Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Evolocumab

Proprietary Product Name: Repatha

Sponsor: Amgen Australia Pty Ltd

March 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AI/pen	Autoinjector/pen(s)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFFAS	Cognitive Function Full Analysis Set
CFPAS	Cognitive Function Primary Analysis Set
CEC	Clinical Events Committee
CI	Confidence interval
CK	Creatine kinase
CRF	Case report form
CTCAE	National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events
CTT	Collaboration Cholesterol Treatment Trialists' Collaboration
CV	Cardiovascular
CVD	Cardiovascular Disease
CYP3A4	Cytochrome P450 3A4 Inhibitor
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay

Abbreviation	Meaning
EOS	End of study
FAS	Full analysis set
FBG	Fasting blood glucose
FOURIER	Study 20110118
GCP	Good clinical practice
GLAGOV	Study 20120153
HbA1c	Haemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HLGT	High Level Group Term
HR	Hazard ratio
hsCRP	High-sensitivity C-reactive protein
IAS	IVUS analysis set
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IP	Investigational product
IPD	Important protocol deviation
IRB	Institutional review board
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDL-C	Low density lipoprotein cholesterol
LFT	Liver function test
LLOQ	Lower limit of quantification
LMC	Lipid monitoring committee
Lp(a)	Lipoprotein a
MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Meaning
MI	Myocardial infarction
NCEP	National Cholesterol Education Program
NYHA	New York Heart Association
PAD	Peripheral artery disease
PAL	Paired associates learning
PALTEA	Paired associates learning total errors adjusted
PCSK9	Proprotein convertase subtilisin/kexin type 9
PEP	Potential endpoint event
PPAS	Per protocol analysis set
NODM	New onset diabetes mellitus
Q2W	Once every 2 weeks
QM	Once monthly
PAV	Percent atheroma volume
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SI	System international
SMQ	Standard MedDRA query
SOC	System organ class
TAV	Total atheroma volume
TIA	Transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
UC	Ultracentrifugation
ULN	Upper limit of normal
VLDL-C	Very low density lipoprotein cholesterol

I. Introduction to product submission

Submission details

Type of submission:	Extension of Indications
Decision:	Approved
Date of decision:	2 August 2018
Date of entry onto ARTG:	6 August 2018
ARTG numbers:	231152 and 273084
, *Black Triangle Scheme*	No
Active ingredient:	Evolocumab
Product name:	Repatha
Sponsor's name and address:	Amgen Australia Pty Ltd 115 Cotham Road, Kew VIC 3101
Dose form:	Solution for injection
Strengths:	140 mg/1 mL (Single use) Pre-filled syringe; and 420 mg /3.5 mL (120 mg/mL) Automated mini-doser
Containers:	Prefilled pen injector or automated mini-doser
Pack sizes:	1s, 2s and 3s (Pre-filled syringe) and 1s (Automated mini-doser)
Approved therapeutic use:	*Prevention of cardiovascular events* *Repatha is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke and coronary revascularisation) in adults with established cardiovascular disease in combination with an optimally dosed statin and/or other lipid lowering therapies (see Clinical Trials).* *Primary hypercholesterolaemia* *Repatha is indicated in adults with primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia and non-familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C):* • *in combination with a statin or statin with other lipid lowering therapies, or* • *alone or in combination with other lipid lowering therapies in patients who are statin intolerant.'*
Route of administration:	Subcutaneous (SC) injection
Dosage:	Primary hypercholesterolaemia and prevention of

cardiovascular events: The recommended dose for Repatha is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent.

Homozygous familial hypercholesterolaemia: The initial recommended dose for Repatha is 420 mg once monthly. The dose can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

Product background

This AusPAR describes the application by the sponsor to extend the indications of Repatha to include the prevention of cardiovascular disease outcomes, and to broaden the population for the hypercholesterolaemia indication.

The sponsor proposes to:

- Add an indication statement to capture that Repatha reduces cardiovascular events in patients with or at risk of atherosclerotic cardiovascular disease.
- Reintroduce into the indication statement the use of Repatha 'alone' or in combination with other lipid lowering therapies following evidence of outcomes data. Treatment using Repatha alone was removed following label negotiation prior to approval of the initial Marketing Application due to lack of outcomes data.
- Reintroduce the monotherapy data to the clinical trial section following evidence of outcomes data. The monotherapy clinical trial data was removed following label negotiation prior to approval of the initial Marketing Application due to lack of outcomes data.
- Include the FOURIER trial and GLAGOV trial data into the clinical trial section.
- Update the Adverse Event section to incorporate the latest safety data.
- Remove 'low LDL-C' as a precaution following the FOURIER trial (Study 20110118).
- Update the 'Renal impairment' patient population found under 'Special populations'.

Currently, Repatha is approved for the treatment of hypercholesterolemia, based on the effects of Repatha to lower low density lipoprotein cholesterol (LDL-C), a surrogate biomarker for cardiovascular risk reduction recognised by health authorities around the world. The currently approved indication is:

> *Repatha is indicated as an adjunct to diet and exercise in:*
>
> *Primary hypercholesterolaemia*
>
> *Repatha is indicated in adults with heterozygous familial hypercholesterolaemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD):*
>
> *in combination with a statin or statin with other lipid lowering therapies, or*
>
> *in combination with other lipid lowering therapies in patients who are statin-intolerant.*
>
> *The effect of Repatha on cardiovascular morbidity and mortality has not been determined.*

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 proposed indication is as follows:

Repatha is indicated as an adjunct to diet and exercise in:

Prevention of Cardiovascular Events

Repatha is indicated to reduce the risk of cardiovascular events in patients with or at risk of atherosclerotic cardiovascular disease

Hypercholesterolaemia

Repatha is indicated in adults with hypercholesterolaemia, alone or in combination with other lipid lowering therapies, to reduce low-density lipoprotein cholesterol (LDL-C).

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 currently approved dosage is as follows:

Primary Hypercholesterolaemia (HeFH or clinical atherosclerotic CVD)

The recommended dose for Repatha is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent.

Homozygous familial hypercholesterolaemia

The initial recommended dose for Repatha is 420 mg once monthly. The dose can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate (stages 2 and 3) renal impairment. Repatha has not been studied in patients with more severe (stages 4 or 5) renal impairment (eGFR < 30 mL/min/1.73m2).

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Repatha has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Elderly patients

No dose adjustment is necessary in elderly patients (age ≥ 65 years).'

The proposed dosage is the same for prevention of cardiovascular events with only a change of subtitle to '*Hypercholesterolaemia and prevention of Cardiovascular Events*'. The dosage for patients with renal impairment has been altered to '*No dose adjustment is necessary in patients with renal impairment*'.

There are no proposed changes to the administration section apart from a change to the indication wording in the table.

Active ingredient

Evolocumab is a human monoclonal immunoglobulin G2 (IgG2) which binds to the proprotein convertase subtilisin/kexin type 9 (PCSK9).

Information on the condition being treated

Cardiovascular (CV) disease includes coronary artery, cerebrovascular and peripheral arterial disease. It is a major cause of mortality and morbidity in Australia and worldwide. Major risk factors include blood lipid abnormalities, smoking, hypertension, diabetes, abdominal obesity and physical inactivity. The European Union guidelines on clinical investigation of medicinal products in the treatment of lipid disorders;[1] state that *a large body of epidemiological evidence now exists demonstrating a strong positive correlation and causal relationship between serum low density lipoprotein cholesterol (LDL-C), and the risk of coronary heart disease (CHD). Other clinical manifestations of atherosclerosis also appear linked to plasma LDL-C levels such as cerebrovascular disease (i.e. stroke) or peripheral vascular disease. In addition, clinical trials have shown that LDL-lowering therapy with HMG-Co A reductase inhibitors reduces risk for CHD.* Treatment choices are guided by a patient's level of risk. The National Vascular Disease Prevention Alliance's Guideline for the management of absolute cardiovascular disease risk (NVDP 2012) states that adults with high absolute risk of CV disease should be treated with lipid and blood pressure lowering pharmacotherapy in addition to lifestyle intervention unless contraindicated or clinically inappropriate.

Current treatment options

Current treatment options for lipid lowering include dietary modification, statins, ezetimibe, bile acid sequestering agents and PCSK9 inhibitors. Statins have by far the most persuasive evidence for risk reduction of the lipid lowering therapies and, as such, are the recommended first line therapy. If the LDL-C levels are not sufficiently reduced on maximum tolerated statin dose, then another agent can be added. Ezetimibe has typically been the second line therapy.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 9 December 2015.

A similar application was submitted in the EU on 25 May 2017 and had been approved in the USA on 1 June 2017. The sponsor stated that the applications were similar. The EU submission included three Studies 20110118, 20130385 and 20120153 but not the renal impairment study, Study 20140213. The USA submission included two parallel submissions, the first included Studies 20110118, 20130385 and 20120153. The second was stated to include 'summary data from the lipid lowering clinical trials in the original filing supporting an expansion of the current LDL-lowering indication' (Studies GAUSS 3 20120332 and renal impairment Study 20140213). The sponsor stated that 'GAUSS-3 was not part of the original Amgen clinical trial program but a study specifically requested by the FDA looking at the definition of statin intolerance'.

[1] EMA/CHMP/748108/2013 Rev. 3: Clinical investigation of medicinal products in the treatment of lipid disorders.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2017
First round evaluation completed	21 December 2017
Sponsor provides responses on questions raised in first round evaluation	27 February 2018
Second round evaluation completed	17 April 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	1 May 2018
Sponsor's pre-Advisory Committee response	15 May 2018
Advisory Committee meeting	1 June 2018
Registration decision (Outcome)	2 August 2018
Completion of administrative activities and registration on ARTG	6 August 2018
Number of working days from submission dossier acceptance to registration decision*	183

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

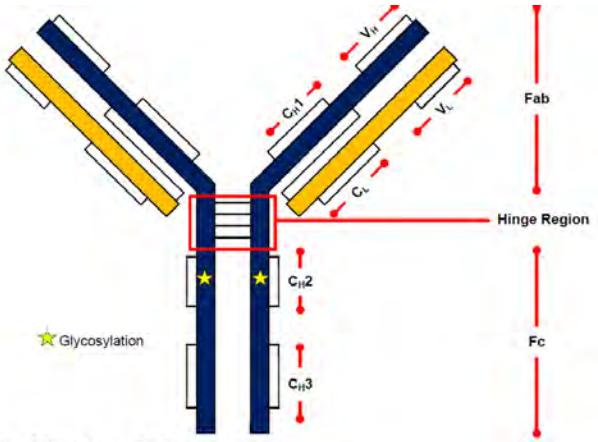
III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

Drug substance (active ingredient)

Repatha is a fully human immunoglobulin G2 (IgG2) monoclonal antibody with high affinity binding to Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). Repatha has an approximate molecular weight of 144 kilo Daltons (kDa) and is produced using recombinant deoxyribonucleic acid (DNA) technology in mammalian (Chinese hamster ovary (CHO)) cells.

Figure 1: Schematic of evolocumab structure



V_H is the variable domain of the heavy chain
C_H1, C_H2, and C_H3 are the constant domains of the heavy chain
V_L is the variable domain of the light chain
C_L is the constant domain of the light chain

Drug product

Repatha is a sterile, preservative free solution, clear to opalescent; colourless to yellowish solution for injection, practically free from particles.

Repatha is provided as a:

- 1 mL solution (140 mg/mL evolocumab) in a single use pre-filled pen with type 1 glass syringe and stainless steel needle; supplied as a 1 pack, 2 pack, and 3 pack.
- 3.5 mL solution (120 mg/mL) in a single-use prefilled cartridge assembly made from Crystal Zenith resin which is co-packaged with an administration device (AMD). The administration device is a compact, sterile, single-use, disposable, injection device intended for use only with the provided 3.5 mL pre-filled cartridge assembly; supplied as a 1 pack.

Note: A 1 mL solution (140 mg/mL evolocumab) in a single use pre-filled syringe made from type I glass with stainless steel needle, supplied as a 1 pack is not available in Australia.

Excipients

Repatha is formulated from proline, glacial acetic acid, polysorbate 80, water for injection and sodium hydroxide.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Clinical rationale

Repatha binds selectively to PCSK9 and inhibits circulating PCSK9 from binding to the low density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9 mediated LDLR degradation. Increasing liver LDLR levels results in associated reductions in serum LDL-C.

There is a medical need for therapies in patients who do not achieve LDL-C control with available therapies and also for those who are intolerant to statins. The sponsor stated in the clinical overview that 25 to 33% of high risk patients are unable to adequately control their lipid levels and that statin intolerance occurs in an estimated 5 to 15% of patients. The sponsor goes on to state that, LDL-C is important in the pathogenesis of atherosclerotic disease and lowering it has benefits in terms of cardiovascular event reduction. Therefore, evolocumab has a clinical place in reducing the risks of atherosclerotic disease for patients on statins who do not achieve LDL-C control as well as for those who are intolerant to them.

Formulation development

The formulation used in the submitted clinical trials is the same as that currently on the market.

Guidance

The sponsor stated that the design of Study 20110118 was discussed with the FDA and the EMA.

Relevant EU guidelines include:

- Guideline on the clinical investigation of medicinal products in the treatment of lipid disorders (EMA 2016); and
- Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMEA 2008).

Contents of the clinical dossier

Scope of the clinical dossier

The clinical submission included literature references and clinical study reports for the following four trials:

- Study 20140213 Phase I in subjects with renal impairment.
- Study 20110118 Phase III cardiovascular outcomes study (the FOURIER trial).
- Study 20130385 Phase III safety (cognitive function) study in a subset of subjects from Study 20110118.
- Study 20120153 Phase III study of the effects on atherosclerosis using intravascular ultrasound (the GLAGOV trial).

Paediatric data

No paediatric data were submitted.

Good clinical practice

The sponsor stated in the clinical study reports that all four clinical trials were conducted according to Good Clinical Practice (GCP) and local ethical and regulatory requirements.

Evaluator's commentary on the background information

Cardiovascular disease is a major cause of morbidity and mortality in our community. Evolocumab, a monoclonal antibody, is in a new class of agents the PCSK9 inhibitors, and has been shown to effectively lower LDL-C levels. The cardiovascular outcome data in this dossier will be critical for positioning this therapy in the treatment of cardiovascular disease.

Pharmacokinetics

Studies providing pharmacokinetic data

There was one submitted PK Study 20140213 in patients with renal impairment.

Evaluator's conclusions on pharmacokinetics

The dossier included one PK study in patients with renal impairment. After a single140 mg SC dose of evolocumab, severe renal impairment (RI) and end-stage renal disease (ESRD) patients had lower exposure to evolocumab while maintaining similar LDL-C lowering. This supports the sponsor's claim that dose adjustments are not necessary for patients with severe resistive index (RI) or ESRD receiving haemodialysis.

The relevant proposed alterations in the PI (Pharmacokinetics (PK), Precautions and Dosage and Administration sections) are acceptable.

Pharmacodynamics

Studies providing pharmacodynamic data

There were no submitted pharmacodynamic studies. Some pharmacodynamic data were available in the PK Study 20140213 in patients with renal impairment.

Evaluator's conclusions on pharmacodynamics

Patients with severe renal impairment and ESRD requiring haemodialysis showed clinically similar LDL-C level lowering compared to those with normal renal function after a single 140 mg SC dose of evolocumab.

Dosage selection for the pivotal studies

No new data submitted. The dosage used in the submitted Phase III studies was the same as the approved dose.

Efficacy

Studies providing efficacy data

There were two studies in the dossier with efficacy data: Study 20110118 assessing CV outcomes and Study 20120153 assessing the effect on atherosclerosis via intravascular ultrasound (IVUS). The CV outcome study has a cognitive function sub study (Study 20130385).

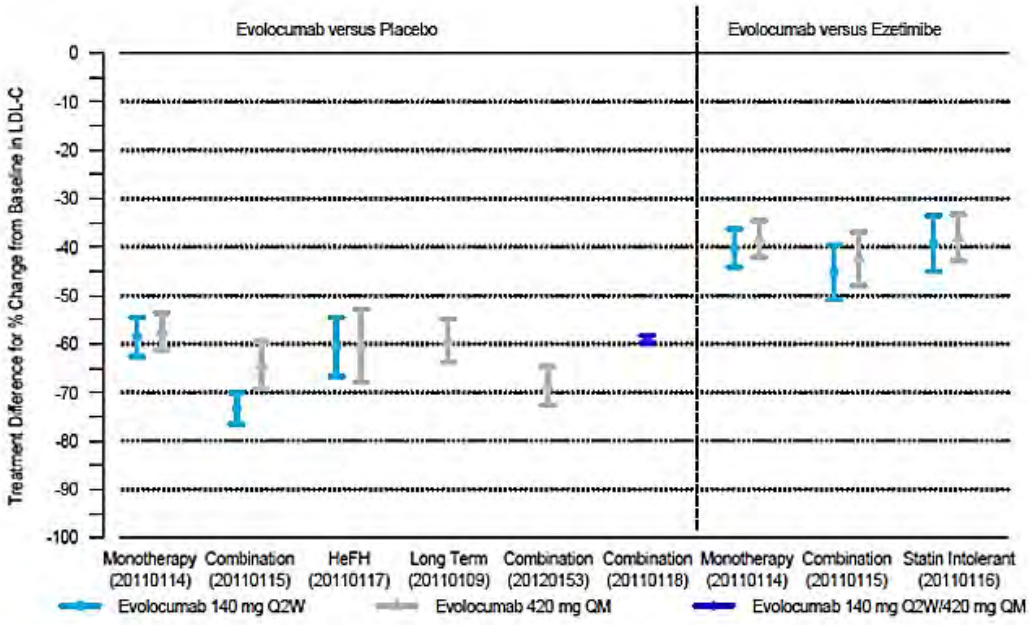
Evaluator's conclusions on efficacy

Study 20110118 was a large cardiovascular outcome study which was well conducted and produced robust results. Outcome data were gathered on an adult population with established cardiovascular disease and risk factors and treatment was on top of moderate to high intensity statins. The large study sample size and a fast event accrual allowed a shorter treatment duration of approximately 2 years which was less than other outcome studies where a four to five year treatment follow up is more typical.

