Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Evolocumab (rch)

Proprietary Product Name: Repatha

Sponsor: Amgen Australia Pty Ltd

May 2016

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.
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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
ACC	American College of Cardiology
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AHA	American Heart Association
AI/Pen	Auto injector/pen
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMD	Automated mini-doser
ANCOVA	Analysis of covariance
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
CABG	Coronary artery bypass graft
CAS	Completer analysis set
CBC	Complete blood count
CEC	Clinical endpoint committee
CETP	Cholesterylester transfer protein
CHD	Coronary heart disease
CK	Creatine kinase
C_{max}	Maximal concentration
CMH	Cochran-Mantel Haenszel statistical test for categorical variables
CRP	C-reactive protein
CSR	Clinical study report

Abbreviation	Meaning
CTCAE	NCI Common Terminology Criteria for AEs
CVS	Cardiovascular system
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DMC	Data monitoring committee
EAS	European atherosclerosis committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study (for individual subject)
EU	European Union
EvoMab	Evolocumab
FAS	Full analysis set
FDA	Food and Drug Administration
FH	Familial hypercholesterolaemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Haemoglobin A1c
HeFH	Heterozygous familial hypercholesterolaemia
HCV	Hepatitis C virus
HDL-C	High density lipoprotein cholesterol
HLGT	High level group term
HoFH	Homozygous familial hypercholesterolaemia
HR	Heart Rate
hsCRP	High sensitivity CRP

Abbreviation	Meaning
IBG	Independent Biostatistical Group
ICH	International Conference on Harmonization
IEAAS	Integrated expansion all-IP period analysis set
IECAS	Integrated extension SOC-controlled period analysis set
IEC/IRB	Independent Ethics Committee / Institutional Review Board
INR	International normalized ratio
IP	Investigational product
IPAS	Integrated parent analysis set
iSAP	Integrated statistical analysis plan
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
IV	Intravenous
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LH	Luteinizing hormone
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
LOCF	Last observation carried forward
Lp(a)	Lipoprotein(a)
LS	Least squares
LSM	Least squares mean
MAS	Monotherapy analysis set
MedDRA	Medical dictionary for regulatory activities

Abbreviation	Meaning
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NYA	New York Heart Association
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PFS	Pre-filled syringe
PK	Pharmacokinetic
PK/PD	Pharmacokinetic / pharmacodynamic
PO	Oral administration
PopPK	Population pharmacokinetics
Q2W	Q2W is defined as every 2 weeks with a window of ± 3 days for each visit
Q4W	Every 4 weeks
QD	Each day
QM	QM is defined as every 4 weeks with a window of ± 3 days for each visit
QT	Interval from start of Q wave to end of T wave
QTc	QT interval corrected for heart rate
QTcB	QT interval using Bazzett's correction
QTcF	QT interval using Fridericia's correction
QW	Every week
RBC	Red blood cells
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SE	Standard error

Abbreviation	Meaning
TIA	Transient ischemic attack
T_{max}	Time to maximum concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WBC	White blood cell

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	4 December 2015
Date of entry onto ARTG	9 December 2015
Active ingredient(s):	Evolocumab (rch)
Product name(s):	Repatha
Sponsor's name and address:	Amgen Australia Pty Ltd 115 Cotham Road, Kew VIC 3101
Dose form(s):	Injection, solution
Strength(s):	140 mg/mL
Container(s):	Single use pre-filled syringe made from Type I glass with stainless steel needle and Single use pre-filled pen with Type I glass syringe and stainless steel needle.
Pack size(s):	1, 2s (pen only) and 3s (pen only)
Approved therapeutic use:	*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.*
Route(s) of administration:	Subcutaneous (SC) injection
Dosage:	***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.

One pre-filled syringe or pre-filled pen (SureClick ®) delivers the 140 mg every 2 week dose, and three pre-filled syringes or three pre-filled pens administered consecutively within 30 minutes delivers the 420 mg once monthly dose.

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. Three pre-filled syringes or three pre-filled pens administered consecutively within 30 minutes deliver the 420 mg once monthly or 420 mg every 2 weeks dose.

ARTG number (s): 231151, 231152

Product background

This AusPAR describes the application by the sponsor to register new monoclonal antibody evolocumab (Repatha) for the treatment of hyperlipidaemia (heterozygous familial and non-familial), mixed dyslipidaemia and homozygous familial hypercholesterolaemia as follows

Primary hyperlipidaemia and mixed dyslipidaemia

Repatha is indicated in patients with primary hyperlipidaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia:

- *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 or for whom a statin is not considered clinically appropriate.*

Homozygous familial hypercholesterolaemia

Repatha is indicated in patients with homozygous familial hypercholesterolaemia in combination with other lipid lowering therapies.

Repatha is proposed to be used as an adjunct to diet when the response to diet and exercise is inadequate. It is proposed for use in adults and children 12 years and over, alone or in combination with other lipid-lowering therapies. Dosage is by subcutaneous (SC) injection, and the maximum proposed dose is 420 mg every 2 weeks (Q2W).

Evolocumab is a first in class fully human Immunoglobulin G2 (IgG2) directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9). It binds selectively to PCSK9 and inhibits circulating PCSK9 from binding to the low density lipoprotein (LDL) receptor on the surface of the hepatocyte. By binding to PCSK9 it increases the concentration of low density lipoprotein receptor (LDLR) on hepatic cells by inhibiting LDLR degradation and promoting recycling of the receptor. The inhibition also increases LDLR expression. Increasing liver LDLR levels results in associated reductions in serum low density lipoprotein-cholesterol (LDL-C). It differs from statins in its mode of action although the action of statins also leads to an increase in LDLR on the hepatocyte cell surface by increasing LDLR expression.

In 2009 about one third of deaths in Australia were the result of cardiovascular disease and 2,027 per 100,000 people were hospitalised with cardiovascular disease as a principal diagnosis in 2009 to 2010 (Australian Institute of Health and Welfare (AIHW)). Although a number of therapeutic options are registered for use in patients with hypercholesterolaemia, they do not universally result in the achievement of target serum lipid levels and have adverse effects that the population for which they are suitable. A reduction in serum lipids as measured by LDL-C has been associated with a reduction in the risk of cardiovascular events and serum lipid reduction is advocated in international guidelines for managing cardiovascular risk.

Homozygous familial hypercholesterolaemia (HoFH) is a rare disorder occurring in approximately 1:1 million births, whereas heterozygous familial hypercholesterolaemia is more common, occurring about 1:500 people. The more common mutations that result in hereditary hypercholesterolaemias are in LDL receptor genes and apolipoprotein B genes. Patients with these mutations present with coronary heart disease (CHD) earlier, have higher pre-treatment serum cholesterol levels that remained higher during treatment with statins and other lipid lowering therapies such as LDL apheresis and partial ileal bypass.[1] There may be differences in Asian and Caucasian populations in the phenotypes that specific mutations cause. PCSK9 gain-of function mutations, such as the D374Y mutation, decrease the number of LDL receptors at the hepatocyte surface and have been associated with autosomal dominant hypercholesterolaemia.

PCSK9 is a member of the mammalian serine proprotein convertase family that functions in the proteolytic processing and maturation of secretory proteins. PCSK9 binds to the epidermal growth factor-like repeat A (EGF-A) domain of the low density lipoprotein receptor (LDLR) inducing LDLR degradation. Although first identified in neuronal cells it was later found that loss of function mutations in the PCSK9 gene in humans lowered plasma LDL-C. These mutations occur in about 3% of the African American population. Nonsense mutations in PCSK9 have been reported to reduce LDL-C by 28% and decrease the frequency of CHD by 88% in those affected.

The European Union (EU) guidelines adopted by the TGA relevant to this submission, in addition to the general guidelines are:

- EMA/CHMP/748108/2013 Guideline on clinical investigation of medicinal products in the treatment of lipid disorders
- EMA/CHMP/494506/2012 (EMEA/CHMP/EWP/213057/2010)Paediatric addendum to CHMP guideline on clinical investigation of medicinal products in the treatment of lipid disorders
- EMEA/CHMP/EWP/311890/2007 Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention
- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a Clinical Investigation of Medicinal Products for Long-Term Use
- CHMP/EWP/89249/2004 Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins.

[1]Naoumova RP, Tosi I, Patel D, Neuwirth C, Horswell SD, Marais AD, van Heyningen C, Soutar AK. (2205). Severe hypercholesterolemia in four British families with the D374Y mutation in the PCSK9 gene: long-term follow-up and treatment response. *Arterioscler Thromb Vasc Biol*. 25:2654 –2660.

Regulatory status

The proposed product is a new biological entity for Australian regulatory purposes. Evolocumab received marketing authorisation in the EU on 17 July 2015 and in the USA on 27 August 2015. The approved indications are as follows:

Europe

Hypercholesterolaemia and mixed dyslipidaemia
Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
In combination with a statin or stain with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
Alone, or in combination with other lipid lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.
Homozygous familial hypercholesterolaemia
Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

USA

Primary hyperlipidaemia
Repatha is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
Homozygous Familial Hypercholesterolemia
Repatha is indicated as an adjunct to diet and other LDL-lowering therapies (E.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

The approved dosage regimens in Europe are the same as those proposed for Australia. The US dosage regimen does not include a 420 mg every 2 weeks (Q2W) dose to coincide with LDL apheresis.

A similar submission to that provided in Australia was provided to Health Canada and Swissmedic on 19 September 2014.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared 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>.

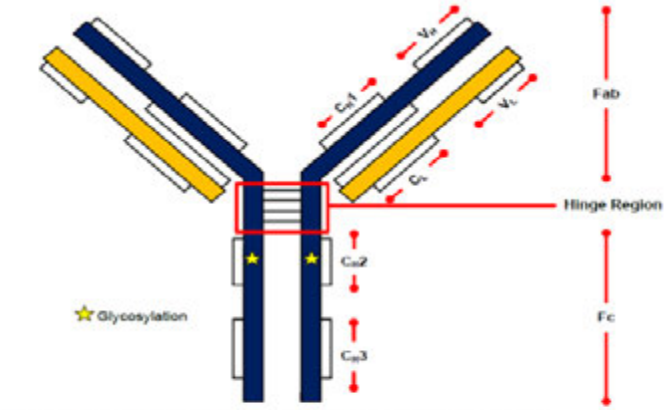
II. Quality findings

Drug substance (active ingredient)

Evolocumab is a human monoclonal antibody comprising 2 heavy chains and 2 light chains of the lambda subclass (Figure 1 and Table 1). Evolocumab contains 36 total cysteine residues involved in both intra-chain and inter-chain disulfide bonds. Each heavy chain contains 441 amino acids with 4 intra-chain disulphides. Each light chain contains 215 amino acids with 2 intra-chain disulphides. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 291.

The molecular formula for the predominant evolocumab heavy chain isoform (C-terminal glycine) is $C_{2140}H_{3313}N_{571}O_{664}S_{21}$, not including N-linked glycans. The molecular formula for evolocumab light chain is $C_{981}H_{1529}N_{263}O_{334}S_7$. The theoretical mass of glycosylated evolocumab containing 2 predominant glycans (1 per heavy chain) is 144,423 Daltons (Da). The experimentally determined predominant evolocumab mass is 144,428 Da, which is in agreement with the theoretical value within experimental error.

Figure 1: Structure of evolocumab



Heavy chains are shown in blue and light chains are shown in orange
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 substance is manufactured using a working cell bank (WCB) of Chinese hamster ovary (CHO) cells containing an expression vector.

The purification process is designed to remove all process related and product related impurities from the harvested cell culture fluid (HCCF) and to produce drug substance of the appropriate purity and concentration in the formulation buffer ready for drug product manufacture.

Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Table 1: General properties of evolocumab

Immunoglobulin subclass	IgG2
Sequence	Human sequence
Biological target	Specific binding to human PCSK9
Physical description	Clear to opalescent; colourless to yellowish; liquid,
Molecular mass	141,540 Da for de-glycosylated molecule 144,428 Da including glycosylation
Cysteines	36
Number of disulfide bonds	18
Glycosylation	N-linked site: Asn291 on each heavy chain

Drug product

The drug product [140 mg/mL] evolocumab is supplied as a sterile, single use, preservative free solution for SC injection in a prefilled syringe (PFS) and a prefilled pen.

Based on stability data collected to date, a shelf-life of 24 months is supported for the 140 mg/mL PFS and 140 mg/mL prefilled pen stored at the recommended storage condition of 5°C. Additionally, to enhance convenience and facilitate dosing compliance, an optional short-term storage at room temperature (controlled, 25°C or less) of not more than 1 month is supported after removal from storage at 5°C.

Biopharmaceutics

Biopharmaceutic data are not required for this product.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. There are no outstanding issues to be addressed.

There are no (further) objections to the registration of Repatha.

Recommended batch release conditions of registration for Delegate

- It is a condition of registration that, as a minimum, the first five independent batches of Repatha evolocumab (rch) 140 mg/mL injection solution syringe or Repatha evolocumab (rch) 140 mg/mL injection solution syringe within a pen injector imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA.

III. Nonclinical findings

Introduction

The nonclinical data submitted to support the application are consistent with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for a biotechnology derived product.[2] While the nonclinical data submitted are considered to be adequate, there is a greater emphasis on clinical safety and efficacy data than would be the case for a conventional small molecular product. Moreover, in addition, it should be noted that our knowledge of the PCSK9 pathway is relatively recent, and so our understanding of its biology is likely to be incomplete.

Pharmacology

Evolocumab is a monoclonal antibody directed against PCSK9, a protein whose role in the regulation of circulating levels of LDL-C (LDL-cholesterol) has emerged only over the past

[2]ICH guideline S6(R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals. June 2011. EMA/CHMP/ICH/731268/1998.

decade. LDL-C is the primary target of lipid lowering therapies, as lowering of LDL-C reduces the risk for coronary heart disease (CHD)[3]. A reduction in LDL-C is considered to be a valid surrogate for reduced risk of cardiovascular disease.[4] However, as discussed in the sponsor's Clinical Overview, other lipid parameters are also thought to be correlated both negatively and positively with pro atherogenic risk. The apolipoprotein B (ApoB) containing particles LDL-C, very low LDL (VLDL) and intermediate-density lipoprotein (IDL) are atherogenic, while the ApoA1 containing high density lipoprotein (HDL-C) is anti atherogenic. The relative impact of pro and anti atherogenic components may be integrated into a single measure by using the ratio of total to HDL cholesterol. Similarly, ApoB and ApoA1 are sometimes taken as positive and negative markers for atherogenic risk. An additional potential target for reducing CHD risk is known as lipoprotein (a) (Lp(a)), and consists of an LDL particle covalently bound to apolipoprotein(a). PCSK9 was first known as neural apoptosis-regulated convertase-1 (NARC-1) or LP251, and was the ninth identified member of the proprotein convertase family, being up-regulated by apoptosis induced by serum deprivation in neuronal cells.[5] Following its identification in neuronal tissue, it was reported that selective mutations in the PCSK9 gene were responsible for autosomal dominant hypercholesterolaemia. Conversely, loss of function (LOF) mutations in PCSK9 (Y142X and C679X) are associated with substantial reductions in serum concentrations of LDL-C .[6] A large bi-racial 15 year prospective study found that nonsense mutations in PCSK9 that reduced LDL-C levels by 28% decreased the frequency of CHD by 88%. In addition, Caucasians with a R46L allele had a 50% reduction in CHD, associated with mean reductions in LDL-C of 15%.[7]

PCSK9 is now known to regulate LDL-C levels by its influence in the recycling and regulation of the LDL receptor (LDLR).[7] The secreted protein is approximately 72 kDa, consisting of a pro domain of approximately 14kDa, bound to the 63 kDa mature protein. Both components undergo tyrosine sulfation in the endoplasmic reticulum before autocatalytic cleavage. Circulating levels of PCSK9 in human plasma are 50 to 600 ng/mL, and the concentration of purified PCSK9 needed to promote LDLR degradation (500 ng/mL) falls within this range.[7] Secreted PCSK9 binds to the first epidermal growth factor (EGF)-like repeat of the LDLR, which is associated with the cell membrane. Binding of PCSK9 inhibits endocytic recycling of the LDLR, and both proteins undergo lysosomal degradation, thus reducing the level of LDL-C clearance from plasma.[8] In the absence of PCSK9, LDLR recycling to the cell surface is facilitated, resulting in increased clearance of LDL-C from plasma.

Based on the above, PCSK9 is considered to be a viable new target for cholesterol lowering therapies, and a number are currently in the pipeline.[9] Evolocumab is the first of these to be evaluated for approval in Australia.

[3]Grundy *et al* (2004). Implications of recent clinical trials for the national cholesterol education program Adult Treatment Panel III guidelines. *Circulation* 110: 227-239.
[4]Cholesterol Treatment Trialists' Collaboration (2010). Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 376 (9753): 1670-1681.
[5]Seidah, N.G. *et al* (2003). The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): Liver regeneration and neuronal differentiation. *Proceedings of the National Academy of Science* 100(3): 928-33.
[6]Cohen, J. *et al* (2005). Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nature Genetics* 37: 161-5.
[7]Horton, J.D. *et al* (2006). Molecular biology of PCSK9: Its role in LDL metabolism. *TRENDS in Biochemical Sciences* 32(2): 71-7.
[8]Lagace, T.A. (2014) PCSK9 and LDLR degradation: regulatory mechanisms in circulation and in cells. *Current opionins in Lipidology* 25: (387-393).
[9]Hudson, V. (2014). The dyslipidaemia market. *Nature Drug Discovery Reviews* 13: 807-8.

Primary pharmacology

The full biological characterisation and immunological properties of evolocumab, including its antigenic specificity, have been submitted and are addressed in the Quality evaluation report.

In nonclinical studies, evolocumab was shown to bind with high affinity to recombinant PCSK9 from human (both 'wild type' and the GOF D374Y mutation), Cynomolgus monkey and hamster (K_D = 16, 7, 8 and 14 pM, respectively). Binding of evolocumab to PCSK9 prevented it from interacting with human recombinant LDLRs in vitro, increased LDLR expression and dose dependently increased LDL-C uptake by human HepG2 cells (a human hepatocyte carcinoma line), with an 50% effective concentration (EC_{50}) of 130 nM. These studies demonstrated the suitability of the hamster and Cynomolgus monkey as models to study the pharmacology and toxicology of evolocumab. The mouse was not a suitable model since evolocumab binding to the mouse protein was much weaker. In vitro studies with the human PCSK9 GOF mutation D374Y are suggestive of potential efficacy of evolocumab in reducing LDL-C levels in patients with this particular mutation, as well as in patients with the normal or wild type PCSK9. No other PCSK9 mutations were examined. It is possible that evolocumab might not bind to other mutations of PCSK9, and so it is not known whether it would be efficacious in such patients.

Both PCSK9 and the LDLR are co-ordinately regulated by sterol regulatory element-binding protein-2 (SREBP-2).[7] Inhibition of cholesterol synthesis by HMG CoA reductase inhibitors induces SREBP-2 expression, resulting in increased expression of LDLRs but PCSK9 mRNA and protein levels are also increased, which may limit the efficacy of statins. Rashid *et al* (2005)[10] showed that the livers of PCSK9 knockout (KO) mice had increased levels of LDLR protein and decreased serum concentrations of cholesterol compared to wild type mice. In addition, the knockout mice showed an enhanced hypocholesterolaemic response to lovastatin, suggesting that pharmacological inhibition of PCSK9 might have additive or synergistic effects with statins with respect to serum cholesterol. This was supported in the current submission by an in vitro study in HepG2 cells in which evolocumab and the HMG CoA reductase inhibitor mevinolin individually both increased LDLR protein expression, while mevinolin also increased the secretion of PCSK9. The two agents in combination had an additive effect of LDLR expression in vitro, supporting the hypothesis that statins and evolocumab might have additive effects in combination therapy. In the 3 month repeat dose toxicity study in monkeys, evolocumab in combination with a sub-efficacious dose of rosuvastatin decreased plasma LDL-C concentrations and thus in this species evolocumab's LDL-C lowering effect was additive with that of rosuvastatin. Therefore the submitted pharmacological studies provide support for the combination of evolocumab with statin therapy.

The cholesterol lowering properties of evolocumab were examined in vivo following administration of single SC doses to male Syrian Golden Hamsters and male Cynomolgus monkeys, or following IV administration of single doses to male mice expressing human PCSK9. Evolocumab administration in these species resulted in reductions in serum LDL-C in monkeys, and in non-HDL-C (LDL- and VLDL-C) in hamsters and mice). The magnitude and/or duration of the hypocholesterolaemic effect were dose dependent and in the hamster were shown to be associated with increased LDLR expression. In the monkey, administration of evolocumab immediately decreased serum unbound PCSK9 to below detection levels, an effect that preceded the decline in serum LDL-C. Both PCSK9 and LDL-C levels recovered with a similar time course. Similar results were obtained in a single dose pharmacokinetic study in monkeys.

[10]Rashid, S. *et al* (2005). Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9. *Proceedings of the National Academy of Sciences* 102(15): 5374-9.

Evolocumab had no effect on serum triglyceride or HDL-C concentration in monkeys. In contrast, HDL-C levels were reduced in the hamster. This appears to be due to a species difference as HDL-C is cleared by the LDLR in this species.[11] Mice transfected with human PCSK9 also showed reductions in serum HDL and triglyceride concentrations following evolocumab administration. These effects contrast with the results obtained in clinical trials with evolocumab, in which serum HDL-C concentrations were increased (sponsor's Clinical Overview). The clinical studies examined a greater range of lipid parameters than were studied in animals, and the sponsor's Clinical Overview concluded that evolocumab reduced serum concentrations of LDL-C, non-HDL-C, ApoB, total cholesterol, Lp(a), VLDL-C, and triglycerides and the ratios of total cholesterol: HDL-C and ApoB:ApoA1 in subjects with primary hyperlipidaemia (heterozygous familial and nonfamilial) and mixed dyslipidaemia, while HDL-C and ApoA1 concentrations were increased. The lack of extensive monitoring of the full range of potential pro-atherogenic markers in the animal studies is appropriate given the evidence of subtle species differences in the effects of PCSK9 inhibition on non-LDL-C markers, but as mentioned above, this places a greater emphasis on the clinical data to support the efficacy of the product. The nonclinical pharmacodynamic data thus provide proof of concept for the use of evolocumab in the treatment of elevated LDL-C but do not provide any evidence for efficacy in the treatment of CHD or improved survival.

It is noted that the animal studies involved only single dose administration to normal male animals (or humanised mice), and did not examine evolocumab in any animal models of cardiovascular disease. The repeat-dose toxicity studies in hamsters and monkeys used both males and females and examined the pharmacodynamic effects of repeated dose administration.

Secondary pharmacodynamics and safety pharmacology

The antigen specificity of evolocumab for PCSK9 and the specificity of binding to PCSK9 over other members of the proprotein convertase family were not addressed. The nonclinical data did not specifically address the potential complement binding properties of evolocumab (as is recommended in the ICH guideline[12]), although no evidence of an adverse effect was observed in repeat-dose toxicity studies.

A safety pharmacology study in Cynomolgus monkeys found that a single IV dose of evolocumab (300 mg/kg) was well tolerated, and showed no notable effects on behaviour, body temperature, cardiovascular parameters or respiration rate. The peak plasma concentration of evolocumab (C_{max}) attained in this study (5850 µg/mL) was approximately 60 times that observed in HoFH patients at Week 8 following evolocumab treatment at 420 mg Q2W (Clinical Study 20110271).

Tissue cross reactivity assays examined the potential binding of evolocumab to non-target antigenic determinants in panels of 33 to 35 tissues from hamster, Cynomolgus monkey and human. The study designs appeared to be appropriate, with suitable controls but the results are difficult to interpret. No staining of hepatic tissue was observed in any of the three species, while extracellular elements which did stain included striated skeletal muscle, cardiomyocytes and smooth muscle myocytes in the skin in all 3 species, in addition to smooth muscle myocytes in the monkey iris. Widespread staining to intracellular elements was also observed but evolocumab is unlikely to access the cytoplasmic compartment and so this is not of toxicological relevance. The repeat dose toxicity studies did not provide any evidence of functional or morphological effects of

[11]Goulinet, S. & Chapman, M.J. (1993). Plasma lipoproteins in the Golden Syrian hamster (*Mesocricetus auratus*): heterogeneity of apoB- and apo-I containing particles. *Journal of Lipid Research* 34, 943-959.
[12] ICH guideline S6(R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals. June 2011. EMA/CHMP/ICH/731268/1998.

evolocumab in cardiac and striated muscle, skin or eye. Additional in vivo investigations in repeat dose studies in the hamster and Cynomolgus monkey included indirect ophthalmoscopy and slit lamp biomicroscopy for detailed examination of the anterior and posterior segments but no adverse effects were observed. Neurobehavioural examination of Cynomolgus monkey infants on postnatal days (PNDs) 7 and 14 in the enhanced pre-postnatal development study found no effects on the pupillary light reflex, nyastagmus or the glabellar tap reflex. Technical limitations of the tissue cross reactivity assay are well known.[13] A survey of such data from 113 monoclonal antibodies found that only 22% and 10% of molecules tested in non-human primates and human tissues, respectively, showed positive staining in more than 95% of tissues known to express the therapeutic target, while false positive results were also common .[14] It is concluded that the results of the tissue cross reactivity assay do not provide any useful information about possible off target or secondary pharmacological activity.

