapy. In the GLAGOV study discontinuation due to adverse events were slightly higher for evolocumab (3.3%) than for placebo (2.3%), mainly due to myalgia (0.2%, 0.6%).

Clinical laboratory evaluations

After review of all available clinical laboratory data, no trends indicative of clinically important treatment related laboratory abnormalities were observed with evolocumab treatment in Study 20110118.

With the exception of serum glucose and serum potassium, the incidence of shifts from baseline grades 0, 1 or 2 to postbaseline grades 3 or 4 in all laboratory values was low and balanced between treatment groups.

There were 179 (1.3%) subjects in the evolocumab group and 130 (1.0%) subjects in the placebo group with increases in potassium from baseline CTCAE grades 0, 1 or 2 to postbaseline grades 3 or 4. The majority of shifts in both treatment groups were from baseline grade 0 to post-baseline grade 3. Potassium values by visit were similar between treatment groups at each time point throughout the study. Median (Q1, Q3) values for potassium at baseline were 4.5 (4.2, 4.7) mmol/L in each treatment group. Median (Q1, Q3) change in potassium from baseline to week 168 was 0.0 (-0.2, 0.3) mmol/L in each treatment group.

Across all subjects, there were 775 (5.6%) subjects in the evolocumab group and 731 (5.3%) subjects in the placebo group with increases in glucose from baseline CTCAE grades 0, 1 or 2 to postbaseline grades 3 or 4; the majority of the difference between groups was attributable to a greater number of subjects in the evolocumab group (417 [3.0%]) than the placebo group (375 [2.7%]) who experienced a 1-grade shift from baseline (from CTCAE grade 2 to 3). Glucose values by visit were similar between treatment groups at each time point. Median (Q1, Q3) values at baseline were 5.7 (5.2, 6.7) mmol/L in both the evolocumab and placebo groups. Median (Q1, Q3) change in glucose from baseline to week 168 was 0.2 (-0.3, 0.8) mmol/L in the evolocumab group and 0.2 (-0.2, 0.8) mmol/L in the placebo group.

Creatine kinase

There were no notable trends in CK concentrations throughout Study 20110118; median (Q1, Q3) change from baseline to week 168 was -1.0 (-26.0, 24.0) IU/L for subjects in the evolocumab group and 1.0 (-27.0, 31.0) IU/L in the placebo group.

A shift in CK from baseline CTCAE grade 0, 1 or 2 to postbaseline grade 3 or 4 occurred in 94 (0.7%) subjects in the evolocumab group and 98 (0.7%) subjects in the placebo group. The number of subjects with 1-grade, 2-grade, 3-grade, and 4-grade shifts from baseline in CK were similar between the evolocumab and placebo groups.

The subject incidences at each scheduled assessment of CK > 5 x ULN and > 10 × ULN in all subjects were balanced between treatment groups.

Table S22: Subject Incidence of Creatine Kinase > 5 x ULN or > 10 x ULN Study 20110118 (Safety Analysis Set - Actual Treatment Group)

	Placebo n (%)	EvoMab n (%)
All Subjects	N = 13756	N = 13769
Baseline		
Subjects with at least one CK test at baseline - N°	13750	13766
CK > 5 x ULN	21 (0.2)	18 (0.1)
CK > 10 x ULN	5 (<0.1)	4 (<0.1)
Any postbaseline visit		
Subjects with at least one postbaseline CK test - N°	13536	13542
CK > 5 x ULN	100 (0.7)	96 (0.7)
CK > 10 x ULN	22 (0.2)	27 (0.2)
Subjects With Normal Baseline	N = 12177	N = 12145
Any postbaseline visit		
Subjects with at least one postbaseline CK test - N°	11987	11945
CK > 5 x ULN	63 (0.5)	55 (0.5)
CK > 10 x ULN	16 (0.1)	18 (0.2)

Liver function tests

There were no notable changes in AST or ALT concentrations from baseline throughout Study 20110118. For AST, median (Q1, Q3) change from baseline to week 168 was 1.0 (-3.0, 5.0) U/L in both the evolocumab and placebo treatment groups. For ALT, median (Q1, Q3) change from baseline to week 168 was -1.0 (-7.0, 4.0) U/L in the evolocumab group and -1.0 (-7.0, 5.0) U/L in the placebo group.

A shift in AST from baseline CTCAE grade 0, 1 or 2 to postbaseline grade 3 or 4 occurred in 45 (0.3%) subjects in the evolocumab group and 52 (0.4%) subjects in the placebo group. A shift in ALT from baseline grade 0, 1 or 2 to postbaseline grade 3 or 4 occurred in 58 (0.4%) subjects in the evolocumab group and 65 (0.5%) subjects in the placebo group. The number of 1-grade, 2-grade, and 3-grade shifts from baseline in ALT and AST values were generally balanced between groups.

The subject incidences of LFT abnormalities in all subjects and in subjects with normal baseline AST or ALT were balanced between treatment groups.

All 4 subjects with post-baseline incidence of (ALT or AST > 3 x ULN) and (total bilirubin > 2 x ULN and ALP < 2 x ULN) among subjects with normal AST and ALT at baseline had alternate etiologies for the hepatic laboratory abnormalities (acute cholecystitis in the evolocumab subject and bile duct stenosis, chronic gastritis, and acute alcohol intoxication in the 3 placebo subjects); no subject met Hy's law criteria.

Table S23: Subject Incidence of Liver Function Test Abnormality Study 20110118 (Safety Analysis Set - Actual Treatment Group)

	Placebo n (%)	EvoMab n (%)
All Subjects	N = 13756	N = 13769
Baseline		
Subjects with at least one liver function test at baseline - N^o	13750	13767
ALT or AST > 3 x ULN	25 (0.2)	32 (0.2)
ALT or AST > 5 x ULN	8 (<0.1)	11 (<0.1)
Total bilirubin > 2 x ULN	11 (<0.1)	14 (0.1)
(ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN and ALP < 2 x ULN)	0 (0.0)	2 (<0.1)
Any postbaseline visit		
Subjects with at least one postbaseline liver function test - N^o	13537	13543
ALT or AST > 3 x ULN	243 (1.8)	240 (1.8)
ALT or AST > 5 x ULN	77 (0.6)	70 (0.5)
Total bilirubin > 2 x ULN	62 (0.5)	43 (0.3)
(ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN and ALP < 2 x ULN)	3 (<0.1)	3 (<0.1)
Subjects With Normal Baseline AST and ALT	N = 11914	N = 11976
Any postbaseline visit		
Subjects with at least one postbaseline liver function test - N^o	11721	11784
ALT or AST > 3 x ULN	143 (1.2)	132 (1.1)
ALT or AST > 5 x ULN	49 (0.4)	47 (0.4)
Total bilirubin > 2 x ULN	54 (0.5)	35 (0.3)
(ALT or AST > 3 x ULN) and (Total bilirubin > 2 x ULN and ALP < 2 x ULN)	3 (<0.1)	1 (<0.1)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; EvoMab = Evolocumab (AMG 145); N = number of subjects randomized and dosed; % = n / N^o * 100; ULN = upper limit of normal

The baseline is defined as the last non-missing value collected prior to or on randomization date.

Renal function tests

No trends indicative of clinically important treatment related renal function laboratory abnormalities were observed between treatment groups in Study 20110118. Urine protein (as determined by dipstick method), at all time points, was negative in the majority of subjects tested. The majority of subjects for both evolocumab (56.5%) and placebo (55.5%) did not have an increase in proteinuria from baseline. The incidence of 4+ proteinuria was low and similar across the 2 treatment groups, with 17 (0.1%) subjects in the evolocumab group and 10 (< 0.1%) subjects in the placebo group having 4+ proteinuria value at some point during the study. The majority of subjects with 4+ proteinuria at some point during the study had a proteinuria value of either 3+ or 4+ at baseline (10 of 17 in the evolocumab group, 7 of 10 in the placebo group).

A similar number of subjects in the evolocumab (11 [0.1%] subjects) and the placebo (8 [0.1%] subjects) treatment groups had a post-baseline 3 grade level increase in creatinine (from grade 0 to 3 or from grade 1 to 4). There was also a similar number of subjects with a 4 grade maximum post-baseline

level increase in creatinine (from grade 0 to 4) in the evolocumab group (1 [0.1%] subjects) and the placebo group (2 [< 0.1%] subjects). The majority of subjects for both evolocumab (80.3%) and placebo (79.8%) did not have an increase in creatinine grade from baseline.