The study was powered for its key secondary endpoint and the risk reduction for time to major cardiac events (cardiovascular death, myocardial infarction (MI) or stroke) was 20%. For the primary five composite endpoints which also included hospitalisation for unstable angina and coronary revascularisation, the risk reduction for time to first event was 15%. The results were driven by an effect on morbidity endpoints (MI, stroke and coronary revascularisation) as there was no significant effect on all cause or cardiovascular mortality. Efficacy was seen in both the first and second year of therapy with no diminution of effect.

The reduction in LDL-C in Study 20110118 was consistent with other studies (Figure 2).

Figure 2: Treatment differences for percent change from baseline in calculated LDL-C in the Phase III evolocumab program



HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; Q2W = every 2 weeks; QM = monthly.

All studies use calculated LDL-C except 20120153 and 20110118 which use reflexive LDL-C.

Least squares means from repeated measures model and associated 95% confidence intervals. Week 12 for all studies except 20110109 at week 52, 20120153 at week 78 and 20110118 at week 48. Results for Study 20110115 are from the random effects meta-analysis pooled results.

Given the population studied and lack of outcome data in adolescents, it follows that any indication should be limited to adults. There are also no CV outcome data on at risk adults who do not yet have established cardiovascular disease or in those taking evolocumab as monotherapy. The evaluator recommends rewording the indication to accurately reflect the population included in the clinical trial.

The IVUS study assessed the effects of 76 weeks evolocumab therapy on atherosclerosis in patients with CV disease on optimised statins. There were statistically significant reductions in percent atheroma volume (PAV) and total atheroma volume (TAV) with evolocumab compared to placebo, although the clinical relevance of the level of effect has been questioned. The added benefit with evolocumab on any degree of regression in PAV and TAV, was noted in 17.0% and 12.5% of subjects respectively, appears modest.

Safety

Studies providing safety data

There were two studies in the dossier with efficacy data: Study 20110118 assessing CV outcomes and Study 20120153 assessing the effect on atherosclerosis via intravascular ultrasound (IVUS). The CV outcome study has a cognitive function sub Study 20130385.

Patient exposure

In Study 20110118, there were 27,525 subjects who received study medication with 13,769 in the evolocumab group and 13,756 in the placebo group. The median duration

of exposure to evolocumab was 24.8 months (mean 24.1 months) and ranged from 0.07 months to 41.5 months. There were 7432 subjects with ≥ 24 months and 593 subjects with ≥ 36 months exposure (Table 1 below).

In Study 20120153, there were 968 subjects with 484 exposed to evolocumab 420 mg once monthly (QM). The median exposure duration was 18.4 months (range 0.95 to 19.65 months). Exposure was balanced between evolocumab and placebo groups.

The sponsor stated in their Summary of Clinical Safety that total exposure to evolocumab in the clinical development program is 24,385 subjects representing 49,755 patient-years of exposure.

Table 1: Study 20110118 Summary of exposure

	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.

Safety issues with the potential for major regulatory impact

Hepatic events, liver function and liver toxicity

Pivotal and/or main efficacy Study 20110118

Hepatobiliary disorder System Organ Class (SOC) adverse events (AEs) were balanced between groups (2.1% versus 1.9%). AEs of transaminase elevation and potential hepatic disorders occurred in 3.0% versus 2.7% of the evolocumab and placebo groups, respectively. Grade 3 and grade 4 events were reported in 0.6% and < 0.1% respectively with the same rate in both groups. The rate of serious events was 0.5% in the evolocumab and 0.4% in the placebo group.

Drug induced liver injury (DILI) was reported in 4 evolocumab and 2 placebo subjects (< 0.1% both groups). None of the evolocumab subjects had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN) or total bilirubin > 2 x ULN at any assessment. There was one non-serious case which occurred 6 days post first dose of evolocumab in a patient with urinary retention and treatment was withdrawn. There were 3 serious cases. One fatal case had alcohol use and ischaemic liver due to heart failure listed as possible contributing factors. The other two serious events included rhabdomyolysis with amiodarone and atorvastatin

interaction, and fever and nausea hospitalisation with suspected DILI. Study treatment was withdrawn in both serious cases.

Shifts from baseline Grade 0, 1 or 2 to post baseline Grade 3 or 4 in ALT and AST were similar between groups (Table 2). Median changes from baseline to Week 168 were minimal and balanced. There were four subjects (3 in the evolocumab group) with normal AST and ALT at baseline who had post baseline increases of > 3 x ULN and total bilirubin > 2 x ULN with ALP <2 x ULN. All had other possible aetiologies. There were no cases meeting Hy's Law criteria (Table 3).

Table 2: Study 20110118 Laboratory toxicity summary of shifts from baseline Grades 0, 1 or 2 to post-baseline Grades of 3 or 4Study 20110118 (Safety analysis set; Actual treatment group)

Panel Laboratory Parameter	Direction of Concentration Change	Baseline Grade	Maximum Post-baseline Grade	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
CHEMISTRY					
Alanine Aminotransferase	Increase	0	3	41 (0.3)	39 (0.3)
Alanine Aminotransferase	Increase	0	4	7 (0.1)	5 (<0.1)
Alanine Aminotransferase	Increase	1	3	16 (0.1)	13 (0.1)
Alanine Aminotransferase	Increase	1	4	1 (<0.1)	0 (0.0)
Alanine Aminotransferase	Increase	2	3	0 (0.0)	1 (<0.1)
Aspartate Aminotransferase	Increase	0	3	31 (0.2)	30 (0.2)
Aspartate Aminotransferase	Increase	0	4	7 (0.1)	4 (<0.1)
Aspartate Aminotransferase	Increase	1	3	13 (0.1)	10 (0.1)
Aspartate Aminotransferase	Increase	2	3	1 (<0.1)	1 (<0.1)
Creatine Kinase	Increase	0	3	47 (0.3)	37 (0.3)
Creatine Kinase	Increase	0	4	16 (0.1)	18 (0.1)
Creatine Kinase	Increase	1	3	20 (0.1)	24 (0.2)
Creatine Kinase	Increase	1	4	6 (<0.1)	5 (<0.1)
Creatine Kinase	Increase	2	3	9 (0.1)	7 (0.1)
Creatine Kinase	Increase	2	4	0 (0.0)	3 (<0.1)
Glucose	Increase	0	3	102 (0.7)	104 (0.8)
Glucose	Increase	0	4	8 (0.1)	3 (<0.1)
Glucose	Increase	1	3	238 (1.7)	240 (1.7)
Glucose	Increase	1	4	6 (<0.1)	8 (0.1)
Glucose	Increase	2	3	375 (2.7)	417 (3.0)
Glucose	Increase	2	4	2 (<0.1)	3 (<0.1)
Potassium	Increase	0	3	91 (0.7)	122 (0.9)
Potassium	Increase	1	3	26 (0.2)	37 (0.3)
Potassium	Increase	2	3	13 (0.1)	20 (0.1)
Potassium	Decrease	0	3	17 (0.1)	11 (0.1)
Potassium	Decrease	0	4	1 (<0.1)	2 (<0.1)
Potassium	Decrease	2	3	6 (<0.1)	1 (<0.1)

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EvoMab = Evolocumab (AMG 145); N = number of subjects randomized and dosed; CTCAE = Common Terminology Criteria for Adverse Events
Grading categories were determined using modified CTCAE version 4.03 without applying clinical context. The worst toxicity grade was assigned if criteria of multiple grades were met.

Table 3: Study 20110118 Subject incidence of liver function test abnormality(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 - Nº	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 - Nº	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 - Nº	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 / Nº * 100; ULN = upper limit of normal
The baseline is defined as the last non-missing value collected prior to or on randomization date.

Study 20120153

The rate of hepatic AEs (narrow search) was 2.5% and 2.1% in the evolocumab and placebo groups, respectively. There were no notable differences in the changes on liver function tests.

Renal function and renal toxicity

Pivotal and/or main efficacy Study 20110118

The rate of renal and urinary disorder SOC events was 6.5% and 6.7% in the evolocumab and placebo groups, respectively. The rate of 4+ proteinuria was 0.1% and < 0.1% in the evolocumab and placebo groups, respectively. The rate of creatinine increase of 3 grades was 0.1% in both groups.

Study 20120153

Renal and urinary disorder SOC AEs occurred at a similar rate (6.8% versus 7.2%) and renal failure/renal impairment was reported in 1.0% of each group. An increase in proteinuria was noted during the study (25.9% versus 19.4% at week 78) which was mainly trace or 1+. There were 14 evolocumab subjects with proteinuria increase from negative, 1 or 2+ to 3 or 4+ and this was often associated with comorbidities. There were no subjects with Grade 4 (4+) proteinuria.

Other clinical chemistry

Pivotal and/or main efficacy Study 20110118

Shift in potassium from Grades 0, 1 or 2 to Grades 3 or 4 occurred in 1.3% of the evolocumab and 1.0% of the placebo group. Shift in these grade for glucose were 5.6% versus 5.3%, in the respective groups (Table 2). The median change from baseline to week 168 in glucose was 0.2 mmol/L in both groups. There were no differences in the change from baseline to Week 168 in median glycated haemoglobin (HbA1c) levels (0.1% in both groups).

Creatine kinase (CK) shifts were similar between groups with 0.7% of each group shifting from Grades 0, 1 or 2 to Grades 3 or 4. CK levels > 5 x and > 10 x ULN were not higher in the evolocumab group (Table 4).

Table 4: Study 20110118 Subject incidence of CK > 5 x ULN or > 10 x ULN (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[a]	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[a]	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[a]	11987	11945
CK > 5 x ULN	63 (0.5)	55 (0.5)
CK > 10 x ULN	16 (0.1)	18 (0.2)

CK = creatine kinase; EvoMab = Evolocumab (AMG 145); N = number of subjects randomized and dosed; % = n / N[a] * 100; ULN = upper limit of normal

The baseline is defined as the last non-missing value collected prior to or on randomization date. Two subjects ([redacted] placebo, [redacted] EvoMab) are considered with at least one postbaseline CK test > 5 x ULN or > 10 x ULN based on the results collected between randomization and first investigational product dose date.

Study 20120153

Shift in glucose from Grade 0, 1, or 2 to Grade 3 or 4 occurred in 2.7% and 2.5% of the respectively groups. A two grade shift was more frequent with evolocumab (1.9% versus 0.8%). These subjects had pre-existing diabetes or elevated glucose and HbA1c at baseline. The median change from baseline to Week 78 was 0.2 and 0.1 mmol/L, respectively. Changes in CK were balanced between groups and unremarkable.

Haematology and haematological toxicity

Pivotal and/or main efficacy Study 20110118

Decreases in white blood cells (WBC) and in platelets were not remarkable.

There was little discussion in the study report CSR on any notable changes or differences between groups in haematology parameters and the sponsor has been asked to address this.

Study 20120153

There was little discussion in the CSR on any notable changes or differences between groups in haematology parameters and the sponsor has been asked to address this.

Electrocardiograph findings and cardiovascular safety

Pivotal and/or main efficacy Study 20110118

There were slightly more evolocumab subjects at baseline with QTcF;[2] >450 ms (7.0% versus 6.0%). Maximum post baseline increases were balanced between groups (Table 5).

Table 5: Study 20110118 QTc interval Fridericia correction maximum postbaseline and maximum increase from baseline categories in ms (ECG analysis set; Actual treatment group)

	Placebo (N = 2014) n (%)	EvoMab (N = 1984) n (%)
Baseline		
≤ 450	1659 (82.4)	1600 (80.6)
> 450 to 480	113 (5.6)	130 (6.6)
> 480 to 500	7 (0.3)	6 (0.3)
> 450	120 (6.0)	138 (7.0)
> 480	7 (0.3)	8 (0.4)
> 500	0 (0.0)	2 (0.1)
Missing	0 (0.0)	0 (0.0)
Maximum postbaseline		
≤ 450	1523 (75.6)	1485 (74.8)
> 450 to 480	181 (9.0)	171 (8.6)
> 480 to 500	12 (0.6)	18 (0.9)
> 450	196 (9.7)	192 (9.7)
> 480	15 (0.7)	21 (1.1)
> 500	3 (0.1)	3 (0.2)
Missing	0 (0.0)	0 (0.0)
Maximum increase from baseline		
≤ 30	1647 (81.8)	1600 (80.6)
> 30 to 60	48 (2.4)	47 (2.4)
> 30	50 (2.5)	52 (2.6)
> 60	2 (<0.1)	5 (0.3)
Missing	22 (1.1)	25 (1.3)

ECG = electrocardiogram; EvoMab = Evolocumab (AMG 145); N = number of subjects in the electrocardiogram analysis set; QTc = QT interval corrected for heart rate
Summary is based on observed data, and observations with the diagnoses or findings of artificial pacemaker, atrial fibrillation, atrial flutter, left bundle branch block, and right bundle branch block are excluded from analysis.

Study 20120153

Post baseline QTcF > 480 ms occurred in 0.4% and 0.2% of the evolocumab and placebo groups, respectively. An increase of 20 to 60 ms was noted in 2.7% versus 3.9% of the respectively groups with one subject in the evolocumab having a maximum post baseline QTcF increase of > 60 ms (466 ms).

Vital signs and clinical examination findings

Pivotal and/or main efficacy Study 20110118

It is noted that 80% of the trial population had a history of hypertension. Changes in vital signs were similar between groups.

[2] The QT interval is a measurement made on an electrocardiogram used to assess some of the electrical properties of the heart. It is calculated as the time from the start of the Q wave to the end of the T wave and approximates to the time taken from when the cardiac ventricles start to contract to when they finish relaxing. An abnormally long or abnormally short QT interval is associated with an increased risk of developing abnormal heart rhythms and sudden cardiac death. The QT interval is dependent on the heart rate in an obvious way (i.e., the faster the heart rate, the shorter the R–R interval and QT interval) and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia. Fridericia proposed an alternative correction formula using the cube-root of RR.

Study 20120153

Baseline history of hypertension was again frequent at 83%. Change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were not remarkable.

Immunogenicity and immunological events

Pivotal and/or main efficacy Study 20110118

Of the 13,769 subjects who received evolocumab, 13,748 had at least one antibody measurement, 12,410 at baseline and 13,343 with at least one post baseline level. At baseline prior to any dosing, 0.3% of the patients were anti-evolocumab binding antibody positive and one subject was positive for neutralising antibodies (negative at all further testing). For those who were antibody negative at baseline or had no result, 0.3% of the patients were positive post-baseline. There were 35 of these 43 subjects who had a single positive result. There were no subjects positive to neutralising antibodies post-baseline. There were no AEs associated with the positive antibody status.

Study 20120153

There were 2 subjects (0.4%) who had antibodies detected at baseline. The rate of post-baseline anti-evolocumab binding antibodies was 0.2% (n = 1). This subject had antibodies detected at one single time point.

Neurocognitive events

Pivotal and/or main efficacy Study 20110118

Neurocognitive AEs were assessed and the rate was similar between groups (1.6% versus 1.5%). Amnesia had a higher rate (0.4% versus 0.2%); however the higher level term of memory loss excluding dementia was similar (1.0% versus 0.9%). Less than 0.1% of each group had a neurocognitive treatment emergent adverse event (TEAE) that was Grade 4 or was a serious AE (SAE). There were more subjects in the evolocumab group (n = 20, 0.1%) who discontinued treatment due to such an event than in the placebo group (n = 9, < 0.1%). Analysis by lowest LDL-C level found no trend with low LDL-C (Table 6).

Table 6: Study 20110118 Incidence of potential neurocognitive TEAEs by lowest post-baseline LDL-C achieved by high level group term (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)

EvoMab = Evolocumab (AMG 145); N = number of subjects randomized and dosed with lowest postbaseline LDL-C < 25, < 40, or ≥ 40 mg/dL achieved on and before 30 days after the last dose of IP date;
MedDRA = Medical Dictionary for Regulatory Activities; LDL-C = low-density lipoprotein cholesterol;
HLGT = high level group term
The potential neurocognitive events are identified using HLGT terms that are deliria (incl. confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders.
Coded using MedDRA version 19.1.

Study 20130385

In the 1204 subjects in the sub Study 20120385, there was no notable effect of evolocumab compared to placebo on cognitive function as measured by the Cambridge Neuropsychological Test Automated Battery (CANTAB) assessments.[3]

Study 20120153

The rate of neurocognitive events was 1.4% and 1.2% in the evolocumab and placebo groups, respectively.

Post-marketing data

The sponsor submitted post-marketing data in their Summary of Clinical Safety up to 17 January 2017. It was estimated that 61,600 subjects were exposed to evolocumab in the post-marketing setting. There have been 14,337 individual case reports received with 74.8% of reports from solicited sources (patient support programs and market research) and the rest spontaneous (24.5%) or from post-marketing studies (0.6%). Of the 36,567 AEs, 88.0% were non-serious and 12% serious, with < 0.1% (n = 185) fatal. The most frequent AEs were drug dose omission, myalgia, injection site pain, back pain and arthralgia. The most frequently reported SAEs were MI, dyspnoea and pneumonia. Fatal events were most frequently MI and cardiac arrest.

The sponsor stated in their Summary of Clinical Safety that the evaluation of the safety data from the post-marketing experience has not resulted in the detection of any new risks or a change in the nature of the risks described in the risk management plan for evolocumab or any updates to the core data sheet or regional prescribing information. Reports of non-serious finger stick events associated with autoinjector use were received which resulted in a revision of the instructions for use in the US.

There have been 49 pregnancies of which 12 had maternal exposure during studies and 3 from post-marketing sources. The sponsor stated that no safety issues were identified.

Evaluator's conclusions on safety

The CV outcome Study 20110118 provided a large safety database of 27,525 subjects of whom 13,769 were exposed to evolocumab and had mean exposure duration of 24.1 months.

TEAEs were reported in 77.4% in both groups with the most frequent being diabetes, hypertension, nasopharyngitis and upper respiratory tract infection (URTI).