The sponsor provided an extensive literature review addressing the potential secondary pharmacodynamic characteristics of evolocumab, based on studies on PCSK9 localisation and function. PCSK9 is expressed most abundantly in liver but has also been localised in small intestine, pancreas and kidney as well as in neurones.[5, 15,16] Thus based on this extra hepatic distribution, PCSK9 may be involved in other roles in addition to its regulation of LDLR expression. The literature review considered the evidence for possible secondary pharmacological activity for PCSK9 inhibitors, including the potential for effects on the brain and cognitive function, interactions with other members of the lipoprotein receptor family, a postulated role in hepatitis C virus (HCV) infectivity, the potential impact on insulin resistance and diabetes risk, possible effects on the hepatobiliary system and intestinal tract and on the immune system as well as the relevance of statin-induced myopathy. Overall the literature review is considered to be extensive and comprehensive. However, some aspects of the biological role of PCSK9 remain to be fully clarified, including possible species differences in PCSK9 regulation. The available evidence to date does not provide a clear signal for potential adverse secondary pharmacological effects with evolocumab treatment but unforeseen long term consequences of PCSK9 inhibition cannot be excluded.

Possible adverse consequences of low serum cholesterol concentration

There have been some concerns expressed in the literature about the possible adverse consequences of very low serum cholesterol concentrations, partly based on some of the theoretical considerations as discussed above and also based on epidemiological studies. It has been argued that average LDL-C levels of approximately 120 to 130 mg/dL (3.10 to 3.36 mmol/L) in Western countries could safely be reduced to 30 to 60 mg/dL (1.552 to 0.776 mmol/L), which are more reflective of 'normal physiological' levels seen in early development or in contemporary hunter gatherer populations.[17, 18] Decreased circulating levels of LDL-C are likely to result in increased cholesterol synthesis in extra hepatic tissues to satisfy local requirements for cholesterol. In addition, evolocumab treatment

[13]Leach, M.W. *et al* (2010). Use of tissue cross-reactivity studies in the development of antibody-based biopharmaceuticals: history, experience, methodology and future directions. *Toxicologic Pathology* 38: 1138-1166.
[14]Bussiere, J.L. *et al* (2011). Survey results on the use of the tissue cross-reactivity immuno-histochemistry assay. *Regulatory Toxicology and Pharmacology* 59: 493-502.
[15]Langhi, C. *et al* (2009). PCSK9 is expressed in pancreatic δ-cells and does not alter insulin secretion. *Biochemical and Biophysical Research Communications* 390: 1288-93.
[16]Poirier, S. *et al* (2006). Implication of the convertase NARC-1/PCSK9 in the development of the nervous system. *Journal of Neurochemistry* 98: 838-50.
[17]Hochholzer, W. and Giugliano, R.P. (2010). Lipid lowering goals: back to nature? *Therapeutic advances in cardiovascular disease* 4(3): 185-91.
[18]LaRosa *et al* (2013). Safety and effect of very low levels of low-density lipoprotein cholesterol on cardiovascular events. *American Journal of Cardiology* 111:1221-1229.

will increase LDLR expression in extra-hepatic tissues, allowing them to take up more cholesterol from the circulation.

The lower levels of serum cholesterol described above are consistent with those observed in people with PCKS9 LOF mutations. As previously discussed, such mutations in humans are associated with substantial reductions in serum concentrations of LDL-C and reduced incidence of CHD.[19] Zhao *et al* (2006)[20] identified one individual with compound heterozygous mutations affecting PCSK9 synthesis and processing/secretion. This individual was reported as having no circulating PCSK9 in her plasma, and had a serum LDL-C concentration of 14 mg/dL (0.362 mM). Despite having no functional PCSK9, this individual was reported to be a healthy, fertile, normotensive woman, with normal neuronal, liver and renal function (including urinalysis). A second individual lacking detectable levels of PCSK9 in his plasma has been reported in the literature.[21] This subject had diabetes mellitus (most likely type II) and moderate liver steatosis but hepatic enzymes and liver function tests were otherwise normal. There was no history of diarrhoea nor eye or neurological abnormalities related to any vitamin deficiency. His serum cholesterol concentration was 16 mg/dL (0.414 mmol/L).

In contrast, other types of genetic disorders associated with hypolipidaemia, such as abetalipoproteinaemia (Bassen-Kornzweig syndrome), hypobetaliporoteinaemia and chylomicron retention disease can be associated with significant adverse developmental and physical symptoms.[22] Symptoms of abetalipoproteinaemia initially include fat malabsorption, steatorrhoea and failure to thrive and can progress to intellectual disability, retinal degeneration, sensory neuropathy, posterior column signs, and cerebellar signs of dysmetria, ataxia, and spasticity which can eventually lead to death.

Potential for secondary effects on the brain and cognitive function

Cholesterol is a major constituent of all cell membranes and also of the myelin sheath. Dysregulation of brain cholesterol metabolism has been associated with a number of neurodegenerative disorders, leading to concerns that lipid lowering agents might adversely affect neuronal function or development. Adverse effects of statins on cognitive performance or memory have been reported and combination therapy with evolocumab and statins has the potential to reduce serum cholesterol levels below those seen with statin monotherapy.

Brain cholesterol is derived almost entirely from de novo synthesis as lipoproteins do not cross the blood brain barrier.[23] Cholesterol homeostasis in the brain is believed to be independent of the rest of the body. Although distribution studies with evolocumab were not submitted, significant central nervous system (CNS) exposure is not anticipated due to its large size (see below, *Pharmacokinetics*). PCSK9 levels in human CSF have been reported to be approximately 60 times lower than in serum and remain stable throughout the day, while serum levels vary due to exhibit diurnal rhythms and postprandial fluctuations. Circulating PCSK9 does not cross the blood brain barrier in mice and pharmacotherapeutic agents which reduce PCSK9 expression are not expected to affect

[19]Cohen, J. *et al* (2005). Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nature Genetics* 37: 161-5.
[20]Zhao Z et al. (2006).Molecular Characterization of Loss-of-Function Mutations in *PCSK9* and Identification of a Compound Heterozygote. The American Journal of Human Genetics Volume 79; 514-523
[21]Cariou, B. *et al* (2009). PCSK9 dominant negative mutant results in increased LDL catabolic rate and familial hypobetalipoproteinaemia. *Arteriosclerosis, Thrombosis and Vascular Biology* 29: 2191-7.
[22]Merck Manual;
http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/lipid_disorders/hypolipidemia.html
[23]Dietschy, J.M. & Turley, S.D. (2004). Cholesterol metabolism in the central nervous system during early development and in the mature animal. *Journal of Lipid Research* 45: 1375-97.

brain PCSK9 concentration.[24] The sponsor's conclusion that evolocumab is expected to lower serum cholesterol without having any effect on cholesterol (or PCSK9) concentrations in the brain appears to be justified. In contrast, statins may reduce CNS cholesterol concentrations through local inhibition of HMG CoA reductase.

As previously mentioned, PCSK9 was originally identified as NARC-1, a potential regulator of neuronal differentiation in cortical neurones. The physiological role of PCSK9 in the brain has not been fully established, although in vitro evidence from animal studies suggests that it may be involved in apoptosis. Inactivation of PCSK9 results in disordered neuronal development and death in zebra fish[7] although PCSK9 knockout mice apparently develop normally[10]. In the enhanced pre-postnatal development study in Cynomolgus monkeys there were no morphological or functional effects on CNS development following maternal treatment with pharmacologically active doses of evolocumab throughout pregnancy. Similarly, case studies in humans with LOF mutations in PCSK9 (including complete absence of detectable PCSK9 in plasma) have not provided any evidence of adverse health or developmental effects. A recent study of approximately 6000 elderly people (70 to 82 years old) exhibiting a single PCSK9 nucleotide polymorphism associated with a 10 to 16% reduction in serum LDL-C, found no effect on cognitive performance, daily activities or non-cardiovascular clinical events.[25] In addition, dense linkage disequilibrium mapping of genes putatively involved in lipid metabolism from 1567 dementia cases (including 1270 with Alzheimer's disease) found no association with genes encoding PCSK9.[26]

The sponsor states that there was no neurocognitive signal in clinical studies with evolocumab. However, a possible neurocognitive signal has recently been reported in a pooled analysis of open label randomised trials of 4465 patients who received evolocumab (140 mg Q2W or monthly) for a median of 11.1 months.[27] Neurocognitive events were defined as delirium or confusion, cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders. They were reported in 27 (0.9%) of evolocumab treated subjects, compared with 4 (0.3%) of subjects receiving standard therapy. The incidence of neurocognitive events in clinical trials with alirocumab, another PCSK9 inhibitor currently under development, were 18 (1.2%), compared with a placebo incidence of 4 (0.5%; p = 0.17)[28]. The latter authors considered that the usefulness of this observation is limited by the lack of formal neurocognitive testing as part of the study design. Although there was no evidence in the submitted nonclinical data for any adverse neurocognitive events in animals, this was not formally studied. The enhanced pre-postnatal development study in monkeys did include a neurobehavioural assessment but this was relatively limited and did not examine learning and memory.

Potential interaction with other LDLR family members

The nonclinical overview reviewed the evidence for evolocumab effects on other members of the LDLR family, including the VLDLR, ApoER2 and LDLR related receptors (LRPs) since these receptors all share a number of structural features. A number of in vitro studies have found that PCSK9 can bind to the VLDLR and ApoER2. In vivo studies have reported

[24]Rousselet, E. *et al* (2011). PCSK9 reduces the protein levels of the LDL receptor in mouse brain during development and after ischaemic stroke. *Journal of Lipid Research* 52: 1383-91.
[25]Postmus, I. *et al* (2013). PCSK9 SNP rs 11591147 is associated with low cholesterol levels but not with cognitive performance or noncardiovascular clinical events in an elderly population. *Journal of Lipid Research* 54(2): 561-66.
[26]Reynolds, C. A. *et al* (2010). Analysis of lipid pathway genes indicates association of sequence variation near SREBF1/TOM1L2/ATPAF2 with dementia risk. *Human Molecular Genetics* 19(10): 2068-78.
[27]Sabatine, M.S. *et al* (2015). Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *New England Journal of Medicine* 372: 1500-1509.
[28]Robinson, J.G. *et al* (2015). Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *New England Journal of Medicine* 372: 1489-1499.

conflicting results. One study in PCSK9 KO mice found no effect on VLDLR and LRP1 protein levels, body weight or adipose depot size but neither was there any change in LDLR levels.[10] In contrast, Roubtsova *et al* (2011)[29] reported a 40 fold increase in surface VLDLR protein in peri gonadal fat and an 80% increase in visceral adiposity. The results of the repeat dose toxicity studies with evolocumab are more consistent with the former study as there were no differences in body fat deposits. As discussed above in the *Pharmacology* section, in the clinical studies there were reductions in triglycerides and VLDL concentrations following treatment with evolocumab. However, the sponsor has suggested that decreased serum VLDL could be the result of its binding to LDLRs following their up regulation which is consistent with the literature presented.

Poirier *et al* (2008)[30] reported that PCSK9 binds to the ApoER2 as well as the VLDLR and suggested that ApoE2R binding by PCKS9 may underlie its neuronal regulatory role. However, the brains of PCKS9 KO or over-expressing mice did not show different levels of expression of ApoER2 protein.[31] In addition, as already discussed, CNS exposure to evolocumab is likely to be minimal and it is therefore not expected to affect CNS levels of PCSK9.

Potential effect of PCSK9 inhibition on Hepatitis C infectivity

The nonclinical overview included a review of the evidence for LDLR up regulation via inhibition of PCSK9 leading to an increase in HCV infectivity. The results of in vitro experiments examining PCSK9 inhibition of the surface expression of CD81 (the major HCV cell entry factor) are contradictory. Labonté *et al* (2009)[32] found increased hepatic expression of CD81 in PCSK9 KO mice. A preliminary report (not peer-reviewed) by Ramanthan *et al* (2013)[33] found no correlation between the amount of secreted, soluble PCSK9 and total or surface CD81 in Huh-7 cells (a human hepatocyte cell line), and treatment with alirocumab (a monoclonal antibody against PCSK9 under development by Regeneron) had no effect on CD81 expression. These authors also reported no changes in hepatic CD81 expression in their strains of PCSK9 KO or hyperlipidaemic ($Pcsk9^{hum/hum}Ldlr^{+/-}$ mice treated with alirocumab). The evidence for a potential increase in HCV infection risk with evolocumab treatment is equivocal. No signal for increased HCV infectivity was noted in the clinical studies, although there were only 3 subjects reported to be infected.

Potential impact on insulin resistance and diabetes risk

The nonclinical overview included a review of the potential impact of evolocumab treatment on insulin resistance and diabetes risk. As mentioned above, PCSK9 is expressed in the pancreas. Associations between low levels of plasma PCSK9 and insulin in humans are most probably driven by dietary influences. Although animal studies have suggested that insulin may regulate PCSK9 expression, studies in humans have reported that subjects with Type 2 diabetes or impaired glucose metabolism did not exhibit differences in plasma PCSK9 concentrations compared to normoglycaemic controls. Studies with PCSK9 KO mice have yielded contradictory results but the incidence of diabetes was not increased in humans with PCSK9 LOF mutations (Y142X or C679X).[6] An association between increased

[29]Roubtsova, A. *et al* (2011). Circulating proprotein convertase subtilisin/Kexin 9 (PCSK9) regulates VLDLR protein and triglyceride accumulation in visceral adipise tissue. *Arteriosclerosis Thrombosis and Vascular Biology* 31:785-9.
[30]Poirier, S. *et al* (2008). The proprotein convertase PCSK9 induces degradation of low density lipoprotein receptor (LDLR) and its closest famility members VLDLR and ApoeER2. *Journal of Biological Chemistry* 283: 2363-72.
[31]Liu, M. *et al* (2010). PCSK9 is not involved in the degradation of LDL receptors and BACE1 in the adult mouse brain. *Journal of Lipid Research* 51:2611-18.
[32]Labonté, P. *et al* (2009). PCSK9 impedes Hepatitis C virus infection *in vitro* and modulates liver CD81 expression. *Hepatology* 50: 17-24.
[33]Ramanathan, A. *et al* (2013). Abstract 12052: Role of Alirocumab on CD81 levels and hepatitis C virus entry into hepatocytes. *American Heart Association* Conference report abstract only.

serum cholesterol and pancreatic islet dysfunction and increased diabetes risk is well known and thus the cholesterol lowering effect of evolocumab might be expected to reduce the risk of diabetes. However, the reverse had been found to be true with statins.[34,35] There was no evidence of increased plasma or urinary glucose concentration or pancreatic histopathology in the repeat dose toxicity studies with evolocumab. The nonclinical data do not provide any evidence of increased risk of diabetes with evolocumab. Clinical studies have included assessments of plasma glucose and glycated haemoglobin (HbA1c).

Potential relevance of statin-induced myopathy for evolocumab

The nonclinical overview reviewed the literature concerning mechanisms underlying statin induced myopathy. It has previously been suggested that this may occur as a result of the cholesterol lowering action of statins and thus any further lowering of serum cholesterol as would occur with an inhibitor of PCSK9 might exacerbate statin induced myopathy. The sponsor provided a study that investigated the mechanism underlying cerivastatin induced myopathy in rats (which manifested as necrosis of type IIB glycolytic fibres of skeletal muscle fibres, associated with serum and urinary biomarkers of skeletal muscle injury). Dietary supplementation with 1% cholesterol was associated with increased serum cholesterol concentration but did not prevent cerivastatin induced myopathy. In contrast, supplementation with 1% mevalonate (the product of HMG CoA reductase, which occurs upstream of the isoprenoid intermediates in the cholesterol synthesis pathway) prevented cerivastatin induced myopathy. This suggests that statin induced myopathy is not a result of cholesterol depletion per se but may be related to depletion of isoprenoid intermediates which occur downstream of mevalonate in the cholesterol synthesis pathway. The study also showed that cerivastatin induced myopathy in this model was associated with increased expression of genes involved in stress, inflammation and autophagy/mitophagy, while genes involved in energy production or mitochondrial biogenesis (PGC-1α) showed reduced expression.

The literature review and the mechanistic study provided support for the hypothesis that statin induced myopathy may be due to depletion of isoprenoid cholesterol precursors that are critical for skeletal muscle viability and mitochondrial function and not directly due to the cholesterol lowering effect. The repeat dose toxicity studies with evolocumab did not provide any evidence of muscle toxicity, including changes in serum concentrations of aspartate aminotransferase (AST), creatine kinase (CK) or aldolase or histopathological changes in skeletal muscle fibres. However, it should be noted that the 3 month repeat dose rosuvastatin and evolocumab combination toxicity study in monkeys used a non-efficacious dose of rosuvastatin.

Metabolic fate of plasma lipoprotein lipids and potential impact on hepatobiliary system and intestinal tract

The submission included a literature review to consider the possible consequences of increased hepatic uptake of LDL-C as a consequence of PCSK9 inhibition by evolocumab. Hypothetical adverse effects include increased hepatocellular lipid accumulation and increased metabolism or excretion of cholesterol leading to increased intracellular bile acid accumulation or increased bile acid excretion. However, potential compensatory mechanisms could include reduced endogenous synthesis of cholesterol or biliary excretion either as free cholesterol or in the form of bile acids. In the repeat dose toxicity studies with evolocumab no evidence of adverse hepatic effects were found, such as histopathological changes in the hepatobiliary tract and intestine, liver steatosis, gallstone

[34]Sampson, U.K. *et al* (2011). Are statins diabetogenic? *Current Opinion in Cardiology* 26: 342-347.
[35]Sattar, N. *et al* (2012). Statins are diabetogenic – Myth or reality? *Atherosclerosis Supplements* 13: 1-10.

formation or increases in serum transaminases. Hepatic triglyceride content in humans with heterozygous PCSK9 LOF mutations was not significantly different from controls.[36]

Rashid *et al* (2005)[10] reported that PCSK9 KO mice had similar liver cholesterol, triglyceride and bile acid content to wild type mice, indicating that such homeostatic mechanisms are in operation in this model. Another PCSK9 KO mouse strain was found to have 1.5 to 2 fold higher level of faecal bile acid excretion compared with wild type mice[37], while faecal sterol levels were similar. These authors examined the combined effect of PCSK9 LOF with statin administration in their KO mouse strain and reported that the reduced serum LDL-C concentration was not associated with changes in liver lipid levels, total bile acid concentration or plasma total bile acid levels but atorvastatin further increased bile acid excretion and also and increased cholesterol excretion via the faeces. The effects of atorvastatin were associated with increased expression of bile acid synthesis genes, without changing bile transporter mRNA levels (sodium taurocholate cotransporter, bile salt export protein, or apical sodium bile acid transporter). The PCSK9 KO mice also had increased expression of bile acid synthesis genes compared with wild type mice, and no change in the expression of these transporters.

The sponsor did not investigate the effect of evolocumab treatment on bile acid secretion or excretion nor on the expression of bile transporters such as the bile salt export protein (BSEP). Studies investigating the possible effects of evolocumab on hepatic lipid and bile acid homeostasis, including the possible up regulation of bile acid transporters would be highly desirable. Altered bile acid transporter expression could have implications for interactions between evolocumab and other pharmacological agents and this has not been addressed in the current application.

It has been proposed that the association between dietary fat intake and increased incidence of colorectal cancer may be mediated through elevated faecal levels of secondary bile acids.[38] These include deoxycholic acid (DCA), lithocholic acid (LCA) and ursodeoxycholic acid (UDCA) which are formed in the large intestine due to the action of enteric bacterial enzymes. Both DCA and LCA can exert tumourigenic effects. There was no evidence of colon carcinogenesis in the 2 year carcinogenicity study in hamsters. Low serum cholesterol concentrations are positively correlated with increased cancer incidence in epidemiological studies but no such association has been found in subjects with LOF mutations in PCSK9 .[39,40]

Potential effects of evolocumab on immune system function

The submission included a literature review of the evidence for the potential of PCSK9 inhibitors to adversely affect the immune system. Lymphocytes responding to immune stimulation require cholesterol for plasma membrane synthesis during clonal expansion, and altered cholesterol content of lipid structures have been associated with altered signal transduction in T-lymphocytes and other immune cells.[41] A number of studies have shown

[36]Kotowski *et al* (2006). A spectrum of PCSK9 alleles contributes to plasma levels of low density lipoprotein cholesterol. *American Journal of Human Genetics* 78: 410-22.
[37]Parker, R.A. *et al* (2013). Bile acid and sterol metabolism with combined HMG-CoA reductase and PCSK9 suppression. *Journal ofLipid Research* 54: 2400-9.
[38]Degirolamo *et al* (2011). Bile acid and colon cancer: solving the puzzle with nuclear receptors. *Trends in Molecular Medicine* 17(10): 564-72.
[39]Benn, M. *et al* (2011). Low-density lipoprotein cholesterol and the risk of cancer: a Mendelian randomisation study. *Journal of the National Cancer Institute* 103(6): 508-19.
[40]Folsom, A.R. *et al* (2007). Sequence variation in proprotein convertase subtilisin/kexin type 9 serine protease gene, low LDL cholesterol and cancer incidence. *Cancer Epidemiology, Biomarkers and Prevention* 16: 2455-8.
[41]Cuthbert, J.A. and Lipsky, P.E. (1987). Provision of cholesterol to lymphocytes by high density and low density lipoproteins. *The Journal of Biological Chemistry* 262(16): 7808-18.

immunosuppressive effects of statins on various aspects of immune function.[42] Thus inhibition of PCSK9 might have adverse effects on the immune system, and this was addressed in the current submission by the inclusion of immunotoxicology endpoints in the 6 month repeat dose study in Cynomolgus monkeys and the 3 month study in which evolocumab was administered in combination with rosuvastatin. Evolocumab treatment (or evolocumab in combination with atorvastatin) had no effect on T-cell dependent antibody responses, peripheral blood immunotyping and natural killer cell (NKC) activity. In addition, lymphoid organ histopathology and haematology examinations were conducted in all repeat dose toxicity studies, with no adverse findings.

Similar findings have recently been reported for another anti-PCSK9 monoclonal antibody (RG7652) administered in combination with atorvastatin in a 12 week repeat dose study in monkeys.[42] These authors also examined delayed type hypersensitivity (DTH) responses following BCG immunisation and subsequent tuberculin challenge. Treatment with the PCSK9 antibody (alone or in combination with atorvastatin) did not significantly reduced DTH responses to tuberculin challenge, although the combined treatment was associated with reduced CD4+ (T-helper lymphocytes) cell content, and there was also a trend towards reduced CD8+ (cytotoxic T-lymphocytes) and CD68+ (macrophage) cell content compared with controls. These results are in keeping with studies showing that exogenous LDL concentrations as low as 0.5 mg/dL (0.013 mmol/L) were sufficient to enable mitogen stimulated lymphocyte proliferation to occur in vitro, even in the presence of a HMG CoA reductase inhibitor.[41] For comparison, serum LDL-C concentrations were ≥ 1 mg/dL (0.026 mmol/L) in clinical trials with evolocumab.

In conclusion, the sponsor has examined the potential for evolocumab (alone or in combination with a statin) to exert immunomodulatory effects by incorporating standard immunotoxicological endpoints in the repeat dose toxicity studies. There was no evidence of an adverse effect on the immune system in these studies.

Pharmacokinetics

The plasma kinetics of evolocumab was examined after single intravenous (IV) or SC doses in male Cynomolgus monkeys. The plasma clearance following IV administration was 129.6 mL/h/kg (approximately 26 mL/h, or 2 fold higher than the human plasma clearance of 12 mL/h). The monkey data showed evidence of non-linear elimination and concentration dependent changes. In humans, clearance of natural immunoglobulin is 6.0 to 8.4 mL/h, and both natural immunoglobulin clearance processes and saturable, target (PCSK9) mediated elimination are both likely to contribute to the overall elimination process. The volume of distribution following IV administration in the monkey was lower than the plasma volume, which is typical of a monoclonal antibody with limited tissue distribution, and consistent with the human data (volume of distribution at steady state (Vss) = 3.3 L). Following SC administration in monkeys and humans, plasma concentrations of unbound evolocumab peaked after 3 to 4 days and bioavailability was high (82% and 72%, respectively). Systemic exposure increases in the monkey were greater than dose proportional and apparent clearance after SC administration decreased with increasing dose, consistent with an antibody with capacity-limited binding. In repeat dose studies in hamsters and monkeys accumulation ratios were up to approximately 3 fold, indicating no time dependent changes in pharmacokinetics and there was a low incidence of anti-evolocumab antibody development. These studies also showed no notable gender differences. The sponsor developed a semi-mechanistic pharmacokinetic/pharmacodynamic model based on the data obtained in the Cynomolgus

[42]Gelzleichter TR (2014). Combined Administration of RG7652, a Recombinant Human Monoclonal Antibody Against PCSK9, and Atorvastatin does not Result in Reduction of Immune Function. Toxicological Sciences. ToxSci Advance Access published May 22, 2014.

monkey to determine a dose for first-in-human trials and to develop exposure response models to apply to clinical studies.