Glycemic parameters

In Study 20110118, HbA1c values were balanced between treatment groups throughout the study. Median (Q1, Q3) values at baseline were 5.9% (5.5, 6.5) in the evolocumab and 5.9% (5.6, 6.5) in the placebo group. There were no meaningful changes in HbA1c throughout the study in either treatment group. Median (Q1, Q3) change in HbA1c from baseline to week 168 was 0.1% (-0.1, 0.3) in the evolocumab group and 0.1% (-0.1, 0.4) in the placebo group (N = 13 at week 192).

In summary, no differences in CK shifts (98 (0.7%) vs 94 (0.7%)) or CK > 5 x ULN (96 (0.7%) vs 100 (0.7%) or > 10 x ULN (27 (0.2%) vs 22 (0.2%) could be observed between evolocumab and placebo. There were no notable differences in ALT/AST shifts or ALT/AST > 3 x ULN (240 (1.8%) vs 243 (1.8%))or > 5 x ULN (70 (0.5%) vs 77 (0.6%)) or total bilirubin > 2 x ULN (3 each). There was no subject with Hy's law criteria. The number of dipstick 4+ proteinuria was low but slightly higher for evolocumab (17 (0.1%)) versus placebo (10 (<0.1%)). Also a slightly higher number had a grade 3 post-basline increase in creatinine (11 vs 8), but grade 4 only occurred in 1 evolocumab patients and 2 placebo patients. Safety data on vitamin E levels show to be within the normal range consistent with the initial dossier. Despite a slightly higher incidence of new onset of diabetes mellitus found for evolocumab (8.1% vs 7.7%), HbA1c values were comparable throughout the study (at baseline 5.9% with change of 0.1% during the study for both treatment arms).

Vital signs

In Study 20110118, there were no notable differences between groups with respect to vital signs, including blood pressure and heart rate. Of note, 80.1% of subjects entered the study with a history of hypertension. The mean changes from baseline in systolic and diastolic blood pressure were similar between groups at each study time point; values ranged from -1.7 to 1.7 mmHg (systolic) and -1.3 to 0.8 mmHg (diastolic) in the evolocumab group and -1.1 to 0.0 mmHg (systolic) and -1.3 to -0.2 mmHg (diastolic) in the placebo group.

Immunological events

Hypersensitivity events

In Study 20110118, analysis of potential hypersensitivity events showed a higher incidence of hypersensitivity events in the evolocumab group than in the placebo group using both narrow (4.7% and 4.2%, respectively) and broad (7.6% and 7.0%, respectively) search strategies. The difference in incidence between the evolocumab and placebo groups within the narrow search strategy was primarily driven by events in the dermatitis and eczema HLT (209 [1.5%] evolocumab subjects, 169 [1.2%] placebo subjects). Within this HLT the vast majority of events, including the most common preferred term eczema (95 [0.7%] evolocumab subjects, 67 [0.5%] placebo subjects), were CTCAE grade 1 or 2 and non serious and rarely led to discontinuation of investigational product; there were no grade 4 events. The remaining high level terms in the narrow search strategy had similar incidence between treatment groups (within 0.1% difference).

Overall, the majority of events in the narrow search strategy for potential hypersensitivity events were CTCAE grade 1 or grade 2. CTCAE grade ≥ 3 events were reported in 59 subjects (0.4%) in the evolocumab group and 41 subjects (0.3%) in the placebo group and grade ≥ 4 events were reported in 7 subjects (< 0.1%) in the evolocumab group and 2 subjects (< 0.1%) in the placebo group. There were no fatal events. No grade 4 hypersensitivity adverse event was considered related to investigational

product by the investigator; all events had alternate etiologies (medication, food, contact allergen), occurred after the last dose of investigational product, or upon medical review were non-hypersensitivity related. For each of the adverse events attributed to an alternate etiology, investigational product was continued without event recurrence.

Overall, the incidence of serious adverse events was similar between groups (34 [0.2%] evolocumab, 25 [0.2%] placebo). There were 2 serious adverse events of anaphylactic shock (2 evolocumab, 0 placebo); 1 event occurred following peanut consumption and evolocumab was continued without further hypersensitivity events; and 1 event occurred after 152 days of exposure to evolocumab and, per the investigator, the most likely diagnosis was vasovagal syncope. However, anaphylactic shock could not be ruled out. There were 5 serious events of anaphylactic reaction (2 evolocumab, 3 placebo) and all were attributed to alternate etiologies (antibiotics, analgesics, bee/wasp sting). There was 1 serious adverse event of Henoch-Schonlein purpura in the evolocumab group considered possibly related to both evolocumab and atorvastatin; the event resolved and evolocumab was continued without further hypersensitivity events. In the placebo group, there were 2 nonserious potential hypersensitivity vasculitis cases (Henoch-Schonlein purpura, hypersensitivity vasculitis).

Eight subjects reported adverse events within the bullous conditions HLT (3 evolocumab, 1 placebo) and exfoliative conditions HLT (4 evolocumab, 0 placebo); the majority (6) of events were grade 1 or 2, nonserious, considered unrelated to investigational product by the investigator, and did not lead to discontinuation of investigational product. The grade 3 events were both in the evolocumab group and included non serious Stevens-Johnson syndrome which occurred 10 months after the last dose of evolocumab and dermatitis exfoliative (scalp, forehead, face, hands) in a subject concurrently using topical minoxidil.

There was no difference between treatment groups in the incidence of angioedema MedDRA SMQ (narrow); the overall incidence within this search strategy was balanced between groups (35 [0.3%] evolocumab subjects, 39 [0.3%] placebo subjects).

The incidence of hypersensitivity adverse events leading to discontinuation of investigational product was 46 (0.3%) subjects in the evolocumab group and 33 (0.2%) subjects in the placebo group. Most adverse events leading to discontinuation were skin-related and grade 1 or 2.

Review of the broad search strategy for hypersensitivity did not yield any additional findings.

Table S24: Treatment Emergent Adverse Events That Occurred in > 0.2% of Subjects in Any Treatment Group by High Level Term Using Narrow Search Strategy for Potential Hypersensitivity Events Study 20110118 (Safety Analysis Set - Actual Treatment Group)

High Level Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
All treatment emergent adverse events	574 (4.2)	653 (4.7)
Dermatitis and eczema	169 (1.2)	209 (1.5)
Rash, eruptions, and exanthemas	188 (1.4)	196 (1.4)
Nasal congestion and inflammations	43 (0.3)	48 (0.3)
Urticarias	41 (0.3)	42 (0.3)
Allergic conditions NEC	34 (0.2)	36 (0.3)

Study 20120153 (GLAGOV)

In Study 20120153, evaluation using SMQs for hypersensitivity terms showed that subjects in the evolocumab group had a slightly higher incidence of hypersensitivity events compared with the placebo group. Using narrow search strategies, 33 (6.8%) subjects in the evolocumab group and 23 (4.8%) subjects in the placebo group had a hypersensitivity event. Using broad search strategies, 53 (11.0%) subjects in the evolocumab group and 38 (7.9%) subjects in the placebo group had a hypersensitivity event.

Events (evolocumab, placebo) that contributed to the difference between groups in these categories, using the narrow search strategy, included known adverse drug reactions for evolocumab of rash (2.3%, 1.9%) and urticaria (0.6%, 0.4%), as well as events of drug hypersensitivity (0.8% , 0%) and drug eruption (0.2% , 0%). All of the drug hypersensitivity and drug eruption events were considered unrelated to evolocumab by the investigator and were attributed to other agents (antibiotics, analgesics, or fraxiparine) and in all subjects evolocumab was continued.

Antibody formation

Of the 13 769 subjects in Study 20110118 who received at least 1 dose of evolocumab, 13 748 subjects had at least 1 on-study antibody result. A total of 12 410 subjects had a result at baseline and 13 343 subjects had a minimum of 1 post-baseline result. Thirty-four (0.3%) subjects tested positive for pre-existing anti-evolocumab binding antibodies at baseline (prior to dosing with investigational product). One (< 0.1%) of these subjects tested positive for pre-existing neutralizing antibodies; however, this subject was negative for post-baseline binding or neutralizing antibodies to evolocumab at all time points beyond baseline.

Among subjects who had negative anti-evolocumab antibodies or no result at baseline, 43 (0.3%) tested positive for anti-evolocumab binding antibodies post-baseline. In the majority of subjects these results were transient; 35 subjects had a single positive anti-evolocumab binding antibody result post-baseline and tested negative by the next assessment; 1 subject had 2 consecutive positive results post-baseline and tested negative at the last study assessment. Of the remaining subjects with positive post-baseline binding antibody to evolocumab, 5 had a single positive binding antibody result at the last blood draw, and 2 subjects had 2 consecutive positive binding antibody results, but no documentation of resolution. No subject tested positive for neutralizing antibodies to evolocumab post-baseline.