There was a small increase in hypersensitivity events (4.7% versus 4.2%) and injection site reactions (1.9% versus 1.5%) with evolocumab treatment.

There was no increase in muscle, demyelination or neuropathy events and no evidence of an increased risk of new onset diabetes mellitus where cases were adjudicated by the Clinical Events Committee (CEC). The statement in the PI relating to musculoskeletal events has been deleted and this is acceptable given the data from Study 20110118. The events of arthralgia, back pain and myalgia have been included in the adverse events table in the PI.

Neurocognitive function was assessed in 1204 subjects in the dedicated sub Study 20130385 of Study 20110118 and there was no significant effect on the measures of cognitive function using CANTAB assessments. In addition, in the full

[3] CANTAB components include SWM strategy 6-8 boxes (SWMS68), PAL total errors adjusted (PALTEA) and RTI median 5-choice reaction time (RTIMDRFT); see more in section Overall Benefit Risk assessment.

outcome study population, there was no increase in risk of potential neurocognitive adverse events noted. As a consequence, the sponsor has deleted the paragraph in the Adverse Effects section on the PI relating to neurocognitive events. This is also acceptable.

Assessment of TEAEs by subgroups of patients achieving lower levels of LDL-C post-baseline did not reveal any increase risk with lower LDL-C levels (< 0.6 mmol/L and < 1.0 mmol/L). A precaution relating to the unknown effects of low LDL-C has been deleted from the PI. The evaluator recommends that as data were only available for an average of 2 years of exposure and treatment could be life-long, the precaution should be retained. A statement could be included that no adverse consequences after 2 years of therapy have been identified.

Laboratory parameters were unremarkable, including CK and liver enzymes. The sponsor has been asked to comment on any relevant haematology findings.

Anti-evolocumab antibodies were present in 0.3% at baseline. Among those negative at baseline, 0.3% had a positive post baseline results for binding antibodies with the majority of these (81%) being transient. No one was positive for neutralising antibodies post baseline and the sponsor stated that no clinical sequelae were noted.

Safety in the IVUS Study 20120153 was in line with Study 20110118.

Subgroup analysis by race and age was unremarkable. Subjects 75 years and older had higher rates of events but no differences were evident between treatment groups. Small numbers with type 1 diabetes made it difficult to draw conclusions, although no risks were apparent. TEAEs in the small subgroup with severe renal impairment were balanced between groups.

Estimated post-marketing exposure is 61,600 patients to January 2017. The sponsor states that no regulatory action has been taken for safety issues. A change in the instructions on the US label was made in relation to needle stick injuries.

The sponsor stated that, with the inclusion of Studies 20110118 and 20120153 in the safety database, the adverse drug reaction profile has not altered apart from further characterisation of injection site reactions (Table 7).

Table 7: Subject incidences of adverse drug reactions

System Organ Class Preferred Term	Evolocumab (N = 18,546) n (%)	Control (N = 16,595) n (%)
Gastrointestinal disorders		
Nausea	327 (1.8)	282 (1.7)
General Disorders and Administration Site Conditions		
Injection site reactions (pain, erythema, bruising, swelling, and hemorrhage)	413 (2.2)	279 (1.7)
Infections and Infestations		
Influenza	586 (3.2)	485 (2.9)
Nasopharyngitis	1367 (7.4)	1176 (7.1)
Upper respiratory tract infection	848 (4.6)	733 (4.4)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia[b]	726 (3.9)	657 (4.0)
Back pain[b]	823 (4.4)	740 (4.5)
Skin and Subcutaneous Tissue Disorders		
Rash	257 (1.4)	220 (1.3)
Urticaria	59 (0.3)	40 (0.2)

N = number of subjects randomized and dosed.
Adverse events were coded using MedDRA version 19.1.
Adverse event summaries do not include deaths or positively adjudicated non-fatal clinical endpoints reported in Study 20110118.
[a] Includes Double-Blinded Studies: 20090158, 20090159, 20101154, 20101155, 20110231, 20110109, 20110114, 20110115, 20110116, 20110117, 20120348, 20120356, 20120332 part B, 20110118, 20120153, 20120122.
[b] Events of arthralgia and back pain continue to be considered adverse drug reactions due to the higher incidence observed in the evolocumab group compared with the control group both in the original evolocumab application and in Study 20110118.

Pregnancy risks still need to be delineated and the sponsor stated that Studies 20150338 and 20150162 are evaluating this.

The CV outcome study was of relatively short duration and data from ongoing open label extension Studies 20130295 and 20160250 will be important for assessment of long term safety.

The sponsor has been asked to comment on any safety data in subjects with hepatitis C which is included as an area of lacking data in the Risk Management Plan (RMP).

First round benefit-risk assessment

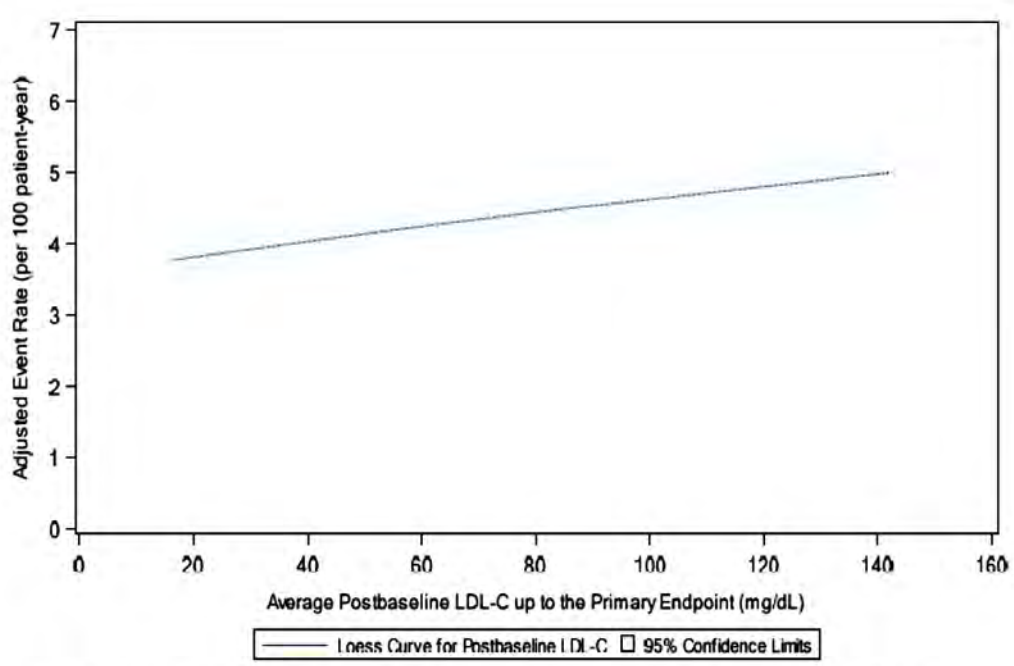
First round assessment of benefits

The cardiovascular outcome Study 20110118 provided evidence that evolocumab on top of moderate to high intensity statin therapy reduces the risk of cardiovascular events in adult patients with established CV disease and risk factors. The study was large, well conducted and produced robust results. After a median follow up of 26 months (59,865 patient years), the level of risk reduction was 15% for the 5 composite endpoint and 20% for CV death, MI and stroke. Risk reduction appeared to commence after around 5 months of therapy and there was some evidence for improvement in risk reduction in the second year of treatment compared to the first year. The benefit was achieved on morbidity endpoints of MI, stroke and coronary revascularisation and there was no impact on CV or all-cause mortality, or on hospitalisation for coronary revascularisation. High use in the trial of other pharmacotherapies which lower CV

mortality could have impacted on this mortality finding. There was no analysis provided on the number needed to treat in order to achieve event prevention and this has been queried.

The relationship between post-baseline LDL-C and the primary composite endpoint was shown (Figure 3), albeit in an exploratory post hoc analysis. The study's findings are consistent with the Cholesterol Treatment Trialists' Collaboration which found that '*further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke*'.[4] Treatment with evolocumab lowered LDL-C below what is achieved with statins and this has resulted in additional clinical benefit.

Figure 3: Study 20110118 Adjusted event rate of primary endpoint (CV Death, MI, hospitalisation for unstable angina, stroke, or coronary revascularisation) by average post-baseline LDL-C up to the primary endpoint (Full analysis set)



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 from the same blood sample, if available
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 endpoint collection date
Adjusted event rate per 100 patient-year is based on a Cox model adjusted by postbaseline LDL-C category and other baseline covariates of age, gender, type 2 diabetes, prior history of myocardial infarction, prior history of stroke, baseline LDL-C, current smoking status and region.

Findings are supported by data from the IVUS study which showed a decrease in atherosclerosis on top of what may be achieved by statins, although the clinical relevance of the level of changes seen has been questioned.

A major limitation of the data is the lack of long term follow up. The median treatment and follow up duration of approximately 2 years was less than the median follow up of 4.8 years in the 21 trials of statin versus control in the CTT meta-analysis. The sponsor stated that this short duration was due to a faster than anticipated accrual of events and further insight into this has been requested.

[4] Cholesterol Treatment Trialists' Collaboration (CTTC), Baigent C Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta- analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-1681

After this median exposure duration of 24 months, analysis of the large safety dataset of 13,769 patients treated with evolocumab did not identify any new safety signals. The rates of death, SAEs, and treatment discontinuation due to an AE were all comparable to that seen with placebo treatment. There was a modest increased risk of hypersensitivity and injection site reactions. Immunogenicity data has been updated in the PI to include the rate of anti-evolocumab antibodies from the CV outcomes study (0.3%). No adverse consequences of this were noted.

At low LDL-C levels there were no evident safety signals. Nonetheless, the evaluator recommends that the relevant precaution is retained as therapy could be life-long and the study only provided data from mean exposure duration of two years. There were comparable rates of neurocognitive TEAEs and non-inferior effects compared to placebo on cognitive function although the clinical significance of the CANTAB changes reported need some explanation. Given the data presented, it is acceptable to delete the statement in the PI relating to neurocognitive effects. The lack of findings on muscular events also supports the sponsor's request to delete an associated paragraph in the PI.

The patient groups in which there is missing safety information have been adequately covered in the RMP. It has been proposed to alter the adverse events table to included only AEs with a frequency of 2% rather than 1%. This change is acceptable, although the presentation of adverse reaction data has been queried.

There are major proposed revisions to the indication for evolocumab. The proposed indication for prevention of cardiovascular events states the '*Repatha is indicated to reduce the risk of cardiovascular events*'. Given the positive data were achieved only for certain events, consideration should be given to rewording this to Repatha is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularisation as has been proposed for the US label. The proposed indication includes '*patients with or at risk of atherosclerotic cardiovascular disease*' and also does not include an age group. The indication needs to reflect the population group studied in Study 20110118 which was adults 40 years and over with established and clinically evident atherosclerotic disease and risk factors. No data were presented in the paediatric population or in adults without clinical atherosclerotic disease. As the risk reduction was achieved on top of moderate to high intensity statin therapy this should also be reflected in the indication.

The sponsor has proposed that evolocumab should be indicated as monotherapy for both CV event prevention and treatment of hypercholesterolaemia. The original registration dossier included monotherapy efficacy data from two short term studies of 12 weeks duration. At this time, the monotherapy indication was not supported due to the lack of longer term monotherapy data, the lack of CV outcome data and availability of alternative therapies. In both trials evaluated in this dossier, evolocumab was used on top of moderate to high intensity statin therapy and no new monotherapy data have been presented. The evaluator contends that there are still insufficient data to support the use of evolocumab without statins in the overall population with established atherosclerotic disease.

For patients who are intolerant of statins there are fewer treatment alternatives. While the study populations were slightly different (coronary artery disease with acute coronary syndrome versus established atherosclerotic disease), the risk reduction with evolocumab (plus statin) was notably higher than the more modest reductions achieved with ezetimibe (plus simvastatin) in the IMPROVE-IT trial (6.4% risk reduction for CV deaths, major cardiac events and non-fatal stroke (Ezetrol (ezetimibe) PI).[5] Given the lack of treatment options for statin intolerant patients, the robustness of the evolocumab data, the level of CV event risk reduction and safety profile of

[5] https://www.ebs.tga.gov.au/

evolocumab, the evaluator believes there is a relevant clinical place for evolocumab monotherapy in this particular group who are unable to take statins.

The evaluator therefore recommends reverting to the current approved indication for hypercholesterolaemia where usage is in combination with a statin or statin and other lipid lowering therapies. Only in those who cannot tolerate statins, it is recommended that evolocumab may be used alone or with other lipid lowering therapies.

The renal impairment study supports the changes to the product information that no dose adjustment is needed in patients with Stage 4 or 5 chronic renal diseases.

In summary, there is a clinical place for ongoing reduction in cardiovascular morbidity and mortality and evolocumab offers an additional therapy option. Evolocumab efficacy data in non-fatal CV event prevention are positive and there are no new safety signals from the expanded clinical trials and post-marketing safety database.

Nevertheless, the benefit-risk balance in the proposed usage is currently not favourable. This is because the proposed indication does not reflect the patient population in which efficacy and safety were demonstrated and a generalised monotherapy indication is not supported. The benefit-risk balance may become favourable if the changes recommended to the indication are adopted and there are satisfactory responses to the questions and comments (see Second round evaluation below).

First round recommendation regarding authorisation

Following the first round evaluation, approval of the changes to the PI for evolocumab is currently not recommended. This is due to the following:

- The indication needs to be altered.
- The Clinical questions (see below) need to be satisfactorily answered.
- Comments on the PI and Consumer Medicine Information (CMI) need to be addressed.

Second round clinical evaluation

The sponsor has submitted responses to the questions following the first round evaluation. These responses are discussed below together with evaluator comments.

Efficacy

Question 1

Please discuss any insights into why the event rate in Study 20110118 was higher than anticipated in the sample size calculations.

Sponsor response

The assumed and actual event rates in Study 20110118 did not differ considerably for either the primary composite or key secondary composite endpoints. The assumed placebo event rate for the key secondary composite endpoint in the power calculation was 2%. The observed placebo event rate for the key secondary composite endpoint in the final analysis was approximately 3% per year based on 1013 placebo subjects experiencing an event with 29930.0 patient-years of follow-up in the overall placebo group. The higher rate observed indicates recruitment of a patient population with a high unmet need, despite current standard of care, as was the purpose of Study 20110118.

Evaluator comment

The explanation is accepted.

Question 2

In Study 20110118, two dose frequencies (fortnightly and monthly) were used. Please comment on if there was any difference in CV event risk dependent on which dose frequency was used.

Sponsor response

The evolocumab 140 mg SC once every 2 weeks (Q2W) and 420 mg SC QM dosing regimens are clinically equivalent, and did not differ with respect to composite cardiovascular endpoints in Study 20110118 (Table 8). It is noted that there are limitations to a comparison of the 2 dosing regimens: the study was not powered for such an analysis; subjects could not initiate treatment with QM until after protocol amendment 4; the majority of subjects remained on Q2W dosing; and subjects could switch dose frequency based on preference. Thus, the estimation of variation for cardiovascular endpoints in the subjects remaining on QM dosing is greater due to the smaller number of subjects in that subgroup.

Table 8: Study 20110118 Subgroup summary of primary and secondary efficacy endpoints subgroups = dose frequency (Full analysis set)

	Q2W				QM			
	Placebo (N = 11882) n (%)	EvoMab (N = 11907) n (%)	Hazard Ratio[c] (95% CI)	Nominal p-value[d]	Placebo (N = 1246) n (%)	EvoMab (N = 1251) n (%)	Hazard Ratio[c] (95% CI)	Nominal p-value[d]
Primary endpoint[a]	1346 (11.33)	1185 (9.95)	0.87 (0.81, 0.94)	0.0006	129 (10.35)	102 (8.15)	0.77 (0.59, 1.00)	0.0462
Key secondary endpoint[b]	882 (7.42)	720 (6.05)	0.81 (0.73, 0.89)	<0.0001	78 (6.26)	60 (4.80)	0.76 (0.54, 1.06)	0.1016

EvoMab = Evolocumab (AMG 145); IVRS = interactive voice response system; N = number of subjects randomised; n = Number of subjects having experienced the endpoint; % = (n/N) x 100; Q2W = once every 2 weeks; QM = once monthly.
Includes the events occurring between the subject randomisation date and the subject last confirmed survival status date, inclusive.
[a] Primary endpoint is the time to cardiovascular death, myocardial infarction, hospitalisation for unstable angina, stroke, or coronary revascularisation, whichever occurs first.
[b] Key secondary endpoint is the time to cardiovascular death, myocardial infarction, or stroke, whichever occurs first.
[c] Based on a Cox model stratified by the randomisation stratification factors collected via IVRS.
[d] 2-sided log-rank test stratified by randomisation stratification factors collected via IVRS.

Evaluator comment

The data limitations, due to low numbers in the monthly dosing group, are noted. Nonetheless, it is reassuring to see similar endpoint rates between the two dose frequency groups.

Question 3

In Study 20110118, has there been any ongoing follow up of subjects beyond the 26 month study period and if so are longer term efficacy and safety data available?

Sponsor response

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 1,226 (4.5%) subjects for ≥ 36 months.

Two open-label extension studies, Studies 20130295 and 20160250 are ongoing to assess the long-term safety and tolerability of evolocumab in subjects who completed Study 20110118. Efficacy is being assessed as a secondary endpoint in these studies. Approximately 5000 subjects are planned for enrolment in Study 20130295, including approximately 2000 subjects with ≥ 2 years of study exposure in the FOURIER trial. A further 1600 subjects have been enrolled in Study 20160250. Both extension studies are designed to collect safety data for up to 260 weeks (5 years). No safety signals have

been identified to date from the review of ongoing data. No clinical study reports are available at this time. Both studies are referenced in and ongoing as part of additional pharmacovigilance activities in the current Australian Risk Management Plan.

Evaluator comment

The sponsor reported no safety signals to date in the ongoing extension studies of Study 20110118, although no specific data were presented. Data from these studies should be submitted when available.