The nonclinical data did not include any studies investigating the tissue distribution or plasma protein binding properties of evolocumab. CNS exposure to antibody is likely to be very low, as only 0.1 to 0.2% of circulating immunoglobulins are found in the brain at steady state.[43]

No formal nonclinical studies were submitted on the metabolism or excretion of evolocumab. The expected consequence of metabolism of biotechnology derived pharmaceuticals is the degradation to small peptides and individual amino acids. Therefore, the metabolic pathways are generally understood and classical biotransformation studies as performed for pharmaceuticals are not needed.[44] Clearance of evolocumab is likely to involve binding and complex formation with the target, PCSK9, as well as interactions with the neonatal Fc receptor and the reticuloendothelial system.[45] The ultimate fate is likely to involve degradation to small peptides and amino acids. While evolocumab itself is unlikely to be renally excreted because of its high molecular weight, peptide fragments and amino acids that are not able to be used for de novo protein synthesis may be excreted by the kidney.

Pharmacokinetic drug interactions

In the 3 month repeat dose toxicity study in Cynomolgus monkeys, evolocumab administration did not affect the systemic exposure of co-administered rosuvastatin. The study design did not specifically examine whether rosuvastatin affected the systemic exposure of evolocumab. No other nonclinical studies were submitted but CYP or P-gp mediated interactions with small molecule therapeutic agents are unlikely with this class of medicine.[45] However, as discussed above, altered hepatic lipid and bile acid homeostasis is expected based on the biological activity of PCSK9. The sponsor did not investigate the effect of evolocumab treatment on bile acid secretion or excretion, nor on the expression of bile transporters such as the bile salt export protein (BSEP). However, the lack of pharmacokinetic interaction between evolocumab and the organic anion-transporting polypeptide B1 (OATP1B1) and Breast Cancer Resistance Protein (BCRP) substrate rosuvastatin argues against any effect of evolocumab on these transporters.

Toxicology

Acute toxicity

Formal single dose toxicity studies were not conducted. There was no evidence of acute toxicity in a single dose safety pharmacology study in Cynomolgus monkeys or after the first dose in repeat dose studies in hamsters and Cynomolgus monkeys (SC doses of up to 300 mg/kg).

Repeat-dose toxicity

Repeat dose toxicity was examined in Syrian Golden hamsters and Cynomolgus monkeys dosed for up to 3 months and 6 months, respectively in Good Laboratory Practice (GLP) compliant studies. In addition, a 3 month repeat dose study in Cynomolgus monkeys

[43]Yu, Y.J. & Watts, R.J. (2013). *Neurotherapeutics* 10: 459-472.
[44]ICH guideline S6(R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals. EMA/CHMP/ICH/731268/1998 (2011)
[45]Keizer, R.J *et al* (2010). Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clinical Pharmacokinetics* 49(8): 493-507.

investigated combined treatment with rosuvastatin. These species had previously been shown to be suitable animal models based on pharmacological activity comparable to that seen with the human target protein in vitro (that is, similar high affinity binding to hamster and Cynomolgus monkey PCSK9) and with the desired surrogate endpoint (lowered serum LDL-C concentrations) demonstrated in vivo. Evolocumab was administered by the clinical route in these studies at a dose frequency that was generally higher than the proposed dosage regime (weekly or biweekly in animals studies, compared with biweekly or monthly in clinical use). Assessments of serum total and LDL-C were included in the repeat-dose toxicity studies. The 13 week hamster study was shorter in duration than is normally expected for a product intended for chronic use and the animal group size of six would limit the power of the study to detect unusual toxicities. However, these deficiencies are somewhat ameliorated by the 2 year carcinogenicity study in this species which had adequate animal numbers and included monitoring of the pharmacodynamic effect throughout the study. With the exception of the 3 month repeat dose study in hamsters, these studies included an extended recovery period, ranging from 16 weeks recovery for the 4 week hamster study to 25 weeks recovery for the 6 month monkey study. This enabled the recovery time course of the pharmacodynamic effect to be determined.

All monkey studies included monitoring of the anti-drug antibody response (including whether they were neutralising or non-neutralising), while in the hamster this was only performed in the 4 week study. However, this is acceptable as no antibodies to evolocumab were detected after dosing had commenced in the 4 week hamster study. In addition, the pharmacodynamic and toxicokinetic data from the 3 month repeat dose and 2 year carcinogenicity studies in this species do not indicate a notable antibody response. Immunotoxicity studies were conducted in the monkey as part of the 6 month repeat dose study and the 3 month repeat dose combination study with rosuvastatin. Overall, the nonclinical toxicology studies submitted were consistent with the relevant ICH guidelines.[46]

Relative exposure

Exposure ratios have been calculated based on unbound evolocumab animal: human plasma area under the concentration versus time curve between time zero and the time of next dosing ($AUC_{0-\tau}$) taking into to account any difference in dosing intervals (Table 2). Human reference values are from severe familial hypercholesterolemia patients dosed at 420 mg biweekly in Clinical Study 20110271. Relative exposures at the high dose level were adequate and justified the dose selections for the repeat dose studies, as there were no dose limiting toxicities.

Table 2: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration (day), dosing frequency	Dose mg/kg/dose	$AUC_{0-\tau}$ mg·h/mL	Exposure ratio#
Hamster (Syrian Golden)	28 days (Day 22) QW	3	38.7	3
		30	134	10
		300	331	26

[46]ICH guideline S6(R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals. EMA/CHMP/ICH/731268/1998 (2011); ICH M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. EMA/CPMP/ICH/286/1995 (2009)

Species	Study duration (day), dosing frequency	Dose mg/kg/dose	$AUC_{0-\tau}$ mg·h/mL	Exposure ratio#
	3 months (Day 85) QW	100	139	11
		300	267	21
	2 years carcinogenicity Week 27 Q2W	10	9.8	0.38
		30	54.9	2
		100	171.5	7
Monkey (Cynomolgus)	6 weeks (Day 36) QW	3	8.6	0.7
		30	103	8
		300	1530	118
	6 months (Day 176) QW	3	13.6	1
		30	270	21
		300	1730	134
Human	Q2W	420 mg	25.9	–

= animal: human plasma $AUC_{0-\tau}$, adjusted for the difference in dose intervals between the animal studies (1 week or 2 weeks) and the human study (2 weeks)

Major toxicities

Evolocumab related effects were limited to the desired pharmacological activity, reducing LDL and total cholesterol. In hamsters, HDL-C was also reduced. This is due to the affinity of the LDLR to ApoE, which is present in higher amounts in HDL-C in the hamster relative to primates.[11] Minimal and sporadic reductions in HDL-C were seen in the repeat-dose studies in Cynomolgus monkeys, while in the clinical studies HDL-C concentrations were increased (sponsor's Clinical Overview). Reductions in serum LDL-C and total cholesterol were reversed in the recovery period with a time course that was consistent with evolocumab clearance from plasma.

Evolocumab was not immunogenic in the hamster, and there was only a very low incidence of anti-evolocumab antibody formation in the monkey studies.

Genotoxicity

The standard battery of genotoxicity studies routinely conducted for pharmaceuticals are not considered to be applicable to biotechnology derived pharmaceuticals.[47] Evolocumab contains no inorganic linkers, synthetic organic linkers or other non-protein portions which might raise concerns regarding deoxyribonucleic acid (DNA) reactivity. The sponsor did not submit any genotoxicity studies with evolocumab. This is acceptable.

[47]ICH guideline S6(R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals. EMA/CHMP/ICH/731268/1998.

Carcinogenicity

Standard carcinogenicity assays are not routinely required for biotechnology derived pharmaceuticals unless there is concern regarding the biological activity of the product.[5] As discussed above in the section under *Secondary pharmacology*, the sponsor provided a detailed and comprehensive literature review of the biology of PCSK9 which included a review of the evidence for an association between low circulating levels of cholesterol and human cancer incidence. Low serum cholesterol concentrations are positively correlated with increased cancer incidence in a number of epidemiological studies.[39,40] Increased cancer incidence has also been associated with administration of lipid lowering pharmacological interventions in rodents and in clinical trials (with clofibrate, and simvastatin in combination with ezetimibe). Folsom *et al* (2007)[40] reported a lack of association between low LDL-C PCSK9 genetic variants and cancer incidence in a prospective study of 13,250 subjects. Benn *et al* (2011)[39] more recently investigated the possible causal relationship between low LDL-C and cancer in over 70,000 subjects by testing for genetic polymorphisms associated with reducing plasma LDL-C. While an association with low plasma LDL-C and cancer was confirmed, the genetic polymorphisms were not associated with cancer risk. The explanation for this discrepancy is unknown.

As discussed above, a plausible biological mechanism may exist for evolocumab treatment leading to colon cancer development as a result of homeostatic mechanisms in operation due to increased hepatocellular cholesterol uptake. PCKS9 KO mice have been reported to have increased faecal excretion of bile acids (Parker et al 2013).[37] Increased bile acid excretion could theoretically increase the possibility of colon carcinogenesis through the formation of secondary bile acids lithocholic acid (LCA) and deoxycholic acid (DCA) which are known to be tumourigenic.

The sponsor submitted a lifetime carcinogenicity study in Golden Syrian hamsters dosed biweekly with evolocumab at up to 100 mg/kg SC, corresponding to systemic exposure levels up to 7 times the maximum clinical exposure. This treatment was associated with reductions in mean serum LDL-C throughout the treatment period, reaching maximums of up to 86% in males and 70% in females, providing evidence of sustained biological activity throughout the animals' lifetime. A single incidence of neoplasia in the colon (a malignant leiomyosarcoma in a high dose (HD) male) does not represent a clear signal of colon carcinogenesis. Although some individual or combined tumour type incidences were higher in treated hamsters compared with controls (adrenal cortical cell carcinoma, thyroid follicular cell adenoma, Harderian gland adenoma and uterine epithelial cell tumours), none of these differences showed statistical significance and the frequency of these tumours within the historical control range. It is concluded that there was no evidence of an effect of treatment with evolocumab on mortality or on neoplastic or non-neoplastic changes.

Reproductive toxicity

The sponsor submitted a fertility and early embryonic development study in male and female hamsters (dosed for 4 and 2 weeks, respectively, from before cohabitation through mating and up until implantation) and an enhanced peri-postnatal study in Cynomolgus monkeys in which mothers were dosed from Gestation Day 20 to 22 through to birth. In addition, male and female fertility endpoints were assessed in the 6 month repeat dose toxicity study in Cynomolgus monkeys. No dedicated embryofetal toxicity study was included but this was addressed in the enhanced pre/postnatal monkey study where a full necropsy of offspring was performed at six months. Extensive fetal exposure to evolocumab during the period of organogenesis is unlikely however, since in nonhuman primates as well as in humans the placental transfer of immunoglobulins is very low

during this period with an increased rate of transfer occurring in the third trimester.[48] Evolocumab was detected in the serum of neonatal monkeys in the pre/postnatal development study up until PND 91, confirming that placental and/or lactational transfer of evolocumab had occurred. Immunoglobulins are normally excreted early on post-partum via colostrum but not later during the lactation period.[5] The amount of evolocumab detected in the serum of these neonatal monkeys (approximately 100 µg/mL) would be expected to be associated with maximal reduction in serum LDL-C in an adult monkey. Overall, the range of studies submitted and the study designs were in accordance with the relevant guidelines[49] and are considered adequate for the purposes of reproductive assessment.

Biweekly treatment of Golden Syrian hamsters with evolocumab at up to 100 mg/kg SC had no effect on male or female fertility, oestrous cycling, sperm parameters or male reproductive organ weights or on embryofetal survival. Toxicokinetic monitoring was not carried out in this study but based on the results obtained in the 2 year carcinogenicity study in this species at the same maximum dose the No observable effect level (NOEL) for fertility and early embryonic toxicity corresponded to a relative exposure level of 7 (compared with a clinical dose of 420 mg Q2W). In addition, there were no adverse effects on reproductive organ weights or histopathology, menstrual cycling or sperm parameters the 6 month repeat dose toxicity study in sexually mature Cynomolgus monkeys following weekly SC administration of evolocumab at doses up to 300 mg/kg, corresponding to relative systemic exposure levels 134 times the maximum anticipated clinical exposure. Low serum cholesterol is generally not thought to be associated with adverse birth outcomes .[50,51] On the other hand, in a study of 9938 women attending for routine prenatal screening, Edison *et al* (2006) reported an association between low second trimester serum total cholesterol concentrations (in the lowest tenth percentile; serum total cholesterol less than 159 mg/dL/4.11 mmol/L) and preterm delivery. In addition, there was a trend for increased incidence of microcephaly in this cohort. However, overall, infants with congenital anomalies were most commonly born to mothers whose serum cholesterol concentration fell within either the lowest 5% or highest 10%.

The dose administered for the enhanced pre-postnatal development study in Cynomolgus monkeys was selected based on previous pharmacodynamic studies where saturation of PCSK9 inhibition was observed at ≥ 3 mg/kg and because the systemic exposure was anticipated to be in excess 10 fold higher than the clinical dose of 420 mg QM. However, the maximum proposed clinical dose is 420 mg Q2W, so the relative exposure achieved in this study was only 5. Maternal treatment with evolocumab from early pregnancy throughout gestation was not associated with any maternal toxicity or adverse effects on gestation or pregnancy or post-partum outcomes. The evolocumab associated reduction in maternal LDL-C was superimposed on a background of lower serum LDL-C in the control animals. This represents a species difference, since in humans the serum concentrations of total cholesterol and LDL-C are increased throughout pregnancy.[51,52] Interestingly, the mean serum LDL-C concentrations in evolocumab treated monkey offspring was only slightly lower than that of controls. Taking into account the levels of evolocumab detected

[48]Kane, S.V. *et al* (2009). Therapeutic monoclonal antibodies to women during conception and pregnancy. *American Journal of Gastroenterology* 104: 228-33.
[49]ICH Topic S5(R2). Detection of toxicity to reproduction for medicinal products and toxicity to male fertility. CPMP/ICH/386/95 (1994); ICH guideline S6(R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals. EMA/CHMP/ICH/731268/1998.
[50]Homianics, G.E. *et al* (1993). Target modification of the apolipoproetin B gene results in hypobetalipoproetinamia and developmental abnormalities in mice. *Proceedings of the National Academy of Sciences* 90: 2389-93.
[51]Connor, W.E. *et al* (1978). The plasma lipids, lipoproteins, and diet of the Tarahumara Indians of Mexico. *American Journal of Clinical Nutrition* 31: 1131-42.
[52]Bartels, A. *et al* (2012). Maternal serum cholesterol levels are elevated from the first trimester of pregnancy: a cross-sectional study. *Journal of Obstetrics and Gynaecology* 32(8): 747-52.

in the serum of these neonatal monkeys (approximately 100 µg/mL) it appears that the offspring are less sensitive to the cholesterol lowering effect of evolocumab than adults.

Maternal treatment with evolocumab during pregnancy had no effect on birth weight, although the offspring of treated mothers showed significantly decreased body weight gain postnatally. However, morphometric measurements showed no remarkable difference other than single time point instances of slightly smaller foot length and head measurements of treated animals which may reflect higher male: female ratio in the control group or differences in the gestation day of delivery. Neurobehavioural assessments on PNDs 7 and 14 found no differences between the offspring of control and treated monkeys, with all scores within the normal range for infant Cynomolgus monkeys. However, as already discussed, this did not include a neurocognitive development assessment of learning and memory. A terminal necropsy of infants at six months found no treatment related effects on organ weights, morphometric measurements or external, visceral or heart evaluation observations.

In conclusion, there were no adverse effects on embryofetal or postnatal development in Cynomolgus monkeys following maternal exposure to evolocumab at systemic exposures approximately five times higher than the maximum anticipated clinical exposure. These exposure levels were associated with approximately 70% reductions in LDL-C. However, the observed species differences between the human and the Cynomolgus monkey with respect to the normal physiological response to pregnancy in terms of changes in serum lipids should be kept in mind when interpreting the results of animal studies.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1[53]. This is appropriate based on the animal data.

Local tolerance

The clinical formulation was well tolerated when administered via the SC route to Golden Syrian hamsters and via the IV route in rabbits. In addition, injection site reactions were unremarkable in the repeat dose toxicity studies.

Immunotoxicity

As discussed above, immunotoxicity studies were conducted in the monkey as part of the 6 month repeat dose study and the 3 month repeat dose combination study with rosuvastatin. It should be noted that the dose of rosuvastatin administered in the latter study was sub-efficacious. All monkey studies included monitoring of the anti-drug antibody response (including whether they were neutralising or non-neutralising). Evolocumab was only weakly immunogenic in the nonclinical studies, with approximately 10% of monkeys exhibiting anti-evolocumab antibodies and approximately half of these being neutralising. Even in the presence of neutralising antibodies evidence of pharmacological activity was detected. The incidence of anti-evolocumab antibodies in clinical studies was only 0.1%. The presence of anti-evolocumab antibodies is not expected to adversely affect its safety or efficacy. As discussed above (*Secondary pharmacology Potential effects of evolocumab on immune system function*) immunotoxicity endpoints included white blood cell counts, T cell dependent antibody responses and peripheral blood immunotyping (total numbers of T cells ($CD3^+$), helper T cells (CD3+CD4+CD8-, cytotoxic T cells (CD3+CD8+CD4-, B cells ($CD3^-CD20^+$), and Natural killer Cell ($CD3^-CD16^+$) activity. In addition, lymphoid organ histopathology and haematology examinations showed no adverse findings. Similar findings for another anti-PCSK9

[53]Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.

monoclonal antibody (RG7652) are discussed above, including a lack of significantly reduced delayed type hypersensitivity response.

Evolocumab administration did not show any evidence of immunosuppression in nonclinical studies. In clinical studies, serum LDL-C levels were an order of magnitude above the threshold level for inhibition of lymphocyte proliferation of 0.5 mg/dL (0.013 mmol/L).[41]

Impurities

Evolocumab is a biotechnology derived product and studies on impurities are not required.

Paediatric use

No dedicated juvenile animal toxicity studies were submitted. The sponsor is proposing that evolocumab be indicated for use in adults and children 12 years of age and over. It was argued in the sponsor's nonclinical overview that the developmental age of animals evaluated in the repeat dose toxicity studies included the 6 week study in monkeys which were 2.5 years of age or older, corresponding to a human age of approximately ten years of age. This study is not considered long enough in duration to be considered adequate to support paediatric use. The monkeys used in the six month repeat dose toxicity study were 4 to 6 years of age and sexually mature at the start which does not support the proposed paediatric use. No adverse toxicological or developmental effects were observed in the enhanced pre and postnatal development study in the offspring of Cynomolgus monkeys following maternal exposure to evolocumab throughout gestation. Neonatal exposure to evolocumab was confirmed up to 91 days post-partum. While this study is supportive of paediatric use, the exposure is again relatively short term. However, hamsters were 5 to 7 weeks old at the start of the 2 year carcinogenicity study, which found no adverse neoplastic or non-neoplastic effects. Overall, the nonclinical data provide limited support for the use of evolocumab in paediatric patients.

Nonclinical summary

- The nonclinical data submitted to support the application were mostly in accordance with the requirements for a biotechnology derived product. The studies were generally well chosen and designed, enabling adequate assessment from a minimum number of animals.
- The role of PCSK9 in the regulation of circulating levels of LDL cholesterol (LDL-C) has emerged only over the past decade. PCSK9 binds to the LDL receptor (LDLR) and inhibits its endocytic recycling. Reduced LDLR expression at the hepatic cell surface reduces LDL-C clearance from plasma. It is proposed that as a result of evolocumab binding to PCSK9, LDLR recycling to the cell surface is facilitated, resulting in increased clearance of LDL-C from plasma.
- Evolocumab binds with high affinity to recombinant PCSK9 from human (both 'wild type' and the gain-of-function D374Y mutation), Cynomolgus monkey and hamster (K_D = 16, 7, 8 and 14 pM, respectively). Binding of evolocumab to PCSK9:
    a. Prevented PCSK9 from interacting with human recombinant LDLRs;
    b. Increased LDLR expression; and
    c. Dose-dependently increased LDL-C uptake in vitro (EC_{50} = 130 nM).

    These studies demonstrated the suitability of the Golden Syrian hamster and Cynomolgus monkey as models to study the pharmacology and toxicology of evolocumab.

- Evolocumab and the HMG CoA reductase inhibitor mevinolin in combination had an additive positive effect on LDLR expression. In the 3 month repeat dose toxicity study in monkeys evolocumab's LDL-C lowering effect was additive with that of rosuvastatin, supporting its combination use with statin therapy.
- Evolocumab reduced serum LDL-C in monkeys, and non-HDL-C (LDL- and VLDL-C) in hamsters and in a humanised mouse model in vivo. The magnitude and/or duration of the hypocholesterolaemic effect were dose dependent and in the hamster were shown to be associated with increased LDLR expression. In the monkey, evolocumab reduced serum unbound PCSK9 concentrations; their subsequent recovery correlated with changes in serum LDL-C. The lack of extensive monitoring of the full range of potential pro-atherogenic markers in the animal studies compared to those measured in the clinical studies is acceptable given the evidence of minor species differences in the effects of PCSK9 inhibition on non-LDL-C markers. The animal data support the use of evolocumab to lower LDL-C in humans.
- A safety pharmacology study in Cynomolgus monkeys found that a single IV dose of evolocumab (300 mg/kg) was well tolerated and showed no notable effects on behaviour, body temperature, cardiovascular parameters or respiration rate.
- The design and conduct of a tissue cross reactivity study examining the potential binding of evolocumab to non-target antigenic determinants in hamster, Cynomolgus monkey and human appeared to be appropriate but did not provide any useful information about possible off target or secondary pharmacological activity. PCSK9 is expressed most abundantly in liver but has also been localised to the small intestine, pancreas and kidney as well as to neurones. A comprehensive and extensive literature review by the sponsor considered possible off-target activity, including the potential for effects on the brain and cognitive function, interactions with other members of the lipoprotein receptor family, hepatitis C virus infectivity, the potential impact on insulin resistance and diabetes risk, possible effects on the hepatobiliary system and intestinal tract and on the immune system. Some aspects of the biological role of PCSK9 remain to be fully clarified, including possible species differences in PCSK9 regulation.
- A mechanistic study in rats provided evidence that statin induced myopathy results from depletion of isoprenoid cholesterol precursors critical for skeletal muscle viability and mitochondrial function and is not directly due to the cholesterol lowering effect. The nonclinical data suggest that clinical use of evolocumab will not be associated with myopathy and it is not expected to exacerbate statin induced myopathy, at least at low statin doses.
- The bioavailability of evolocumab following SC administration to Cynomolgus monkeys was high (82%), and similar to that in humans (72%), with a time to peak plasma concentration (T_{max}) of 3 to 4 days. Systemic exposure increases in the monkey were greater than dose proportional, and apparent clearance after SC administration decreased with increasing dose, consistent with an antibody having capacity-limited binding. Natural immunoglobulin clearance processes and saturable, target mediated elimination are both likely to contribute to the overall elimination process. The volume of distribution (Vss = 3.3 L) was lower than the plasma volume, consistent with limited tissue distribution (and with the human data) but tissue distribution and plasma protein binding were not examined directly. In repeat dose studies in hamsters and monkeys there were no remarkable time dependent changes in pharmacokinetics. These studies also showed no notable gender differences.
- Evolocumab administration did not affect the systemic exposure of co-administered rosuvastatin in a 3 month repeat dose study in monkeys but the study design did not specifically examine whether rosuvastatin affected the systemic exposure of evolocumab. No other nonclinical studies were submitted. The possibility that

homeostatic changes in bile acid excretion could affect expression of bile transporter proteins (which could have implications for drug interactions) was not investigated.

- Repeat dose toxicity studies were performed in Syrian Golden hamsters and Cynomolgus monkeys and were designed and conducted in accordance with ICH guidelines. Assessments of serum total cholesterol and LDL-C were included in the repeat-dose toxicity studies. Most studies included an extended recovery period, enabling the recovery time course of the pharmacodynamic effect to be determined. Evolocumab was not immunogenic in the hamster and there was only a very low incidence of anti-evolocumab antibody formation in the monkey studies, which did not adversely affect its pharmacodynamic or pharmacokinetic effects. The systemic exposure levels (based on AUC) achieved in the repeat dose studies in hamsters and monkeys were approximately 20 and 130 times that anticipated in clinical studies at a dose of 420 mg Q2W. Evolocumab related effects were limited to the desired pharmacological activity, that is, reducing LDL- and total cholesterol, with no evidence of evolocumab mediated toxicity. In hamsters, HDL-C was also reduced which is a species-specific effect and contrasts with the increase in HDL seen in clinical studies. Reductions in serum LDL-C and total cholesterol were reversed in the recovery period with a time course that was consistent with evolocumab clearance from plasma.
- Administration of evolocumab to monkeys in the 6 month repeat dose study (relative exposure 130) was not associated with any effects indicative of immunosuppression, including T cell dependent antibody responses and peripheral blood immunotyping, lymphoid organ histopathology or haematology examinations. Immunotoxicity endpoints were also studied in the 3 month combination study with a sub-therapeutic dose of rosuvastatin in this species and showed no adverse effects.
- Genotoxicity studies are not required for this type of product and none were submitted. A theoretical biological mechanism may exist for evolocumab treatment leading to colon cancer as a result of homeostatic mechanisms in operation due to increased hepatocellular cholesterol uptake, resulting in increased formation of secondary bile acids DCA and LCA which are known to be tumourigenic. A 2 year carcinogenicity study in hamsters (relative exposure of 7) found no evidence of an effect of treatment with evolocumab on mortality or on neoplastic or non-neoplastic changes.
- A fertility study in male and female hamsters found no adverse effects of treatment with evolocumab (estimated relative exposure 7) on male or female fertility, oestrous cycling, sperm parameters or male reproductive organ weights or on embryofetal survival. In addition, there were no adverse effects on reproductive organ weights or histopathology, menstrual cycling or sperm parameters in the 6 month repeat dose toxicity study in sexually mature Cynomolgus monkeys (relative systemic exposure 130).
- An enhanced pre/postnatal development study in Cynomolgus monkeys examined embryofetal and postnatal development following maternal exposure to evolocumab from gestation day 20 to 22 through until birth, at systemic exposures approximately five times higher than the maximum anticipated clinical exposure. There were no adverse effects on pregnancy outcomes, although postnatally the offspring of treated mothers showed significantly decreased body weight gain. Neurobehavioural assessments were all within the normal range for infant Cynomolgus monkeys, although they did not include neurocognitive endpoints such as learning and memory. No treatment related effects on organ weights, morphometric measurements or external, visceral or heart evaluation observations were seen at the terminal necropsy of infants at six months. Treatment of mothers with evolocumab was associated with approximately 70% reductions in LDL-C, superimposed on a physiological reduction in serum LDL-C in the control group. This is in contrast with the physiological

hyperlipidaemia observed during pregnancy in humans and highlights the possibility of interspecies differences in lipid metabolism. Evidence of placental transfer of evolocumab was provided in the offspring post-partum up until PND 91.