Among subjects who tested positive for any anti-evolocumab antibody post-baseline, no adverse events were determined to be associated with a positive antibody result. None of the postbaseline anti-evolocumab positive subjects had an adverse event in the system organ class of immune system disorders and very few had events within the narrow hypersensitivity SMQ (4 subjects) or the broad search strategy for injection site reactions (2 subjects). Overall, the majority of adverse events in subjects who tested positive for any anti-evolocumab antibody post-baseline were CTCAE grade 1 or 2 and non serious. In summary, among subjects with post-baseline positive anti-evolocumab antibody results, there was no pattern of adverse events indicative of a safety concern.

Study 20120153 (GLAGOV)

In Study 20120153, the incidence of post-baseline anti-evolocumab binding antibodies was very low (0.2%) with no neutralizing antibodies detected in any subject on evolocumab. One (0.2%) subject in the evolocumab group had post-baseline anti-evolocumab binding, non-neutralizing antibodies detected at a single time point (week 24); samples from this subject obtained at week 52 and week 78 were negative for binding antibodies. Two (0.4%) additional subjects had pre-existing anti-evolocumab antibodies detected at baseline; no other samples for these 2 subjects tested positive for binding antibody. The presence of anti-evolocumab binding antibodies had no effect on serum unbound evolocumab concentrations for these subjects, as their serum evolocumab concentrations were within the range

observed for other subjects at the same time points. A total of 479 subjects in the evolocumab group had at least 1 on-study binding antibody assay result available and 466 subjects had a baseline result available.

In summary, a slightly higher incidence for hypersensitivity events was observed for evolocumab (4.7% vs 4.2%), mostly eczema (96(0.7%) vs 67 (0.5%)). Also a slightly higher number led to discontinuation (46 (0.3%) vs 33 (0.2%)). Serious adverse events were approximately similar (34 (0.2%) vs 25 (0.2%)). The 5 anaphylactic reactions that occurred were not attributed to medication. No difference was found in the incidence of angioedema (35(0.3%) vs 39 (0.3%)). In the GLAGOV study, similar higher incidence for evolocumab was found for hypersensitivity events. A small proportion tested positive for anti-evolocumab binding antibodies post-baseline (n=43), but these were in the majority transient and not associated adverse events were associated with this. None had immune system disorder adverse events, while only 4 patients had hypersensitivity events and 2 injection site reactions. No neutralizing antibodies were detected. Comparable findings were obtained in the initial dossier.

Safety in special populations

Elderly

The types and incidences of adverse events within each age group were generally similar between the evolocumab and placebo groups. As expected, the overall incidence of adverse events, serious adverse events and adverse events leading to discontinuation in both the evolocumab and placebo groups was higher in subjects ≥ 65 years of age and in subjects ≥ 75 years of age than in subjects < 65 years of age. The most commonly reported adverse events in ≥ 65 year group (evolocumab, placebo) were hypertension (8.3%, 8.7%), nasopharyngitis (7.6%, 7.9%), and diabetes mellitus (6.6%, 6.6%); similarly, the most commonly reported adverse events in ≥ 75 year group were hypertension (8.2%, 8.3%), nasopharyngitis (7.5 %, 7.1%), and urinary tract infection (7.5%, 6.9%), which are generally consistent with events observed in the older age group and comorbidities of the study population. Adverse events that were > 1% higher in the evolocumab group in subjects ≥ 75 years of age were dizziness (5.5%, 4.0%) and diarrhea (4.7%, 3.6%); no adverse events were > 1% higher in the evolocumab group in subjects ≥ 65 years of age. The events of diarrhea and dizziness in subjects ≥ 75 years of age were generally mild to moderate in severity, non-serious and did not lead to treatment discontinuation.

Table S25: Summary of Subject Incidence of Treatment Emergent Adverse Events in Subjects < 65, ≥ 65, and ≥ 75 Years of Age Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Subgroup	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
Subjects < 65 Years of Age	N = 7678	N = 7615
All treatment emergent adverse events	5793 (75.4)	5767 (75.7)
Serious adverse events	1689 (22.0)	1717 (22.5)
Leading to discontinuation of investigational product	252 (3.3)	259 (3.4)
Subjects ≥ 65 Years of Age	N = 6078	N = 6154
All treatment emergent adverse events	4851 (79.8)	4897 (79.6)
Serious adverse events	1715 (28.2)	1693 (27.5)
Leading to discontinuation of investigational product	321 (5.3)	349 (5.7)
Subjects ≥ 75 Years of Age	N = 1237	N = 1286
All treatment emergent adverse events	1005 (81.2)	1045 (81.3)
Serious adverse events	417 (33.7)	418 (32.5)
Leading to discontinuation of investigational product	73 (5.9)	93 (7.2)

Renal impairment

No safety concern was identified from the evaluation of subjects with renal impairment in the studies included in this submission. Study 20110118 included subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). The number of subjects with severe renal impairment was small (122 evolocumab, 82 placebo); therefore, data should be interpreted with caution. Total emergent adverse events were comparable (83.6% vs 87.8%) and serious adverse events (45.1% vs 48.8%). The most commonly (≥ 10% of subjects in either treatment group) reported events (evolocumab and placebo) are events that would be expected in subjects with severe renal failure, e.g., hypertension (13.1%, 7.3%) and diabetes mellitus (10.7%, 13.4%). Overall incidence of adverse events, and serious adverse events were comparable between the evolocumab and placebo groups.

Gender

The types and incidences of adverse events within each gender were similar between the evolocumab and placebo treatment groups. The overall incidence of adverse events, serious adverse events and adverse events leading to discontinuation in both the evolocumab and placebo groups was slightly higher in women than in men.

Table S26: Summary of Subject Incidence of Treatment Emergent Adverse Events by Sex Study 20110118 (Safety Analysis Set - Actual Treatment Group)

Subgroup AE Category	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
Men	N = 10382	N = 10385
All treatment emergent adverse events	7887 (76.0)	7939 (76.4)
Serious adverse events	2478 (23.9)	2484 (23.9)
Leading to discontinuation of investigational product	399 (3.8)	396 (3.8)
Women	N = 3374	N = 3384
All treatment emergent adverse events	2757 (81.7)	2725 (80.5)
Serious adverse events	926 (27.4)	926 (27.4)
Leading to discontinuation of investigational product	174 (5.2)	212 (6.3)

In conclusion, no particular safety concerns exist with the treatment with evolocumab in elderly patients. The incidence of adverse events was approximately similar for older patients compared to younger patients. Also the type of adverse events was found to be similar. Limited data is available for patients > 75 years of age. Similarly, no particular safety concern could be identified in patients (n=204) with renal impairment, although number of patients were very limited. Slightly more events occurred in women than in men (80.5% vs 76.4% in the evolocumab group).

2.5.1. Discussion on clinical safety

In the initial submitted data 6026 patients were exposed to evolocumab representing 5246 patient years of exposure. With the current submission of the pivotal study (FOURIER) with a total of 27525 subjects, and the GLAGOV study with 968 patients included, the overall exposure data from clinical studies has substantially increased, although exposure in the pivotal study was limited to a median of 26 months. A long-term follow-up study (FOURIER-OLE) including patients from the pivotal FOURIER study is currently ongoing and will present data in 2023 earliest. Further, it has been estimated that 61 600 subjects have been exposed to evolocumab in the postmarking setting.

Consistent with the initial submission, evolocumab generally displays a **safety profile** similar to that of the control group of statin and other lipid lowering therapy (77.4% each for incidence of adverse events). Diabetes mellitus (8.8%, 8.2%), hypertension (8.0%, 8.7%), nasopharyngitis (7.8%, 7.4%), upper respiratory tract infection (5.1%, 4.8%), and back pain (4.9%, 4.7%) were the most commonly reported adverse events. In the original submitted dossier nasopharyngitis, upper respiratory tract infection and back pain were also the most frequently reported, although generally with a lower incidence (2.5%-5.9%).

No difference was found in the incidence of **serious adverse events** between evolocumab and placebo (24.8% vs 24.7%). Most frequently reported serious adverse events were found in the group of ischemic coronary artery disorders with most serious adverse events being unstable angina (1.7%, 2.0%), angina pectoris (1.5%, 1.6%), pneumonia (1.1% in each group), atrial fibrillation (0.9%, 1.0%), and non-cardiac chest pain (0.8% 1.0%), which were not different in frequency between both treatment groups. No difference in the incidence of cancer was observed.