Question 4

There was no analysis provided on the number needed to treat in order to achieve event prevention in Study 20110118. Please provide and discuss relevant data.

Sponsor response

The sponsor noted that that *there are limitations to evaluating cardiovascular risk using attributable risk reduction (ARR), outlined as follows:*

- *ARR is dependent on the risk of the underlying patient population, ie, the higher the risk of the cohort, the greater the ARR.*
- *Additionally, ARR is time-dependent, ie, it increases over time due to accumulating risk.*

Since NNT is the reciprocal of the point estimate for ARR, the limitations of ARR also apply to NNT. While ARR and NNT may provide incremental information about a treatment, these limitations reiterate why RRR is the best measure for use in primary analyses to evaluate the cardiovascular risk in pivotal cardiovascular outcome studies.

For the primary composite endpoint the number needed to treat was 142.8, 65.6 and 48.4 at 12, 24 and 36 months, respectively (Table 9). For the key secondary endpoint (time to CV death, MI or stroke) the NNT was 172.1, 73.9 and 49.4 at 12, 24 and 36 months respectively (Table 9). The relative risk reduction (RRR) was 0.15 and 0.20 for the primary and key secondary composite endpoints, respectively (Table 10).

Table 9: Study 20110118 Absolute risk reduction (placebo evolocumab) and number needed to treat over time for the primary composite endpoint and key secondary composite endpoints (Full analysis set)

	ARR (95% CI) – percentage Number Needed to Treat		
Efficacy Endpoint (N = 27,564)	**12 months**	**24 months**	**36 months**
Time to composite event of cardiovascular death, myocardial infarction, hospitalisation for unstable angina, stroke, or coronary revascularisation	0.70 (0.15, 1.25) 142.8	1.52 (0.79, 2.25) 65.6	2.07 (0.85, 3.29) 48.4
Time to cardiovascular death, myocardial infarction, or stroke	0.58 (0.15, 1.01) 172.1	1.35 (0.76, 1.94) 73.9	2.02 (0.96, 3.08) 49.4

ARR = absolute risk reduction (placebo K-M estimate – evolocumab K-M estimate); CI = confidence interval; K-M = Kaplan Meier.

Table 10: Study 20110118 Relative risk reduction for the primary composite endpoint and key secondary composite endpoints (Full analysis set)

Efficacy Endpoint (N = 27,564)	RRR (95% CI)
Time to composite event of cardiovascular death, myocardial infarction, hospitalisation for unstable angina, stroke, or coronary revascularisation	0.15 (0.08, 0.21)
Time to cardiovascular death, myocardial infarction, or stroke	0.20 (0.12, 0.27)

CI = confidence interval; HR = hazard ratio; IVRS = interactive voice response system; RRR = relative risk reduction (1 – HR where HR is based on a Cox model stratified by the randomisation stratification factors collected via IVRS).
Source: FOURIER_ARR_NNT.

Evaluator comment

Based largely on the CTT Collaborators' meta-analysis[6], it has been reported on the review website NNT.com that after 5 years of statin therapy in patients with known heart disease the NNT was 83, 39 and 125 to prevent one death, one non-fatal MI and one stroke, respectively. For primary prevention of cardiovascular disease, the number needed to treat for 5 years with a statin has been reported at 138 for all-cause mortality and 49 for fatal and non-fatal cardiovascular disease events.[7] Data from the JUPITER trial of rosuvastatin, reported a 3 year NNT of 49 for the primary end point of MI, stroke, hospitalisation for unstable angina, arterial revascularisation, or cardiovascular death and a 3 year NNT for MI, stroke and any death was 54.[8]

The data for evolocumab indicate that about 50 patients with established CV disease need to be treated for 3 years to prevent one CV event in the composite endpoint. The evaluator agrees with the sponsor's caution in the interpretation of the NNT analysis. Data are not directly comparable due to differing patient populations, differing therapy duration (three versus five years) and varying endpoints. In addition, the data for evolocumab are in combination with moderate to high intensity statin therapy and separation of the effects of each component is not possible. A comparative review of the number needed to treat is beyond the scope of this evaluation, however it can be concluded that results seen with evolocumab are within the range of that seen with statins alone.

Question 5

In Study 20120153, while the results on PAV and TAV reduction with evolocumab were statistically significant, please comment on the clinical relevance and benefit of this level of reduction in coronary atherosclerosis.

Sponsor response

The sponsor discussed the results from Study 20130153 and the relationship between changes in PAV and LDL-C levels. The relationship between LDL-C and CV risk was discussed. However '*to date, there are no randomised controlled trials where both IVUS endpoints (PAV and TAV) and cardiovascular outcomes have been evaluated within the same study evaluating the effect of LDL-C lowering therapy*'.

[6] Cholesterol Treatment Trialists' (CTT) Collaboration (2005). Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet*. 366: 1267-1278.
[7] Taylor FC, Huffman M, Ebrahim S (2013). Statin therapy for primary prevention of cardiovascular disease. *JAMA.* 310 (22) 2451-2452
[8] Ridker PM, MacFadyen JG, Fonseca FAH et al. (2009). Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Circ Cardiovasc Qual Outcomes*. 2: 616-623

The '*results from Study 20120153 demonstrate a positive, measurable, statistically significant biologic and clinically relevant effect of evolocumab on atherosclerosis, beyond what is achievable with optimised statins alone. The data supplement the cardiovascular outcomes data from Study 20110118 by providing insight on the effect of evolocumab on underlying disease, at the vessel wall and plaque level'.*

Evaluator comment

The results of Study 20120153 show an impact of evolocumab on the atherosclerosis disease process. The clinical benefit of the level of PAV and TAV reduction was not discussed and only inferred from the results of Study 20110118.

Safety

Question 6

In Study 20130385, the clinical study report stated that the cognitive function efficacy endpoints were the 'change from baseline' but it does not state up to what time point. Was it change from baseline to end of study? Please confirm.

Sponsor response

The efficacy endpoints for Study 20130385 evaluated the change in cognitive function between baseline and the average of post-baseline observations.

Evaluator comment

The clarification is noted.

Question 7

The sample size for the primary endpoint in Study 20130385 was 1204 which was less than the 1500 target. Please comment on the implications of this reduced sample size.

Sponsor response

There was no impact on the primary objective evaluation as non-inferiority was demonstrated with the 1204 subjects included in the CFPAS (cognitive function primary analysis set). Approximately 1200 subjects in the CFPAS would provide approximately 93% power.

Evaluator comment

The reduced sample size still gave the study adequate power.

Question 8

In Study 20130385, there was no significant treatment difference between evolocumab and placebo on the three cognitive assessments, while there were some small changes from baseline in both groups. Please comment on the clinical significance, if any, of these changes over time seen in both treatment groups.

Sponsor response

The changes in cognitive function over time were small and *'are approximately an order of magnitude smaller than those associated with mild cognitive impairment (Saunders et al, 2011),*[9] *which is itself typically subclinical. The sponsor concluded that the parallel changes in cognitive test performance observed in the placebo- and evolocumab-treated groups over the course of Study 20130385 are small, expected, and of no clinical significance in the interpretation of the study results'*.

[9] Saunders NL, Summers MJ. Longitudinal deficits to attention, executive, and working memory in subtypes of mild cognitive impairment. *Neuropsych*. 2011;25(2):237-234

Evaluator comment

The evaluator accepts the explanation that the cognitive changes seen in both groups are unlikely to have clinical significance.

Question 9

In Study 20110118, apart from device-related events, the rates of treatment-related AEs were not discussed in the study report. Please discuss treatment-related events and comment on any differences between treatment groups.

Sponsor response

The rate of treatment-related AEs was 9.7% and 9.0% in the evolocumab and placebo groups, respectively. The rate of grade ≥ 3 treatment-related AEs was 1.4% in both groups (Table 11).The most frequent treatment-related events occurring in ≥ 0.1% of subjects were myalgia (0.9%, 0.8%), diabetes mellitus (0.5%, 0.4%), diarrhoea (0.4% in each group) and fatigue (0.4% in each group) (Table 12).

Table 11: Study 20110118 Summary of subject incidence of treatment-emergent adverse events related to investigational product (Safety analysis set; Actual treatment group)

	Placebo (N = 13756)	EvoMab (N = 13769)
All treatment-related adverse events	1240 (9.0)	1341 (9.7)
Grade ≥ 2	676 (4.9)	718 (5.2)
Grade ≥ 3	191 (1.4)	198 (1.4)
Grade ≥ 4	21 (0.2)	20 (0.1)
Serious adverse events	107 (0.8)	117 (0.8)
Leading to discontinuation of investigational product	204 (1.5)	229 (1.7)
Serious	25 (0.2)	38 (0.3)
Device-related adverse events	84 (0.6)	111 (0.8)
Grade ≥ 2	11 (< 0.1)	15 (0.1)
Grade ≥ 3	2 (< 0.1)	1 (< 0.1)
Grade ≥ 4	1 (< 0.1)	0
Serious	1 (< 0.1)	0

EvoMab = Evolocumab (AMG 145); MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects randomised and dosed.
Data are presented as number (%) of subjects. All death events were adjudicated independently by an external Clinical Events Committee and were not included in the adverse events tables. Coded using MedDRA version 19.1.
Source: Table 14-6.602.402-gah of Study 20110118.

Table 12: Study 20110118 Treatment-emergent adverse events related to investigational product and reported for ≥ 0.1% of subjects in any treatment group (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 randomised 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.
Source: Table 14-6.602.2-G of Study 20110118.

Evaluator comment

There were no evident safety signals on analysis of treatment-related AEs in Study 20110118.

Question 10

In Study 20120153, the rates of treatment-related AEs were also not discussed in the study report. Please discuss these and comment on any differences between treatment groups.

Sponsor response

The rate of treatment-related AEs in Study 20120153 was 14.0% and 16.5% in the evolocumab and placebo groups, respectively. The rate of Grade ≥ 3 treatment-related AEs was 2.5% and 1.7% in the respective groups (Table 13). The most frequent event was myalgia (1.9% versus 2.5%).

Table 13: Study 20120153 Summary of subject incidence of treatment emergent adverse events related to investigational product (Full analysis set; Actual treatment group)

	Placebo QM (N = 484) n (%)	EvoMab 420 mg QM (N = 484) n (%)
All treatment emergent adverse events	80 (16.5)	68 (14.0)
Grade ≥ 2	36 (7.4)	32 (6.6)
Grade ≥ 3	8 (1.7)	12 (2.5)
Grade ≥ 4	1 (0.2)	0 (0.0)
Serious adverse events	6 (1.2)	9 (1.9)
Leading to discontinuation of investigational product	6 (1.2)	11 (2.3)
Serious	1 (0.2)	1 (0.2)
Non-serious	5 (1.0)	11 (2.3)
Fatal adverse events	0 (0.0)	0 (0.0)
Device related adverse events	6 (1.2)	7 (1.4)
Grade ≥ 2	1 (0.2)	3 (0.6)
Grade ≥ 3	0 (0.0)	1 (0.2)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious	0 (0.0)	0 (0.0)

N = number of subjects randomised and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous)
Coded using MedDRA version 19.0
Source: Table 14-6.604.1 of Study 20120153

Evaluator comment

There were no evident safety signals on analysis of treatment-related AEs in Study 20120153.

Question 11

There was little discussion in the clinical study reports for Studies 20110118 and 20120153 on any notable changes or differences between groups in haematology parameters. Please discuss any relevant haematological findings (laboratory and adverse event) from these two studies.

Sponsor response

A review of available haematology laboratory data did not identify any trends indicative of clinically important treatment related laboratory abnormalities with evolocumab treatment in either study. Specifically, haematocrit, haemoglobin, mean corpuscular haemoglobin, mean corpuscular volume, platelets, red blood cells, red cell distribution width, and white blood cells by scheduled visit were reviewed.

In Study 20110118, haematological adverse events and serious adverse events were similar between treatment groups and no risk related to haematology adverse events was identified. In Study 20120153, too few subjects had haematological adverse events to allow meaningful comparison between treatment groups.

Data on TEAEs in the SOC of blood and lymphatic system disorder and haematological investigations are presented in Table 14 (Study 20110118) and Table 15 (Study 20120153).

Table 14: Study 20110118 Blood and lymphatic system disorder and haematological investigations; SOC TEAEs by Preferred Term reported by > 0.1% of subjects in any treatment group (Safety analysis set; Actual treatment group)

System Organ Class Preferred Term	Placebo (N = 13756) n (%)	EvoMab (N = 13769) n (%)
Number of subjects reporting treatment emergent adverse events	10644 (77.4)	10664 (77.4)
Blood and lymphatic system disorders	482 (3.5)	459 (3.3)
Iron deficiency anaemia	42 (0.3)	44 (0.3)
Anaemia	282 (2.1)	269 (2.0)
Leukocytosis	23 (0.2)	18 (0.1)
Lymphadenopathy	20 (0.1)	13 (<0.1)
Thrombocytopenia	34 (0.2)	29 (0.2)
Investigations		
Platelet count decreased	17 (0.1)	11 (<0.1)
Haemoglobin decreased	17 (0.1)	15 (0.1)

N = number of subjects randomised and dosed; EvoMab = Evolocumab (AMG 145)
Coded using MedDRA version 19.1.

Table 15: Study 20120153 Blood and lymphatic system disorder and Haematological investigations SOC TEAEs treatment emergent adverse events by Preferred term (Full analysis set; Actual treatment)

System Organ Class Preferred Term	Placebo QM (N = 484) n (%)	EvoMab 420 mg QM (N = 484) n (%)
Number of subjects reporting treatment emergent adverse events	386 (79.8)	372 (76.9)
Blood and lymphatic system disorders	9 (1.9)	17 (3.5)
Anaemia	4 (0.8)	7 (1.4)
Haemorrhagic anaemia	0 (0.0)	1 (0.2)
Microcytic anaemia	0 (0.0)	1 (0.2)
Normochromic normocytic anaemia	0 (0.0)	1 (0.2)
Increased tendency to bruise	1 (0.2)	0 (0.0)
Eosinophilia	1 (0.2)	1 (0.2)
Leukocytosis	0 (0.0)	1 (0.2)
Lymphocytosis	1 (0.2)	0 (0.0)
Lymphopenia	0 (0.0)	2 (0.4)
Leukopenia	1 (0.2)	1 (0.2)
Neutropenia	2 (0.4)	0 (0.0)
Polycythaemia	0 (0.0)	1 (0.2)
Macrocytosis	0 (0.0)	1 (0.2)
Thrombocytopenia	2 (0.4)	0 (0.0)
Investigations		
Red cell distribution width increased	1 (0.2)	0 (0.0)
Eosinophil count increased	2 (0.4)	1 (0.2)
Lymphocyte count increased	0 (0.0)	1 (0.2)
Monocyte count increased	0 (0.0)	1 (0.2)
Monocyte count decreased	1 (0.2)	0 (0.0)
White blood cell count increased	1 (0.2)	0 (0.0)

N = number of subjects randomised and dosed; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous).
Coded using MedDRA version 19.1.

Evaluator comment

There were no notable safety findings related to haematological parameters or adverse events in either study.

Question 12

Please comment on any safety data in subjects with hepatitis C from Study 20110118.

Sponsor's response

A total of 108 subjects out of 27 525 subjects had a pre-existing history of hepatitis C in Study 20110118. The numbers of subjects with a pre-existing history of hepatitis C are small (47 evolocumab, 61 placebo); therefore, the data should be interpreted with caution.

TEAE rates were not higher in the evolocumab group (85.1% versus 90.2%) nor were Grade ≥ 3 TEAEs (38.5% versus 47.5%). There were four Grade 4 events, three in the evolocumab group (adenocarcinoma of colon, CPK increased, hepatic cirrhosis) and one in the placebo group (cardiac arrest). In subjects with hepatitis C, there were more discontinuations due to an AE in the evolocumab group (12.8% versus 6.6%). Adverse events occurring in ≥ 10% of subjects in either treatment group (evolocumab, placebo) were depression (17.0%, 1.6%), hypertension (14.9%, 6.6%), sinusitis (12.8%, 1.6%), upper respiratory tract infection (10.6%, 8.2%), and nasopharyngitis (8.5%, 11.5%). Serious adverse events occurring in ≥ 2 subjects in either treatment group (evolocumab, placebo) were acute kidney injury (4.3%, 3.3%), iron deficiency anaemia (4.3%, 0.0%), peripheral arterial occlusive disease (4.3%, 1.6%), angina unstable (2.1%, 3.3%), and abdominal pain (0.0%, 3.3%).

Evaluator comment

The small number of subjects with hepatitis C makes interpretation of data difficult and so further monitoring of this population is warranted.

Second round benefit-risk assessment

Second round assessment of benefits

Following evaluation of the sponsor's responses to the questions raised after the first round evaluation, the benefits of evolocumab remain unchanged.

Second round assessment of risks

Following evaluation of the sponsor's responses to the questions raised after the first round evaluation, the risks of evolocumab remain unchanged.

Second round assessment of benefit-risk balance

Following request, the sponsor undertook a number needed to treat (NNT) analysis. This showed that in order to prevent one event contained in the primary composite endpoint approximately 143 patients would need to be treated for one year and 48 for three years. To prevent one event in the secondary composite endpoint (CV death, MI or stroke) approximately 172 subjects would need treatment for one year and 49 for three years. The evaluator notes the sponsor's statement that the '*relative risk reduction may provide the best measure for use in primary analyses to evaluation the cardiovascular risk in pivotal cardiovascular outcome studies*'. Nevertheless, the NNT analysis is useful in gauging the clinical impact of the medication.

The CV outcome study found that at low LDL-C levels there were no evident safety signals. The sponsor stated that to date 373 patients have been exposed to evolocumab for at least 5 years with no ill effect. Given this, the sponsor has proposed to delete the precaution relating to low LDL-C levels. Despite this, the evaluator recommends that, until long term safety data are submitted for evaluation, this precaution is retained.