- The clinical formulation was well tolerated when administered via the SC route to Golden Syrian hamsters, and via the IV route in rabbits. In addition, injection site reactions were unremarkable in the repeat dose toxicity studies.

Nonclinical conclusions

- The nonclinical data submitted to support the application were consistent with the ICH guideline for a biotechnology derived product.
- The primary pharmacology studies support the proposed indication with respect to LDL-C lowering (both alone and in combination with a statin) but due to interspecies differences in lipid metabolism a full range of pro-atherogenic markers were not monitored in animal studies. The effect of evolocumab in animal models of CHD was not investigated.
- The available evidence to date does not provide a clear signal for potential adverse secondary pharmacological effects with evolocumab treatment but unforeseen long term consequences of PCSK9 inhibition cannot be excluded as some aspects of the biological role of PCSK9 remain to be fully clarified.
- The sponsor did not investigate the metabolic fate of increased hepatic uptake of cholesterol, which is likely to be via increased faecal excretion of bile acids and which may involve increased expression of bile acid transporters.
- Mechanistic data suggest that evolocumab is not expected to elicit myopathy or to exacerbate statin induced myopathy.
- Evolocumab was only weakly immunogenic in repeat dose toxicity studies in hamsters and monkeys; the development of anti-evolocumab antibodies did not affect the assessment of safety and efficacy. There was no evidence of toxicity in these studies, which also included immunotoxicity endpoints and the pharmacodynamic response was shown to be reversible.
- Evolocumab (as a biotechnology derived product) is not expected to be genotoxic and there was no evidence of carcinogenicity or toxicity in a lifetime study in hamsters.
- Reproductive toxicity was adequately investigated but these and other studies provide only limited evidence to support the proposed use in children 12 years and over.
- Although the nonclinical data are generally supportive of efficacy and safety, further investigation of potential homeostatic mechanisms in response to increased hepatic uptake of cholesterol, including the potential for drug interactions based on bile acid transporters is recommended.
- There was no evidence in the submitted nonclinical data for any adverse neurocognitive events in animals, in contrast to recently reported clinical findings. However, the neurobehavioural assessment in monkeys was relatively limited in scope and did not examine learning and memory.
- Amendments to the draft PI were also recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The following clinical rationale was provided in the sponsor's letter of application:

> *Cardiovascular disease (CVD) remains the leading cause of death and disability in both the developed and developing world. The causes of CVD are varied, but atherosclerosis and hypertension are common. Hyperlipidaemia is a major modifiable risk factor for atherosclerosis. However, despite the availability of existing therapies to treat hyperlipidaemia, approximately 25% of all patients, and 33% of high-risk patients, are unable to adequately control their lipid levels. Thus, despite current, widely available lipid-lowering therapies, there is a large unmet medical need to provide new and more effective therapies, which can be used to improve patient outcomes*.

The clinical rationale is considered acceptable.

Contents of the clinical dossier

Scope of the clinical dossier

The submission included comprehensive clinical data provided to support the registration of evolocumab for the proposed indications. The clinical program included 26 clinical individual clinical studies:

- 10 clinical pharmacology studies (3 Phase I studies evaluating the pharmacokinetics and initial tolerability of evolocumab in healthy subjects; three Phase 0 studies evaluating the initial tolerability of drug product presentations containing placebo; 1 Phase I study evaluating the pharmacokinetics and initial tolerability of evolocumab in subjects with primary hyperlipidaemia and mixed dyslipidaemia; 1 Phase I study evaluating the pharmacokinetics of evolocumab in subjects with mild or moderate hepatic impairment; 2 Phase I biopharmaceutic studies [PK equivalence studies] in healthy subjects).
- 2 population PK modelling and simulation analyses.
- 4 pivotal Phase III clinical efficacy and safety studies in subjects with primary hyperlipidaemia and mixed dyslipidaemia.
- 4 supportive Phase II dose ranging clinical efficacy and safety studies in subjects with primary hyperlipidaemia and mixed dyslipidaemia
- .
- 3 long-term efficacy and safety studies (2 x Phase III, 1 x Phase II) in subjects with primary hyperlipidaemia and mixed dyslipidaemia.
- 2 supportive Phase III efficacy and safety studies in subjects with primary hyperlipidaemia assessing user ability to self-administer evolocumab.
- 2 Phase II/III clinical efficacy and safety studies in subjects with homozygous familial hypercholesterolaemia (including 1 study in subjects with severe FH and HoFH).

- 1 Integrated Immunogenicity Report, 1 Statistical Analysis Plan for the Integrated Summary of Efficacy, 1 Integrated Summary of Efficacy (tables and figures), 1 Statistical Analysis Plan for the Integrated Summary of Safety, 1 Integrated Summary of Safety (tables and figures).

Overview of the studies

- The submission include four, pivotal Phase III clinical efficacy and safety studies of 12 weeks duration supporting evolocumab for the treatment of patients with primary hyperlipidaemia (HeFH and non-FH) and mixed dyslipidaemia (see Table 3, below). In this submission, primary hyperlipidaemia was defined as elevated LDL-C cholesterol only and mixed dyslipidaemia was defined as elevated LDL-C along with high triglycerides or low HDL-C. Specifically, mixed dyslipidaemia was defined as triglycerides (≥ 1.7 mmol/L), triglycerides (≥ 2.3 mmol/L) or HDL-C (< 1.0 mmol/L in males or < 1.3 mmol/L in females).
- The four pivotal Phase III studies were of similar design, had the same co-primary endpoints of percent change from baseline in reflexive LDL-C at week 12 and mean percent change from baseline in reflexive LDL-C at weeks 10 and 12, and evaluated the same two evolocumab dose regimens (140 mg SC Q2W and 420 SC QM) against placebo and/or against ezetimibe. Each of the four, pivotal Phase III studies assessed the efficacy of evolocumab in four separate therapeutic settings (that is, in combination with statins; as monotherapy; in statin intolerant subjects; and in subjects with HeFH).

Table 3: Pivotal Phase III studies in patients with primary hyperlipidaemia (HeFH and non-FH) and mixed dyslipidaemia.

ID	Name	Evolocumab	N *	Title of Study
20110115	LAPLACE -2	In combination with statin	1899	A Double-blind, Randomised, Placebo and Ezetimibe Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 [evolocumab] on LDL-C in Combination With Statin Therapy in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia.
20110114	MENDEL-2	Monotherapy	615	A Double-blind, Randomised, Placebo- and Ezetimibe-controlled, Multicenter Study to Evaluate Safety and Efficacy of Lipid Lowering Monotherapy With AMG 145 [evolocumab] in Subjects With a 10-Year Framingham Risk Score of 10% or Less.
20110116	GAUSS-2	In statin intolerant subjects.	307	A Double-blind, Randomised, Multicenter Study to Evaluate Safety and Efficacy of AMG 145 [evolocumab], Compared With Ezetimibe, in

ID	Name	Evolocumab	N *	Title of Study
				Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor.
20110117	RUTHER FORD-2	HeFH	331	A Double-blind, Randomised, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 [evolocumab] on LDL-C in Subjects With Heterozygous Familial Hypercholesterolemia

N * = number of subjects randomised to investigational product (IP).

- The submission also included four, Phase II studies, of 12 weeks duration which were the 'parent' studies to the four pivotal Phase III studies. These studies were identified as 20101155 (LAPLACE-1), Study 20101154 (MENDEL-1), 20090154 (GAUSS-1) and 20090158 (RUTHERFORD-1). In addition to the 4 'parent' Phase II studies of 12 weeks duration, the submission also included a Phase II study of 12 weeks duration in Japanese patients.
- The submission also included a pre-specified Integrated Summary of Efficacy (ISE) analysing pooled data from the 4 pivotal Phase III 12 week studies (20110114, 20110115, 20110116, and 20110117) in subjects with primary hyperlipidaemia and mixed dyslipidaemia. In addition, the submission included the Statistical Analysis Plan (SAP) for the ISE and a comprehensive list of Tables and Figures relating to the integrated analysis.

The efficacy data have been evaluated separately for each of the 4 pivotal Phase III studies with emphasis on the primary and secondary endpoints. In addition, the integrated efficacy data from the 4 pivotal Phase III studies have also been reviewed. The efficacy data for each of the parent Phase II studies have been evaluated a supportive data. In addition, 2 long-term Phase III studies, 1 long-term Phase II study have been evaluated, and 2 Phase III studies assessing home use of evolocumab have been evaluated.

Paediatric data

The submission included limited data to support the use of evolocumab in adolescents aged 12 to < 18 years with HoFH. A total of 14 adolescent subjects (≥ 12 to < 18 years) with HoFH were enrolled in Studies 20110233 and 20110271 of the evolocumab clinical program. All adolescent subjects from 20110233, with the exception of 1 adolescent subject in Part B, continued in the 20110271 extension study. Three additional adolescent subjects, who did not participate in the 20110233 parent study, were also enrolled in Study 20110271. Of the 10 HoFH adolescents in Study 20110233 Part B, 7 subjects received evolocumab 420 mg QM, and 3 subjects received placebo. The submission included no data in subjects aged < 18 years with primary hyperlipidaemia and mixed dyslipidaemia.

The sponsor states that it has an agreed Paediatric Investigation Plan (PIP) with the EU for studies in a population aged 'from 12 to less than 18 years' for the treatment of elevated cholesterol in patients with heterozygous and homozygous familial hypercholesterolaemia. The PIP required the first study to be completed by October 2012.

The sponsor states that a waiver from the EU exists for the paediatric population 'from birth to less than 12 years' for the treatment of elevated cholesterol on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. In addition, the sponsor states that a waiver from the EU exists for the paediatric population 'from birth to less than 18 years' for the treatment of mixed dyslipidaemia on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

The sponsor states that it has a Pediatric Study Plan (PSP) under review by the FDA.

The sponsor indicates that two clinical studies (20120123 and 20120124) are planned to evaluate evolocumab paediatric patients in order to accord with regulatory requirements.

Good clinical practice

The sponsor's studies were stated to have been conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations and guidelines.

Pharmacokinetics

Studies providing pharmacokinetic data Overview of the studies

The submission included 10 key clinical studies providing PK data (8 clinical pharmacology plus 2 biopharmaceutic PK equivalence studies). These studies are listed below in Table 4. In addition, 15 of the 16 Phase II and III clinical efficacy and safety studies included sparse or limited PK data. Each of the studies with PK data also included PD data relating primarily to shifts from baseline in PCSK9 and LDL-C concentrations following treatment with evolocumab. The submission also included 2 population PK modelling and simulation studies (116744 [evolocumab from Phase I and II studies]; 119663 [update for evolocumab from Phase I, II and III studies]). The submission also included an Integrated Immunogenicity Report. All relevant PK and PD data provided in the submission has been reviewed and evaluated in this CER.

Table 4: Individual clinical pharmacokinetic studies provided in the submission.

ID	Topic	N	Study Objectives
20080397 Phase I	PK and initial tolerability	56 HS	To assess safety, tolerability, PK, PD and immunogenicity of evolocumab at 5 ascending single SC doses and 2 ascending single IV doses. Evolocumab administered to 42 subjects, placebo to 14 subjects
20110121 Phase I	PK and initial tolerability	32 HS	To assess safety, tolerability, PK, PD and immunogenicity at 3 ascending single SC doses in Japanese subjects, and compare the results with white subjects. Evolocumab administered to 18 Japanese and 2 white subjects, placebo administered to 6 Japanese and 6 white subjects.
20120136 Phase I	PK intra-subject variability	20 HS	To determine intra-subject variability in the PK and PD of evolocumab 140 mg SC 2-doses separated by 56 days in a cross-over design; to evaluate the safety, tolerability, and

ID	Topic	N	Study Objectives
			immunogenicity of evolocumab.
20110234 Phase 0	Tolerability of placebo	48 HS	To compare pain scores with various SC infusion rates of 3.5 mL viscous placebo buffer across infusion rates with 1.2 mL rapid SC injection administered as single doses; to assess tolerability of the infused buffer.
20120101 Phase 0	Tolerability of placebo	36 HS	To compare pain scores and adverse events of placebo buffers of different volumes, strengths, and viscosities administered as single doses.
20120135 Phase 0	AMD placebo performance	100 HS	To assess SC delivery, performance, safety, and tolerability of 3.5 mL AMD; single dose administered as 3 SC injections into abdominal wall at different sites.
20080398 Phase I	PK and initial tolerability	56 Patients	To evaluate the safety, tolerability, PK, PD and immunogenicity of multiple ascending doses of evolocumab in adult patients with hyperlipidaemia taking a statin or adults with HeFH.
2012031	Hepatic impairment	24	To evaluate the safety, tolerability, PK, PD and immunogenicity of single SC doses of evolocumab in subjects with mild or moderate hepatic impairment.
20110168	Comparative BA & BE SC injection	292 HS	Primary: to demonstrate PK equivalence of the personal injector AMD (420 mg; 3.5 mL of 140 mg/mL) SC to the AI/pen (3 x 140 mg/mL) SC; Secondary: (a) to evaluate single-dose safety, tolerability, and additional PK parameters of evolocumab; (b) to compare LDL-C responses; (c) to assess complete delivery of 3.5 mL personal injector AMD and 3 x AI/pens.
20120133	Comparative BA & BE SC injection	96 HS	Primary: to demonstrate the PK equivalence of the PFS to the AI/pen following single-dose evolocumab 140 mg SC. Secondary: (a) to evaluate single-dose safety, tolerability, and additional PK parameters of evolocumab; (b) to compare LDL-C responses; (c) to assess complete delivery of AI/pen.

Notes: N = number of subjects; SC = subcutaneous; BA = bioavailability; BE = bioequivalence; HS = healthy subjects; PK = pharmacokinetics; PFS = pre-filled syringe; AI/pen = pre-filled auto-injector pen; AMD = automated mini-doser LDL-C = low density lipoprotein cholesterol.

Evaluator's conclusions on pharmacokinetics

- The pharmacokinetics of evolocumab following SC administration have been adequately characterised in 8 Phase I clinical pharmacology studies, 2 PK equivalence studies, 2 population PK modelling and simulation studies, and 15 Phase II and III clinical efficacy and safety studies including limited or sparse PK data in subjects with hyperlipidaemia.
- The available data from cross-study comparisons indicates that the pharmacokinetics of evolocumab are similar in healthy subjects and subjects with primary hyperlipidaemia (HeFH and nonfamilial) and mixed dyslipidaemia (Studies 2000397 [healthy subjects], 20110168 [healthy subjects], 20120133 [healthy subjects], 20101154, 20101155, 20090158, 20090159, and 20110231 [patients]). The data also show that the pharmacokinetics of evolocumab are similar in subjects with and without HeFH (Study 20080398).
- Cross-study comparisons also show that unbound evolocumab trough serum concentrations following evolocumab 420 mg SC QM for 12 weeks in subjects with HoFH not on apheresis are similar to those in subjects with primary hyperlipidaemia (Studies 20110115, 20110271, and 20110115). In subjects with HoFH on apheresis, unbound evolocumab trough serum concentrations were approximately 20% to 30% lower than before apheresis (Study 20110271). In adolescents with HoFH not on apheresis (n=9), unbound evolocumab trough serum concentrations were highly variable, but fell within the range of adult subjects with primary hyperlipidaemia and mixed dyslipidaemia.
- In the Phase II clinical efficacy and safety Studies 20101154 (evolocumab monotherapy) and 20101155 (evolocumab combined with statin) in subjects with primary hyperlipidaemia and mixed dyslipidaemia, comparison of Week 12 to Week 2 unbound evolocumab trough serum concentrations demonstrated an approximately 3-fold accumulation for the 140 mg SC Q2W dose, and comparison of week 10 to week 2 unbound evolocumab trough serum concentrations demonstrated a less than 2-fold accumulation for the 420 mg QM dose. Similar accumulation was observed in the Phase III Studies 20110114 (evolocumab monotherapy) and 20110115 (evolocumab combined with statin) in patients with primary hyperlipidaemia and mixed dyslipidaemia for the 140 mg SC Q2W dose based on unbound evolocumab trough serum concentrations at Weeks 2, 10, and 12, and for the 420 mg SC QM dose based on unbound evolocumab trough serum concentrations at Weeks 2 and 10.
- In the long-term Phase III study in subjects with primary hyperlipidaemia and mixed dyslipidaemia (Study 20110109), unbound evolocumab trough serum concentrations remained relatively stable over 52 weeks dosing with evolocumab 420 mg SC QM, with steady state being achieved at Week 12. In the Phase II and III clinical efficacy and safety studies of 12 weeks duration in subjects with primary hyperlipidaemia and mixed dyslipidaemia, steady state unbound evolocumab trough serum concentrations approached steady state by week 12 in subjects being treated with evolocumab alone (Studies 20110114 and 20101154) or evolocumab in combination with a statin (Studies 20101155 and 20110115).
- The pharmacokinetics of unbound evolocumab demonstrated moderate intersubject variability in both healthy subjects and subjects with mixed hyperlipidaemia and dyslipidaemia (e.g., CVs for AUC of 51% and 70%, respectively, and CVs for C_{max} 39.7% and 61.7%, respectively, following 140 mg SC in studies 20120133 and 20101154). Moderate intra-subject variability was also demonstrated in healthy subjects following a single SC evolocumab dose of 140 mg (that is, CV approximately 33% for C_{max} and 45% for $AUC_{(last)}$) (Study 20120136).

- There were no absolute bioavailability studies following SC dosing. The absolute bioavailability of evolocumab after SC administration was estimated to be 72% in the population PK analysis (Study 119633), and the mean absorption time was estimated to be approximately 3 days. In the Nonclinical Overview (Module 2.4), the absolute bioavailability of evolocumab following SC administration was stated to be approximately 82% in monkeys.
- A single dose of evolocumab 420 mg SC administered with the AMD presentation at 120 mg/mL with a 3.5 mL fill was pharmacokinetically equivalent to the reference presentation of 3 x AI/pens (3 x 140 mg/mL) in healthy subjects (Study 20110168). A single dose of evolocumab 140 mg SC administered with the PFS presentation at 140 mg/mL with a 1 mL fill was pharmacokinetically equivalent to the reference presentation of 1 x AI/Pen (1 x 140 mg/mL) in healthy subjects (study 20120133). Following single SC evolocumab doses of 140 mg or 420 mg, median peak serum concentrations (T_{max}) were attained in 3 to 4 days. Although not directly compared, the PK equivalence of a single SC dose of evolocumab 420 mg administered using 3 x PFS injections or 1 x AMD injection can be reasonably inferred from the results of studies 20110168 and 20120133. SC administration of evolocumab was into the abdominal wall (three quadrants when a total dose of 420 mg SC was administered). There were no bioavailability data comparing SC administered into different anatomical sites.
- The PK data consistently showed that unbound evolocumab displays non-linear pharmacokinetics across a wide dose range (7 to 420 mg SC). In Study 20080397, neither the SC doses (7, 21, 70, 210, and 420 mg) nor the IV doses (21 or 410 mg) were dose proportional over the dose ranges tested in healthy subjects. The slopes of the power model used to assess dose proportionality in study 20080397 exceeded unity for C_{max}, AUC_{inf}, and $AUC_{(last)}$ following SC administration and for AUC_{inf} and $AUC_{(last)}$ following IV administration. Non-linearity was more pronounced at low than at high evolocumab doses, with the mean dose-normalised $AUC_{(0-t)}$ being approximately 22 times higher for single dose 210 mg SC compared to single dose 21 mg SC and approximately 1.2 fold higher for single dose 420 mg SC compared to single dose 210 mg SC. The dose normalised data from Study 20080397 showed that single-doses of 210 mg SC and 420 mg SC were approximately dose proportional, based on $AUC_{(0-t)}$ and C_{max}.
- The exposure data are consistent with 2 mechanisms of elimination for unbound evolocumab: (1) PCSK9 target-mediated non-linear (saturable) elimination predominating at low evolocumab serum concentrations and saturating when PCSK9 is fully suppressed; and (2) linear (non-saturable) elimination by endogenous IgG clearance mechanisms involving nonspecific catabolism in cells of the reticuloendothelial system at higher evolocumab serum concentrations. PopPK modelling predicts that approximately 77% and 51% of a single-dose of 140 mg SC Q2W and 420 mg SC QM, respectively, is eliminated through the target-mediated (that is, PCSK9) non-linear pathway. The model predicted effective half-lives for the 140 mg SC Q2W and the 420 mg QM doses are 11.4 and 16.8 days, respectively.
- The Vss (mean ± SD) following evolocumab 420 mg IV in healthy subjects (n=6) was 3.340 ± 0.460 L (Study 20080397). The Vss is similar to plasma volume suggesting that evolocumab is not extensively distributed to the tissues and remains predominantly in the intravascular space. However, estimated Vss might be an underestimation of the true Vss.
- In Study 20080397, the systemic clearance (mean ± SD) of evolocumab was 68.3 ± 16.0 mL/h following a single IV dose of 21 mg and 11.6 ± 2.26 mL/h following a single IV dose of 420 mg. The results show that the systemic clearance of evolocumab is dose dependent, indicating that systemic clearance is nonlinear. However, the results for the apparent clearance (mean ± SD) of evolocumab following single SC evolocumab

doses of 210 mg and 420 mg were similar (25.6 ± 6.86 and 24.2 ± 12.5 mL/h, respectively), and lower than for evolocumab 70 mg SC (101 ± 120 mL/h). Overall, the results suggest that apparent clearance is linear over the SC dose range 210 mg to 420 mg, but non-linear over the SC dose range 70 mg to 420 mg.

- There were no clinical studies investigating the metabolism of evolocumab. However, it can be predicted that evolocumab will be metabolised to peptides and amino acids via catabolic pathways in various body tissues. Mass balance studies are considered to be not useful for determining the excretion pattern of therapeutic proteins.[54] There were no data on renal clearance. However, given the large molecular weight of evolocumab (144 kDa) it can be predicted that renal elimination of the intact molecule will be negligible.
- There were no data on subjects with renal impairment. However, as mentioned above, renal elimination of evolocumab is not anticipated and, consequently, increased systemic exposure to evolocumab is not expected in subjects with renal impairment. PopPK modelling showed mild to moderate renal impairment had no significant effects on unbound evolocumab trough serum concentrations at week 12 following evolocumab 140 mg SC Q2W and evolocumab 420 mg SC QM. There were no data on subjects with severe hepatic impairment, but PK data in subjects with mild and moderate hepatic impairment demonstrated decreased systemic exposure to unbound serum evolocumab as assessed by both $AUC_{(last)}$ and C_{max}. However, no significant difference in pharmacodynamics or safety were observed in subjects with mild or moderate hepatic impairment compared to healthy subjects, which suggests that no dose adjustment in these subjects is required.
- No formal PK drug-drug interaction clinical studies were undertaken. No in vitro permeability, in vitro metabolism, or in vitro metabolic drug-drug interaction studies that used human biomaterials were undertaken. Data in subjects with hyperlipidaemia showed that exposure to unbound evolocumab was lower when evolocumab was administered with a statin compared to evolocumab administration without a statin, and that the effect was more pronounced with co-administration of high-dose statin compared to low-dose statin (Study 20080398). However, as discussed later in this evaluation, the pivotal clinical efficacy and safety data show that evolocumab administered as monotherapy and in combination with statins has similar effects on lowering LDL-C concentrations, with comparable safety profiles. Therefore, the dose of evolocumab does not need to be adjusted when the drug is administered with statins.
- Based on population pharmacokinetic and pharmacodynamic analyses, unbound evolocumab pharmacokinetics did not appear to be significantly affected by sex, age (but limited HoFH data in subjects aged ≥ 12 to < 18 years, no data in subjects with HoFH aged < 12 years, and no data in subjects with primary hyperlipidaemia mixed dyslipidaemia aged < 18 years), or race (but limited data on all subjects apart from whites). Exposure to unbound evolocumab decreased with increasing body weight, but this did not affect the pharmacodynamic endpoint of LDL-C reduction.
- The incidence of anti-evolocumab binding antibodies was low in the integrated analysis from 14 Phase II and III studies (0.1% of subjects [7/4846]) (Integrated Immunogenicity Report). None of the 7 anti-evolocumab antibody positive subjects tested positive for neutralising antibodies.