Adverse events leading to **discontinuation** was a minor part of all discontinuations (12.4%) and approximately similar between evolocumab treatment and placebo (4.4% vs 4.2%, respectively). Discontinuations were mainly attributed to myalgia (37 [0.3%] ; 46 [0.3%]), fatigue (12 [< 0.1%]; 23 [0.2%]), and arthralgia (14 [0.1%]; 13 [< 0.1%]) for evolocumab and placebo, respectively. As can be expected, discontinuation was twice more than during the initial submitted studies, apparently not directly related to initiation of therapy.

Of particular interest was whether patients achieving **very low levels of LDL-C** would display a different safety profile to patients with less low LDL-C levels achieved, in particular, as very low levels of LDL-C have been associated with increased risk of cancer, hemorrhagic stroke, non-cardiovascular death and neurocognitive abnormalities and could affect steroid production. No such signs could be identified in the original submitted dossier. Consistent with this original submitted dossier, the incidence of adverse events for patients achieving very low levels of LDL-C was not different from patients with higher LDL-C levels (overall adverse events 68.4% < 25 mg/dL, 73.2% < 40 mg/dL, 73.6% and 77.7% in evolocumab and placebo LDL-C ≥ 40 mg/dL, respectively). Also for serious adverse events the pattern was not different from placebo (overall serious adverse events 20.7% < 25 mg/dL, 23.0% < 40 mg/dL, 23.7% and 24.8% in evolocumab and placebo LDL-C ≥ 40 mg/dL, respectively). The incidence of **neurocognitive adverse events** was generally similar between treatment arms (1.6% vs 1.5 %, evolocumab vs placebo). Amnesia was numerically higher in the evolocumab group compared with

placebo (51 [0.4%], 33 [0.2%], however, when reported in the grouped term memory loss (memory impairment, amnesia, transient global amnesia, amnestic disorder and retrograde amnesia), incidence was only slightly higher (133 [1%] evolocumab, 118 [0.9%] placebo). Of particular interest, for patients achieving very low LDL-C levels, the incidence of these adverse events was approximately similar to placebo (1.1% - 1.5%). Additionally, specific attention has been given to possible **neuropsychological effects** when treated with evolocumab by testing a representative subset of the pivotal study through cognitive evaluation of CANTAB assessment (also known as the EBBINGHAUS study). No difference in effect on the cognitive domain of executive function could be observed, as analysed according to a non-inferiority analysis. Furthermore, no clear difference according to subgroups could be observed. Also, no difference was found for other cognitive domains (working memory, memory function, and psychomotor speed; all secondary endpoints). Also no difference in effect on the cognitive domain of executive function could be observed for subgroups with very low level of LDL-C. The change from baseline over time in Reaction Time Index Median Five-Choice Reaction Time (RTIMDFRT) was slightly higher for the evolocumab group compared with the placebo group, however, this difference was not considered clinically relevant. However, it is questioned whether the study duration of 96 weeks is sufficient to pick up changes for evaluation of potential cognitive effects of evolocumab treatment considering that cognitive dysfunction due to (possible) amyloid accumulation develops slowly. No effect on the incidence of potential **demyelination adverse events** could be observed as this was slightly higher for placebo than for evolocumab (143 [1.0%], 102 [0.7%],). Also, these events were similar or lower in evolocumab-treated subjects with LDL-C < 25 mg/dL (0.6%) or < 40 mg/dL (0.7%) than in evolocumab or placebo (0.7% and 1.1%, respectively). Serious demyelination adverse events were higher for placebo (16 [0.1%]) than evolocumab (11 [< 0.1%]) and not considered related to study drug.

As expected, **injection site reactions** occurred at a higher overall incidence in the evolocumab group than in the placebo group using both narrow (1.9% evolocumab, 1.5% placebo) and broad (2.0% evolocumab, 1.5%, placebo) search strategies and generally non-serious. There were 2 subjects with positive anti-drug antibody (ADA) tests who reported an injection site reaction during the study, without any consequence for treatment continuation. **Device related events** occurred slightly more for evolocumab (156, 1.1% vs 132, 1.0%) mainly classified as non-serious.

Specific attention was given to musculoskeletal and connective tissue disorders, hepatic disorders, renal disorders, and diabetes, as these are known to be associated with treatment with several lipid lowering agents. For **musculoskeletal and connective tissue disorders**, no difference could be observed (3350 [24.3%] evolocumab, 3354 [24.4%] placebo), while in the initial dossier a slightly higher incidence was observed (14.7% vs 13.7%). The most common of these events, as also known from the original submitted dossier, were back pain (673 [4.9%] evolocumab and 651 [4.7%] placebo), arthralgia (605 [4.4%] evolocumab and 589 [4.3%] placebo), myalgia (555 [4.0%] evolocumab and 527 [3.8%] placebo) and pain in extremity (428 [3.1%] evolocumab and 451 [3.3%] placebo). This was supported by laboratory findings of creatin kinase (CK) and absence of imbalance in rhabdomyolysis. No differences in CK shifts (98 (0.7%) vs 94 (0.7%)) or CK > 5 x ULN (96 (0.7%) vs 100 (0.7%) or > 10 x ULN (27 (0.2%) vs 22 (0.2%) could be observed between evolocumab and placebo. Overall, there were 19 events of rhabdomyolysis. Of the 13 serious events, 11 were rhabdomyolysis (5 evolocumab, 6 placebo) and 2 were myopathy (both evolocumab). One of the serious rhabdomyolysis events was considered related, but was also considered related to statin and occurred in a subject who had started weight lifting 2 weeks prior to the event onset. The 2 myopathy events were attributed to other agents (statin, chemotherapy, steroids) and were considered unrelated to evolocumab.

No clear effect on **hepatic disorders** of evolocumab could be observed. Hepatic events were slightly more reported for evolocumab than placebo ((296 [2.1%] evolocumab, 256 [1.9%] placebo)), while this was not different in the initial dossier (0.9% vs 0.8%). Also, slightly more serious hepatic events occurred

(72 [0.5%] vs 58 [0.4%]. Six subjects reported serious grade 4 events of hepatic failures (3 evolocumab, 1 placebo), hepatorenal syndrome (1 evolocumab), and hepatic cirrhosis (1 evolocumab), all not considered related to study drug. However, there were no notable differences in ALT/AST shifts or ALT/AST > 3 x ULN (240 (1.8%) vs 243 (1.8%)) or > 5 x ULN (70 (0.5%) vs 77 (0.6%)) or total bilirubin > 2 x ULN (3 each). There was no subject with Hy's law criteria. Eight serious events had a fatal outcome, but could be explained by an alternative etiology. There were 6 reports of suspected DILI (4 [< 0.1%] evolocumab, 2 [< 0.1%] placebo) without any elevation in liver enzymes of AST or ALT > 5 x ULN or total bilirubin > 2 x ULN. Of the 3 serious events in evolocumab, one fatal event noted alcohol use and ischemic liver due to heart failure as possible contributing factors; and 1 event occurred in the setting of rhabdomyolysis and the events were attributed to a drug interaction between atorvastatin and amiodarone and considered unrelated to evolocumab; evolocumab and statin were discontinued and the events resolved. The third event occurred in a subject who reported being hospitalized with fever and nausea and diagnosed with drug-induced hepatitis/ suspected DILI; liver enzymes from study centre visits were normal and no laboratory data or other medical records were made available to the investigator to support the diagnosis. Evolocumab and statin were withdrawn per protocol.

Concerning the **renal function**, the number of dipstick 4+ proteinuria was low but slightly higher for evolocumab (17) versus placebo (10). Also a slightly higher number had a grade 3 post-baseline increase in creatinine (11 vs 8), but grade 4 only occurred in 1 evolocumab patients and 2 placebo patients. No safety data on renal adverse events have been provided, however, no effect in the initial dossier could be observed, which can be expected as evolocumab is not cleared by the kidneys.

The overall incidence of **new onset of diabetes mellitus** (NODM) was slightly higher for evolocumab 8.1% vs 7.7%. This is different from what has been reported in the incidence of diabetes (8.8% vs 8.2%) due to history of diabetes for the population included. NODM in both treatment groups were lower for subjects with normoglycemia at baseline (4.8%, 4.4%) than for subjects with either metabolic syndrome (11.6%, 11.3%) or impaired fasting glucose (13.3%, 12.8%) at baseline. Despite a slightly higher incidence of new onset of diabetes mellitus found for evolocumab (8.1% vs 7.7%), HbA1c values were comparable throughout the study (at baseline 5.9% with change of 0.1% during the study for both treatment arms). However NODM was lower in the overall clinical program for evolocumab compared with the control treatment. Considering that DM reporting was lower in the overall program and differences in percentages in reporting in the FOURIER study were < 1% difference it is acceptable not to include diabetes mellitus as AE in section 4.8 of the SmPC.