In relation to the proposed indication for prevention of cardiovascular events, the sponsor has agreed to specify that use is in adults. It has also been agreed to change the population from those 'with or at risk of atherosclerotic cardiovascular disease' to those 'with established cardiovascular disease' so as to reflect the population studied. The evaluator accepts that the words 'moderate to high intensity' in relation to statins could be viewed as ambiguous, however the intention and requirement of the CV outcome trial was that the statin dose should be optimised to 'at least an effective dose' prior to adding on evolocumab. Where locally approved, the highly effective statin therapy was defined as at least atorvastatin 40 mg daily or equivalent. Therefore, evaluator recommends that this statin dose requirement is reflected in the indication.

In relation to the wording 'reduce the risk of cardiovascular events' it is noted that the recently approved indication in the US lists the three event types with reduced risk: '*In adults with established cardiovascular disease, Repatha is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization'.* The evaluator acknowledges the precedent set for Ezetrol (ezetimibe) where the indication wording is '*in the expectation of a modest further reduction in the risk of cardiovascular events following at least one year of therapy'.* Nonetheless, the evolocumab data clearly show no beneficial effect on CV mortality so it is still recommended that the indication state the events on which evolocumab had a positive effect.

For the LDL-C lowering indication, usage is together with statins as the sponsor has agreed to remove the monotherapy indication except in the situation of statin intolerance. Given the data now available from the CV outcome study, it is felt acceptable to broaden this indication beyond 'HeFH and clinical atherosclerotic cardiovascular disease' to populations studied in the clinical development program. It is, however, recommended that classification remain as 'primary hypercholesterolaemia'.

After the first round evaluation, the benefit-risk balance in the proposed usage was not favourable as the proposed indication did not reflect the patient population in which efficacy and safety were demonstrated and a generalised monotherapy indication was not supported. The sponsor has satisfactorily answered questions and comments from the first round evaluation. The indication has been reworded and the monotherapy indication dropped apart from in patients who are intolerant to statins. While the evaluator now finds that the benefit-risk balance for evolocumab is favourable, there remain several recommendations on the indication which still need to be adopted. Until this is finalised, the evaluator does not recommend authorisation.

Second round recommendation regarding authorisation

Following the second round evaluation, it is not recommended to approve the changes to the PI for evolocumab. If the following four points on the PI are satisfactorily resolved, then the extensions of the indications are approvable.

- The indication for prevention of cardiovascular events should specify the statin dose used in the pivotal study which was moderate to high intensity and optimised for the individual patient to at least an effective dose.
- The indication for prevention of cardiovascular events should specify the events which were prevented; myocardial infarction, stroke and coronary revascularisation.

- The indication for reduction of LDL-C should specify primary hypercholesterolaemia.
- The precaution relating to low LDL-C levels should be retained.

Suggested wording for the indication is:

> *Repatha is indicated as an adjunct to diet and exercise in:*
>
> *Prevention of Cardiovascular Events*
>
> *Repatha is indicated to reduce the risk of myocardial infarction, stroke and coronary revascularisation in adults with established cardiovascular disease in combination with a statin and/or other lipid lowering therapies (see CLINICAL TRIALS). Statin dose should be optimised prior to commencing Repatha.*
>
> *Primary Hypercholesterolaemia*
>
> *Repatha is indicated in adults with primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C):*
>
> *-in combination with a statin or statin with other lipid lowering therapies, or*
>
> *-alone or in combination with other lipid lowering therapies in patients who are statin-intolerant.*
>
> *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.*

VI. Pharmacovigilance findings

Risk management plan

- In support of this application to extend the indications of Repatha, the sponsor submitted EU-RMP version 2.0 (dated 15 May 2017; Data Lock Point (DLP) 17 January 2017) and Australian Specific Annex (ASA) version 5.0 (dated 13 June 2017).
- In their response to the TGA's request for further information, the sponsor submitted EU-RMP version 2.3 (dated 6 December 2017; DLP 17 January 2017) and ASA version 6.0 (dated 13 February 2018).

The proposed sponsor's Summary of ongoing Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 16.

Table 16: Summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	None	–	–	–	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important potential risks	Hypersensitivity	ü	–	ü	–
Missing information	Use in pregnant/lactating women	ü	ü	ü	–
	Use in paediatric patients	ü	–	ü	–
	Use in patients with severe hepatic impairment (Child-Pugh class C)	ü	–	ü	–
	Use in patients with hepatitis-C	ü	ü	–	–
	Use in patients with HIV	ü	ü	–	–
	Long-term use including effects of LDL-C < 40mg/dL (< 1.03 mmol/L)	ü	ü	–	–

- Additional pharmacovigilance activities include seven clinical trials to collect further information on items of missing information, as outlined in the table above. Three of these studies (Studies 20120138, 20120332 and 20130286) will involve Australian patients.
- For Missing Information: Use in pregnant/lactating women additional pharmacovigilance activities include an observational study and an Organization of Teratology Information Specialists (OTIS) pregnancy exposure registry, pregnancy surveillance study (Patients from United States and Canada)
- There are no additional risk minimisation activities, as previously, which is acceptable. Similarly, the omission of routine risk minimisation for some areas of missing information has not changed and continues to be acceptable.

New and outstanding recommendations

There are no outstanding issues at after the second round evaluation.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently

available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Repatha EU-Risk Management Plan (RMP) (version 2.3, dated 6 December 2017, data lock point 17 January 2017), with Australian Specific Annex (version 6.0, dated 13 February 2018), included with submission PM-2017-02229-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval for evolocumab subject to the following conditions:

- The indication for prevention of cardiovascular events should specify the statin dose used in the pivotal study which was moderate to high intensity and optimised for the individual patient to at least an effective dose.
- The indication for prevention of cardiovascular events should specify the events which were prevented, that is, myocardial infarction, stroke and coronary revascularisation.
- The indication for reduction of LDL-C should specify primary hypercholesterolaemia.
- The precaution relating to low LDL-C levels should be retained.

The evaluator's recommended indication reads:

> *Repatha is indicated as an adjunct to diet and exercise in:*
>
> *Prevention of Cardiovascular Events*
>
> *Repatha is indicated to reduce the risk of myocardial infarction, stroke and coronary revascularisation in adults with established cardiovascular disease in combination with a statin and/or other lipid lowering therapies (see Clinical Trials). Statin dose should be optimised prior to commencing Repatha.*
>
> *Primary Hypercholesterolaemia*
>
> *Repatha is indicated in adults with primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C):*

- *in combination with a statin or statin with other lipid lowering therapies, or*
- *alone or in combination with other lipid lowering therapies in patients who are statin-intolerant.*

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 clinical evaluator had no objection to the proposed dosage regimen for the new indication.

The clinical dossier included the following data:

- Study 20140213: a Phase I study in subjects with renal impairment
- Study 20110118: a Phase III cardiovascular outcomes study (FOURIER trial)
- Study 20130385: a Phase III safety (cognitive function) study in patient subset from Study 20110118
- Study 20120153: a Phase III study of effects on atherosclerosis using intravascular ultrasound (GLAGOV trial)

Pharmacology

Study 20140213 enrolled 18 adult patients, 6 patients each with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2), severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) and end-stage renal disease (ESRD) requiring haemodialysis with a LDL-C of 1.8 to 4.9 mmol/L and on stable statin dose for ≥ 3 months before screening.

Table 17: Study 20140213 Unbound evolocumab after administration of 140 mg SC

Parameter	Descriptive Statistics	Normal Renal Function (N = 6)	Severe RI (N = 6)	ESRD Requiring Hemodialysis (N = 5 - 6)
t_{max} (day)	Median	3.1	4.0	4.9[a]
	(Min – Max)	(3.0 – 7.0)	(3.0 – 7.0)	(3.0 – 5.0)
C_{max} (µg/mL)	Mean ± SD	21.3 ± 9.00	15.1 ± 8.86	11.7 ± 7.20
	(Min – Max)	(12.8 – 33.2)	(4.81 – 27.4)	(0.00 – 19.9)
AUC_{last} (day•µg/mL)	Mean ± SD	185 ± 92.5	141 ± 109	102 ± 80.1
	(Min – Max)	(103 – 316)	(27.9 – 297)	(0.00 – 238)

AUC_{last} = area under the drug concentration-time curve from time zero to time of last quantifiable concentration; C_{max} = maximum observed drug concentration; ESRD = end-stage renal disease; RI = renal impairment; SD = standard deviation; t_{max} = time to reach C_{max}.
Values are reported as 3 significant figures except for t_{max}, which was rounded to 2 significant figures.
[a] One subject did not have quantifiable concentrations and therefore did not an evaluable t_{max}.

During the first two weeks of therapy the effect on LDL-C and PCSK-9 levels were similar between the three groups.

Efficacy

Study 20110118 (FOURIER trial)

This was a double blind, randomised, placebo controlled, parallel group, multicentre, event driven, Phase III study that randomised 27,564 patients and treated 27, 525

patients, conducted in 49 countries between February 2013 and January 2017. It aimed to assess the impact of the LDL-C reduction from evolocumab, in addition to statin therapy on major cardiovascular events as a secondary prevention. Eligible patients were aged 40 to 85 years with clinically evident cardiovascular disease (prior MI, prior non haemorrhage stroke or symptomatic peripheral artery disease (PAD) and ≥ 1 major risk factors or ≥ 2 minor risk factors.[10] They required had LDL-C values >1.8 mmol/L or non-HDL-C values ≥ 2.6 mmol/L on ≥ 2 weeks of stable lipid lowering therapy at final screening (after 15 weeks of therapy). Fasting triglycerides (TG) were to be ≤ 4.5 mmol/L. High to moderate intensity lipid lowering background therapy at randomisation (at least atorvastatin 20 mg or equivalent) was required (atorvastatin 40 mg or equivalent recommended where locally approved). If needed background lipid therapy was optimised prior to the final screening visit. Investigators had to attest higher dose statin therapy was not appropriate for patients with LDL-C ≥ 2.6 mmol/L not on high intensity statin therapy.

The main exclusion criteria were MI or stroke within 4 weeks, the New York Heart Association (NYHA) Class III or IV symptoms;[11] or last known left ventricular ejection fraction (LVEF) < 30%, uncontrolled or recurrent ventricular tachycardia, SBP > 180 mmHg or DBP > 110 mmHg, uncontrolled thyroid disease, estimated glomerular filtration rate (GFR) < 20 mL/min/1.73m^2; AST or ALT > 3 x ULN; creatine kinase (CK) > 5 x ULN; use of a cholesteryl ester transfer protein inhibitor; mipomersen or lomitapide within 12 months; prior use of PCSK9 inhibition treatment other than evolocumab or use of evolocumab < 12 weeks prior the final lipid screening.

Evolocumab was administered as 140 mg SC every 2 weeks (Q2W) given by pre filled syringe or autoinjector pen for the first 24 weeks after which patients could, if desired, change to 420 QM (3 x 140 mg SC injections by AI pen) at 3 monthly time points thereafter could change regimen. A protocol amendment allowed either dosage regimen on commencement.

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[10] FOURIER trial; Major and Minor Risk Factors
Major risk factors were: established diabetes (type 1 or type 2), age ≥65 years, a qualifying MI or stroke within 6 months of screening, current daily cigarette smoking, an additional prior MI or non-haemorrhagic stroke (excluding the qualifying diagnosis) or symptomatic PAD if enrolled with history of MI or non-haemorrhagic stroke. Minor risk factors were: history of non-MI related coronary revascularisation, residual coronary artery disease with ≥40% stenosis in ≥2 large vessels, high-density lipoprotein cholesterol (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. Metabolic syndrome was defined as ≥3 of the following:

- waist circumference >102 cm (>40 in.) for men and > 88 cm (> 35 in.) for women (Asian men, including Japanese > 90 cm; Asian women, except Japanese > 80 cm; Japanese women > 90 cm)
- triglycerides ≥ 150 mg/dL (1.7 mmol/L) by central laboratory at final screening
- HDL-C < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women by central laboratory at final screening (Note: if the HDL-C level is one of criterion used to make the diagnosis of metabolic syndrome, it cannot be used as a separate risk factor)
- SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or hypertension treated with medication
- Fasting glucose ≥ 100 mg/dL (≥ 5.6 mmol/L) by central laboratory at final screening

[11] New York Heart Association (NYHA) Classification of Heart Failure:

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Randomisation was stratified by baseline LDL-C (< or ≥ 2.2 mmol/L) and geographical region. Identical devices were used for allocated treatment dosing, and investigators were not informed of lipids, lipoprotein or high-sensitivity C - reactive protein (hsCRP) levels. Investigators were asked to check compliance with study medications if LDL-C exceeded a prespecified limit and were informed to allow treatment if triglycerides (TG) was ≥ 11.3 mmol/L.

Power calculations were conducted for both primary and secondary endpoints but the sample size calculation was based on the composite secondary endpoint:

- 3550 events for the primary endpoint would give 99.8% power to demonstrate superiority over placebo;
- Assuming a placebo rate of 2% per year, a 26 month enrolment period, a 3% loss to follow-up over the study duration of approximately 56 months, an expected hazard ratio (HR) of 0.8 for the endpoint, a 3 month treatment lag at trial commencement and 10% annual noncompliance over the course of the study, $\alpha = 0.05$,based on a two-sided log rank test for superiority of evolocumab over placebo, a sample size of 27,500 patients with 1630 events in a key secondary endpoint event would give the study 90% power. The occurrence of 1630 outcome events in the key secondary endpoint was as the trigger for study conclusion.

The protocol was amended 6 times. The main changes were: use of the prefilled autoinjector/pen, increasing allowed screening time from 12 to 15 weeks, clarifying the potential endpoints were not SAEs, review of all fatal endpoints, change of secondary endpoint to the key triple composite event (amendment 2), increasing upper age limit from 80 to 85 years (amendment 3), allowing statins other than atorvastatin, allowing QM dosing from time of randomisation (amendment 4), increasing enrolment to 27,500 from 22,500 (amendment 5), adding adjudication of new onset diabetes, allowing addition of ezetimibe in subjects with acute coronary syndrome (amendment 6). The first 3 amendments occurred prior to the enrolment of the first patient. Major protocol deviations occurred in 5.4% and 5% of the evolocumab and placebo groups, respectively, of which approximately ½ were related to the study product received.

Patients were mostly male (75.4%), White (85.1%) with a mean age of 62.5 years, mean baseline LDL-C 2.5 mmol/L, mean PCSK9 approximately 5 nmol/L and mean estimated GFR (eGFR) approximately 76 mL/min/1.73 m^2. At screening 60.2% were on high intensity statins and 32.9% on moderate intensity. After baseline 69.3% were on high intensity and 30.4% were on moderate intensity statins. Most patients (79.1%) were taking atorvastatin. MI (81.1%), non-haemorrhagic stroke (19.4%) and symptomatic PAD (13.2%) were the most common events among the 99.9% patients ≥ 1 CV event. Other preventative therapies included antiplatelet agents (92.3%), beta blockers (75.6%) and angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) ± aldosterone antagonist (78.2%). Age, diabetes and smoking were the most common major risk factors and the most common minor risk factors were metabolic syndrome, low HDL and high hsCRP. Hepatobiliary dysfunction (7%) and 6% patients had Stage 3 to early Stage 4 Chronic Kidney Disease (CKD).

Mean time in the study was 26.1 months (median 26 months interquartile range (IQR) 22 to 30 months). Study treatment discontinuations occurred in 12.4% overall, with similar proportions in each group, mostly due to patient request (5.7% evolocumab versus 6.4% placebo) and AE (4.6% evolocumab versus 4.2 % placebo). Statin discontinuation occurred in about 6% of each group. Despite the discontinuations, 99.2% completed the study.

The primary composite efficacy endpoint was the first event of CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation.

- Evolocumab: 1344 events (9.8%)
- Placebo: 1563 events (11.3%)
- HR (95%CI): 0.85 (0.79, 0.92); p<0.0001
- Differences between evolocumab and placebo were seen in the landmark analyses in Year 1 and after Year 1 and from 5 months in the Kaplan-Meier (KM) estimates. Events were driven by MI and stroke and to a lesser extent coronary revascularisation. Cardiovascular deaths as a first event occurred in 1.17% and 1.03% of the evolocumab and placebo groups, respectively.
- Subgroup analyses were generally consistent with the primary analysis and controlling for covariates of final screening LDL-C level, geographic region, age, gender, race, prior MI, baseline PCSK9 level, baseline LDL-C and ezetimibe use at baseline did not impact the outcome.

The key secondary composite endpoint was the first events of CV death, MI and stroke

- Evolocumab: 816 events (5.92%)
- Placebo: 1013 events (7.35%)
- HR (95%CI): 0.80 (0.73, 0.88); p<0.0001
- Differences between evolocumab and placebo were seen in the landmark analyses in Year 1 and after Year 1 and from 5 months in the KM estimates. Events were driven by MI and stroke.
- Subgroups analyses were consistent and controlling for covariates did not impact the results.

A table of outcomes for the individual components of the cardiovascular events is included in the Table 18.

Table 18: FOURIER trial incidence of adjudicated cardiovascular events (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)

EvoMab = Evolocumab (AMG 145); MI = myocardial infarction; N = number of subjects randomized; PCI = percutaneous coronary intervention
Include the events occurring between the subject randomization date and the subject last confirmed survival status date, inclusive.

Based on the statistical testing hierarchy none of the other secondary endpoint could be claimed as statistically significant, however based on the Cox model and 2 sided log rank tests (nominal p values only) there was no apparent difference between the two treatments for time to cardiovascular death, time to death by any cause time to cardiovascular death, first hospitalisation for worsening heart failure or the post hoc analysis of time to first hospitalisation for unstable angina. The HRs were favourable for evolocumab in time to first fatal or non-fatal myocardial infarction, time to first fatal or non-fatal stroke, time to first coronary revascularisation and time to first ischaemic fatal or non-fatal stroke or transient ischaemic attack (TIA).

From a mean baseline of 2.53 mmol/L the mean LDL-C at week 48 in the evolocumab group was 1.02 mmol/L. The mean percent change from baseline for evolocumab was -64% to -70% compared to -5% to -1% for placebo.