[54]CHMP/EWP/89249/2004: Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins.

Pharmacodynamics

Studies providing pharmacodynamic data

Pharmacodynamic data were provided in 3 Phase I studies in healthy subjects, 1 Phase I study in patients with hyperlipidaemia, 1 Phase I study in patients with hepatic impairment, 11 Phase I and II efficacy and safety studies in primary hyperlipidaemia and mixed dyslipidaemia, 2 Phase III efficacy and safety studies patients with HoFH and 2 Phase III efficacy and safety studies assess home use of the device. In addition to the individual studies containing PD data, the submission also included pooled data from subjects from 4 Phase II studies and a population PK/PD analysis based on pooled Phase II data (Study 116744).

The two key PD parameters were LDL-C serum concentrations and unbound PCKS9 serum concentrations. In each study, a central laboratory (Amgen or a designated contract research organisation) conducted pharmacodynamic assessments. Serum LDL-C concentrations and other lipid parameters were quantified using standard laboratory procedures. A direct measure of LDL-C by ultracentrifugation (UC) was also used in each study. A validated ELISA was used to quantify unbound PCSK9 serum concentrations. The review of pharmacodynamics in this clinical evaluation focuses on the data from the dedicated clinical pharmacology studies and the PK/PD analysis. Reductions in LDL-C concentrations from baseline were the primary efficacy endpoint for the Phase II and III studies and have been examined in full in the evaluation of efficacy provided in this CER.

Evaluator's conclusions on pharmacodynamics

The PD results consistently showed that in subjects with hyperlipidaemia and mixed dyslipidaemia (with and without HeFH) evolocumab, at the proposed doses of 140 mg Q2W and 420 mg once monthly (QM), markedly reduced LDL-C serum concentrations from baseline and achieved maximal inhibition of PCSK9. In addition, PD data in subjects with HoFH showed that evolocumab at the proposed dose of 420 mg QM can reduce LDL-C serum concentrations and unbound PCSK9 serum concentrations.

Dosage selection for the pivotal studies

Dose selection for the pivotal Phase III studies was based on an interim integrated analysis of the safety, tolerability and efficacy data from four, Phase II, placebo-controlled, dose-escalating studies (20090158, 20090159, 20101154, and 20101155). Based on these data, the 140 mg Q2W and 420 mg QM doses provided the greatest effects on LDL-C and other lipid parameters and were clinically equivalent with respect to effects on these parameters. In addition, the safety and tolerability profiles of the 140 mg SC Q2W and 420 mg SC QM dosing regimens were comparable to those of the other 4 lower dose regimens tested in the Phase II studies (70 and 105 mg Q2W and 280 and 350 mg QM). As a result, the 140 mg Q2W and 420 mg QM doses were selected for the pivotal Phase III studies. The results of the interim integrated analyses were confirmed by the final analyses of the Phase II studies. In addition, based on PK/PD modelling, doses of 140 mg SC Q2W and 420 mg SC QM were predicted to achieve approximately 80% of the model-predicted maximal reduction in calculated LDL-C at the mean of Weeks 10 and 12.

Efficacy

Studies providing efficacy data

Primary hyperlipidaemia and mixed dyslipidaemia

Overview of the studies

The submission include four, pivotal Phase III clinical efficacy and safety studies of 12 weeks duration supporting evolocumab for the treatment of patients with primary hyperlipidaemia (HeFH and non-FH) and mixed dyslipidaemia (see Table 5, below). In this submission, primary hyperlipidaemia was defined as elevated LDL-C cholesterol only and mixed dyslipidaemia was defined as elevated LDL-C along with high triglycerides or low HDL-C. Specifically, mixed dyslipidaemia was defined as triglycerides (≥ 1.7 mmol/L), triglycerides (≥ 2.3 mmol/L) or HDL-C (< 1.0 mmol/L in males or < 1.3 mmol/L in females).

The four pivotal Phase III studies were of similar design, had the same co-primary endpoints of percent change from baseline in reflexive LDL-C at Week 12 and mean percent change from baseline in reflexive LDL-C at Weeks 10 and 12, and evaluated the same two evolocumab dose regimens (140 mg SC Q2W and 420 SC QM) against placebo and/or against ezetimibe. Each of the four, pivotal Phase III studies assessed the efficacy of evolocumab in four separate therapeutic settings (that is, in combination with statins; as monotherapy; in statin intolerant subjects; and in subjects with HeFH).

Table 5: Pivotal Phase III studies in patients with primary hyperlipidaemia (HeFH and non-FH) and mixed dyslipidaemia.

Study ID	Name	Evolocumab	N *	Title of Study
20110115	LAPLACE-2	In combination with statin	1899	A Double-blind, Randomised, Placebo and Ezetimibe Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 [evolocumab] on LDL-C in Combination With Statin Therapy in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia.
20110114	MENDEL-2	Monotherapy	615	A Double-blind, Randomised, Placebo- and Ezetimibe-controlled, Multicenter Study to Evaluate Safety and Efficacy of Lipid Lowering Monotherapy With AMG 145 [evolocumab] in Subjects With a 10-Year Framingham Risk Score of 10% or Less.
20110116	GAUSS-2	In statin intolerant subjects.	307	A Double-blind, Randomised, Multicenter Study to Evaluate Safety and Efficacy of AMG 145 [evolocumab], Compared With Ezetimibe, in

Study ID	Name	Evolocumab	N *	Title of Study
				Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor.
20110117	RUTHERFORD-2	HeFH	331	A Double-blind, Randomised, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 [evolocumab] on LDL-C in Subjects With Heterozygous Familial Hypercholesterolemia

N * = number of subjects randomised to investigational product (IP).

The submission also included four, Phase II studies, of 12 weeks duration which were the 'parent' studies to the four pivotal Phase III studies. These studies were identified as 20101155 (LAPLACE-1), Study 20101154 (MENDEL-1), 20090154 (GAUSS-1) and 20090158 (RUTHERFORD-1). In addition to the 4 'parent' Phase II studies of 12 weeks duration, the submission also included a Phase II study of 12 weeks duration in Japanese patients.

The submission also included a pre-specified Integrated Summary of Efficacy (ISE) analysing pooled data from the 4 pivotal Phase III 12 week studies (20110114, 20110115, 20110116 and 20110117) in subjects with primary hyperlipidaemia and mixed dyslipidaemia. This analysis was provided in the sponsor's Summary of Clinical Efficacy and Clinical Overview). In addition, the clinical submission included the Statistical Analysis Plan (SAP) for the ISE and a comprehensive list of Tables and Figures relating to the integrated analysis.

In this evaluation, the efficacy data have been evaluated separately for each of the 4 pivotal Phase III studies with emphasis on the primary and secondary endpoints. In addition, the integrated efficacy data from the 4 pivotal Phase III studies have also been reviewed. The efficacy data for each of the parent Phase II studies have been evaluated as supportive data. In addition, 2 long-term Phase III studies, 1 long-term Phase II study have been evaluated, and 2 Phase III studies assessing home use of evolocumab have been evaluated.

Evaluator's conclusions on clinical efficacy

for primary hyperlipidaemia (heterozygous familial or non-familial) or mixed dyslipidaemia

General conclusions

- The submitted data have satisfactorily established the efficacy of evolocumab 140 mg SC Q2W and 420 mg SC QM for the sponsor's proposed indication of primary hyperlipidaemia (including heterozygous familial and non-familial) defined by elevated LDL-C only, or mixed dyslipidaemia defined by elevated LDL-C along with high triglycerides or low HDL-C.
- In the integrated efficacy analysis (n=3152), efficacy was assessed in three sub-groups of subjects with different definitions for mixed dyslipidaemia, namely, definition 1 elevated LDL-C and screening triglycerides ≥ 1.7 mmol/L in a total of 1148 subjects

(36.4%), definition 2 elevated LDL-C and screening triglycerides ≥ 2.2 mmol/L in a total of 535 subjects (17.0%), and definition 3 elevated LDL-C and screening HDL-C < 1.0 mmol/L in men and < 1.3 mmol/L in women in a total of 855 subjects (27.1%). Based on the number of subjects with mixed dyslipidaemia in the integrated efficacy population it can be calculated that 614 (19.4%) subjects in the integrated efficacy analysis had primary hyperlipidaemia (elevated LDL-C). The integrated efficacy analysis also included a sub-group analysis in subjects with hypercholesterolaemia defined as calculated LDL-C ≥ 4.1 mmol/L at screening while receiving a statin or ≥ 6.2 mmol at screening without receiving a statin.

- The efficacy of evolocumab for primary hyperlipidaemia and mixed dyslipidaemia was demonstrated in 4 pivotal Phase III studies of 12 weeks duration, 5 supportive studies of 12 weeks duration (including 1 in Japanese subjects), 3 long-term studies of ≥ 52 weeks duration (2 Phase III and 1 Phase II), and 2 Phase III studies of evolocumab in a home-use setting. The results of the studies consistently demonstrated that evolocumab at the proposed doses significantly reduced the primary efficacy endpoint of LDL-C from baseline concentrations, and notably improved other secondary lipid parameters of interest.
- The co-primary efficacy endpoints in each of the pivotal, Phase III studies was percent change from baseline in reflexive LDL-C at Week 12 and mean percent change from baseline in reflexive LDL-C at Weeks 10 and 12, and the co-secondary efficacy endpoints included change from baseline at the same time-points for other lipid parameters of clinical interest. In the Phase II studies, percent change from baseline in LDL-C at Week 12 was the primary efficacy endpoint, and change from baseline at this time-point in other lipid parameters of clinical interest were secondary efficacy endpoints.
- As mentioned above, the pivotal Phase III studies had two co-primary efficacy endpoints. The sponsor states that treatment with evolocumab results in a U-shaped LDL-C-reduction curve over the dosing interval, due to the inhibition of unbound PCSK9 and continued endogenous production of PCSK9 which eventually depletes the unbound evolocumab. As the unbound PCSK9 levels return towards pre-treatment levels, the LDL-C follows suit approximately 1 week later. The nadir and duration of LDL-C lowering with evolocumab are dependent on both the dose and the dosing interval. Using the area under the curve approach, the time-averaged effect (TAE) of evolocumab treatment (calculated as Week 8 percent change from baseline plus the average incremental percent change from baseline over Weeks 8 to 12) was determined from weekly LDL-C assessments in PK/PD sub-studies in the Phase II Study 20101154 (evolocumab alone as an adjunct to diet) and the Phase II Study 20101155 (evolocumab in combination with statins with or without ezetimibe). The data from these two PK/PD sub-studies along with the population PK/PD data from the evolocumab Phase II studies were used to evaluate the time-averaged LDL-C reduction and its relationship to other lipid parameters. The analyses revealed that the mean percent change from baseline at Weeks 10 and 12 in LDL-C and other lipid parameters was representative of the time-averaged effect and characterised LDL-C reduction and other lipid parameters better than the percent change at Week 12 alone. In addition, the Phase II data showed that evolocumab 140 mg Q2W and 420 mg QM were clinically equivalent in terms of their effects on LDL-C and other lipid parameters over time. The sponsor concludes that the mean percent change from baseline in LDL-C at Weeks 10 and 12 provides a practical and easily understood alternative to calculating LDL-C TAE over a dosing interval.
- Although the sponsor's rationale for the mean of Weeks 10 and 12 data is acceptable, in practice the results for co-primary efficacy endpoints appear to be highly correlated, with the difference in outcome between the co-primary endpoints being clinically

insignificant. For example, in the integrated Phase III analysis, the fixed effects treatment difference between evolocumab 140 mg Q2W and placebo in reflexive LDL-C from baseline to the mean of Weeks 10 and 12 was -65.7% (95% CI: -70.9%, -60.6%) and from baseline to Week 12 was -66.7% (95% CI: -72.2%, -61.2%). Similarly, the fixed effects treatment difference between evolocumab 420 mg QM and placebo in reflexive LDL-C from baseline to the mean of Weeks 10 and 12 was -65.0% (95% CI: -69.5%, -60.5%) and from baseline to Week 12 was -60.4% (95% CI: -64.6%, -56.2%).

- In the four, pivotal Phase III studies of 12 weeks duration, statistical analysis of the co-primary efficacy endpoints was by a repeated measures linear effect model on subjects randomised and receiving at least one dose of IP. The primary analysis model compared evolocumab with placebo and/or ezetimibe and included terms for treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit. The co-secondary efficacy endpoints were analysed using a CMH (adjusted for stratification factors) for the categorical LDL-C response endpoint, and repeated measures linear effects models for the endpoints of percent change from baseline. Appropriate adjustments for multiplicity were made to control the family-wise error rate at 0.05 for all co-primary and co-secondary endpoints.
- None of the pivotal Phase III or supportive Phase II studies included primary or secondary efficacy endpoints relating to cardiovascular morbidity and mortality. The TGA adopted Guideline on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (EMA/CHMP/748108/2013) state that '[a] relative reduction in LDL-C level is acceptable as a primary efficacy endpoint in patients with primary hypercholesterolaemia, provided that claims in the label are restricted to a lipid lowering effect.' In addition, the guidelines state that for medicinal products acting on LDL-C [other than statins] 'at least a detrimental effect on mortality and morbidity should also be excluded prior to registration'. As discussed later in this CER (see Attachment 2), the safety data suggest that that evolocumab does not appear have detrimental effects on mortality and morbidity. In the submission, the sponsor refers to the sponsor's Clinical Overview which provides a rationale for the use of LDL-C as a 'therapeutic target and validated surrogate for cardiovascular outcomes'. The rational refers to epidemiological data showing that LDL-C is a strong independent predictor of CHD across diverse patient populations, genetic data showing an association between LDL-C life-long exposure arising from genetic polymorphisms in the gene coding for LDL-C and cardiovascular risk, and interventional studies with LDL-C lowering therapies showing reduced cardiovascular risk. Overall, it is considered that the use of LDL-C as a surrogate marker of cardiovascular morbidity and mortality in the submission is acceptable.
- The sponsor is seeking approval of evolocumab for the treatment of primary hyperlipidaemia (heterozygous familial and non-familial) or mixed dyslipidaemia. However, the majority of the Phase II and III studies referred to patients with hypercholesterolaemia rather than hyperlipidaemia. In addition, the inclusion criteria and primary efficacy outcomes referred specifically to subjects with LDL-cholesterol. Furthermore, the term hypercholesterolaemia more clearly defines the target population than the term hyperlipidaemia. Based on these considerations it is recommended that the relevant indication for evolocumab should be for the treatment of patients with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia. The wording of the proposed indication is consistent with the wording of the other indication being sought by the sponsor, namely, homozygous familial hypercholesterolaemia. In addition, the use of the term hypercholesterolaemia rather than hyperlipidaemia is in keeping with the approved indications for the statins. It is noted that the relevant indication being sought by the sponsor in the EU is primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, while in the USA the relevant indication sough is

hyperlipidaemia or mixed dyslipidaemia and in Canada the relevant indication being sought is primary hyperlipidaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

Evolocumab in combination with a statin

- Evolocumab in combination with a statin was investigated in one, pivotal, Phase III study (LAPLACE-2 [n=1896]) of 12 weeks duration in subjects with primary hypercholesterolaemia (HeFH or non-FH) or mixed dyslipidaemias, with fasting LDL-C ≥ 2.1 mmol/L (subjects on intensive statin), ≥ 2.6 mmol/L (subjects on non-intensive statin), or ≥ 4.0 mmol/L (subjects not on statin) and fasting triglycerides ≤ 4.5 mmol/L. In this study, both doses of evolocumab in combination with a statin demonstrated significantly superior efficacy compared to placebo in combination with a statin and to ezetimibe in combination with a statin. The data in the pivotal study were supported by one, Phase II study (LAPLACE-1 [n=629]) of 12 weeks duration. LAPLACE-2 and LAPLACE-1 were also identified as Studies 20110115 and 20101155, respectively.
- In LAPLACE-2, both co-primary efficacy endpoints demonstrated statistically significant reductions in reflexive LDL-C in the evolocumab 140 mg Q2W and 420 mg QM groups compared to the placebo group when treatments were administered in combination with atorvastatin 10 mg, atorvastatin 80 mg, rosuvastatin 5 mg, rosuvastatin 40 mg, or simvastatin 40 mg ($p < 0.001$, adjusted for multiplicity). In addition, both co-primary efficacy endpoints demonstrated statistically significant reductions in reflexive LDL-C for evolocumab 140 mg Q2W and 420 mg QM compared to ezetimibe when the treatments were administered in combination with atorvastatin 10 mg or 80 mg ($p < 0.001$, adjusted for multiplicity)
- In LAPLACE-2, the co-secondary efficacy endpoints relating to changes from baseline in reflexive LDL-C, non-HDL-C, ApoB, TC/HDL-C ratio, ApoB/ApoA1 ratio, and Lp(a), both evolocumab 140 mg Q2W and 420 mg QM showed statistically significant improvements compared to placebo when the treatments were administered with all statin cohorts, and compared to ezetimibe when the treatments were administered with the atorvastatin cohorts. However, no statistically significant difference was seen between treatments for the co-secondary efficacy endpoints of triglycerides and VLDL-C (evolocumab 140 mg Q2W in combination with atorvastatin 10 mg and 80 mg compared to placebo), triglycerides and VLDL-C (evolocumab 140 mg Q2W and 420 mg QM in combination with atorvastatin 10 mg and 80 mg compared to ezetimibe), and HDL-C (evolocumab 140 mg Q2W in combination with atorvastatin 80 mg compared to placebo).
- In addition, subgroup analyses of the co-primary efficacy endpoints in LAPLACE-2 showed that both proposed doses of evolocumab were effective in all subgroups compared to placebo when the treatments were administered with a statin (all cohorts), and compared to ezetimibe when the treatments were administered with the atorvastatin cohorts. No notable differences treatment effect were in observed between subgroups based on age, sex, race, geographical region, Type 2 diabetes mellitus , metabolic syndrome, baseline median LDL-C concentration, screening LDL-C concentration, BMI, hypertension, current smoking status, baseline CHD risk factors, family history of CHD risk, baseline PCSK9 concentration, baseline median triglyceride concentration, baseline triglyceride concentrations, NCEP high-risk, and entry statin therapy.
- The data from LAPLACE-2 support the sponsor's proposal that evolocumab be administered with a statin, without reference to specific statins. In this study, evolocumab was administered with high and low dose rosuvastatin (5 mg and 40 mg),

high and low dose atorvastatin (10 mg and 80 mg) and moderate dose simvastatin (40 mg), and was similarly effective in combination with all statins. Therefore, it can reasonably be inferred that evolocumab at the proposed doses will be effective irrespective of the particular statin with which it is combined. Consequently, it is considered that specifying the statin by name in the indication is not required. The data from LAPLACE-2 also support administration of both proposed doses of evolocumab in combination with high and low dose atorvastatin (10 mg and 80 mg) and ezetimibe 10 mg QD. The results support the sponsor's proposal that evolocumab be administered in combination with a statin with other lipid lowering therapies. The issue of whether the indication should specifically refer to the statin and the other lipid lowering therapy when administered in combination with evolocumab is discussed below.

Evolocumab in combination with a statin and other lipid lowering therapies

- Evolocumab in combination with a statin and other allowed lipid-regulating medications was investigated in subjects with heterozygous familial hypercholesterolaemia (HeFH) with fasting LDL-C ≥ 2.6 mmol/L and fasting triglycerides ≤ 4.5 mmol/L in one pivotal Phase III study (RUTHERFORD-2 [n=329]). In this study, both doses of evolocumab demonstrated significantly superior efficacy to placebo when the treatments were administered in combination with a statin and other allowed lipid-regulating medications. The pivotal study was supported by one Phase II study (RUTHERFORD-1 [n=167]) of 12 weeks duration in subjects with HeFH. RUTHERFORD-2 and RUTHERFORD-1 were also identified as Studies 20110117 and 20090158, respectively.
- In RUTHERFORD-2, both co-primary efficacy endpoints demonstrated statistically significant reductions in reflexive LDL-C in the evolocumab 140 mg Q2W and 420 mg QM groups compared to the placebo group when the treatments were administered in combination with statin and other allowed lipid-regulating medications ($p < 0.001$, multiplicity adjusted). In addition, evolocumab 140 mg Q2W and 420 mg QM resulted in significant improvement for all co-secondary efficacy lipid endpoints compared to placebo when the treatments were administered in combination with a statin and other allowed lipid-regulating medications ($p < 0.001$, multiplicity adjusted). Both proposed doses of evolocumab were also effective in reducing LDL-C concentrations in all subgroups relative to both placebo and ezetimibe when the treatments were administered in combination with statin and other allowed lipid-regulating medications. The subgroups were identical to, or consistent with those described above for LAPLACE-2.
- The sponsor is proposing that evolocumab be approved for the treatment of primary hyperlipidaemia or mixed dyslipidaemia when administered with a statin in combination with other lipid lowering therapies. The proposed indication does not identify either statins by name (discussed above) or other lipid lowering therapies by name. RUTHERFORD-2 included subjects with HeFH who were on a stable dose of an approved statin and on stable doses of other lipid regulating-relating medications for at least 4 weeks before screening. All 329 subjects in the study were on statins (n=109 [100%] placebo versus n=220 [100%] evolocumab), 204 (62.0%) subjects were on ezetimibe (n=69 [60.9%] placebo versus n=135 (61.4%) evolocumab), 26 (n=7.9%) subjects were on bile acid sequestrants (n=8 [7.3%] placebo versus n=18 [8.2%] evolocumab), 15 (4.6%) subjects were on fish oil (n=4 [3.7%] placebo versus n=11 (5.0%) evolocumab), 7 (2.1%) subjects were on nicotinic acid and derivatives (n=2 [1.8%] placebo versus n=5 [2.3%] evolocumab), and small numbers of subjects were on a wide variety of other lipid-regulating medications. The data indicate that the majority of subjects in the study were on a statin in combination with ezetimibe, with

only a small number of subjects being on a statin combined with other lipid-regulating medications.

- In view of the small number of subjects in RUTHERFORD-2 on lipid lowering medications (other than ezetimibe) in combination with statins, the issue arises of whether the indication should refer to a statin with other lipid lowering therapies (unspecified) or whether the indication should refer to a statin specifically with ezetimibe. In the submission, the sponsor comments that *'[w]hile the number of subjects in the clinical trial program who used lipid-modifying therapies such as fish oil, niacin, and bile acids is small, analyses demonstrate that these subjects had similar LDL-C reductions with evolocumab as compared with the overall integrated analysis population*'. In the Clinical Overview, it is stated that these '*additional lipid lowering therapies have different mechanisms of action and thus, were not anticipated to adversely interact with evolocumab'*.
- Review of data from the integrated efficacy analysis supports the efficacy of evolocumab in combination with fish oil or baseline acid sequestrants but the number of patients in the relevant analyses are small. The percent change from baseline to Week 12 in reflexive LDL-C (mg/dL) for subjects receiving concomitant fish oil at baseline was -86.3% for the evolocumab group (n=77), -30.9% for the ezetimibe group (n=19) and -9.5% for the placebo group (n=23). The percent change from baseline to Week 12 in reflexive LDL-C (mg/dL) for subjects receiving concomitant bile acid sequestrants at baseline was -48.50% for the evolocumab group (n=26), -15.98% for the ezetimibe group (n=5) and 6.98% for the placebo group (n=9). The data in RUTHERFORD-2 did not included subgroup analyses of subjects taking different lipid-regulating medications in combination with a statin. On balance, it is considered that the data support the sponsor's proposal for evolocumab to be used in combination with statin with other lipid lowering therapies without specifying the therapies.

Evolocumab as monotherapy

- Evolocumab as monotherapy was investigated in subjects with a 10 year Framingham risk score of ≤ 10% and fasting LDL-C ≥ 2.6 mmol/L and < 4.9 mmol/L and fasting triglycerides ≤ 4.5 mmol/L in one, pivotal Phase III study of 12 weeks duration (MENDEL-2 [n=613]). In this study, evolocumab monotherapy at both doses being proposed for registration was significantly more effective in lowering LDL-C and other lipid concentrations than both placebo and ezetimibe. This study was supported by one Phase II study of 12 weeks duration in subjects with hypercholesterolaemia and a 10 year Framingham risk score of ≤ 10% (MENDEL-1 [n=406]). MENDEL-2 and MENDEL-1 were also identified as Studies 20110114 and 20101154, respectively. The submitted data support evolocumab as monotherapy for the treatment of primary hypercholesterolaemia of mixed dyslipidaemia.
- In MENDEL-2, both co-primary efficacy endpoints demonstrated statistically significant greater reductions in reflexive LDL-C in the evolocumab 140 mg Q2W and 420 mg QM groups compared to the placebo and ezetimibe groups when the treatments were administered as monotherapy ($p < 0.001$, multiplicity adjusted). In addition, treatment with evolocumab 140 mg Q2W and 420 mg QM resulted in statistically significant greater improvements compared to placebo and ezetimibe for all Tier 1 co-secondary efficacy endpoints (reflexive LDL-C, non-HDL-C, ApoB, TC/HDL-C ratio, ApoB/ApoA1 ratio), and selected Tier 2 secondary co-efficacy endpoints (Lp(a)) ($p < 0.001$, multiplicity adjusted). There were no statistically significant differences between evolocumab and placebo and evolocumab and ezetimibe for the Tier 2 co-secondary efficacy endpoints of triglycerides, VLDL-C, or HDL-C. Evolocumab 140 mg Q2W and 420 mg QM were effective in all subgroups relative to placebo and ezetimibe, with no notable differences for the co-primary

efficacy endpoints being observed between subgroups. The subgroups were identical to or consistent with those described above for LAPLACE-2.