Specific attention has also been given **to immunological disorders**. A slightly higher incidence for **hypersensitivity events** was observed for evolocumab (4.7% vs 4.2%), mostly eczema (96(0.7%) vs 67 (0.5%)). Also a slightly higher number led to discontinuation (46 (0.3%) vs 33 (0.2%)). Serious adverse events were approximately similar (34 (0.2%) vs 25 (0.2%)). The 5 anaphylatic reactions that occurred were not attributed to medication. No difference was found in the incidence of angioedema (35(0.3%) vs 39 (0.3%)). A small proportion tested positive for **anti-evolocumab binding antibodies** post-baseline (n=43), but these were in the majority transient and no adverse events were associated with this. None of the patients with anti-evolocumab binding antibodies had immune system disorder adverse events, while only 4 patients had hypersensitivity events and 2 had injection site reactions. No neutralizing antibodies were detected. Comparable findings were obtained in the initial dossier.

Deaths in the pivotal study were adjudicated by a CEC and have been reported and discussed in the efficacy section. Number of deaths in the GLAGOV study were limited with 5 deaths (3 evolocumab, 2 placebo), none of which were considered related to evolocumab.

Safety data on **vitamin E levels** were found to remain within normal levels comparable to the initial submission.

No clinical meaningful changes were found for changes in blood pressure between treatment arms during the study.

Some safety data have been provided on **special populations** including elderly and patients with renal impairment and sex difference. No particular safety concerns exist with the treatment with evolocumab in elderly patients. The incidence of adverse events was approximately similar for older patients compared to younger patients. Also, the type of adverse events was found to be similar. Limited data is available for patients > 75 years of age. Similarly, no particular safety concern could be identified in patients (n=204) with renal impairment, although number of patients were very limited. Slightly more events occurred in women than in men (80.5% vs 76.4% in the evolocumab group).

The incidence profile of adverse events in the **GLAGOV study** was slightly different than for FOURIER, with angina pectoris (7.4%, 8.9%), myalgia (7.0%, 5.8%), chest pain (7.0%, 5.4%), hypertension (6.0%, 7.6%), and non-cardiac chest pain (5.8%, 3.7%) reported as most commonly reported adverse events, with slightly different incidence for evolocumab versus placebo. These were not reported to be related to study medication. The most serious adverse events were also reported in the cardiovascular system. The most frequent serious adverse events were angina pectoris (3.5%, 2.3%), non-cardiac chest pain (2.3%, 1.2%) and unstable angina (1.7%, 1.4%) and slightly reported more for evolocumab. Discontinuation due to adverse events were slightly higher for evolocumab (3.3%) than for placebo (2.3%), the incidence highest in myalgia (0.2%, 0.6%). A higher incidence of injection site reactions were reported for evolocumab. In the GLAGOV study, similar higher incidence for evolocumab was found for hypersensitivity events.

2.5.2. Conclusions on clinical safety

The **overall exposure** data from clinical studies has **substantially increased** from 6026 patients in the initial dossier to an additional 27525 subjects treated in the pivotal study (FOURIER), and the GLAGOV imaging study which included 968 patients. Further, it has been estimated that 61 600 subjects have been exposed to evolocumab in the postmarking setting.

Consistent with the initial submission, evolocumab generally displays a **safety profile similar to that of the control group** of statin and other lipid lowering therapy with both at 77.4% reported incidence of adverse events. Comparable to the initial dossier (except for diabetes), the most common adverse events were diabetes mellitus (8.8%, 8.2%), hypertension (8.0%, 8.7%), nasopharyngitis (7.8%, 7.4%), upper respiratory tract infection (5.1%, 4.8%), and back pain (4.9%, 4.7%) for evolocumab and placebo, respectively. **Serious adverse events** between evolocumab and placebo were also similar (24.8% vs 24.7%).

The overall incidence of **new onset of diabetes mellitus (NODM)** was slightly higher for evolocumab 8.1% vs placebo 7.7%. However NODM was lower in the overall clinical program for evolocumab compared with the control treatment.

Exposure in the pivotal study was **limited to a median of 26 months**; this may be too short to exclude long term effects. A long-term follow-up study including patients from the pivotal FOURIER study is currently ongoing.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 2.5 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

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 2.5 with the following content:

Safety concerns

Important identified risks	none
Important potential risks	hypersensitivity
Missing information	use in pregnant/lactating women
	use in paediatric patients
	use in patients with severe hepatic impairment (Child-Pugh class C)
	use in patients with hepatitis-C
	use in patients with HIV
	long-term use including effects of LDL-C < 40 mg/dL (< 1.03 mmol/L)

Pharmacovigilance plan

Study/Activity Title and category (1 - 3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20110110 Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab (AMG 145) Category 3	• To characterize the safety and tolerability of long-term administration of evolocumab • To characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio in subjects with hypercholesterolaemia	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Ongoing	Q2 2019
20110271 Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of Evolocumab (AMG 145) on LDL-C in Subjects with Severe Familial Hypercholesterolaemia (including HoFH) Category 3	• To characterize the safety and tolerability of long-term administration of evolocumab among subjects with severe familial hypercholesterolaemia (including HoFH) • To characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C and non-HDL-C, Lp(a), ApoB, total cholesterol/HDL-C ratio, ApoB/ ApoA1 ratio, and response of LDL-C reduction (15% or greater) in subjects with severe familial hypercholesterolaemia (including HoFH)	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Ongoing	Q1 2021

Study/Activity Title and category (1 - 3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20120138 A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab (AMG 145) Category 3	• To characterize the safety and tolerability of long-term administration of evolocumab • To characterize efficacy of long-term administration of evolocumab as assessed by LDL-C in subjects with primary hyperlipidaemia and subjects with mixed dyslipidaemia	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Ongoing	Q3 2019
20120332 A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Evolocumab (AMG 145), Compared With Ezetimibe, in Hypercholesterolaemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects (Part C only) Category 3	• To evaluate the long-term safety and efficacy of AMG 145 in statin-intolerant subjects (Part C).	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Ongoing	Part C: Q2 2018

Study/Activity Title and category (1 - 3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20150162 A Multi-national Observational Study to Evaluate the Safety of Repatha® in Pregnancy Category 3	• To evaluate outcomes of pregnancy in females diagnosed with FH, exposed to Repatha® during pregnancy.	Use in pregnant women	Study initiation Q2 2016	Periodic updates with each PSUR Feasibility Report: Q3 2019 Final Report: Q2 2027
20130295 A Multicenter, Open-label Extension Study to Assess Long-Term Safety and Efficacy of Evolocumab Therapy in Patients with Clinically Evident Cardiovascular Disease (FOURIER-OLE) Category 3	• To characterize the safety and tolerability of extended long-term administration of evolocumab in subjects having received evolocumab or placebo in the completed FOURIER trial	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Study initiation Q3 2016	Q3 2022

Study/Activity Title and category (1 - 3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20130286 A Double Blind, Randomized, Placebo Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab in HIV Positive Patients with Hyperlipidemia and Mixed Dyslipidemia Category 3	• Evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in HIV positive subjects with hyperlipidemia or mixed dyslipidemia	Use in patients with HIV	Study initiation Q2 2017	Q2 2020
20160250 A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safety of Evolocumab Therapy in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries Category 3	• To describe the safety and tolerability of long-term administration of evolocumab in a cohort of Western European subjects having received evolocumab or placebo in the completed FOURIER trial	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Study initiation Q1 2017	Q3 2023
20150338 Repatha (evolocumab) Pregnancy Exposure Registry: An OTIS Pregnancy Surveillance Study. Category 3	• To estimate the overall combined rate of major structural defects, as well as to evaluate any pattern of anomalies, in infants of women with atherosclerotic cardiovascular disease (ASCVD) and/or familial hypercholesterolemia (FH) exposed to evolocumab during pregnancy when used to treat hypercholesterolemia.	Use in pregnant/lactating women	Ongoing	Q2 2031

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks: not applicable		
Important Potential Risks		
Hypersensitivity	SmPC: • Section 4.3, Contraindications • Section 4.8, Undesirable effects PIL: • What you need to know before you use Repatha • Possible side effects	None
Missing Information		
Use in pregnant/lactating women	SmPC: • Section 4.6, Fertility, pregnancy and lactation PIL: • What you need to know before you use Repatha	None
Use in paediatric patients	SmPC: • Section 4.2, Posology and method of administration • Section 4.8, Undesirable effects PIL: • What you need to know before you use Repatha	None
Use in patients with severe hepatic impairment (Child-Pugh class C)	SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use	None
Use in patients with Hepatitis-C	None	None
Use in patients with HIV	None	None
Long-term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	None	None

2.7. Update of the Product information

Extension of the indication to adult patients with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors based on the results of the FOURIER study. As a consequence sections 4.1, 4.2, 4.4 4.8, 5.1 and 5.2 of the SmPC were updated. The Package Leaflet is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 5.1 of the SmPC to include mechanistic information for healthcare professionals based on Study 20120153 (GLAGOV study).