Study 20120153 (GLAGOV trial)

This was a double blind, randomised, multicentre, placebo controlled, parallel-group study randomised 970 adults (484 evolocumab, 486 placebo) with an indication for coronary angiography, on optimised statin therapy or intolerant to statins with a LDL-C of 2.07 mmol/L, or 1.55 to 2.07 mmol/L in the presence of 1 major or 3 minor risk factors (≤ 25% of total enrolment) to assess the effects of evolocumab on atherosclerotic disease burden as measured by intravascular ultrasound (IVUS). The main exclusion criteria were clinically significant heart disease likely to need coronary artery bypass graft (CABG), Percutaneous Coronary Intervention (PCI) cardiac transplantation, percutaneous valve repair and/or replacement during the study, NYHA

Class III or IV symptoms or last known LVEF < 30%, CABG < 6 weeks before qualifying IVUS. The patients were mostly White (93.8%), European (68.5%), males (72.2%) with a mean age of 59.8 years and a mean baseline LDL-C of 2.4 mmol/L. most (94%) had a high CV risk, a history of baseline coronary artery disease (CAD) (92%) and 11% had cerebrovascular or peripheral arterial disease. High (58.9%) or moderate (39.4%) intensity statins were taken with 42.9%/36.0%/17.3% on atorvastatin 40 mg/20 mg/80 mg or equivalents.

Baseline mean PAV were 36.4% (evolocumab) and 37.2% (placebo). TAV were 187.0 mm^3 (SD 81.18) (evolocumab) and 191.4 mm^3 (SD 85.7) placebo.

The study had a 2 to 4 week run-in period with stabilisation of statin therapy before patients received either placebo SC QM or evolocumab 420 mg SC QM. Of the 968 patients who received study treatment, 423 in each treatment group had evaluable IVUS results. Endpoints were measured at Week 78 (after 76 weeks of therapy).

Table 19: GLAGOV Change from baseline to Week 78 Primary and secondary efficacy endpoints (IVUS analysis set)

Endpoint	Summary type	Placebo QM (n=423)	Evol. 420 mg QM (n=423)	Treatment difference Evol. Placebo	P value
Primary endpoint					
Change in PAV (%)	LSM (95% CI)	0.053 (-0.319, 0.424)	-0.955 (-1.327, -0.582)	-1.007 (-1.375, -0.640)	<0.0001
Secondary endpoints					
Change in TAV (mm^3)	LSM (95% CI)	-0.94 (-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

Evol.=Evolocumab

The exploratory endpoint of mean (SD) reduction in LDL-C from baseline was 61.6 % (21.6%) at week 76 and 68.0% (30.1%) to Week 78.

Safety

Safety data were provided from all studies in the dossier. Study 20130385 was a primary safety study.

Study 20130385

This was a sub-study of the FOURIER trial, was a double blind, placebo controlled, multicentre non-inferiority study to assess the effect of evolocumab on cognitive function in 1,974 patients with clinically evident CVD receiving optimised statin background therapy. There was no separate randomisation for this study. Patients self-selected for entry into the study at enrolment into the FOURIER trial. Patients were from Europe (69%) and North America (24.3%), mostly White (92.4%) and male (71.8%). The mean age was 62.7 years, and mean years of education 12.7 (48% > 12 years). Baseline characteristics were similar apart from statin therapy at baseline: the evolocumab group had more moderate intensity (31.9% versus 26.5%) and fewer high intensity statin therapy patients (68.1% versus 73.5%) than the placebo group.

Patients were assessed with three of the CANTAB neuropsychological tests; Spatial Working Memory (SWM) a working memory assessment; Paired Associates Learning (PAL) for memory function; and Reaction Time for psychomotor speed. Tests were administered at baseline and Weeks 24 and 48, then every 48 weeks and at the last study visit. A sample size of 1500 would give the study 97% power to show the upper limit of the 95% CI for the mean baseline-adjusted treatment difference was < 20% of the standard deviation of the mean baseline adjusted change in the placebo group (the non-inferiority margin). Patients were assessed at baseline before the first administration of the study. Patients with a baseline assessment could enrol in this study any time up to the week 12 visit.

Of the 1,974 patients who started the study, and the 1,921 who completed the study, 1,204 (538 evolocumab and 618 placebo) had baseline cognitive function assessment prior to the first dose of study medication and at least one post baseline cognitive assessment.

The primary endpoint was the treatment difference in change from baseline using a repeat measures mixed effect linear model that included stratification factors the FOURIER study (final screening LDL-C and geographical region), age, education level, baseline SWM strategy index, treatment group, visit, and treatment by visit interaction.

- SWMS68 Z score least squares mean (LSM) change from baseline (95% CI) (higher score = better performance):
- Evolocumab 0.11 (0.05, 0.18); placebo 0.12 (0.05, 0.19)
- Treatment difference placebo-evolocumab 0.01 (-0.07, 0.08)
- Upper bound 95% CI < 0.19 (non-inferiority met).

The SWM strategy index of executive function (SWMS68);[12] scores differences between placebo and evolocumab were not statistically significantly different.

For the secondary endpoints of mean baseline-adjusted change in SWM between-errors score (SWMBE48) and Paired Associates Learning total errors adjusted (PALTEA);[13]

[12] SWM strategy 6-8 boxes (SWMS68) raw score. This is the number of times that a subject begins a search with a different box in a Spatial Working Memory test having six boxes or more. A high score represents an inefficient use of strategy and planning and a low score represents an efficient use of strategy. SWMS68 is a discrete ordinal variable with a range of 4 to 28. 'Executive function' of the brain refers to central control, planning, strategy and flexible thinking.

[13] The PALTEA is comprised of the number of errors committed by a subject in a Paired Associates Learning test plus an adjustment for the estimated number of errors the subject would have made on any

testing working memory and psychomotor speed were similar between the two treatment groups over time, while a higher Reaction Time Median 5-choice Reaction Time (RTIMDRFT);[14] raw score in the evolocumab group compared to the placebo group was not statistically significant.

Additional analyses were planned for the patients with at least one post-baseline LDL-C < 25 mg/dL (< 0.65 mmol/L) for the primary and secondary endpoints. While there no significant differences between the < 0.65 mmol/L evolocumab group and placebo were noted, and scores were consistent over time, a slightly better performance was seen across all tests in patients on evolocumab with a post-baseline LDL-C > 1.0 mmol/L than in the placebo group with a post-baseline LDL-C > 1.0 mmol/L.

Overall safety

The safety data was not integrated and is presented by study.

The Fourier trial

TEAEs occurred in 77.4% of each treatment group, with similar proportions of Grade 2, 3 and 4 events. The most frequent AEs, comparing the evolocumab and placebo groups, were diabetes (8.8% versus 8.2%), hypertension (8.0% versus 8.7%), nasopharyngitis (7.8% versus 7.4%) and URTI (5.1% versus 4.8%). The overall TEAE rate was 68.4%, 73.2%, 73.6% and 77.7% in the evolocumab patients with LDL-C < 0.65mmol/L, < 1.03 mmol/L, ≥ 1.03 mmol/L and placebo patients with LDL-C ≥ 1.03 mmol/L, respectively. The treatment groups had similar TEAEs rates in subjects < 65 years and ≥ 65 years and in males and females.

TEAEs of hypersensitivity in the evolocumab and placebo groups were 4.7% versus 4.2% using the narrow SMQ and 7.6% versus 7.0% using the broad SMQ. The main events were dermatitis and eczema (1.5% versus 1.2%). There were two events of anaphylactic shock in the evolocumab group (none in the placebo group) with one due to peanut consumption and the other after 152 days of treatment exposure. The 5 serious events of anaphylaxis (2 evolocumab and 3 placebo subjects) had other precipitants. Angioedema occurred in 0.3% in both groups. Treatment discontinuation due to hypersensitivity events occurred in < 0.1% of both groups. Musculoskeletal and connective tissue SOC events were similar between groups. New onset diabetes mellitus occurred in 8.1% and 7.7% in the evolocumab and placebo groups, respectively. The lowest rate of new onset diabetes mellitus (NODM) in the evolocumab group was in the lowest post-baseline LDL-C evolocumab groups. Infections occurred in similar proportions of each group.

Deaths occurred in 3.22% versus 3.09% of the evolocumab and placebo groups, respectively, with CV death in 1.82% versus 1.74%, non-cardiovascular death 1.08% versus 1.03% and undetermined cause in 0.32% of both groups. No between-group differences in the profile of non-cardiovascular deaths were seen.

The rate of SAEs was 24.8% and 24.7% in the evolocumab and placebo groups, respectively. The most frequent SAEs were unstable angina (1.7% versus 2.0%), angina pectoris (1.5% versus 1.6%), pneumonia (1.1% each), atrial fibrillation (0.9% versus 1.0%) and non-cardiac chest pain (0.8% versus 1.0%). There were no notable differences between groups in SAE rates. By post-baseline LDL-C subgroup SAEs were less frequent in the < 0.65 mmol/L evolocumab group (20.7%) compared to < 1.0 mmol/L and ≥ 1.0 mmol/L evolocumab groups and the ≥mmol/L placebo groups

stages that were not reached. A lower score indicates better performance. PALTEA is a discrete ordinal variable with a range of 0 to 70.

[14] RTIMDFRT is the median duration between the onset of the stimulus and the release of the button in a Reaction Time test. A lower score indicates better performance. RTIMDFRT is a continuous variable with a range of 100 to 5100 ms.

(23.0%, 23.7% and 24.8%, respectively). The most frequent SAEs in all post-baseline LDL-C subgroups were angina pectoris, unstable angina, pneumonia, atrial fibrillation and non-cardiac chest pain.

Treatment discontinuation due to an AE occurred in 4.4% versus 4.2% of the evolocumab and placebo groups, respectively, most frequently due to myalgia (0.3% both groups), fatigue (< 0.1% versus 0.2%) and arthralgia (0.1% versus < 0.1%).

The GLAGOV trial

TEAEs occurred in 76.9% of the evolocumab versus 79.8% of the placebo group. The most frequent events were angina pectoris (7.4% versus 8.9%), myalgia (7.0% versus 5.8%), chest pain (7.0% versus 5.4%), hypertension (6.0% versus 7.6%) and non-cardiac chest pain (5.8% versus 3.7%). Hypersensitivity events occurred in 6.8% versus 4.8% using the narrow Standardised MedDRAQueries (SMQs);[15] and 11.0% versus 7.9% using the broad SMQ of the evolocumab and placebo groups, respectively. Muscle related AEs were reported in 13.6% and 12.6% of the evolocumab and placebo groups, respectively. Fewer evolocumab patients reported neoplasms (3.5% versus 5.0%). Infections and infestation SOC events were similar between groups (29.5% versus 28.5%).

Deaths occurred in 0.6% (n = 3) versus 0.4% (n = 2) in the evolocumab and placebo groups, respectively. SAEs occurred in 27.9% and 29.3% in the evolocumab and placebo groups respectively, and the most frequent were angina pectoris (3.5% versus 2.3%), non-cardiac chest pain (2.3% versus 1.2%) and unstable angina (1.7% versus 1.4%). The one treatment related SAE was a stroke in a placebo group patient. Treatment discontinuation due to a TEAE occurred in 3.3% versus 2.3% of the evolocumab and placebo groups, most frequently myalgia (0.2% versus 0.6%).

Study 20140213

TEAEs occurred in 17%, 17% and 33% in the normal renal function, severe renal injury, and end stage renal disease (ESRD) groups, respectively. There was one SAE of hyperkalaemia related to chronic kidney disease (CKD) and no deaths.

Events of special interest

Injection site reactions

In the FOURIER trial, injection site reactions (ISRs) occurred 1.9% and 1.5% in the evolocumab and placebo groups, respectively, the majority of which were injection site pain, bruising and haematoma. No events were Grade 4 or serious and discontinuation of treatment from such events occurred in 0.1% of the evolocumab group (compared to < 0.1% in the placebo group). In the GLAGOV trial, ISRs were more common with evolocumab (2.9% versus 1.9% using the narrow search).

Immunogenicity

Few patients developed anti-drug antibodies.

Hepatic

In the FOURIER trial, drug induced liver injury (DILI) was reported in 4 evolocumab and 2 placebo subjects (< 0.1% both groups). Four subjects (3 in the evolocumab group) with normal baseline AST and ALT had post-baseline increases of > 3 x ULN and total bilirubin > 2 x ULN with ALP < 2 x ULN, all with other possible aetiologies. No evolocumab subject had an AST or ALT > 5 x ULN or total bilirubin > 2 x ULN at any assessment and there were no Hy's Law cases. In the GLAGOV trial, hepatic AEs

[15] Medical Dictionary for Regulatory Activities

(narrow search) occurred in 2.5% versus 2.1% of the evolocumab and placebo groups, respectively.

Neurocognitive

Neurocognitive AEs were similar between groups (1.6% versus 1.5%) and < 0.1% of each group had a Grade 4 neurocognitive TEAE or SAE. Amnesia had a higher rate the evolocumab group (0.4% versus 0.2%) however the higher level term of memory loss excluding dementia was similar (1.0% versus 0.9%). More of the evolocumab group (n = 20, 0.1%) discontinued treatment due to a neurocognitive event than placebo (n = 9, < 0.1%). Events rates by lowest LDL-C level were similar between the treatment groups.

Demyelination

In the FOURIER trial potential demyelination events occurred in similar proportions with evolocumab and placebo (0.7% versus 1.0%), with serious events in < 0.1% and 0.1% in the respective groups and no increased risk with low LDL-C levels.

Reactivation of hepatitis C

In the FOURIER trial 47 evolocumab and 61 placebo patients had pre-existing hepatitis C. Reactivation was note reported among the adverse events for these patients.

Cataracts

In the FOURIER trial, cataract AEs occurred in 1.5% and 1.6%, and cataract SAEs in 0.1% and 0.2% in the evolocumab and placebo groups, respectively. In the GLAGOV trial cataract occurred 0.6% versus 1.0% of the evolocumab and placebo groups, respectively.

Post-market data

Post-market data were submitted that included the period from first market authorisation to 17 January 2017. An estimated 61,600 subjects were exposed to evolocumab in the post-marketing setting. There have been 14,337 individual case reports received, 74.8% from solicited sources (patient support programs and market research) 24.5% were spontaneous reports and 0.6% from post-marketing studies. The cases yielded 36,567 AEs, 88.0% non-serious, 12% serious, and < 0.1% (n = 185) fatal. The most frequent AEs were drug dose omission, myalgia, injection site pain, back pain and arthralgia. The most frequently reported SAEs were MI, dyspnoea and pneumonia. Fatal events were most frequently MI and cardiac arrest.

Use in pregnancy

No safety issues were identified in 49 pregnancy exposures of which 12 maternal exposures were during studies and 3 were from post-marketing sources.

Risk management plan

The TGA accepted the EU Risk Management Plan for Repatha (evolocumab) version 2.3 dated 6 December 2017, data lock point 17 January 2017and Australian Specific Annex version 6.0 dated 13 February 2018. No outstanding issues were identified by the evaluator.

Risk-benefit analysis

Delegate's considerations

Two clinical studies have been provided to support the proposal to extend the indication for evolocumab to include the prevention of cardiovascular outcomes. The sponsor has also relied on the main study for this submission to expand the hypercholesterolaemia indication to include all patients with hypercholesterolaemia.

The FOURIER trial was large event driven study with composite endpoints for its primary and key secondary endpoints that was specifically powered for the secondary endpoint. The study included patients with demonstrated cardiovascular disease and either moderate to high intensity statin therapy at baseline or with statin therapy optimised according to individual patient factors prior to randomisation to additional evolocumab or placebo using the dosage regimen currently registered for primary hypercholesterolaemia. The mix of patients was reasonably representative of patients for whom evolocumab would be indicated. The composite primary and key secondary outcomes are of clinical relevance.

As outlined in the protocol, event numbers to power the study for the secondary endpoint was the trigger for the conclusion of the study, although the event numbers needed for the study to be powered for the primary endpoint in accordance with the sample size and power calculations had not been collected. The study patients continued on treatment for a mean of 26.7 months (median 24.8 months). The reduction in LDL-C was consistent with previous studies of evolocumab.

The primary and key secondary composite endpoints both driven by improvements in MI and stroke rates showed a statistically significant risk reduction of 15% and 20%, respectively for evolocumab over placebo. The primary endpoint also showed a reduction in risk of coronary revascularisation, although hospitalisation for unstable angina, and CV death did not show a benefit for evolocumab. Statistically there was no difference between evolocumab and placebo for CV death or all-cause mortality. While the numerical differences between the groups are small, the events numbers for these components are slightly higher in the evolocumab groups. A longer study may have shown more definitive outcomes for cardiovascular death, however this is speculative. The absolute differences were about 1.5% between the evolocumab and placebo groups for both the primary or secondary composite endpoints, and while modest, this effect is in addition to the reduction in events from statins and was seen in the median treatment duration of 24.8 months. There is uncertainty regarding the sustainability of the CV benefit of evolocumab over time because of the relatively short study duration, and although the KM curves do not converge there is less certainty in the estimates from 30 months onwards due to reduced patient numbers. There was no clear evidence that any one particular patient subgroup was at greater benefit than the remainder.

The evolocumab effect on cardiovascular disease was also shown by imaging in the GLAGOV trial. A reduction in atheroma volume was demonstrated. A minimal clinically important difference (MCID) for this population was not discussed and the clinical meaningfulness of the results is difficult to ascertain, therefore the Advisory Committee on Medicines (ACM) advice regarding the clinical significance of these findings and their weight in considering the evidence of CV event reduction is sought.

Overall the effect size for cardiovascular events is similar to that seen in with statins for primary prevention, noting that cross-comparisons of statins are often for 3 or 5 years therapy. The IMPROVE-IT trial of simvastatin and ezetimibe supporting an extension of indication for CV disease prevents showed a risk reduction of 6.4% in the composite endpoint over 7 years.