Evolocumab in statin-intolerance

- Evolocumab was investigated in one, pivotal Phase III study (GAUSS-2 [n=307]) in statin-intolerant subjects with screening LDL-C ≥ 2.6 mmol/L (with CHD or CHD risk equivalent), ≥ 3.4 mmol/L (diagnosed CHD or CHD risk equivalent and ≥ 2 risk factors), ≥ 4.1 mmol/L (without diagnosed CHD or CHD risk equivalent and with 1 risk factor), or ≥ 4.9 mmol/L (without diagnosed CHD or CHD risk equivalent and no risk factors) and fasting triglycerides ≤ 4.5 mmol/L. The results of the pivotal study were supported by one Phase II study of 12 weeks duration (GAUSS-1 [n=157]). GAUSS-2 and GAUSS-1 were also identified as Studies 20110116 and 20090159, respectively. The submitted data support treatment with evolocumab alone or in combination with other lipid-lowering medications in patients who are statin-intolerant or for who a statin is not considered clinically appropriate.
- In GAUSS-2, efficacy in two analysis sets was investigated (FAS and MAS). The FAS included all subjects who received at a least one dose of IP (evolocumab, ezetimibe, placebo), and included subjects who were taking approved lipid-regulating medications (that is, approved statins, bile-sequestrants, or stanols). The FAS included 307 subjects (102 in the ezetimibe groups and 205 in the evolocumab groups). A total of 37 (18.0%) subjects in the evolocumab groups and 19 (18.6%) subjects in the ezetimibe groups reported statin usage at baseline, and all of these subjects remained on concomitant statin therapy post-baseline. A total of 47 (15.3%) subjects in the evolocumab groups and 12 (11.8%) subjects in the ezetimibe groups received a non-statin lipid modifying therapy at baseline, and all of these subjects remained on these non-statin therapies post-baseline and none received a statin therapy post-baseline. The most commonly administered non-statin lipid modifying therapy was fish oil, which was taken by 39 (19%) subjects in the evolocumab groups and 14 (13.7%) subjects in the ezetimibe groups. The MAS included FAS subjects who did not take any baseline lipid-regulating medications at study entry. The MAS included a total of 205 subjects (71 in the ezetimibe groups and 134 in the evolocumab groups).
- In GAUSS-2, in both the FAS and the MAS both the co-primary endpoints demonstrated statistically significant reductions in reflexive LDL-C for evolocumab 140 mg Q2W and 420 mg QM compared to ezetimibe ($p < 0.001$, multiplicity adjusted). In addition, treatment with evolocumab 140 mg Q2W and 420 mg QM resulted in statistically significant improvements compared to ezetimibe for the co-secondary efficacy endpoints of reflexive LDL-C (absolute change), percent of subjects with reflexive LDL-C < 1.8 mmol/L, percent reduction of non-HDL-C, percent reduction of ApoB, percent reduction of TC/HDL-C ratio, percent reduction of ApoB/ApoA1 ratio, and percent reduction in Lp(a) ($p < 0.001$, multiplicity adjusted). Statistically significant improvements in other co-secondary endpoints of HDL-C, triglycerides, and VLDL-C for evolocumab relative to ezetimibe were not observed. In the FAS, evolocumab 140 mg Q2W and 420 mg QM were also effective in all subgroups of interest relative to placebo and ezetimibe for the co-primary endpoints, with no notable differences being observed between subgroups.

Long-term efficacy

- The submission included long-term efficacy data from three studies in subjects with primary hyperlipidaemia and mixed dyslipidaemia. In DESCARTES (Study 20110109), evolocumab 420 mg SC QD (n=599) was statistically superior to control (n=302), comprising pooled background lipid lowering treatments, in reducing LDL-C (UC,

reflexive, calculated) and improving other lipid parameters from baseline (end of lipid lowering period) at Week 52. In addition, reductions in LDL-C observed at Week 12 were consistent with those observed at Week 52, indicating that the effect of evolocumab was maintained over long-term use. In OSLER-1 (Study 20110110), an interim 1 year analysis showed that evolocumab 420 mg QM (n=882) compared to standard of care (n=442) statistically significantly lowered calculated LDL-C from parent study baseline to extension study Weeks 12 and 52. In addition, the reductions in calculated LDL-C at Weeks 12 and 52 of the extension study were similar, indicating that the effect of evolocumab was maintained over long-term use. The study also showed that the effect of evolocumab on all other lipids (secondary efficacy endpoints) was statistically significantly superior to standard of care at both Weeks 12 and 52. In OSLER-2 (Study 20120138), an interim analysis including 2928 randomised subjects (1951 to evolocumab 140 mg Q2W or 420 mg QM; 977 to control standard of care) showed that percent change in reflexive LDL-C from parent study baseline to Weeks 12 and 24 of the extension study was notably greater in the evolocumab than in the control arm for each of the 4 different treatment combinations based on treatment received in the parent (control or evolocumab) and extension (parent or evolocumab) studies. An analysis of the treatment difference between pooled groups showed that evolocumab significantly reduced calculated LDL-C from baseline at Weeks 12 and 24 compared to control standard of care ($p<0.001$). Evaluator's conclusions on clinical efficacy for subjects with HoFH

Evaluator's conclusions on clinical efficacy for subjects with HoFH

- The efficacy of evolocumab for the treatment of patients with HoFH has been demonstrated in one randomised, placebo-controlled, double-blind study in 50 subjects with HoFH (n=33 evolocumab, n=17 placebo) (Study 20110233; Part B), and one long-term, open-label study in 96 subjects with HoFH (Study 20110271). However, the analysis of ongoing Study 2011271 was an interim analysis.
- In Study 20110233, treatment with evolocumab 420 mg QM in combination other lipid-regulating medications (n=33) resulted in a statistically significant reduction (treatment difference ± standard error (SE)) from baseline at Week 12 in UC LDL-C compared to placebo (n=16) of 30.9% ± 6.4% ($p < 0.001$, multiplicity adjusted; 95% CI [18.0%, 43.9%]). The mean ± SE reduction in UC LDL-C in the evolocumab group compared to placebo remained constant from Week 4 (24.7% ± 3.7%) through Week 12 (30.9% ± 6.4%). The results for calculated LDL-C were consistent with the results for UC LDL-C. In general, the results for the secondary efficacy lipid endpoints analyses supported the results for the primary efficacy analysis of change in LDL-C concentration. Subgroup analyses in the total population of change in LDL-C concentration from baseline through to Week 12 supported the superiority of evolocumab compared to placebo.
- In Study 20110233, there was no statistically significant difference in adolescent subjects between evolocumab 420 mg QM (n=7) and placebo (n=3) in mean change in UC LDL-C from baseline at Week 12 (-26.0% versus -0.7%, respectively, p=0.14, nominal). However, the comparison was underpowered due to the small number of subjects in the two treatment groups. The percent reduction in UC LDL-C in the evolocumab 420 mg QM group from baseline through to Week 12 was consistent in adolescent subjects and all subjects (26.0% versus 23.1%, respectively).
- In Study 20110271, the open-label, single-arm interim data showed that evolocumab 420 mg QM in combination with other lipid-regulating medications (predominantly statins) was effective in maintaining LDL-C reductions through to 48 weeks in subjects with HoFH (n=96). Compared to baseline, LDL-C reductions of approximately 19% (n=68), 23% (n=45), 26% (n=29) and 19% (n=11) were observed at Weeks 12, 24, 36

and 48 weeks respectively. However, the Week 48 data should be interpreted cautiously due to the smaller number of subjects with data at this time-point. In the subset of 13 adolescent subjects with HoFH, mean ± SE percent reductions from baseline in UC LDL-C at OLE weeks 12, 24, and 36 were 15.0% ± 8.1%, 21.5% ± 8.9%, and 33.3% ± 9.6%, respectively.

- In Study 20110271, compared to baseline, LDL-C reductions of approximately 25% in HoFH subjects not on apheresis (n=32) and approximately 20% in HoFH subjects on apheresis (n=13) were maintained at Week 24 with evolocumab 420 mg QM. The small number of subjects in the apheresis group at Weeks 36 and 48 (3 and 2, respectively) preclude meaningful comparison with non-apheresis subjects at these two later time-points. Increasing the frequency of dosing from 420 mg QM for 12 weeks to 420 mg Q2W for 12 weeks in subjects with HoFH resulted in an approximately 6% greater reduction of LDL-C (that is, from approximately 16% QM to 22% Q2W). Improvements in other lipid parameters were also achieved and maintained with long-term evolocumab treatment in HoFH subjects.

Safety

Studies providing safety data

The submission included an Integrated Summary of Safety (ISS) of data from the 14 Phase II and Phase III clinical efficacy and safety studies in subjects with primary hyperlipidaemia and mixed dyslipidaemia. The ISS analysis was pre-specified in an Integrated Statistical Analysis Plan (iSAP) dated 27 September 2013. The methodology used for the ISS analysis is considered to be sound and comprehensively addresses the safety of evolocumab for the treatment of primary hyperlipidaemia and mixed dyslipidaemia. Therefore, in this CER the evaluation of the safety of evolocumab for the treatment of primary hyperlipidaemia and mixed dyslipidaemia focuses on the data presented in the ISS. The safety data for subjects with severe FH (Study 20110271) were not included in the ISS data set for patients and have been evaluated separately in this CER.

The 14 Phase II and III studies included in the ISS analysis were grouped into three safety analysis sets: the Integrated Parent Analysis Set (IPAS), the Integrated Extension SoC-controlled Period Analysis Set (IECAS), and the Integrated Extension All-Investigational Product Period Analysis Set (IEAAS). The three safety analysis sets are summarised below in Table 6.

Table 6: Safety analysis sets in the ISS analysis of the primary hyperlipidaemia and mixed dyslipidaemia studies.

Analysis Set	General Description	Source of Data	Additional Information
Integrated **P**arent **A**nalysis **S**et (IPAS)	phase 2 and phase 3 parent studies (including all data up to the end of the parent study)	• subjects in primary hyperlipidemia and mixed dyslipidemia studies (20101154, 20101155, 20090158, 20090159, 20110114, 20110115, 20110116, 20110117) • subjects in device home-use studies (20120348 and 20120356) • Japanese subjects with primary hyperlipidemia and mixed dyslipidemia in Study 20110231 • subjects in the double-blind, placebo-controlled long-term parent study (20110109)	• Studies 20110114, 20110115, 20110116, and 20110117 in the IPAS were used to analyze device related adverse events with the AI/pen. • The analyses of change from baseline in ECG intervals excluded device home-use Studies 20120348 and 20120356 because these studies had ECG data at screening only.
Integrated **E**xtension SoC-**C**ontrolled Period **A**nalysis **S**et (IECAS)	year 1 of the OLE studies (controlled period)	• subjects randomized in year 1 of the long-term, controlled, OLE Studies 20110110 and 20120138	• Both studies are ongoing with a 01 April 2014 data cutoff date for the submission. • Does not include subjects in Study 20120138 with < 12 weeks of potential follow-up time (the restriction on potential follow-up was implemented to prevent operational bias that may occur by differences in visit schedules during the first 12 weeks of the study).
Integrated **E**xtension **A**ll-Investigational Product Period **A**nalysis **S**et (IEAAS)	year 2+ of the OLE studies (open label period)	• subjects who were on study at the start of the all-IP period in Studies 20110110 and 20120138 and dosed at least once in that period.	• Analysis set primarily comprises subjects from Study 20110110.

Evolocumab exposure

The ISS included 6026 subjects with total exposure of 6165 patient-years (see Table 7 below).

Table 7: Overall summary of exposure in subjects with hyperlipidaemia and mixed dyslipidaemia (IPAS, IECAS, IEAAS)

	Control		EvoMab		
	Any Placebo	Any Control [a]	EvoMab 140 mg Q2W or 420 mg QM	Any EvoMab	Total
Number of Subjects	1526	3027	4783	4971	6026
Total pt-year exposure	604	1737	4242	4427	6165
Number of Subjects					
≥ 3 months	1501	2988	4654	4839	5904
≥ 6 months	294	1444	3276	3286	4571
≥ 12 months	287	718	1760	1797	2430
≥ 18 months	1	55	843	881	1405
≥ 24 months	0	1	598	611	920
≥ 30 months	0	0	61	165	328
≥ 36 months	0	0	0	0	0

Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356, 20110110 and 20120138.
a Any includes placebo, ezetimibe, or standard of care. Patients can contribute data to more than one treatment group. pt-year = patient years, where years are calculated as the sum of period durations for the treatment group across subjects divided by 365.25. Months are calculated by multiplying the patient years by 12 and rounding to the nearest whole month.

The integrated parent studies (IPAS) included 5981 subjects exposed to any Investigational product (IP), comprising 3946 subjects exposed to any evolocumab for a mean ± SD of 3.95 ± 3.21 months (range: 0, 12.3 months), and 2035 subjects exposed to any control for a mean ± SD of 3.99 ± 3.19 months (range: 0.1, 12.3 months). The *integrated parent studies (IPAS)* included 1245 subjects exposed to evolocumab 140 mg Q2W and 1956 subjects exposed to evolocumab 420 mg QM. The mean ± SD durations of evolocumab exposure in the 140 mg Q2W and 420 mg QM groups were 2.57 ± 0.55 months (range: 0, 3.3 months) and 5.29 ± 4.13 months (range 0.4, 12.3 months), respectively. The longer exposure reported in subjects treated with evolocumab 420 mg QM compared to evolocumab 140

mg Q2W is accounted for by inclusion of subjects from the long-term Study 20110109 treated only with the 420 mg QM dose. Exposure in the IPAS treatment groups is summarised below in Table 8.

Table 8: IPAS - Summary of exposure during the integrated parent studies.

	Control			EvoMab			
	Placebo SC Q2W (N = 586)	Placebo SC QM (N = 940)	Ezetimibe QD (N = 554)	Other EvoMab Dose (N = 715)	140 mg Q2W (N = 1245)	420 mg QM (N = 1956)	420 mg QM + Ezetimibe QD (N = 30)
Duration of SC IP exposure (months)							
n	586	940	509	715	1245	1956	30
Mean	2.73	5.47	2.70	2.74	2.57	5.29	2.76
SD	0.35	4.22	0.40	0.29	0.55	4.13	0.18
Median	2.79	2.79	2.79	2.79	2.79	2.79	2.79
Q1, Q3	2.76, 2.83	2.79, 11.93	2.76, 2.79	2.76, 2.79	2.73, 2.79	2.76, 11.89	2.76, 2.83
Min, Max	0.3, 3.4	0.1, 12.3	0.5, 3.4	0.5, 3.3	0.0, 3.3	0.4, 12.3	1.9, 2.9
Duration of study exposure (months)							
n	586	940	554	715	1245	1956	30
Mean	3.24	5.69	3.01	2.99	3.07	5.56	2.81
SD	0.35	4.31	0.36	0.31	0.54	4.24	0.07
Median	3.25	2.83	2.86	2.86	3.25	2.83	2.79
Q1, Q3	3.22, 3.29	2.79, 11.96	2.79, 3.25	2.79, 3.25	3.19, 3.29	2.79, 11.96	2.76, 2.83
Min, Max	0.3, 4.8	0.1, 17.5	0.5, 5.5	1.0, 6.2	0.0, 5.6	0.4, 17.6	2.6, 3.0

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Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356.
N = number of subjects randomized in the integrated parent analysis set; EvoMab = Evolocumab (AMG 145); QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous; IP = investigational product; IPAS = Integrated Parent Analysis Set.

The Year 1 SoC-controlled period of the OLE studies (IECAS) included a total of 4252 subjects from the two long-term extension studies (20110110; 20120138). For subjects assigned to control during the parent study and evolocumab plus SoC during the extension study, the mean ± SD duration of evolocumab exposure was 8.06 ± 3.09 months. For subjects assigned to evolocumab in the parent study and evolocumab plus SoC during the extension study, the mean ± SD exposure to evolocumab was 8.35 ± 3.35 months. The summary of exposure in treatment groups in the IECAS is provided below in Table 9.

Table 9: IECAS - Summary of exposure during the 1 year SoC-controlled period of the extension studies

	Control in Parent Study		EvoMab in Parent Study	
	SoC (N = 472)	EvoMab + SoC (N = 943)	SoC (N = 947)	EvoMab + SoC (N = 1890)
Duration of SC IP exposure (months)				
n	472	940	947	1890
Mean	0.00	8.06	0.00	8.35
SD	0.00	3.09	0.00	3.35
Median	0.00	7.29	0.00	7.38
Q1, Q3	0.00, 0.00	5.59, 10.58	0.00, 0.00	5.59, 12.65
Min, Max	0.0, 0.0	0.0, 13.1	0.0, 0.0	0.1, 13.1
Duration of study exposure (months)				
n	472	943	947	1890
Mean	8.13	8.23	8.55	8.56
SD	3.03	3.04	3.28	3.29
Median	7.18	7.39	7.79	7.56
Q1, Q3	5.78, 10.56	5.78, 10.87	5.75, 12.65	5.75, 12.78
Min, Max	0.0, 13.1	0.0, 13.1	0.0, 13.1	0.1, 13.1

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Includes the following studies: 20110110, 20120138.
N = number of subjects randomized in the integrated extension SoC-controlled period analysis set; EvoMab = Evolocumab (AMG 145); SoC = Standard of Care; SC = subcutaneous; IP = investigational product.

The year 2+ of the OLE period of the extension studies (IEAAS) included a total of 954 subjects from the two long-term extension studies (20110110; 20120138). The mean ± SD for the total evolocumab plus SoC group was 12.64 ± 2.92 months (range 0, 16.9 months). The summary of exposure in the treatment groups in the IEAAS is provided below in Table 10.

Table 10: IEAAS - Summary of exposure during the year 2+ OLE period of the extension studies

	SoC in SoC-Controlled period	EvoMab + SoC in SoC-Controlled Period	
	EvoMab + SoC (N = 312)	EvoMab + SoC (N = 642)	Total (N = 954)
Duration of SC IP exposure (months)			
n	312	642	954
Mean	12.60	12.66	12.64
SD	2.98	2.89	2.92
Median	12.91	13.04	12.94
Q1, Q3	12.19, 14.08	12.22, 14.26	12.22, 14.23
Min, Max	0.0, 16.8	0.0, 16.9	0.0, 16.9
Duration of study exposure (months)			
n	312	642	954
Mean	12.75	12.89	12.84
SD	2.77	2.53	2.62
Median	12.91	13.08	13.04
Q1, Q3	12.24, 14.21	12.25, 14.42	12.25, 14.29
Min, Max	0.0, 16.8	0.0, 16.9	0.0, 16.9

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Includes the following studies: 20110110, 20120138.
N = number of subjects randomized and in the integrated extension all-IP period analysis set; EvoMab = Evolocumab (AMG 145); SoC = Standard of Care; IP = investigational product.

The longer duration of exposure to evolocumab in the OLE extension studies (IECAS; IEAAS) compared to integrated parent studies (IPAS) means that direct comparison of the frequency of adverse events (AEs) across the three data sets should be undertaken cautiously. In general, the data showed that the frequency of AEs reported in subjects treated with evolocumab increased with the duration of exposure. Therefore, the frequency of AEs was greater in the IEAAS compared to the IECAS and the IPAS, and the frequency of AEs in the IECAS was greater than the frequency in the IPAS.

Patient exposure

Total exposure in the clinical development program (both indications)

A total of 6801 subjects (including studies for both intended indications) were treated with evolocumab (alone or in combination with other lipid-regulating medications, primarily statins), placebo, or any control (including standard of care [SoC]) in the clinical development program for both proposed indications. A total of 5710 subjects were exposed to any dose of evolocumab representing 4638 patient-years of exposure. The number of subjects exposed to evolocumab across all studies for ≥ 6 months and ≥ 12 months was 3350 and 1824, respectively. The exposure data for the clinical development program for both proposed indications are summarised below in Table 11.

Table 11: Overall exposure (Phase I, II and III studies) on the clinical development program (both indications).

	Control		EvoMab		
	Any Placebo	Any Control[a]	EvoMab 140 mg Q2W or 420 mg QM or 420mg Q2W[b]	Any EvoMab	All Unique Subjects
Overall					
Number of Subjects	1578	3079	5456	5710	6801
Total pt-year exposure	617	1750	4437	4638	6388
Number of Subjects					
< 3 months	25	39	287	294	280
≥ 3 months	1553	3040	5169	5416	6521
≥ 6 months	294	1444	3340	3350	4638
≥ 12 months	287	718	1787	1824	2462
≥ 18 months	1	55	854	892	1416
≥ 24 months	0	1	601	614	923
≥ 30 months	0	0	61	165	328
≥ 36 months	0	0	0	0	0

Subjects with the following conditions have been treated with any evolocumab for at least 1 year: (a) 407 subjects (1079 patient-years) with established CVD; (b) 559 subjects (1427

patient-years) at National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) high risk for CVD; (c) 162 subjects (429 patient-years) with NCEP ATP III moderately high risk for CVD; (d) 213 subjects (525 patient-years) with type II diabetes mellitus; 649 subjects (1577 patient-years) with metabolic syndrome; (e) 503 subjects (1268 patient-years) on concomitant high intensity statin; (f) 605 subjects (1612 patient-years) on concomitant, moderate intensity statin; and (g) 486 subjects (1255 patient-years) ≥ 65 years old.

Postmarketing data

Not applicable.

Evaluator's conclusions on safety

Overall extent of exposure is summarised above and also in Attachment 2 under *Evaluator's conclusions on safety*.

IPAS (integrated parent studies)

The IPAS comprised integrated data from the Phase II and III, 12 week studies in addition to the Phase III, 52 week study (20110109). The IPAS included a total of 6025 subjects, including 3946 in the any evolocumab group and 2080 in the any control group. AEs were reported in a similar proportion of subjects in the any evolocumab and any control groups (51.1% versus 49.6%, respectively). The majority of AEs in both the any evolocumab and any control groups were National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) Grade 1 or 2 in severity, with CTCAE Grade ≥ 3 events being reported in 3.7% of subjects in the any evolocumab group and 3.2% of subjects in the any control group and CTCAE Grade ≥ 4 events being reported in 0.6% and 0.3% of subjects, respectively.

The only AE reported in ≥ 5% of subjects in the any evolocumab and any control groups was nasopharyngitis (5.9% versus 4.8%, respectively). AEs reported in ≥ 2% of subjects in the any evolocumab group and more frequently than in the any control group were nasopharyngitis, upper respiratory tract infection, back pain, arthralgia, influenza, nausea and cough. The sponsor identified nasopharyngitis, upper respiratory tract infection, back pain, arthralgia, influenza and nausea as adverse reactions based on the criteria of AEs reported in > 2% of subjects in the any evolocumab group and more frequently than in the any control group.

Serious AEs (SAEs) occurred infrequently and with a similar incidence in subjects in the any evolocumab and any control groups (2.8% versus 2.1%, respectively). No SAEs in either treatment group were reported in ≥ 0.2% of subjects.

More details on AEs and SAEs in IPAS, IECAS and IEAAS can be found in Attachment 2 *Evaluator's conclusion on safety*.

Deaths

There were 15 (0.2%) deaths reported in the 6801 unique subjects included in the clinical program for both indications. All 15 deaths occurred in the subjects with hyperlipidaemia and mixed dyslipidaemia. Of the 15 deaths, 4 occurred during the parent study period (IPAS), 7 occurred during the 1 year controlled period (IECAS), 2 occurred during the Year 2+ OLE period (IEAAS) and 2 occurred after the end of the studies. Only 1 sudden death in a 69 year-old subject receiving evolocumab 420 mg QM and SoC in the IECAS was reported by the investigator to be related to the investigational product. The investigator reported the cause of sudden death as unknown but presumed it to be myocardial infarction.

Of the 15 deaths, 11 were positively adjudicated by the independent CEC to be due to cardiovascular causes. Overall, in the total clinical program (both indications) it can be

estimated that there were 8 (0.14%) cardiovascular deaths in the 5710 subjects treated with evolocumab and 3 (0.10%) cardiovascular deaths in subjects treated with control. There appears to be no increased risk of cardiovascular death in subjects treated with evolocumab relative to control. The high proportion of cardiovascular deaths relative to all deaths in the clinical program is not expected, given the characteristics of the subject population enrolled in the studies.