An updated RMP version 2.5was also submitted in order to add two category 3 studies in the RMP (Study 20160250 and Study 20150338), as well as to update the milestones of five category 3 studies (20110110, 20110271, 20120138, 20130286, 20130295).

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

2.7.1. 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 results were bridged to the user consultation performed for the initial MA for Repatha. The justification submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Evolocumab 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.

In the initial submission, evolocumab 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 and in patients with homozygous familial hypercholesterolemia. Evolocumab has demonstrated an acceptable safety profile. Based on these observations the following indication was approved:

Hypercholesterolaemia and mixed dyslipidaemia

Repatha 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 contra-indicated.*

Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

In the current group of variations, the following indication was proposed by the MAH mainly based on the submitted results of the **FOURIER study** (n= 27564), a double-blind, randomized, placebo-controlled, multicentre study assessing the impact of additional LDL-cholesterol reduction on major cardiovascular (CV) events when evolocumab is used in combination with statin therapy in patients with clinically evident cardiovascular disease:

Repatha is indicated to reduce atherosclerotic cardiovascular disease risk in:

- *adults with high cardiovascular risk, or*
- *adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, or*
- *adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia*

as an adjunct to diet when used:

- *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.*

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

A supportive **imaging study** (GLAGOV, n= 968) was also submitted, which was a double-blind, randomized, placebo-controlled study to determine the effects of evolocumab on Atherosclerotic Disease Burden as Measured by Intravascular Ultrasound (IVUS) in patients undergoing coronary catheterization.

3.1.1. Disease or condition

According to the World Health Organization, **cardiovascular disease is the leading cause of death and disability**, accounting for approximately 31% of all deaths and 46% of deaths from non-communicable diseases worldwide (WHO, 2014). Of deaths related to cardiovascular disease, approximately 80% are from myocardial infarction or stroke (WHO, 2014). In the European Union, nearly half of all deaths are from cardiovascular disease (Nichols et al, 2012). Survivors of myocardial infarction or stroke also have a substantial risk of recurrent events. Depending on sex and clinical outcome, survivors of a myocardial infarction have a chance of cardiovascular-related illness and death that is 1.5-fold to 15-fold greater compared with the general population (Roger et al, 2012). Among myocardial infarction survivors, approximately 50% will have another cardiovascular event within 1 year and up to 75% will have a recurrent event within 3 years (Bansilal et al, 2015). Patients hospitalized for an ischemic stroke are approximately 13-fold more likely to have a repeat stroke hospitalization compared with matched controls (Roberts et al, 2009).

Elevated cholesterol, in particular **LDL-C, is a modifiable independent cardiovascular risk factor** (Silverman et al, 2016; The Emerging Risk Factors Collaboration, 2009; Prospective Studies Collaboration, 2007). The seminal role of LDL-C in cardiovascular morbidity and mortality is deeply rooted in the biology of atherosclerosis. Influx of LDL-C particles into the arterial wall activates a deleterious inflammatory process, resulting in atheroma formation and progression (coronary atherosclerosis)

(Moore and Tabas, 2011). Whether in the coronary, cerebrovascular, or peripheral arteries, progression of atherosclerosis leads to morbidity and/or mortality through acute or chronic ischemic disease. Epidemiologic and genetic studies and meta-analyses support this biologic relationship by demonstrating **a proportional and continuous relationship between lipid levels and cardiovascular event rates** across multiple patient groups and countries (Emerging Risk Factors Collaboration, 2009; Prospective Studies Collaboration, 2007).

3.1.2. Available therapies and unmet medical need

Treatment guidelines focus on lipid lowering as an appropriate clinical strategy for the reduction of cardiovascular events, acknowledging that **statins are the first line therapeutic option to reduce LDL-C** (Stone et al, 2014; Reiner et al, 2011; Grundy et al, 2004; Expert Panel, 2001; Expert Panel, 1993; Expert Panel, 1988). Clinically, it is **an individual patient's absolute risk** that determines appropriateness and intensity of hypercholesterolemia treatment.

While many patients achieve LDL-C control with currently available therapies, including statins, an unmet medical need exists for new therapies, particularly in patients who cannot achieve LDL-C control with statins and/or other lipid-lowering therapies (e.g., ezetimibe, bile acid sequestering agents).

3.2. Favourable effects

In the **FOURIER study** evolocumab demonstrated a **significant reduction** on the composite primary endpoint of time to CV death, MI, hospitalization for unstable angina, stroke, and coronary revascularization, whichever occurred first (1344 [9.8%] vs 1563 [11.3%]; HR of 0.85 (95% CI 0.79, 0.92; p < 0.0001)) after a mean of 26 months of treatment with the beneficial effect starting at approximately 5 months of treatment and primarily **driven by MI and stroke and coronary revascularization**. This translated in an absolute risk reduction of approximately 2% for the entire study period for the primary endpoint. Included were **patients at very high CV risk** identified by documented CV disease of MI, stroke and/or peripheral artery disease (PAD) and additional CV risk factors and an elevated LDL-C level in need for LLT according to practical guidelines. This effect was consistent with an observed LDL-C reduction of 48-63% from a starting median level of 2.28 mmol/L in LDL-C in patients primarily **treated with high to moderate statin** background therapy. A **sensitivity analysis** using all-cause mortality in place of cardiovascular mortality showed similar results.

The primary and key secondary endpoints demonstrated a **consistent beneficial effect** across a wide range of subgroups. Also, a comparable effect as for the primary endpoint for evolocumab could be demonstrated (18% reduction) when multiple events were considered. Further, a continuous relationship between the level of achieved LDL-C and adjusted CV event rates could be demonstrated. Notably, at the lowest end of LDL-C, patients were still at risk of 2.5 events per 100/patient years without a clear cut-off.

These results were further supported by an imaging study in 986 patients demonstrating a moderate effect on percent atheroma volume after 78 weeks (-0.96% (0.58, 1.33) for evolocumab vs 0.05% (-0.32, 0.42)) for placebo representing a **reduction of coronary atherosclerotic burden**.

3.3. Uncertainties and limitations about favourable effects

Slightly non-significant **increased hazard ratios for CV death** (251 vs 240; HR 1.05 (0.88, 1.25) and **overall mortality** (444 vs 426 events; HR 1.04 (0.91, 1.19) were observed. When looking more in detail into CV death events, these were mostly attributed to sudden cardiac death, and therefore cannot be well clarified for most of the cases. Moreover, for 88 deaths the cause remained undetermined. For non-CV

death, no specific pattern could be observed to clarify any difference in effect. It cannot be excluded that these observations are due to a chance finding. Also, study duration may have been too short to observe any significant beneficial (or detrimental) effect of evolocumab treatment on these endpoints.

The inclusion of **hospitalization for unstable angina, or coronary revascularization** in the primary endpoint are considered less robust in particular with respect to objective definitions and may introduce bias in relation to clinical decision making (see also SAWP advice in 2012 (EMA/CHMP/SAWP/561197/2012 [EMEA/H/SA/2377/1/2012/II]). However, the sample size was determined based on the key secondary endpoint of cardiovascular death, myocardial infarction, and stroke.

Despite an adequate representation of EU participants, the **treatment effect for Europe** (n=17335; HR 0.90, 95%CI 0.90-1.01) is less than for other regions, in particular US (n=4571; HR 0.62, 95%CI 0.51-0.76). No reasonable explanation could be identified. Further, there seems to be potentially differential result in the race subgroup. The treatment effects for several of the subgroup analyses appear to be counterintuitive and not consistent with expected determinant-effect relationship including e.g. LDL-C level, age, history of stroke, and diabetes. In contrast, some other subgroup display the expected relationship.

There was a limited representation of **patients above 75 years** (only 9.2%) and a limited number of patients with **renal insufficiency**. No data on patients with **liver insufficiency** have been presented.

3.4. Unfavourable effects

The **overall exposure** data from clinical studies has **substantially increased** from 6026 patients in the initial dossier to an additional 27525 subjects treated in the pivotal study (FOURIER), and the GLAGOV imaging study which included 968 patients. Further, it has been estimated that 61 600 subjects have been exposed to evolocumab in the postmarking setting.