The safety data from the FOURIER trial include 59,865 patient years of follow-up, and were consistent with the previous safety profile of evolocumab. The neurocognitive outcomes study did not demonstrate a concern with the use of evolocumab and although effects over time are yet to be established there is no strong signal arising from the study providing some reassurance. The committee is requested to comment on the 'learnability' of these tests with repeated measurements and their sensitivity in detecting small differences between groups in this setting. There were no apparent safety signals from patients with very low post-baseline LDL-C, but long term data are not yet available. The sponsor notes that there are ongoing long term extension studies that will provide clinical trial safety data for up to 7 years exposure.

The sponsor has also made an application to expand the population of patients for whom the hypercholesterolaemia indication applies to include a broader patient group and to include monotherapy with evolocumab. No new data have been provided. One of the principal concerns with the initial submission was the short duration of the studies demonstrating the lipid lowering of evolocumab, with the majority of the main studies of only 12 weeks duration and the lack of demonstrated cardiovascular benefit with evolocumab at that time. The clinical evaluator for this submission agreed that there were now sufficient data supporting cardiovascular benefit and contributing additional safety data to allow broadening of the patient group to all adults with primary hypercholesterolaemia but that the limitations of the monotherapy data set had not been addressed with the new data in the current submission for all patients with established cardiovascular disease. Based on the population mix of the initial submission, the extrapolation of benefit from the FOURIER trial, and the sustained effect in the GLAGOV trial albeit in an exploratory endpoint, the Delegate's preliminary view is that for primary hypercholesterolaemia this is reasonable. The committee is requested to comment on the sponsor's request to include all patients with hypercholesterolaemia.

The evaluator considered patients with hypercholesterolaemia unable to take statins the only suitable group for evolocumab monotherapy. The monotherapy study in the original submission was designed to include only patients with low to moderate cardiovascular risk, mostly because a cardiovascular benefit had not been established for evolocumab. A small number of patients in the DESCARTES trial had monotherapy. Monotherapy would have been outside the protocols for the other Phase III studies, and the majority were of short duration. It remains unclear whether sufficient data have been generated to support monotherapy in all statin-intolerant patients; however LDL-C reductions and cardiovascular risk reductions are greater than those achieved with ezetimibe, the most likely alternative therapy for patients that are unable to take statins. A conclusion has not been reached on this aspect of the requested revision of the hypercholesterolaemia and the view of the ACM is sought.

The sponsor also wishes to remove the statement that the effect of Repatha on cardiovascular morbidity and mortality has not been determined. The FOURIER trial provides data in support of this modification of the indication.

Indication

Prevention of cardiovascular events

In the current proposal, as included in the PI provided with the sponsor's responses, the sponsor proposes to restrict the indication for the prevention of cardiovascular events to adults with established cardiovascular disease in combination with a statin and/or other lipid lowering therapies. It does not propose to list the individual components of the composite endpoints that were favourable for evolocumab, but refers to the Clinical Trials section where the individual components of the endpoint are tabulated. There was no statistical difference between the mortality outcomes for

evolocumab and placebo for cardiovascular death, or time to hospitalisation for unstable angina in the primary endpoints. MI and stroke were the drivers of the outcomes. This approach would seem reasonable. Other recent modifications to the proposed indication are the inclusion of established cardiovascular disease to better reflect the clinical trial population and to include concomitant therapies making clear that evolocumab is not a first-line therapy in the reduction of cardiovascular risk. The preliminary assessment, prior to review by the ACM, is that this approach would be acceptable.

Hypercholesterolaemia

Given the patient mix in the original submission, the cardiovascular outcomes from the FOURIER trial and the longer term efficacy from the GLAGOV trial, it may be reasonable to broaden the indicated population of patients with hypercholesterolaemia to include all patients with hypercholesterolaemia. Pending advice from the ACM, inclusion of monotherapy for patients unable to take statins may be reasonable.

The statement about cardiovascular morbidity and mortality was placed in the indication at the time of the initial approval of evolocumab to alert prescribers to the absence of cardiovascular outcome data. Data have now been provided and the removal of the statement is acceptable.

Dose

No change to the currently approved dosage regimen arises from this submission, and the sponsor proposes that no dose adjustment is needed in patients with renal impairment, based on the PK study. Compared to patients with normal renal function the area under the plasma concentration versus time curve to the last time point (AUC_{last}) and peak plasma concentration (C_{max}) were each 24% and 45% lower in those with severe RI and ESRD. The pharmacodynamic results however were similar for all groups up to Day 14. Based on the pharmacodynamic data there is no objection to the proposed change to the wording of the dosing advice for CKD patients.

Data deficiencies

The FOURIER trial was concluded after accumulation of sufficient events to assess the key secondary endpoint. The mean duration in the study was only approximately 26 months, with only 717 placebo patients and 713 evolocumab available to contribute events to the 36 month time point in the Kaplan-Meier analysis. A longer study may have drawn more definitive conclusions regarding cardiovascular deaths.

A major deficiency in the data set overall is the lack of long term safety outcomes. As noted above, longer term data are being generated.

The very elderly were not included in the studies in the original submission, with an upper age limit of 80 years in the shorter studies and 75 years in the DESCARTES trial. The FOURIER trial has included patients aged 40 to 85 years.

There are limited data in patients taking evolocumab as monotherapy, as outlined above.

Conditions of registration

The following is a proposed condition of registration for evolocumab if the extension of indications is approved:

> *The Repatha EU-Risk Management Plan (RMP) (version 2.3, dated 6 December 2017, data lock point 17 January 2017), with Australian Specific Annex (version 6.0, dated 13 February 2018), included with submission PM-2017-02229-1-3, and*

any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Summary of issues

The FOURIER trial was an event driven study. Both the primary and key secondary endpoints were favourable for evolocumab but the absolute risk reduction between treatment groups was modest. The risk reductions were 15% and 20% respectively based on the Cox model HRs. Given the relatively short duration of this study for a cardiovascular outcomes study there is uncertainty about the strength or sustainability of the effects over a longer period.

The 1% atheroma volume reduction in the GLAGOV trial is difficult to interpret. The sponsor has not discussed a MCID for this outcome. This study was not powered to demonstrate differences in clinical outcomes. Fewer patients than in the FOURIER trial had a prior MI (35% versus 81%) so extrapolation of the study results from one patient population to the other is limited.

In providing advice on the original submission for hypercholesterolaemia indications for evolocumab the TGA's advisory committee advised a narrower indication than that requested by the sponsor. In the current submission the sponsor has revisited this indication, requesting a broadening of the population to all adults with hypercholesterolaemia. Because the evidence in monotherapy is limited it is still unclear whether it is sufficient to support the sponsor's proposal. It is also unclear whether there is sufficient evidence to support an indication broader than primary hypercholesterolaemia.

The neurocognitive outcomes study showed similar results with time for both the treatment groups. It is not clear whether the CANTAB test measurements are influenced by 'learning' the test with repeated measurements. However if this is the case the effect should be equal between the two groups. It is also unclear whether this is sufficiently sensitive to detect small differences between the groups.

Proposed action

The Delegate had no reason to say, at this time, that the application for evolocumab should not be approved for registration for the modified indication

Repatha is indicated as an adjunct to diet and exercise in

Prevention of Cardiovascular Events

Repatha is indicated to reduce the risk of cardiovascular events in adults with established cardiovascular disease in combination with a statin and/or other lipid lowering therapies (See Clinical Trials).

Primary hypercholesterolaemia

Repatha is indicated in adults with hypercholesterolaemia, (including heterozygous familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C):

- in combination with a statin or statin with other lipid lowering therapies, or

- alone or in combination with other lipid lowering therapies, to reduce low-density lipoprotein cholesterol (LDL-C).

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.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Please comment on the effect size and clinical significance of the outcomes of the primary and key secondary endpoints in the FOURIER trial.
2. Please comment on the clinical significance of the outcomes of the GLAGOV trial.
3. The primary and key secondary composite endpoints are driven by myocardial infarction and stroke with no statistically significant difference between evolocumab and placebo for cardiovascular, coronary or all-cause mortality. The sponsor's requested Indication makes a claim about 'cardiovascular events' and references to the clinical trials for details about the endpoints. The clinical evaluator favoured specific component claims in the indication. Please comment.
4. There are two changes proposed for the indication for hypercholesterolaemia. The sponsor proposes to broaden the population to all adults with hypercholesterolaemia and to include monotherapy for statin intolerant patients. Has sufficient evidence now been provided to support this broader indication?
5. The neurocognitive outcomes sub study did not demonstrate differences between the two treatment groups. Please comment on the suitability of CANTAB testing to detect small differences between treatment groups in a study of this size.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Question for the sponsor

The sponsor is requested to address the following issues in their pre ACM response.

1. The sponsor proposes to include evolocumab monotherapy for patients who are statin intolerant in the hypercholesterolaemia indication. Were any patients in the FOURIER trial taking evolocumab as monotherapy during the study? If so, how many, and what were their outcomes?

Note for the sponsor

As noted in previous correspondence, a comment on the wording of the indication proposed in this overview, this may be included as a separate attachment in the pre-ACM response.

Response from sponsor

The indications proposed with the initial application were

Repatha is indicated to reduce the risk of cardiovascular events in patients with or at risk of atherosclerotic cardiovascular disease and

Repatha is indicated in adults with hypercholesterolaemia, alone or in combination with other lipid lowering therapies, to reduce low-density lipoprotein cholesterol (LDL-C).

In this response, the sponsor agrees with the Delegate's proposal for the cardiovascular indication and proposes to remove the word 'Primary' from the heading of the lipid lowering indication as shown below:

~~*Primary*~~ *Hypercholesterolaemia*

Repatha is indicated in adults with hypercholesterolaemia (including heterozygous familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C) in combination with a statin or statin with other lipid lowering therapies, or alone or in combination with other lipid lowering therapies in patients who are statin-intolerant'.

Delegate's comments to ACM

FOURIER trial (Study 20110118) (Questions 1 and 3):

CVD is the leading cause of death and disability worldwide. In Australia, CVD affects more than 3.7 million people. Of these, 1.2 million suffer from disability because of CVD. Approximately 1 million Australians with high risk of CVD (1 in 3) do not adequately reduce their LDL-C levels despite using lipid lowering therapy.

In 2014 and 2015, an estimated 643,000 adults had coronary heart disease, including angina and previous heart attack, and 308,000 were living with the effects of stroke or other cerebrovascular diseases.[16],[17] The effect of evolocumab on CV risk measured by the primary and key secondary composite endpoints in the FOURIER trial (Study 20110118) evaluated events that are associated with increased mortality, morbidity and disability. Reduction of the risk of these events will directly impact patient lives by reducing the associated morbidity and disability.

With advances in CV care over the last quarter century, the rate of death due to MI or stroke has declined markedly[18][19],making it difficult to observe a CV mortality benefit, in clinical studies of lipid lowering therapies, especially over a median duration of 26 months of follow-up. The lack of effect on CV mortality was observed in studies of other lipid lowering therapies: 3 of 21 placebo controlled statin studies demonstrated a statistically significant effect on CV mortality.[20],[21],[22],[23] All these studies were designed to evaluate mortality, had a median duration of at least 5 years, and were completed before 2002. Recent studies comparing more versus less intensive lipid lowering therapies have been unable to demonstrate a statistically significant CV mortality benefit;[20,24],[25,26] despite a median duration of follow-up that exceeded 5 years.

[16] Australian Institute of Health and Welfare. Australia's health 2016. ISBN 978-1-74249-924-6 (PDF).
[17] Australian Institute of Health and Welfare. Trends in cardiovascular deaths. Bulletin 141. September 2017. ISBN 978-1-76054-187-3 (PDF).
[18] Roth GA, Forouzanfar MH, Moran AE, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med*. 2015;372:1333-1341.
[19] Yang Q, Cogswell ME, Flanders WD, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA*. 2012;307:1273-1283
[20] Cholesterol Treatment Trialists' Collaboration (CTTC), Baigent C Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta- analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-1681.
[21] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22
[22] Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-1357
[23] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
[24] Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387-2397
[25] Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin QD in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010;376:1658-1669

Considering the pivotal role LDL-C plays in CVD, the demonstrated CV outcomes benefits achieved through LDL-C reduction, and limitations of available therapies related to their efficacy and/or tolerability, new therapies are needed to provide robust additional LDL-C lowering and further reduce CV risk. The compelling efficacy results and excellent overall safety profile provide a favourable benefit-risk profile for the use of evolocumab in the prevention of CVD.

Comments to address the Delegate's questions to the ACM in relation to the Study 20110118 are provided in Points 1 and 2 below:

1. *Comment on the effect size and clinical significance of the outcomes of the primary and key secondary endpoints in the FOURIER trial.*

Study 20110118 results provide compelling evidence of the evolocumab benefit-risk profile. Study 20110118 was designed to demonstrate a significant reduction in CV events based on the primary and key secondary composite endpoints. The patient population consisted of patients with very high CV risk, despite optimised lipid lowering therapy, and demonstrated high utilisation of evidence-based CV therapies known to decrease CV morbidity and mortality.

Evolocumab significantly reduced the risk of CV events with a 15% and 20% reduction in the primary and key secondary composite endpoints, respectively.

The Kaplan-Meier curves for the primary and key secondary composite endpoints show time to event rates began to separate between treatment groups at approximately 5 months after randomisation. The magnitude of the absolute risk reduction (ARR) grew steadily over time with continued accrual of ARR through the median 2.2 years of study follow-up. The ARR for the primary and key secondary composite endpoints were 1.52% and 1.35% at 2 years and 2.07% and 2.02% at 3 years, respectively. Landmark analyses were conducted showing that evolocumab reduced the risk of the primary composite endpoint by 12% in year 1 (hazard ratio (HR) = 0.88 (95% CI: 0.80, 0.97)) and by 19% after year 1 (HR = 0.81 (95% CI: 0.73, 0.89)) and the key secondary composite endpoint by 16% in year 1 (HR = 0.84 (95% CI: 0.74, 0.96)) and by 25% after year 1 (HR = 0.75 (95% CI: 0.66, 0.85)), indicating greater CV benefit with longer duration of treatment. These benefits were observed in patients who were already receiving standard of care with other CV therapies, including statins.

In addition, large reductions in LDL-C (median 63.8% to 69.5%) observed during evolocumab treatment were maintained over the course of Study 20110118 with no attenuation.

Furthermore, the relationship between reduction of LDL-C and reduction in CV event rates with evolocumab therapy was aligned with the results from studies for other lipid lowering therapies that upregulate the LDL receptor.[20,27] The hazard ratios for major CV events per 1.0 mmol/L reduction in LDL-C with evolocumab in Year 1 and Year 2 were similar to those reported previously per 1.0 mmol/L reduction with a statin in the corresponding years.[20,28] Notably, the statin studies included in the CTTC analysis supported the authorisation by regulatory authorities worldwide of those therapies to reduce both LDL-C and CV risk.

[26] LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *NEJM*. 2005;352:1425- 1435

[27] Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. *JAMA*. 2016;316:1289-1297.

[28] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713-1722

In summary, the effect size observed in this study is clinically compelling and consistent with what has been observed for other lipid lowering therapies indication for prevention of CVD.

The Delegate noted the lack of long-term safety outcomes as a data deficiency. Although longer term data is being generated, the current safety profile of evolocumab is well characterised and includes significant long-term exposure. A total of 24,824 subjects (46,009 subject-years exposure) have been exposed to evolocumab; this includes 13,769 subjects from the Study 20110118. Data from Study 20110118 represent a large increase in long-term exposure to evolocumab since the original application. With this application, subjects exposed to evolocumab for at least 1 year has increased to 18,334 subjects; subject exposed for 2 years has increased to 12,445 subjects, and data are now available from completed and ongoing studies for subjects who have received evolocumab for at least 3, 4 or 5 years from 3246, 750, and 373 subjects, respectively. The safety profile of evolocumab remains similar regardless of treatment duration; no new safety findings were identified with extended treatment, including up to 5 years (Table 20).

Table 20: Summary of exposure to evolocumab in Phases I, II, and III studies (ongoing and completed)

	Evolocumab (N=24824)	
Duration of exposure	Number of Subjects	Subject Years
Total population		
>= 1 year	18334	44271.78
>= 2 years	12445	34568.22
>= 3 years	3246	11865.88
>= 4 years	750	3632.88
>= 5 years	373	1951.76

Completed studies include: 20080397, 20110121, 20120136, 20120133, 20110168, 20120341, 20150111, 20080398, 20140213, 20130194, 20090158, 20090159, 20101154, 20101155, 20110231, 20110109, 20110114, 20110115, 20110116, 20110117, 20120348, 20120356, 20110233, 20110118, 20120153, 20120122, 20120332 part B.
Ongoing studies include: Data cutoff date of 17 January 2017 for Studies 20110110, 20120138, 20110271, 20120332 part C, 20140128, 20120123, 20120119, 20130293, 20130287, 20140234, 20120124, 20130295, and 20140316, and data cutoff date of 27 January 2017 for Studies 20150353 and 20120134.

2. *Comment on the Indication statement reflecting 'cardiovascular events' with a cross references to the clinical trials section for details about the endpoints.*

Based on European authority scientific advice and guidelines;[29],[30] Study 20110118 was designed and powered to demonstrate that evolocumab administration (when added to lipid lowering therapy) would produce a significant reduction in CV events on the primary and key secondary composite endpoints. Study 20110118 was not powered to evaluate the effect of evolocumab on individual components of the composite endpoints.

Even though there was no significant effect of evolocumab on CV death, there was a numerical reduction in fatal myocardial infarction and fatal stroke, which is consistent with the expectations of a lipid lowering therapy. The patient population demonstrated high utilisation of evidence based CV therapies known to decrease CV mortality, such as anti-platelet agents, beta blockers and ACE inhibitors/ARB (75% to 93% utilisation). The clinical evaluator acknowledged that the high use of other pharmacotherapies lowering CV mortality could have impacted the mortality results in Study 20110118.