Safety across therapeutic settings (monotherapy, combined with statins or statin intolerant)

In the integrated parent studies (IPAS), all AEs, SAEs and AEs leading to discontinuation were reported in a similar or lower proportion of subjects in the monotherapy cohort and the combination with statin cohort compared to the entire integrated population. In contrast, in the statin intolerant cohort, all AEs, SAEs and AEs leading to discontinuation were reported in a greater proportion of subjects in the any evolocumab and any control groups compared to the entire integrated population. However, in the statin intolerant cohort, all AEs were reported more frequently in the any control group compared to the any evolocumab group (69.4% versus 64.5%, respectively). In the statin intolerant cohort, SAEs were reported with similar frequencies in the any evolocumab and any control groups (3.3% versus 3.0%, respectively), while AEs leading to discontinuation were reported more frequently in the any control group compared to the any evolocumab group (11.2% versus 6.4%). Overall, the data from the IPAS indicates that the safety profile of evolocumab is satisfactory in the monotherapy, combined with statins and statin intolerant cohorts. In the 1 year SoC-controlled period (IECAS) and the Year 2+ OLE period (IEAAS), the safety profile of the evolocumab plus SoC is considered to be satisfactory in the three therapeutic settings.

AEs of regulatory interest

AEs of special interest were analysed in various organ systems. No significant safety issues associated with evolocumab were identified in these analyses. The incidence of positively adjudicated cardiovascular events was similar in subjects treated with evolocumab or control. No significant safety issues were identified for hepatic, renal, haematological or immune system disorders. Medical review by the sponsor identified rash, urticaria and injection site reactions as adverse reactions. There were 2 cases of glomerulonephritis and 1 case of IgA nephropathy associated with evolocumab.

AEs of special interest with evolocumab using broad and narrow search strategies

AE events known or suspected to be associated with approved lipid-lowering therapies were monitored in clinical studies with evolocumab (that is, muscle related events, liver related events, events potentially related to low levels of LDL-C, diabetes related events, and neurocognitive events). Other events of special interest monitored in the studies were those known to be associated with injectable proteins (hypersensitivity events, injection site reactions) and events that could theoretically be associated with PCSK9 inhibition/LDLR up-regulation (hepatitis C events).[55]

More details on this can be found in Attachment 2 under the same heading.

A summary of *Laboratory and investigations and immunogenicity* and *Vital signs and ECG* changes are also included in Attachment 2.

Safety in special groups

The short-term interim safety data from subjects (n=102) with severe FH from Study 20110271 were consistent with the safety data for patients with hyperlipidaemia and

[55]Labonté P, Begley S, Guevin C, et al. PCSK9 impeded hepatitis C virus infection in vitro and modulates liver CD81 expression. Hepatology. 2009; 50(1):17-24.

mixed dyslipidaemia from the ISS. The analysis of the sub-group data from the IPAS, IECAS and IEASS for subjects with severe hypercholesterolaemia and mixed dyslipidaemia of varying severity showed that AEs, SAEs and AEs leading to discontinuations of IP, and deaths were consistent across the sub-groups and with the overall integrated analysis population.

No clinically significant safety differences were seen between subjects aged ≥ 65 years and ≥ 75 years; there were limited data in subjects aged < 18 years of age (see *Homozygous familial hypercholesterolaemia* below). There were no clinically significant safety differences between male and female subjects. The majority of subjects were White (83.9%) with most of the other subjects being Asian. No clinically significant safety differences were seen in the different racial groups.

There were no safety data in subjects with hepatic or renal impairment (the studies excluded subjects with eGFR < 30 mL/min/1.73 m^2). No studies on potential drug-drug or drug-food interactions were conducted with evolocumab. However, it is considered that the absence of specific studies in these special patient groups should not preclude registration of evolocumab.

Homozygous familial hypercholesterolaemia

The submission included substantially less safety data in subjects with HoFH. This is not unexpected as HoFH is a rare disease with an estimated prevalence of 1 in 1 million persons. However, the general AE profile of evolocumab in subjects with HoFH was consistent with that in subjects with primary hyperlipidaemia and mixed dyslipidaemia.

More details on the safety data and exposure collected in this population are included in Attachment 2.

The HoFH data included safety data on a total of 14 adolescent subjects (≥ 12 to < 18 years). All adolescent subjects from Study 20110233 with the exception of 1 subject in Part B continued in the 20110271 extension study. Three additional adolescent subjects who did not participate in the parent Study 20110233 were enrolled into Study 20110271. Of the 10 HoFH adolescents in Study 20110233 Part B, 7 subjects received evolocumab 420 mg QM and 3 subjects received placebo. In the subgroup of adolescent subjects, AEs were reported in 3 (42.9%) subjects in the evolocumab group and 2 (66.7%) subjects in the placebo group. Overall, the number of adolescent subjects with HoFH treated with evolocumab is too small to specifically evaluate the safety in this patient group. However, there is no biological reason to expect that the safety profile of evolocumab in subjects with HoFH aged ≥ 12 years to < 18 years will significantly differ from subjects aged > 18 years. Therefore, the limited safety data in adolescents aged ≥ 12 to < 18 years with HoFH should not preclude registration of evolocumab in these subjects.

First Round Benefit-Risk Assessment

First round assessment of benefits

Primary hyperlipidaemia and mixed dyslipidaemias

General comments

- The benefits of evolocumab administered by SC injection for the treatment of patients with primary hypercholesterolaemia (HeFH and nonfamilial) or mixed dyslipidaemia have been satisfactorily demonstrated in the four pivotal Phase III studies of 12 weeks duration, supported by the four Phase II studies of 12 weeks duration, and the three long-term studies at least 52 weeks duration (2x Phase III, 1x Phase II).
- The benefits of treatment with evolocumab primarily relate to reductions in LDL-C serum concentrations, while improvements in other lipid parameters have also been observed. There were no clinical data demonstrating that evolocumab reduces

cardiovascular morbidity and mortality. However, elevated serum LDL-C concentrations are an accepted surrogate marker for cardiovascular morbidity and mortality.

More details on the studies and findings are included in Attachment 2 under the same heading.

Long-term benefits of treatment with evolocumab

In DESCARTES (long-term, Phase III study), compared to placebo (n=264) the reduction (treatment difference) in UC LDL-C from baseline observed at week 52 with evolocumab 420 mg QM (n=542) for all background therapies combined was 57% (95% CI: 53, 61); multiplicity adjusted $p < 0.001$. The difference between placebo and evolocumab 420 mg QM was present at the week 12 visit and was maintained through week 52. The benefits of evolocumab 420 mg QM compared to placebo were demonstrated for each of the four background therapies. Compared to placebo, the reductions (treatment difference) in UC LDL-C from baseline to week 52 for the evolocumab 420 mg QM treatment group were 56% (95% CI: 47%, 64%) in the diet alone group, 62% (95% CI: 56%, 67%) in the diet plus atorvastatin 10 mg group, 57% (95% CI: 46%, 67%) in the diet plus atorvastatin 80 mg group, and 49% (95% CI: 38%, 59%) in diet plus atorvastatin 80 mg plus ezetimibe 10 mg group; multiplicity adjusted $p < 0.001$ for each comparison between evolocumab and placebo. Results of the subgroup analyses for reductions in UC LDL-C baseline to week 52 demonstrated that evolocumab 420 mg QM was effective across all subgroups. Results of the secondary efficacy analyses for all lipid parameters showed that statistically significant improvements occurred for all parameters in the evolocumab 420 mg QM group compared to placebo from baseline to Week 12, and that these improvements were maintained through Week 52.

Homozygous Familial Hyperlipidaemia (HoFH)

The benefits of evolocumab 420 mg QM in combination with other lipid-regulating medications (predominantly statins) in reducing LDL-C and other lipids in subjects with HoFH have been satisfactorily demonstrated in the submitted data.

More details are included in Attachment 2 under the same heading.

First round assessment of risks

Primary hyperlipidaemia and mixed dyslipidaemia

- No significant safety issues associated with evolocumab treatment emerged from the clinical program. The study population (n=6026) included subjects with a prior history of coronary artery disease (18.9%), cerebrovascular disease (8.4%), Type 2 diabetes mellitus (13.3%), metabolic syndrome (≥ 3 factors) without diabetes (33.2%) and hypertension (51.4%). The majority of the subjects had normal renal function, with 11.2% having renal impairment (eGFR < 60 mL/min/1.73 m^2). Of the total study population, 33.7% of subjects were categorised as high risk for CHD based on NCEP criteria.
- In the total clinical study program investigating evolocumab for the treatment of hypercholesterolaemia, 5710 subjects were exposed to any dose of evolocumab. Based on the 'rule of threes', it can be estimated that the number of subjects exposed to evolocumab was sufficient to identify ADRs with an incidence of ≥ 0.05% (3/5710) with 95% confidence. No subjects in the clinical program were exposed to evolocumab for ≥ 3 years, 1824 were exposed for ≥ 12 months and 614 were exposed for ≥ 24 months.

More details are included in Attachment 2 under this same heading.

- No significant safety issues with the potential for major regulatory impact were identified (that is, hepatic toxicity, haematological toxicity, serious skin reactions, cardiovascular safety, unwanted immunological events). Positively adjudicated cardiovascular events were reported infrequently in the clinical program, and were reported with a similar incidence in subjects with primary hyperlipidaemia or mixed dyslipidaemia in the evolocumab and control groups. The sponsor identified rash and urticaria as adverse reactions. Glomerulonephritis was reported in 2 subjects treated with evolocumab, and there was a temporal relationship between the onset of these events and the administration of evolocumab. However, it is possible that the association between evolocumab and these events may have been confounded by pre-existing renal disease. There was one case of IgA nephropathy associated with evolocumab.
- No significant risks of AEs known to be associated with approved lipid-lowering therapies were identified, including muscle related events (that is, myopathy, rhabdomyolysis), liver related events, events potentially related to low LDL-C concentrations, diabetes related events, and neurocognitive events. No significant risks of AEs known to be associated with approved other injectable protein therapies were identified (that is, hypersensitivity events, injection site reactions). The sponsor identified injection site reactions associated with evolocumab as adverse reactions. However, the incidence of these reactions was low and none appear to have been reported as SAEs. No significant risks of AEs that could theoretically be associated with PCSK9 inhibition/LDLR up-regulation were identified (that is, hepatitis C events).
- There appears to be no significant risk of increased CK, AST or ALT levels associated with evolocumab treatment. In addition, evolocumab does not appear to significantly affect serum vitamin E levels or steroid hormone levels (adrenocorticotropic hormone (ACTH), cortisol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), or testosterone).
- There appears to be no significant risks of changes in vital signs or electrocardiogram (ECGs) associated with evolocumab treatment. Evolocumab does not appear to prolong the QTc interval.
- In view of concerns arising from some studies suggesting that very low levels of LDL-C might increase the risk of cancer, haemorrhagic stroke and non-cardiovascular death, the risks of treatment with evolocumab in patients with low LDL-C was investigated in the clinical development program. In the any evolocumab group (IPAS) and the evolocumab plus SoC group (IECAS), AEs and SAEs were reported in similar proportions of subjects who achieved LDL-C levels < 0.6, < 1.0 mmol/L, ≥ 1.0 mmol/L and in the entire integrated population. However, in the year 2+ OLE period (IEAAS), AEs and SAEs were reported more frequently in subjects in the LDL-C < 0.6 mmol/L subgroup compared to the LDL-C < 1.0 and ≥ 1.0 mmol/L subgroups and the entire integrated population. The difference appears to be related to a higher percentage of subjects in the LDL-C < 0.6 mmol/L subgroup with cardiac disorders (SOC) and neoplasms benign, malignant and unspecified (SOC). However, associations were not observed in the two other safety analysis sets (that is, IPAS and IECAS). Furthermore, the absolute number of patients contributing to the observed difference in the incidence of subjects with these events in the IEAAS is small. There was no evidence of neurocognitive impairment associated with low LDL-C levels. Analyses of vitamin E and steroid analytes were performed by LDL-C subgroup, and the analyses were consistent across the subgroups.
- The risks of treatment with evolocumab in subjects with severe hypercholesterolaemia and in patients with mixed dyslipidaemia defined by different criteria are consistent with the risks in the total population of subjects with primary hypercholesterolaemia and mixed hyperlipidaemia.

- The risks of treatment with evolocumab were similar when the drug was administered as monotherapy, or in combination with statins (IPAS; IECAS), and were consistent with the risks of treatment observed in the entire integrated population. However, in statin resistant subjects, the safety profile of evolocumab appeared to be inferior to the safety profiles in subjects treated with evolocumab as monotherapy and in combination with statins. Nevertheless, the safety of evolocumab in statin intolerant subjects is considered to be satisfactory.
- The risks of treatment with evolocumab are similar in subjects aged > 65 years and > 75 years, and in both males and females. There are no data on the risks of treatment with evolocumab in patients with hepatic or renal impairment. However, evolocumab was not associated with hepatic or renal toxicity. There was no formal drug-drug interaction studies conducted with evolocumab. However, evolocumab was well tolerated when administered with statins and other lipid-regulating medications. Furthermore, throughout the Phase II and III studies investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except for those specified in the protocols. Therefore, it is likely that a wide range of commonly used medications were administered with evolocumab during the clinical trial program.

Homozygous familial hypercholesterolaemia

- The number of subjects with HoFH was substantially less than the number of subjects treated with primary hyperlipidaemia and mixed dyslipidaemia. However, the safety profile in subjects with HoFH was similar to the safety profile in subjects with primary hyperlipidaemia and mixed dyslipidaemia. No additional safety issues were observed in subjects with HoFH. There were limited data in adolescent subjects aged ≥ 2 to < 18 years with HoFH (n=7).

First round assessment of benefit-risk balance

The benefit-risk balance of evolocumab, given the proposed usage is favourable. The benefits of treatment with evolocumab relate to significant reductions in LDL-C serum concentrations and improvement in other lipid parameters compared to statins, ezetimibe, and other lipid-regulating medications. There were no data on whether evolocumab reduces cardiovascular morbidity and/or mortality. However, the safety data suggest that evolocumab does not increase the risk of death from all causes or death due to cardiovascular events, or significantly increase the risk of cardiovascular morbidity compared to statins, ezetimibe, or other lipid-regulating medications.

First Round Recommendation Regarding Authorisation

It is recommended that Repatha (evolocumab) be approved for the following indications:

Repatha should be used as an adjunct to diet when the response to diet and exercise is inadequate.

Repatha is indicated in patients with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia:

- *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 or for whom a statin is not considered clinically appropriate.*

Repatha is indicated in patients with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Clinical Questions

Pharmacokinetics

1. Please provide a justification for not submitting an absolute bioavailability study in humans for evolocumab following SC injection.

Safety

2. Please comment on the two cases of hypomagnesaemia reported in the any evolocumab group in the integrated parent studies (primary hyperlipidaemia and mixed dyslipidaemia).
3. Please comment on the two cases of glomerulonephritis and the one case of IgA nephropathy associated with evolocumab in subjects with primary hyperlipidaemia and mixed dyslipidaemia. Does the sponsor consider that these cases represent a signal for glomerular pathology associated with evolocumab?
4. In the subgroup analysis of subjects with LDL-C levels < 25 mg/dL (<0.6 mmol/L) in the integrated extension SoC controlled period analysis set, the tabulated summary of AEs provided two values for the incidence of diabetes mellitus in the evolocumab plus SoC group under Metabolism and Nutrition Disorders (that is, 0.2%, n=1 and 1.7%, n=11). Please account for this apparent discrepancy.
5. In the Year 2+ OLE period (IEAAS) subgroup analysis of subjects who achieved LDL-C levels < 0.6 mm/L, < 1.0 mmol/L and ≥ 1.0 mmol/L, the percentage of subjects with AEs (all) and SAEs was higher in subjects in the LDL-C < 0.6 mmol/L subgroup than in subjects in the higher LDL-C level subgroups and in the entire integrated patient population. The difference in the results for SAEs appears to be driven primarily by the higher proportion of subjects with cardiac disorders (System Organ Class (SOC)) and neoplasms benign, malignant and unspecified (SOC) in the LDL-C < 0.6 mmol/L subgroup compared to the LDL-C < 1.0 and ≥ 1.0 mmol/L subgroups. Please comment on this observation.
6. Please comment on the potential safety of evolocumab when administered with drugs other than statins and other lipid-lowering medications. For the ISS population, please provide a summary of drugs taken by subjects during the studies (other than statins and other lipid lowering medications).

Second round evaluation of clinical data submitted in response to questions

The details of the sponsor's responses to the *Clinical questions* and the clinical evaluator's comments on the sponsor's responses are detailed in Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefit

After consideration of the responses to the clinical questions, the benefits of evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia, and homozygous familial hypercholesterolaemia remain unchanged from those identified in the first round.

Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia, and homozygous familial hypercholesterolaemia remain unchanged from those identified in the first round.

Second round assessment benefit-risk balance

The benefit-risk balance of evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia and homozygous familial hypercholesterolaemia is favourable. The benefits of treatment with evolocumab relate to significant reductions in LDL-C serum concentrations and improvement in other lipid parameters compared to statins, ezetimibe and other lipid-regulating medications. There were no data on whether evolocumab reduces cardiovascular morbidity and/or mortality. However, the safety data suggest that evolocumab does not increase the risk of death from all causes or death due to cardiovascular events or significantly increase the risk of cardiovascular morbidity compared to statins, ezetimibe or other lipid-regulating medications.

Second round recommendation regarding authorisation

It is recommended that Repatha (evolocumab) be approved for the following indications:

> *Repatha should be used as an adjunct to diet when the response to diet and exercise is inadequate.*
>
> *Primary hypercholesterolaemia and mixed dyslipidaemia*
>
> *Repatha is indicated in patients with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia:*
>
> - *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 or for whom a statin is not considered clinically appropriate.*
>
> *Homozygous familial hypercholesterolaemia*
>
> *Repatha is indicated in patients with homozygous familial hypercholesterolaemia in combination with other lipid lowering therapies.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 1.0 (dated 31 July 2014) and Australian Specific Annex Version 1.0 (dated 16 October 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 12.

Table 12: Sponsor's summary of ongoing safety concerns

Important identified risks	None
Important potential risks	Hypersensitivity Immunogenicity
Missing information	Use in pregnant/lactating women Use in paediatric patients

	Use in elderly patients ≥ 75 years old Use in patients with severe renal impairment Use in patients with severe hepatic impairment (Child-{ugh Class C) Use in patients with Hepatitis C Long-term use including effects in LDL-C < 40 mg/dL (<1.03 mmol/L)

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all ongoing safety concerns. In addition, two clinical studies are part of the pharmacovigilance plan and are ongoing at the time of this evaluation, addressing the missing information of 'Use in paediatric patients'.

Follow-up questionnaires for anaphylactic reaction and pregnancy outcome are also proposed relating to the ongoing safety concerns of 'Hypersensitivity', 'Immunogenicity' and 'Use in pregnant/lactating women'. Follow-up questionnaires are also proposed for 'Medication error' which is currently not listed as ongoing safety concern.

It appears that the ongoing safety concerns of 'Immunogenicity', 'Use in patients with severe renal impairment (eGFR<30 mL/min/1.73 m^2)', 'Use in patients with Hepatitis-C' and 'Long term use including effects of LDL-C <40 mg/dL or <1.03 mmol/L' are addressed through ongoing clinical trials, although the sponsor incorrectly only describes 'routine pharmacovigilance' in the 'overview of pharmacovigilance actions' section in the EU-RMP.

Regarding the missing information of 'Use in pregnant/lactating women' the sponsor states: '*…women who become pregnant during evolocumab treatment are encouraged to enroll in Amgen's Pregnancy and Lactation Surveillance Programmes*.'

Risk minimisation activities

The sponsor proposes routine risk-minimisation in the form of provision of information in the Australian PI/Consumer Medicine Information (CMI). No routine risk-minimisation activity is proposed for the missing information of 'Use in patients with Hepatitis C'.

Reconciliation of issues outlined in the RMP report

Table 13 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the TGA's evaluation of the sponsor's responses.

Table 13: Reconciliation of issues outlined in the round 1 RMP evaluation report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration	*The sponsor can confirm that any recommendations and safety considerations raised through the consolidated request and/or Nonclinical and Clinical Evaluation Reports, and accepted by the sponsor, have been addressed in the updated European Risk*	The sponsor's response is satisfactory. The nonclinical evaluator has provided comments regarding the safety

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*Management Plan (EU RMP) (version 1.2), the updated Australia-Specific Annex (ASA) (Version 2.0) to the EU RMP, and the PI and CMI where relevant.*	specification of the RMP. The sponsor should correct the relevant part of the RMP consequently.
2. Amendments to the safety specification section of the RMP and to the table of ongoing safety concerns.	*Conclusion of response* *The sponsor has developed a global pharmacovigilance strategy, and maintain that the safety concerns identified within Module SVIII (Summary of the Safety Concerns) of the current final agreed version of the EU RMP as important identified risks, important potential risks, and missing information associated with evolocumab use are in alignment with the currently available data. The EU RMP was agreed upon by the Medicines Agency Pharmacovigilance Risk Assessment Committee (EMA PRAC) as part of the Committee for Medicinal Products for Human Use (CHMP) opinion adopted on May 21, 2015. The sponsor has conducted and will continue to conduct ongoing safety surveillance through comprehensive pharmacovigilance activities, including monitoring of adverse events from clinical studies, postmarketing experience, and literature, in order to detect potential new safety signals. Based upon these assessments, The sponsor will determine whether any such safety signals (change in nature of existing risks and/or new identified risks) should be included as important identified risks or important potential risks for evolocumab per the definitions described*	The sponsor has adequately discussed the issue of 'medication error' in its response with the updated EU-RMP and ASA. As the adverse events in question have been included in the PI and the sponsor has committed to ongoing monitoring and reporting of adverse events, the sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	within the European Medicines Agency Guideline on Good Pharmacovigilance Practices, Module V, Risk Management Systems, dated 15 April 2014.	
3. The sponsor should revise the Table *Overview of pharmacovigilance activities* to outline that additional pharmacovigilance activities are carried out in the form of clinical trials for 'Immunogenicity', 'Use in patients with severe renal impairment (eGFR<30 mL/min/1.73 m^2)', 'Use in patients with Hepatitis-C' and 'Long term use including effects of LDL-C <40 mg/dL or <1.03 mmol/L'. Furthermore, all the studies which address the above ongoing safety concerns should be included in the pharmacovigilance plan of the EU-RMP. These amendments should also be reflected in the pharmacovigilance section of the ASA.	*Conclusion of sponsor response* *The previously submitted EU-RMP for evolocumab (version 1) has been updated to accurately reflect all ongoing or planned pharmacovigilance activities for all important potential risks and missing information. Appropriate revisions have also been incorporated into the ASA to the EU RMP. Updated versions of the EU RMP (version 1.2) and the ASA (version 2.0) to the EU RMP are provided.*	The sponsor's response is satisfactory.
4. The sponsor should provide an update on the current medical/scientific knowledge regarding the effects of PCSK9 inhibition on neurocognitive function.	*Conclusion of sponsor's response* *Consistent with nonclinical data, up-to-date information in the literature regarding the effects of PCSK9 inhibition on neurocognitive function does not suggest that evolocumab would impact brain cholesterol levels either by local direct effects on PCSK9 within the central nervous system or by indirect effects via reduction in circulating levels of cholesterol or PCSK9. A comprehensive review of a more recent (01 July 2014) dataset since the MA found no safety risk for neurocognitive events with evolocumab use.* *Neurocognitive events will continue to be carefully monitored in collaboration with regulatory agencies, using a comprehensive search*	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	strategy in ongoing studies and a dedicated sub-study using a validated instrument.	
5. The sponsor should provide clarification as to how patients who become pregnant will be enrolled into the pregnancy and lactation surveillance programme, and should provide a detailed description of this surveillance program in the RMP.	*Conclusion of sponsor's response* *In conclusion The sponsor has a surveillance process as part of routine signal detection for pregnancy exposures in which cases are reviewed individually and in aggregate, compared to background rates in relevant populations in the literature, and reported in the PSUR. The sponsor feels this process is sufficient for evaluating exposures in pregnancy in the postmarketing setting. Lactation exposures are also monitored as part of signal detection. As additional information is gathered on exposure during pregnancy, the sponsor will continue to assess the adequacy of our current surveillance process and update as needed.* *Standard questionnaires are included in the EU-RMP.* *A description of the pregnancy and lactation pharmacovigilance activities has been added to the ASA.*	The sponsor's response is satisfactory considering the product's Category B1 rating.
6. Currently no post-marketing data is available as Repatha is not approved in any other jurisdiction, and the indication proposed in Australia may attract a very large patient population. Therefore, the RMP evaluator questions whether the pharmacovigilance plan in its proposed form, without any additional activities, is sufficient to comprehensively monitor the safety of the product in a real world setting. Advice regarding the appropriateness of the pharmacovigilance plan will be sought by ACSOM.	*Conclusions of sponsor's response* *The planned pharmacovigilance activities in both ongoing clinical trials and in the postmarketing setting are comprehensive and sufficient to monitor the safety of evolocumab in a real-world setting.*	The sponsor's response is acceptable. It should be noted that the pharmacovigilanc e plan, as part of an RMP, is a live system that needs to be reviewed and updated to reflect the pattern of use, safety profile and local practice. The sponsor should submit the