Consistent with the initial submission, evolocumab generally displays a **safety profile similar to that of the control group** of statin and other lipid lowering therapy with both at 77.4% reported incidence of adverse events. Comparable to the initial dossier (except for diabetes), the most common adverse events were diabetes mellitus (8.8%, 8.2%), hypertension (8.0%, 8.7%), nasopharyngitis (7.8%, 7.4%), upper respiratory tract infection (5.1%, 4.8%), and back pain (4.9%, 4.7%) for evolocumab and placebo, respectively. **Serious adverse events** between evolocumab and placebo were also similar (24.8% vs 24.7%). Most frequently reported serious adverse events were found in the group of ischemic coronary artery disorders at comparable frequency between both treatment groups.

Evolocumab was well tolerated with acceptable numbers of **discontinuations** (12.2% evolocumab vs 12.7% placebo) with less **due to adverse events** (4.4% evolocumab vs 4.2% placebo). This included myalgia (0.3%, 0.3%), fatigue (< 0.1%, 0.2%), and arthralgia (0.1%, < 0.1%), respectively.

Consistent with the initial dossier, the incidence of adverse events for patients achieving **very low levels of LDL-C** was not different from patients with higher LDL-C levels (68.4% < 25 mg/dL, 73.2% < 40 mg/dL, 77.7% LDL-C ≥ 40 mg/dL placebo), also for serious adverse events (20.7% < 25 mg/dL, 23.0% < 40 mg/dL, 24.8% LDL-C ≥ 40 mg/dL placebo). The incidence of **neurocognitive adverse events** was consistent with this (1.4% < 25 mg/dL, 1.4% < 40 mg/dL, 1.5% LDL-C ≥ 40 mg/dL placebo). For potential **demyelination adverse events**, these events were also similar or lower in evolocumab-treated subjects with LDL-C < 25 mg/dL (0.6%) or < 40 mg/dL (0.7%) versus placebo (1.1%).

For **musculoskeletal adverse events**, no difference could be observed in the rate (24.3%, 24.4%) nor the specific pattern of adverse events. Also, comparable differences in CK shifts and elevations were observed. There was no imbalance in rhabdomyolysis (5 evolocumab, 6 placebo), while the 2 reported myopathy events were attributed to other agents (statin, chemotherapy, steroids) and were considered unrelated to evolocumab.

No clear effect on **hepatic disorders** of evolocumab could be observed, but there were slightly more AEs reported for evolocumab than placebo ((296 [2.1%], 256 [1.9%]), and for serious hepatic events (72 [0.5%] vs 58 [0.4%], but no notable differences in ALT/AST shifts or increases. There was no subject with Hy's law criteria. Eight serious hepatic events had a fatal outcome (6 evolocumab and 2 placebo), but could be explained by an alternative aetiology.

A slightly higher incidence of new onset of **diabetes mellitus** (NODM) was observed for evolocumab (8.1% vs 7.7%). However, HbA1c values were comparable throughout the study (at baseline 5.9% with change of 0.1% during the study for both treatment arms). Considering that DM reporting was lower in the overall program and differences in percentages in reporting in the FOURIER study were < 1% difference it is acceptable not to include diabetes mellitus as AE in section 4.8 of the SmPC.

For **immunological disorders**, slightly more **hypersensitivity events** were noticed for evolocumab (4.7% vs 4.2%), but serious adverse events were approximately similar ([34] 0.2% vs [25] 0.2%). Comparable to the initial dossier, the numbers tested positive for **anti-evolocumab binding antibodies** were low (n=43), and not associated with adverse events. No neutralizing antibodies were detected.

Device-related events occurred slightly more with evolocumab than placebo ([156] 1.1% vs [132] 1.0%) in accordance with a higher incidence of **injection site reactions** (1.9% vs 1.5%).

No clinically meaningful changes were found for changes in **blood pressure** between treatment arms during the study.

The incidence profile of adverse events in the **GLAGOV study** was generally in line with the findings of the pivotal FOURIER study, although with slightly different most commonly reported adverse events than in the FOURIER study (angina pectoris (7.4%, 8.9%), myalgia (7.0%, 5.8%), chest pain (7.0%, 5.4%), hypertension (6.0%, 7.6%), and non-cardiac chest pain (5.8%, 3.7%)).

3.5. Uncertainties and limitations about unfavourable effects

Exposure in the pivotal study was **limited to a median of 26 months**; this may be too short to exclude long term effects. A long-term follow-up study including patients from the pivotal FOURIER study is currently ongoing.

The applicant provided the results of treatment related adverse events. These were consistent with those already observed as treatment emergent adverse events. The most observed events in both groups combined (evolocumab, placebo) were myalgia (0.9%, 0.8%), diabetes mellitus (0.5%, 0.4%), diarrhea (0.4% in each group), and fatigue (0.4% in each group).

Deaths in the pivotal study were slightly more for evolocumab (444 vs 426 patients), although this was not found to be significantly different as reported and discussed in the efficacy section.

In a subset of the pivotal study (EBBINGHAUS study) **neuropsychological effects** were not different for evolocumab as assessed by the *cognitive domain of executive function* part of the CANTAB assessment and analysed according to a non-inferiority analysis. Also, no difference in effect on the cognitive domain of executive function could be observed for subgroups with very low level of LDL-C. However, it is

questioned whether the study duration of 96 weeks is sufficient to pick up changes for evaluation of potential cognitive effects of evolocumab treatment considering that cognitive dysfunction due to (possible) amyloid accumulation develops slowly.

Relative limited safety data is available for patients **> 75 years of age** (n=1286), although this can be considered sufficient in absolute terms. No particular safety concern could be identified in patients (n=204) with **renal impairment**, although number of patients were very limited.

No safety data on **renal adverse events** have been provided. The number of dipstick 4+ proteinuria was low but slightly higher for evolocumab (17) versus placebo (10). In the initial dossier the effect of evolocumab on renal function was considered limited. Evolocumab is not cleared by the kidneys.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Previously, evolocumab 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 and in patients with homozygous familial hypercholesterolemia.

Evolocumab has demonstrated a beneficial effect of **reducing cardiovascular events primarily on MI and stroke in a selected patient group with very high cardiovascular risk** as identified by documented cardiovascular disease. This effect on mainly ischemic events (stroke, MI) can be considered **clinically relevant**, despite that no effect could be demonstrated 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 patients still at risk of a 2.5 events per 100 patient-years at even the lowest LDL-C levels achieved. There seems to be no lower limit of LDL-C at which potential benefit disappears.

Regarding safety, evolocumab displayed **an acceptable safety profile** with a comparable or slightly higher incidence of adverse events to that of the comparator therapy (statin and other lipid lowering therapy), with very limited patients discontinuing treatment or showing serious adverse events. In addition, evolocumab 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.

For a lifelong treatment, **a follow-up period of 26 months can be considered limited**. Longer term data will be generated with **the follow-up study (FOURIER-OLE)** intended to be finalised by 2023, although these data are open-label and not controlled.

3.6.2. Balance of benefits and risks

The applicant has conducted **an outcome study to address and confirm the cardiovascular safety and efficacy of evolocumab** in a patient population primarily identified on their CV risk profile (very high CV risk based on established CV disease). In agreement with clinical practice guidelines 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 a history of a cardiovascular event.

A further reduction of LDL-C on top of existing therapy options has been demonstrated in the initial

submitted dossier. However, given the hypothetical benefit of a further reduction of LDL-C on CVS outcomes was only based on the assumption of possible CV risk reduction by the LDL-C surrogacy concept a statement was added in the SmPC during initial MAA that "the effect of Repatha on cardiovascular morbidity and mortality has not yet been determined". It was agreed to delete this sentence in the current procedure.

Despite that included patients were in need for lowering LDL-C levels according to their very high cardiovascular risk profile as recommended in the European clinical practice guideline (e.g. *2016 ESC/EAS Guideline on cardiovascular disease prevention in clinical practice),* **the effect could be considered moderate with a 15% reduction of the primary endpoint and a 2% absolute risk reduction achieved over 26 months of treatment**. This was primarily achieved by reduction in ischemic events of MI and stroke. No effect on CV death and overall mortality could be demonstrated, however, this has been the case with other lipid lowering therapies as well (e.g. ezetimibe, atorvastatin). Moreover, patients were further enriched by defining additional CV risk factors in the inclusion criteria.

The FOURIER study supports treating to LDL-C ''*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*). 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**.