[29] European Medicines Agency. Committee for Human Medicinal Products. Guideline on the evaluation of medicinal products for cardiovascular disease prevention. London, 25 September 2008. Doc. Ref. EMEA/CHMP/EWP/311890/2007.
[30] European Medicines Agency. Committee for Human Medicinal Products. Guideline on clinical investigation of medicinal products in the treatment of lipid disorders. London, 23 June 2016. Doc. Ref. EMA/CHMP/748108/2013, Rev 3

The proposed indication statement for evolocumab, based on the results of Study 20110118, is aligned with regulatory precedent in Australia. The approved Australian indication for ezetimibe based on the IMPROVE-IT trial, which had a similar study design to Study 20110118, states it is indicated for 'reduction in risk of cardiovascular events'. It does not state specific component claims in the indication statement.[31] It should be noted that the magnitude of benefit observed with evolocumab in Study 20110118 was much greater than that observed with ezetimibe.

The sponsor therefore believes it is appropriate to reflect the composite endpoint and use 'cardiovascular events' in the indication statement with a reference to the clinical trials for details about the endpoints, instead of using specific component claims in the indication. This proposal is consistent with guidelines adopted by the TGA.[29,30] The sponsor agrees with the indication statement proposed by the Delegate.

The GLAGOV trial (Study 20120153) (Question 2)

Atherosclerosis is a progressive disease and halting progression or inducing regression stops the inflammatory process that ultimately leads to growth of the plaque, necrotic regions within plaques, and plaque rupture with thrombus formation which results in adverse clinical sequelae. Regression or stabilisation of coronary atherosclerosis is therefore an important clinical goal of therapy, independent of CV risk reduction.

The GLAGOV trial (Study 20120153) demonstrated the effect of evolocumab on CVD shown by imaging and, in conjunction with Study 20110118, provides a comprehensive assessment of atherosclerosis. Study 20120153 utilised intravascular ultrasound, which is a proven and reliable imagining technique offering important advantages. PAV and TAV represent reproducible endpoints measuring the entirety of a coronary atherosclerotic plaque, rendering it suitable for examining the effects of lipid lowering therapies on coronary atherosclerosis.

Study 20120153 demonstrated that when evolocumab is added to optimised statin therapy, 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. In Study 20120153, evolocumab reduced LDL-C from 60% to 68% throughout the study (Week 78). A relationship has been established between lowering LDL-C, regression (or slowing the progression) of atherosclerosis, and lower risk of major adverse CV events.[20,32,33]

Overall, the results from Study 20120153 demonstrate a positive, measurable, statistically significant biologic and clinically relevant effect of evolocumab on atherosclerosis, beyond what is achievable with optimised statins alone.

[31] Ezetrol (ezetimibe) AUSPAR. Department of Health. Therapeutic Goods Administration. Australian Public Assessment Report for ezetimibe and ezetimibe/simvastatin. 26 June 2017. https://www.tga.gov.au/sites/default/files/auspar-ezetrol-vytorin-170626.pdf Accessed 10 May 2018
[32] Puri R, Nissen SE, Ballantyne CM, et al. Factors underlying regression of coronary atheroma with potent statin therapy. *Eur Heart J*. 2013;34:1818-1825.
[33] Pitt B, Facc J, Ellis, S, et al. Pravastatin limitation of atherosclerosisin the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol*. 1995; 26:1133-1139

Alongside the results of Study 20110118, the Study 20120153 results provide a comprehensive assessment of the biological and clinical effect of evolocumab on the underlying disease of atherosclerosis which, upon progression, manifests as CV events. The statistically significant results observed for the primary and key secondary composite endpoints in Study 20110118 are presumed to result from plaque regression in most subjects treated with evolocumab. Progression and rupture of atherosclerotic plaque trigger the transition of atherosclerotic disease to clinical manifestations, and reducing LDL-C is of key importance in the medical management of clinical atherosclerotic CVD.

Hypercholesterolaemia indication (Question 4)

The sponsor proposed an indication for '*hypercholesterolaemia'* and including monotherapy for statin-intolerant patients. The sponsor believes sufficient evidence is provided in the original submission and the recently submitted application to support such an indication.

At the time of registration, the CV outcomes Study 20110118 was ongoing. In the absence of an established CV benefit of evolocumab, the hypercholesterolaemia indication was restricted to patients with the highest risk and unmet need, including patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic CVD. Results from Study 20110118 demonstrated that evolocumab reduces CV risk. Furthermore, the reductions in LDL-C observed in Study 20110118 were consistent with those of the lipid lowering studies included in the original marketing application. Thus, it can be concluded that patients with HeFH and those with and without established atherosclerotic CVD will benefit from evolocumab and it is reasonable to expand the indicated patient population for hypercholesterolaemia to include a broader patient population. The sponsor disagrees with the Delegate's proposal to reflect '*Primary hypercholesterolaemia*' as the heading of the indication. The sponsor proposes that the word 'primary' be deleted and that the heading be 'hypercholesterolaemia' for the reasons stated above and for consistency with other products. This proposal aligns with the regulatory precedent for another PCSK9 inhibitor, alirocumab, which is indicated for patients with hypercholesterolemia, and was studied in a similar patient population as evolocumab for lipid lowering. The sponsor believes the same approach should be followed for Repatha.

In the original application, results were submitted from evolocumab studies in statin intolerant patients and from studies that evaluated evolocumab as monotherapy. Two 12 week studies (Phase II Study 20090159 and Phase III Study 20110116) were conducted in statin intolerant subjects receiving evolocumab with non-statin background therapy including ezetimibe. In addition, two 12 week studies (Phase II Study 20101154 and Phase III Study 20110114) and the diet only arm of one 52 week study (Phase III Study 20110109) were performed to understand efficacy and safety of evolocumab in the absence of potential confounding factors from statins and statin intolerance (that is, as monotherapy). Evolocumab demonstrated superiority to ezetimibe and placebo for lipid lowering across all studies, thus supporting monotherapy in the indication for statin intolerant patients.

For the reasons mentioned above, the sponsor proposes the following indication:

> *Hypercholesterolaemia*
>
> *Repatha is indicated in adults with hypercholesterolaemia (including heterozygous familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C) in combination with a statin or statin with other lipid lowering therapies, or alone or in combination with other lipid lowering therapies in patients who are statin-intolerant.*

Neurocognitive outcomes sub-study (Question 5)

The CANTAB assessments are highly sensitive and were suitable to evaluate small differences. CANTAB is also an FDA validated method to evaluate neurocognitive outcomes.[34]

The CANTAB has been shown to be sufficiently sensitive to detect small differences in subclinical effects on cognitive function such as those due to age, education level, and gender, with statistical significance. The individual tests chosen for this study were chosen to assess the cognitive domains of psychomotor speed/attention, episodic memory and working memory/executive function and have been shown to be sensitive to drug induced impairment or improvement in performance.[35,36,37,38,39,40] The CANTAB platform has been used in interventional clinical studies to test (and demonstrate) both cognitive impairment and enhancement.[35,36,37,38,39,40,41] The subtests of the CANTAB selected for this study have established sensitivity to cognitive dysfunction in amnestic clinical syndromes such as mild cognitive impairment and Alzheimer's disease;[42] and have also been used to demonstrate cognitive safety drug therapy.[43]

As an example, the CANTAB assessment showed that the paired associates learning total errors adjusted learning task increases by 0.6 per year of age.[44] The CANTAB normative dataset also showed that working memory errors increases by approximately 0.4 errors per year of age and reaction time by approximately 1.1 ms per year of age. Hence, the CANTAB assessments are highly sensitive and were suitable to detect small differences between evolocumab and placebo in cognitive function in Study 20130385.

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Delegate's questions to the sponsor

1. *Were any patients in the FOURIER trial taking evolocumab as monotherapy during the study? If so, how many, and what were their outcomes?*

Due to the requirement in Study 20110118 that subjects be receiving background therapy with statins unless they could not tolerate statin therapy, only 11 subjects received evolocumab as monotherapy. A table of outcomes for these subjects is provided in Table 21.

Table 21: Study 20110118 Subject incidence of adjudicated cardiovascular events for subjects who took investigational product as monotherapy during study

	Placebo (N = 10) n (%)	EvoMab (N = 11) n (%)
Number of subjects with any positively adjudicated cardiovascular event	2 (20.00)	3 (27.27)
Death	0 (0.00)	1 (9.09)
Cardiovascular	0 (0.00)	0 (0.00)
Coronary death	0 (0.00)	0 (0.00)
Non-cardiovascular	0 (0.00)	0 (0.00)
Undetermined	0 (0.00)	1 (9.09)
Myocardial infarction (fatal and non-fatal)	0 (0.00)	0 (0.00)
Fatal	0 (0.00)	0 (0.00)
Non-fatal	0 (0.00)	0 (0.00)
Hospitalization for unstable angina	1 (10.00)	0 (0.00)
Coronary revascularization	1 (10.00)	1 (9.09)
PCI	1 (10.00)	1 (9.09)
Related to MI or unstable angina event	1 (10.00)	0 (0.00)
Surgical	0 (0.00)	0 (0.00)
Related to MI or unstable angina event	0 (0.00)	0 (0.00)
Cerebrovascular event	0 (0.00)	1 (9.09)
Transient ischemic attack	0 (0.00)	0 (0.00)
Stroke (fatal and non-fatal)	0 (0.00)	1 (9.09)
Fatal	0 (0.00)	0 (0.00)
Ischemic	0 (0.00)	0 (0.00)
Ischemic with hemorrhagic conversion	0 (0.00)	0 (0.00)
Hemorrhagic stroke	0 (0.00)	0 (0.00)
Type undetermined	0 (0.00)	0 (0.00)
Non-fatal	0 (0.00)	1 (9.09)
Ischemic	0 (0.00)	1 (9.09)
Ischemic with hemorrhagic conversion	0 (0.00)	0 (0.00)
Hemorrhagic stroke	0 (0.00)	0 (0.00)
Type undetermined	0 (0.00)	1 (9.09)

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N = number of subjects who received at least 1 dose of investigational product and without post-baseline (on-study) statin; EvoMab = Evolocumab (AMG 145); PCI = percutaneous coronary intervention
Include the events occurring between the subject randomisation date and the subject last confirmed survival status date, inclusive

Study 20110118 was not designed to evaluate evolocumab as a monotherapy. However, in prior lipid lowering evolocumab studies, placebo adjusted reductions in LDL-C of approximately 55% to 75% were consistently observed with evolocumab and this effect was detected in subjects with hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidaemia as monotherapy or as an add-on therapy to statins, including in subjects who could not tolerate doses of a statin. The LDL-C reductions observed in Study 20110118 and Study 20120153 fall within the range of

those observed in the lipid lowering studies included in the original application. Based on the results of Study 20110118 and Study 20120153, combined with those in the original evolocumab application, there is justification to use evolocumab in all populations and treatment settings studied. Given the association between reduction of LDL-C and reduction in both atherosclerotic plaque burden and CV events with evolocumab treatment, it is reasonable to conclude that LDL-C reduction with evolocumab would translate into CV benefits in other populations of patients who require reduction of CV risk with pharmacologic therapy including evolocumab as a monotherapy and in combination with other lipid lowering therapies.

Conclusion

Results from Study 20110118 were highly statistically significant and demonstrated clinically relevant reductions in CV events in the primary and key secondary composite endpoints with evolocumab treatment. All sensitivity and covariate analyses showed treatment effects consistent with the main analyses, further confirming the robustness of the study results.

The benefit-risk profile supports the use of evolocumab to reduce the risk of CV events in patients with established CVD. In addition, the benefit-risk profile supports removal of any limitations of use and supports the use of evolocumab in all the populations studied where evolocumab demonstrated lipid lowering.

Advisory Committee Considerations[45]

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Repatha injection prefilled pen, injection prefilled syringe and injection solution mini-doser containing 140 mg/1 mL injection solution (pre-filled syringe), 140 mg/1 mL injection solution (pre-filled pen), 420 mg /3.5 mL (120 mg/mL) injection solution (mini-doser) of evolocumab to have an overall positive benefit-risk profile for the amended indication:

Repatha is indicated as an adjunct to diet and exercise in:

Prevention of Cardiovascular Events

Repatha is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke and coronary revascularisation) in adults with established cardiovascular disease in combination with an optimally dosed statin (see Clinical Trials) and/or other lipid lowering therapies

No effect of Repatha on cardiovascular mortality has been demonstrated.

Primary Hypercholesterolaemia

Repatha is indicated in adults with primary hypercholesterolaemia, (including heterozygous familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C):

[45] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- *in combination with an optimally dosed statin or*
- *alone or in combination with other lipid lowering therapies in patients who are statin intolerant*

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 providing this advice the ACM:

- Expressed concern that one of the limitations of the FOURIER trial was the relatively short duration of follow-up (approximately 2 years) as compared with other lipid lowering trials, which have follow-up periods of approximately 5 years. It is possible that the shorter duration of the trial may have contributed to the negative trial result regarding the endpoint of cardiovascular death.
- Noted the FOURIER trial was powered for the secondary endpoint but was underpowered for the primary endpoint. Event numbers to power the study for the secondary endpoint was the trigger for the conclusion of the study. More events were required for the study to be powered for the primary endpoints but the study was stopped before that number could be reached.
- Noted that the primary and key secondary composite endpoints were mainly driven by the reduction in myocardial infarction and stroke. There were no statistically significant differences between the evolocumab and placebo group for cardiovascular death or all-cause mortality.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised the following:

- Add a statement in the *Clinical Trials* section of the PI to reference the absolute risk reduction of the end points in the FOURIER trial.
- Add a statement in the PI to more accurately reflect the validity of the methodology used in the cognitive sub-study.
- The information regarding the GLAGOV trial should be moved to the *Mechanism of Action* section of the PI and it should clarify the study did not have any clinical outcomes data.
- In the *Clinical Trials* section, 'the study was not designed to detect such a difference' should be removed from 'No significant difference was seen on overall cardiovascular mortality; the study was not designed to detect such a difference.' Cardiovascular death data was collected as part of the primary and key secondary endpoints. A difference may not have been detected in the study, possibly because there was no effect or because the trial length was relatively short, however data on this endpoint was collected.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Please comment on the effect size and clinical significance of the outcomes of the primary and key secondary endpoints in the FOURIER trial.*

In the FOURIER trial, there were a 15% relative risk reduction in the composite primary endpoint of CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation; and a 20% relative risk reduction in the secondary end point of cardiovascular death, myocardial infarction or stroke over 2.2 years. The relative risk reduction in the primary end point was mainly driven by reductions in MI and stroke. There were no statistically significant differences between the evolocumab and placebo group for cardiovascular death or all-cause mortality. The absolute risk reductions for both the primary and secondary endpoints were only about 1.5%. The ACM was of the view that although the effect of CV events observed in FOURIER trial was small; it was of a similar size to CV risk reduction observed in other statin studies for primary prevention.

2. *Please comment on the clinical significance of the outcomes of the GLAGOV trial.*

The GLAGOV trial was a double blind, randomised control trial which assessed the effects of evolocumab on atheroma as measured by intravascular ultrasound (IVUS) over 78 weeks of treatment. The regression in atheroma from baseline in the evolocumab group was statistically significantly larger than the placebo group. The committee was of the view that IVUS data were more useful in drug development (as supported by the EMA 2016 guideline). The study did not collect clinical outcomes data. The committee recommended moving the information regarding the GLAGOV trial to the *Mechanism of Action* section of the PI and a clarification that the study did not have any clinical outcome data.

3. *The primary and key secondary composite endpoints are driven by MI and stroke with no statistically significant difference between evolocumab and placebo for cardiovascular, coronary or all-cause mortality. The sponsor's requested Indication makes a claim about 'cardiovascular events' and references to the clinical trials for details about the endpoints. The clinical evaluator favoured specific component claims in the indication. Please comment.*

The committee agreed with the clinical evaluator that the component claims (MI, stroke and coronary revascularisation) should be specified in the indication. This will clarify that the reduction in the primary and key secondary endpoints were driven by specific cardiovascular events in the composite endpoints.

4. *There are two changes proposed for the Indication for Hypercholesterolaemia. The sponsor proposes to broaden the population to all adults with hypercholesterolaemia and to include monotherapy for statin intolerant patients. Has sufficient evidence now been provided to support this broader indication?*

The ACM was of the view that the reduction in LDL-C demonstrated by evolocumab was sufficient evidence to support the extension of the indication to include all adults with primary hypercholesterolaemia either as an adjunctive treatment to an optimally dosed statin or as monotherapy for statin intolerant patients.

5. *The neurocognitive outcomes sub-study did not demonstrate differences between the two treatment groups. Please comment on the suitability of CANTAB testing to detect small differences between treatment groups in a study of this size.*

As stated in the EU guidelines on the clinical investigation of medicine for the treatment of Alzheimer's disease, a large number of methods for evaluation of cognitive and functional changes are available, but no one particular test has emerged as the acceptable reference technique. The rationale for the choice of test should be provided and justified. The CANTAB test is not a commonly known test and may not be validated. The committee was of the view that a statement that will more accurately reflect the validity of the methodology used in the neurocognitive outcome sub-study should be included in the PI. This may need to be recognised as an unknown in the PI.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Repatha (evolucumab) 140 mg/1 mL (Pre-filled syringe and Pre-filled pen) and 420 mg /3.5 mL (120 mg/mL) Automated mini-doser for SC injection 140 mg every 2 weeks or 420 mg once monthly, indicated for:

> *Prevention of cardiovascular events*
>
> *Repatha is indicated to reduce the risk of cardiovascular events (myocardial infarction, stroke and coronary revascularisation) in adults with established cardiovascular disease in combination with an optimally dosed statin and/or other lipid lowering therapies (see Clinical Trials).*
>
> *Primary hypercholesterolaemia*
>
> *Repatha is indicated in adults with primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia and non-familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C):*
>
> - *in combination with a statin or statin with other lipid lowering therapies, or*
> - *alone or in combination with other lipid lowering therapies in patients who are statin intolerant.'*

Specific conditions of registration applying to these goods

The Repatha EU-Risk Management Plan (RMP) (version 2.3, dated 6 December 2017, data lock point 17 January 2017), with Australian Specific Annex (version 6.0, dated 13 February 2018), included with submission PM-2017-02229-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Repatha approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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