In the FOURIER study, there is some evidence that treating lower LDL-C levels than currently recommended by the ESC clinical practice guideline (*2016 ESC/EAS Guidelines for the Management of Dyslipidaemias*) provide CV benefit. This is because the data suggest that even lower levels of LDL-C than the inclusion criteria (> 1.81 mmol/L (> 70 mg/dL) provide CV benefit, as there were t**wo thousand patients included with a lower LDL-C level than the inclusion criteria (> 1.81 mmol/L (> 70 mg/dL) showed a relative reduction in the primary and secondary composite endpoints to a similar extent as those patients meeting the inclusion criteria**. These data thus further **challenge the current clinical practice guideline recommendations** and **challenge the current treatment definition of "hypercholesterolemia" as currently included in the indication**. In this respect the study 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 "normocholesterolemia" and "hypercholesterolemia" 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 26 month treatment period **could still be considered too short** to reveal certain consequences of lifelong very low LDL-C levels or other evolocumab effects. It remains important to follow-up this 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, hemorrhagic 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 was considered reassuring. For other safety aspects, including adverse events specifically known to be associated with existing lipid lowering therapy, including **muscle related events, hepatic events, and renal events**; these have been closely monitored within the current study as well, and **did not give rise to specific concerns**. Following the RMP, adverse events of hypersensitivity and immunological events have been followed-up without any clear safety signs with evolocumab treatment. The applicant provided the results

of treatment related adverse events. These were consistent with those already observed as treatment emergent adverse events and were already included in the product information.

3.6.3. Additional considerations on the benefit-risk balance

The CHMP extensively discussed the initially proposed extension of the indications:

Repatha is indicated to reduce atherosclerotic cardiovascular disease risk in:

- *adults with high cardiovascular risk, or*
- *adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, or*
- *adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia*

as an adjunct to diet when used:

- *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 Repatha on cardiovascular morbidity and mortality has not yet been determined.*~~ *For study results with respect to effects on LDL-C, cardiovascular events, and populations studied see section 5.1.*

This indication aimed to include **the reduction of atherosclerotic cardiovascular disease risk in adults with high cardiovascular risk**. The CHMP questioned whether the cardiovascular effects demonstrated in the population of patients included in the FOURIER study could be extrapolated to the high cardiovascular risk population at large and specifically, if a similar effect size can be expected in European patients.

The applicant provided more insight in the study population and associated treatment effects. A proposal for an amended indication by including a **statement on prevention of cardiovascular disease** was made by the MAH as follows:

Hypercholesterolaemia and mixed dyslipidaemia

Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) 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.

Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

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

Prevention of cardiovascular disease

Repatha is indicated in adults with established cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease), 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.
For study results with respect to effects on LDL-C, cardiovascular events, and populations studied see section 5.1.

This proposed indication identifies patients eligible for further lipid lowering treatment based on their CV risk profile ("patients with established cardiovascular disease") but the following consideration need to be taken into account.

It was noted that **comparable statements were previously included in the SmPCs of statins**. However statin therapy is a **first line treatment in lipid lowering therapy** and also indicated for **primary prevention** of cardiovascular disease. Including the separate underlined statement of *"prevention of cardiovascular disease''* may give the impression that evolocumab could also be used 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 Fourier study**.

The FOURIER study was **restricted to patients with an established cardiovascular disease** (prior myocardial infarction, prior stroke, or symptomatic peripheral artery disease) **plus other risk factors** that predisposed them to a high likelihood of a future cardiovascular event. The applicant has presented the **data on absolute risk reduction according to predefined subgroups following different cardiovascular risk conditions** including the results according to the number of risk factors. Presentation according to risk factors demonstrated that patients with ≥ 1 major + ≥ 2 minor risk factors (n=16203) showed a larger treatment effect than patients with ≥ 1 major + < 2 minor risk factors (N = 9488). Subgroups of 0 major and ≥ 2 minor risk factors (N = 1763) and 0 major risk factor + < 2 minor risk factors demonstrated an unexpected larger treatment effect than for the subgroup of ≥ 1 major + < 2 minor risk factors, however, both subgroups were substantially smaller and the results should be interpreted with caution. Further, in term of **absolute risk reduction the trial results were of modest magnitude**, especially in patients with lower cardiovascular risk, but inconsistencies in relative

treatment effects were observed. Finally, **no effect was demonstrated on CV mortality (and overall mortality)** and a **less convincing effect size was seen in the European subgroup**. All these factors were the reason why the explicit description of the selected patient population studied in the Fourier study was considered of great importance.

In addition, in the FOURIER study there seems to be no lower limit of LDL-C at which potential benefit disappears. Consequently, patients with established CV disease, may be appropriate candidates for Repatha given that there is some evidence that lowering LDL-C levels than currently recommended by the ESC clinical practice guideline (*2016 ESC/EAS Guidelines for the Management of Dyslipidaemias*) provide CV benefit. These patients are not usually considered as having primary hypercholesterolaemia or requiring further LDL-C reduction.

On the basis of the argumentation above and in order to address the concerns raised by the CHMP, the applicant submitted a revised product information, proposing the following wording for the indication:

Hypercholesterolaemia and mixed dyslipidaemia

Repatha 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.*

Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Established atherosclerotic cardiovascular disease

Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial 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

The proposed indication was considered to **identify a patients population not covered by the already approved indication eligible for (further) lipid lowering treatment based on their CV risk profile** as has been selected and studied in the FOURIER study (patients with established atherosclerotic cardiovascular disease plus other risk factors that predisposed them to a high likelihood of a future cardiovascular event on top of maximum tolerated statin therapy). Of note, patients with established atherosclerotic cardiovascular disease and statin-intolerant or for whom statin is contra-indicated could also be treated based on this indication. Although, such data have not been

provided or evaluated, this would then be acceptable based on extrapolation from LDL-C lowering data from the initial submission.

3.7. Conclusions

The overall B/R of Repatha is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by a majority of 25 out of 31 the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
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
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	I and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None

C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None

Extension of the indication to adult patients with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors based on the results of the FOURIER study. As a consequence sections 4.1, 4.2, 4.4 4.8, 5.1 and 5.2 of the SmPC were updated. The Package Leaflet is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 5.1 of the SmPC to include the effects of evolocumab on atherosclerotic disease burden as measured by intravascular ultrasound based on Study 20120153 (GLAGOV study).

The RMP is updated to version 2.5 in order to add two category 3 studies (Study 20160250 and Study 20150338), as well as to update the milestones of five category 3 studies (20110110, 20110271, 20120138, 20130286, 20130295).

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

These conditions do fully reflect the advice received from the PRAC.

Divergent positions to the majority recommendation are appended to this report.

5. EPAR changes

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

Scope

Extension of the indication to adult patients with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors based on the results of the FOURIER study. As a consequence sections 4.1, 4.2, 4.4 4.8, 5.1 and 5.2 of the SmPC were updated. The Package Leaflet is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 5.1 of the SmPC to include the effects of evolocumab on atherosclerotic disease burden as measured by intravascular ultrasound based on Study 20120153 (GLAGOV study).

The RMP is updated to version 2.5 in order to add two category 3 studies (Study 20160250 and Study 20150338), as well as to update the milestones of five category 3 studies (20110110, 20110271, 20120138, 20130286, 20130295).

Summary

Please refer to the Scientific Discussion Repatha (EMEA/H/C/3766/II/017/G)

APPENDIX

DIVERGENT POSITION DATED 22 March 2018

DIVERGENT POSITION DATED 22 March 2018

Repatha EMEA/H/C/003766/II/0017/G

The below listed members of the CHMP did not agree with the CHMP's positive opinion recommending the extension of the indication to the marketing authorisation of Repatha as below (additions ***in bold;*** *deletions ~~strikethrough~~*):

Hypercholesterolaemia and mixed dyslipidaemia

Repatha 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.*

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Established atherosclerotic cardiovascular disease

Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial 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.

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

The reasons for divergent opinion were the following:

The new indication based on the results of the Fourier study is not supported since both the aim of the treatment as well as the target population in that study can be considered as already covered by the currently approved indication.

• The main aim of lipid lowering treatment is to reduce the risk of primary and/or secondary cardiovascular events and LDL-lowering is in general considered as an acceptable surrogate marker for lowering of this risk. This was confirmed by the Fourier study.

• The target population covered by the current indication includes (implicitly) both patients with and without established cardiovascular disease who have hypercholesterolemia or mixed dyslipidemia and are in need for additional lipid lowering treatment. This is considered to cover the study population in the Fourier study

In view of the above considerations the delegates listed below consider the benefit risk of this extension indication to be negative:

Bruno Sepodes

Kristina Dunder

Koenraad Norga

Christophe Focke

Sinan B. Sarac

Agnes Gyurasics