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
		protocols for planned Studies 20130295, 20130286 to the TGA for review when they become available.
7. There is potential that the product be used for paediatrics ≤12 years, in particular for HoFH patients. The sponsor is requested to provide comment on the appropriateness of the pharmacovigilance plan to monitor off-label use in this age group. If any additional pharmacovigilance activities were to be implemented then data relating to off-label use in paediatrics ≤12 years should be collected and reported.	*Evolocumab is proposed for use in adults and adolescents 12 to < 18 years of age with homozygous familial hypercholesterolaemia (HoFH). Off-label use of evolocumab in children < 12 years of age with HoFH in Australia is anticipated to be very rare. Data suggest that very few children < 12 years of age in Australia are diagnosed with HoFH and the use of evolocumab in this age group in Australia will be very rare.* *Pharmacovigilance and Risk Management for Paediatric Patients* *Routine pharmacovigilance will be used to monitor adverse events after evolocumab use outside the labelled indications. As part of The sponsor's routine pharmacovigilance, reports of off-label use with, or without, associated adverse events are routinely collected in the Amgen Global Safety Database, collated, and analysed to assess patterns of off-label use and to determine any emerging areas for further investigation. Periodic safety update reports to the TGA will include a summary of off-label use for patients of any age. Individual reports of adverse events associated with off-label use will be reported to the TGA if they meet reporting requirements (such as serious, related) for patients of any age.*	The sponsor's response is acceptable. In comparison to the wording for indication in the PI, the approved Summary of product Characteristics (SmPC) makes explicit mention of adolescents aged 12 years and over as follows: '*Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.*' It is recommended that the Delegate considers the adequacy of the wording in the PI.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	As of the data cut-off date of 01 April 2014 for the marketing application, the safety profile for evolocumab in Study 20110271 was similar between adolescents and adults. To date, there has been no evidence of age related safety issues that would warrant special monitoring beyond routine pharmacovigilance for off-label use of evolocumab in children < 12 years of age. *Two additional clinical studies are planned to further evaluate the safety and efficacy of evolocumab in adolescents, in accordance with regional regulatory requirements:* *Study 20120123 and* *Study 20120124.Risk management for paediatric patients will be addressed by the clear age restrictions for the labelled indications: ≥ 18 years of age in patients with primary hypercholesterolaemia or mixed dyslipidaemia and ≥ 12 years of age in patients with HoFH.*	
8. ASA should be revised to include a risk minimisation activities table detailing all planned risk minimisation measures in the Australian context and the EU-RMP context. This table should include a comparison of the actual content and wording of the EU SmPC and the proposed Australian PI and CMI for all of the specified ongoing safety concerns and missing information to identify and provide reasons for any observed differences, particularly where it appears the EU SmPC is more restrictive.	*The ASA will be updated to include a table itemising ongoing safety concerns and missing information and detailing how risk minimisation activities will be implemented in Australia, including any differences between the EU and Australian activities with justification.*	The sponsor's response is satisfactory. The evaluator has noted the updated ASA.
9. In regard to the proposed routine risk minimisation activities, the draft CMI be revised	*1) The sponsor addressed the question on whether to add Hepatitis C language to the*	The evaluator has noted the sponsor's

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
as follows: 1). The sponsor should include routine risk-minimisation in the Australian PI for the missing information of 'Use in patients with hepatitis C', or provide compelling justification for not doing so. 2). The indication statement in the PI contains the following information: *Repatha should be used as an adjunct to diet when the response to diet and exercise is inadequate.* It appears that the 'What is Repatha used for' section in the CMI does not reflect the indication statement in the PI, as there is currently no reference to exercise in the proposed CMI. It is recommended that the following statement in the 'What is Repatha used for' section be amended as follows: *Repatha is used in patients who cannot control their cholesterol levels by cholesterol lowering diet and exercising alone. You should stay on your cholesterol lowering diet and exercise as directed by your doctor while taking this medicine.* A similar reference to exercise should also be included in the first paragraph of the 'When to use it' section of the CMI.	*'Precaution' section of the Product Information and concluded that based on review of clinical data, no safety issues were found to warrant precautions in the product label with the use of evolocumab for potential hepatitis C events. Additionally, evidence from published scientific literature support the conclusion that evolocumab mediated PCSK9 inhibition is unlikely to increase HCV infection risk (viral entry or replication).* *2) The sponsor agrees to update the CMI and include the reference to exercise as described above by TGA.*	comments regarding the recommendations on PI and CMI. The recommendations remain for consideration by the Delegate.

Summary of recommendations

It is considered that the sponsor's response to the TGA has adequately addressed most of the issues identified in the RMP evaluation report.

Issues in relation to the RMP

Recommendation 7: The sponsor's response is acceptable. In comparison to the wording for indication in the PI, the approved SmPC makes explicit mention of adolescents aged 12 years and over as follows:

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

It is recommended that the Delegate considers the adequacy of the wording in the PI.

Recommendation 9: The evaluator has noted the sponsor's comments regarding the recommendations on PI and CMI. The recommendations remain for consideration by the Delegate.

***Advice from the** Advisory Committee on the Safety of Medicines (ACSOM)*

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA the sponsor provided an updated EU-RMP version 1.2 dated 28 April 2015 and ASA version 2.0 dated 21 June 2015. Key changes from the version evaluated in the first round evaluation are summarised below (Table 14).

Table 14: Key changes to the EU-EMP and ASA

	Key change
Safety specification	'Use in patients with type I diabetes' and 'use in patients with HIV' have been added as 'missing information'.
Pharmacovigilance activities	Study 20110118 – 'A Double-blind, Randomized, Placebo-controlled, Multi center Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy in Patients with Clinically Evident Cardiovascular Disease' has been proposed to monitor 'use in patients with type I diabetes'. Study 20130286 – 'A Double Blind, Randomized, Placebo Controlled, Multi center Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab in HIV Positive Patients with Hyperlipidemia and Mixed Dyslipidemia' has been proposed to monitor 'use in patients with HIV'.

The sponsor has provided further details of the changes in the updated EU-RMP and ASA (see sponsor's response to Recommendation 3 in Table 13 Reconciliation of issues outlined in the RMP Evaluation Report).

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

- Implement EU-RMP version 1.2 dated 28 April 2015 with Australian Specific Annex version 2.0 dated 21 June 2015 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality evaluator had no objections to the registration of evolocumab. Evolocumab contains 2 heavy and 2 light chains that are covalently linked by 18 disulfide bonds. It has a molecular weight of 141.534 kDa. Evolocumab is manufactured using a working cell bank Chinese Hamster Ovary cell containing an expressing vector.

The quality evaluators have reviewed the manufacturing processes and have concluded the cell banking processes are satisfactory. The infectious disease safety evaluator has concluded that the risks related to the adventitious presence of infectious viral, prion and mycoplasma agents in the manufacturing of evolocumab have been controlled to an acceptable level.

Stability data support a shelf life of the 24 months for the drug substance stored at -30°C. The drug product is supplied as a sterile, single-use, preservative-free solution for subcutaneous injection in a prefilled syringe (PFS) or as an integral component of an auto-injector pen (AI/pen). Stability data support a shelf-life of 24 months when stored at 2 – 8°C. Additional data support an optional short-term storage at room temperature (≤ 25°C).

Nonclinical

The nonclinical evaluator concluded that the nonclinical data were generally supportive of efficacy and safety of evolocumab but recommended further investigation of potential homeostatic mechanisms in response to increased hepatic uptake of cholesterol, including the potential for drug interactions based on bile acid transporters.
Evolocumab binds with high affinity to recombinant PCSK9 from human (both 'wild type' and the gain-of-function D374Y mutation), Cynomolgus monkey and hamster (K_D = 16, 7, 8 and 14 pM, respectively). Binding of evolocumab to PCSK9:

a. Prevented PCSK9 from interacting with human recombinant LDLRs; 2
b. Increased LDLR expression; and
c. Dose-dependently increased LDL-C uptake *in vitro* (EC_{50} = 130 nM).

Evolocumab lowered LDL-C (both alone and in combination with a statin) in a dose-dependent manner but due to interspecies differences in lipid metabolism a full range of pro-atherogenic markers were not monitored in animal studies and the effect of evolocumab in animal models of CHD was not investigated. Evolocumab and the HMG CoA reductase inhibitor mevinolin in combination had an additive positive effect on LDL receptor expression.

The sponsor did not investigate the metabolic fate of increased hepatic uptake of cholesterol which is likely to be via increased faecal excretion of bile acids and which may involve increased expression of bile acid transporters. There was no evidence in the submitted nonclinical data for any adverse neurocognitive events in animals although the neurobehavioural assessment in monkeys was relatively limited in scope and did not examine learning and memory. Mechanistic data in rats suggest that because statin induced myopathy results from depletion of isoprenoid cholesterol precursors critical for skeletal muscular viability and is not directly due to the cholesterol lowering effect evolocumab is not expected to elicit myopathy or to exacerbate statin-induced myopathy, at least at low doses.

Evolocumab was weakly immunogenic in repeat dose toxicity studies and the development of anti-evolocumab antibodies did not affect the assessment of safety and efficacy. There was no evidence of toxicity in these studies, which also included immunotoxicity endpoints, and the pharmacodynamic (PD) response was shown to be reversible. The sponsor considered potential off-target activity, including the potential for effects on the brain and cognitive function, interactions with other members of the lipoprotein receptor family, hepatitis C virus infectivity, the potential impact on insulin resistance and diabetes risk, possible effects on the hepatobiliary system and intestinal tract and on the immune system. Aspects of the biological role of PCSK9 remain to be fully clarified, including possible species differences in PCSK9 regulation. Evolocumab is not expected to be genotoxic and there was no evidence of carcinogenicity or toxicity in a lifetime study in hamsters. Reproductive toxicity was adequately investigated but these and other studies provide only limited evidence to support the proposed use in children 12 years and over. The nonclinical evaluator concluded that the proposed Pregnancy Category B1 was appropriate based on the animal data.

A safety pharmacology study in Cynomolgus monkeys found that a single IV dose of evolocumab (300 mg/kg) was well tolerated and showed no notable effects on behaviour, body temperature, cardiovascular parameters or respiration rate. The absolute bioavailability of evolocumab following SC administration was stated to be approximately 82% in monkeys.

Clinical

The clinical evaluator has recommended approval for evolocumab with a revised indication of:

> *Repatha should be used as an adjunct to diet when the response to diet and exercise is inadequate.*
>
> ***Primary hypercholesterolaemia and mixed dyslipidaemia***
>
> *Repatha is indicated in patients with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia:*
>
> - *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 or for whom a statin is not considered clinically appropriate.*
>
> ***Homozygous familial hypercholesterolaemia***
>
> *Repatha is indicated in patients with homozygous familial hypercholesterolaemia in combination with other lipid lowering therapies.*

The evaluator recommended acceptance of the sponsor's proposed dosage regimen.

Pharmacology

The pharmacokinetics (PK) of evolocumab following SC administration have been characterised in the clinical pharmacology studies, population PK modelling and simulation studies and limited/sparse PK data in subjects with hypercholesterolaemia from Phase II and III clinical efficacy and safety studies.

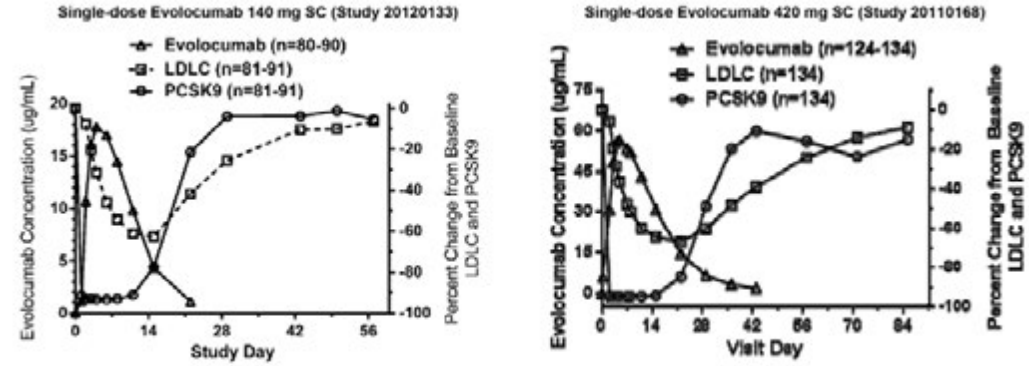
- Absolute bioavailability was estimated to be 72% in the population PK analysis mean. T_{max} was estimated to be approximately 3 to 4 days. The Vss (mean ± SD) of evolocumab 420 mg IV was 3.340 ± 0.460 L. Steady state concentration was approached by Week 12 and unbound evolocumab trough serum concentrations remained relatively stable over 52 weeks dosing with evolocumab 420 mg SC monthly

(QM). A post hoc analysis showed absorption of SC dosing is similar in the upper arm, abdomen and thigh.

- Two mechanisms of elimination for unbound evolocumab are proposed: (1) PCSK9 target-mediated non-linear (saturable) elimination predominating at low evolocumab serum concentrations and saturating when PCSK9 is fully suppressed; and (2) linear (non-saturable) elimination by endogenous IgG clearance mechanisms involving nonspecific catabolism in cells of the reticuloendothelial system at higher evolocumab serum concentrations. Target mediated (non-linear) elimination is predicted to account for approximately 77% and 51% of a single-dose of 140 mg SC second weekly (Q2W) and 420 mg SC QM. The predicted effective half-lives for the 140 mg SC Q2W and the 420 mg QM doses are 11.4 and 16.8 days, respectively. An approximately 3 fold accumulation of unbound evolocumab for the 140 mg SC Q2W dose comparing Week 12 to Week 2, and a less than 2 fold accumulation for the 420 mg QM dose. Similar accumulation was observed with evolocumab monotherapy and combined with a statin.
- Systemic clearance (mean ± SD) was 11.6 ± 2.26 mL/h following a single IV dose of 420 mg. Apparent clearances (mean ± SD) of evolocumab following single SC evolocumab doses of 210 mg and 420 mg were similar (25.6 ± 6.86 and 24.2 ± 12.5 mL/h, respectively) and lower than for evolocumab 70 mg SC (101 ± 120 mL/h).
- Moderate intersubject variability in both healthy subjects and subjects with mixed hypercholesterolaemia and dyslipidaemia for AUC and C_{max}.
- Unbound evolocumab displays non-linear pharmacokinetics across a wide dose range (7 to 420 mg SC) and was more pronounced at low than at high evolocumab doses. The SC doses (7, 21, 70, 210, and 420 mg) and the IV doses (21 or 410 mg) were not dose proportional in healthy subjects but dose-normalised data that single-doses of 210 mg SC and 420 mg SC were approximately dose proportional for $AUC_{(0\text{-}t)}$ and C_{max}.
- Renal elimination is likely to be negligible given the large molecular weight of evolocumab (144 kDa). PopPK modelling showed mild to moderate renal impairment had no significant effects on unbound evolocumab trough serum concentrations at Week 12 following evolocumab 140 mg SC Q2W and evolocumab 420 mg SC QM.
- Subjects with mild and moderate hepatic impairment demonstrated decreased systemic exposure to unbound serum evolocumab as assessed by both $AUC_{(last)}$ and C_{max}. There were no data on subjects with severe hepatic impairment.
- PK of evolocumab was similar in healthy subjects, patients with primary hypercholesterolaemia (HeFH and non-familial) and mixed dyslipidaemia, and patients with HoFH not on apheresis. Adolescents with HoFH not on apheresis had highly variable unbound evolocumab trough serum concentrations that fell within the range of adult subjects with primary hyperlipidaemia and mixed dyslipidaemia. Patients with HoFH on apheresis, unbound evolocumab trough serum concentrations were approximately 20% to 30% lower than before apheresis.
- No formal PK drug-drug interaction clinical studies were undertaken. In subjects with hypercholesterolaemia exposure to unbound evolocumab was lower on moderate dose statin that when evolocumab was administered with high dose statin (AUC_{last} 0.74 (95% CI: 0.29, 1.9).
- A single dose of evolocumab 140 mg SC administered with the PFS presentation at 140 mg/mL with a 1 mL fill was bioequivalent to 1 x AI/Pen (1 x 140 mg/mL) in healthy subjects. SC administration of evolocumab was into the abdominal wall (three quadrants when a total dose of 420 mg SC was administered).

- The PD was measured using unbound PCSK9 serum concentration and LDL-C levels (Figure 2). Reductions in PCSK9 were measured within 4 hours of dosing and within 2 to 8 days of a single dose of evolocumab 140 or 420 mg SC evolocumab were reduced by approximately 90% to 94%. Similar effects were seen in healthy subjects, those with hepatic impairment (140 mg SC), and patient with hypercholesterolaemia (with or without HeFH) and mixed hyperlipidaemia. There was a dose dependent effect on PCSK9 in these patients (36% lower with 420 mg SC dose). In HoFH (Study 21000233) 420 mg SC QM produced the greatest reduction (about 90%) in PCSK9 activity was in the first 6 weeks, although there was a sustained reduction of approximately 27% after 12 weeks of 420 QM dosing.

Figure 2: Mean unbound evolocumab serum concentrations and geometric mean percent change from baseline in UC LDL-C and unbound PCSK9 in healthy subjects.



LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SC = subcutaneous.
Evolocumab was administered with a prefilled autoinjector/pen in Study 20120133 and with an automated mini-doser in Study 20110168.

- Based on population PK and PD analyses, unbound evolocumab PK did not appear to be significantly affected by gender, age or race although there were limited data in some subgroups. Exposure to unbound evolocumab decreased with increasing body weight but this did not affect the pharmacodynamic endpoint of LDL-C reduction.
- *Immunogenicity:* Across 16 Phase II and Phase III studies binding antibodies occurred in 7 of the 4942 patients (0.1%) and were transient in 4 patients. Binding antibodies were also detected at baseline suggesting the presence of cross-reacting antibodies to evolocumab and another protein.

Efficacy

Study 20110115 (LAPLACE 2) This Phase III, multinational, multicentre, randomised, double blind, double dummy, placebo and ezetimibe controlled study was designed to evaluate the effect of 12 weeks of evolocumab SC administered Q2W or QM by AI/pen (*in combination with a statin,* diet and exercise) on percent change from baseline in LDL-C in 1899 subjects with primary hypercholesterolaemia and mixed hyperlipidaemia. Adult patients ≤ 80 years of age with triglycerides ≤ 4.5 mmol/L and hypercholesterolaemia defined as a fasting LDL-C on no treatment (≥ 4.0 mmol/L), on a non-intensive statin (≥ 2.6 mmol/L) or on intensive statin (high dose or any statin plus ezetimibe combination) (≥ 2.1 mmol/L).

Exclusion criteria were extensive but included inability to tolerate statins, NYHA III or IV heart failure[56] (or LVEF <30%), myocardial infarction, unstable angina or nterventions for coronary artery disease in the previous 6 months or planned intervention, uncontrolled arrhythmia within 3 months, uncontrolled hypertension/hyperthyroidism, eGFR < 30 mL/min/1.73 m^2, type I or recently diagnosed/poorly controlled Type 2 diabetes, CK > 3 times ULN at screening.

There was a two-step randomisation process. Patients were randomised to open label statin (atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg) followed by a 4 week lipid stabilisation period (n=2067), after which eligible patients were randomised within each statin dose cohort to blinded evolocumab 140 mg Q2W or QM SC injection or placebo injection SC Q2W or QM. In the atorvastatin arms only, those allocated placebo SC injection also received either oral placebo or ezetimibe in addition and those allocated evolocumab (either treatment regimen) received oral placebo. The patients in the rosuvastatin and simvastatin cohorts were allocated with placebo or evolocumab injection (either dosage regimen) but did not receive oral placebo. Stratification was based on statin use at study entry. All continued their allocated background statin medication. Dose adjustment of the blinded medications was not permitted but if the statin was discontinued for medical reasons the blinded medications could be continued. Concomitant medications were permitted with the exception of additional lipid lowering agents, high dose niacin or omega-3 supplements and red yeast rice, potent CYP3A4 inhibitors, amphetamines and amphetamine-like derivatives and weight loss medications, and colchicine. The study was powered to detect a reduction of LDL-C of at least 20% (± 20%) over ezetimibe with a family-wise error of 0.05, allowing for drop-outs and statin discontinuation. A hierarchical testing strategy was adopted to adjust for multiplicity. Major protocol variations occurred in 2.3% of the patients and were similar across the treatment groups. Most (1896, 99.8%) received at least one dose of statin and study drug, 1807 completed treatment and 1826 completed the study. Most discontinued early because of withdrawn consent (2.1%) or early enrollment in the extension study prior to the last study visit (1.4%).

The patients were mostly White (94%) men (54.2%) with a mean age of 59.8±9.9 years (64.6% < 65 years) with a mean body mass index (BMI) of 29.4±5.4 kg/m^2. The mean baseline serum LDL-C was 2.81± mmol/L and the distribution of other lipid parameters was similar between the groups. About 69% used statins at baseline (atorvastatin 26%, simvastatin 21.9% and rosuvastatin 16%), with 8.4% ezetimibe and 3.1% fish oil use.

The co-primary endpoints were percent change in LDL-C (reflexive) at Week 12 and mean percent change from baseline in LDL-C at Weeks 10 and 12 (Table 15).

Sensitivity analyses using completer and nonparametric analyses of the co-primary endpoints were consistent with the primary efficacy analyses. Subgroup analyses adjusted for the covariates of age (<65 year or ≥ 65 years), gender, race, geographical region, baseline LDL-C, BMI, glucose tolerance status, hypertension, smoking (current) baseline CHD risk factors for CHD, family history of premature CHD, PSCK9 level at baseline,

[56]The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent 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.

triglycerides and National Cholesterol Education Program NCEP) high risk, were consistent with the primary efficacy analysis.

The combined statin analyses showed that fixed effect treatment differences for percent change in LDL-C (reflexive) for evolocumab Q2W versus placebo was -70.79% (95% CI -74.3%, -67.44%) at Week 12 and -69.22% (95% CI: - 72.19%, -66.25%) for the mean of Weeks 10 and 12, with corresponding results for evolocumab QM versus placebo being -62.18% (95% CI: - 65.93%, -58.43%) and -67.33% (95%CI: - 70.88%, -63.98%) with p<0.001 for each comparison.

Table 15: Primary analysis of the co-primary endpoints for percent change from baseline in reflexive LDL-C

		EvoMab 140 mg Q2W vs Ezetimibe QD or Placebo Q2W		EvoMab 420 mg QM vs Ezetimibe QD or Placebo QM	
Statin Therapy	Treatment Difference	Week 12	Week 10/12	Week 12	Week 10/12
Atorvastatin 10 mg	Treatment difference vs Ezetimibe [a]				
	Estimate (SE)	-39.60 (3.15)	-37.53 (2.79)	-41.10 (3.41)	-43.49 (3.15)
	95% CI	(-45.81, -33.40)	(-43.03, -32.03)	(-47.83, -34.37)	(-49.70, -37.28)
	nominal p-value	<0.001	<0.001	<0.001	<0.001
	adjusted p-value [b]	<0.001		<0.001	
	Treatment difference vs Placebo [a]				
	Estimate (SE)	-71.42 (3.11)	-69.95 (2.76)	-59.16 (3.44)	-62.82 (3.17)
	95% CI	(-77.55, -65.29)	(-75.38, -64.51)	(-65.94, -52.38)	(-69.06, -56.57)
	nominal p-value	<0.001	<0.001	<0.001	<0.001
	adjusted p-value [b]	<0.001		<0.001	
Atorvastatin 80 mg	Treatment difference vs Ezetimibe [a]				
	Estimate (SE)	-47.20 (5.24)	-44.95 (4.75)	-38.88 (4.73)	-43.81 (4.19)
	95% CI	(-57.54, -36.86)	(-54.32, -35.57)	(-48.21, -29.56)	(-52.06, -35.55)
	nominal p-value	<0.001	<0.001	<0.001	<0.001
	adjusted p-value [b]	<0.001		<0.001	
	Treatment difference vs Placebo [a]				
	Estimate (SE)	-76.29 (5.36)	-74.92 (4.85)	-70.51 (4.72)	-74.81 (4.15)
	95% CI	(-86.87, -65.72)	(-84.49, -65.35)	(-79.81, -61.20)	(-83.00, -66.62)
	nominal p-value	<0.001	<0.001	<0.001	<0.001
	adjusted p-value [b]	<0.001		<0.001	
Rosuvastatin 5 mg	Treatment difference vs Placebo [a]				
	Estimate (SE)	-68.21 (3.30)	-66.88 (2.93)	-64.49 (3.21)	-66.58 (3.05)
	95% CI	(-74.72, -61.70)	(-72.67, -61.08)	(-70.84, -58.14)	(-72.60, -60.56)
	nominal p-value	<0.001	<0.001	<0.001	<0.001
	adjusted p-value [b]	<0.001		<0.001	
Rosuvastatin 40 mg	Treatment difference vs Placebo [a]				
	Estimate (SE)	-68.31 (4.42)	-65.66 (3.81)	-54.98 (5.23)	-62.91 (4.27)
	95% CI	(-77.04, -59.57)	(-73.19, -58.12)	(-65.31, -44.65)	(-71.37, -54.46)
	nominal p-value	<0.001	<0.001	<0.001	<0.001
	adjusted p-value [b]	<0.001		<0.001	
Simvastatin 40 mg	Treatment difference vs Placebo [a]				
	Estimate (SE)	-70.56 (3.12)	-69.43 (2.74)	-60.41 (4.41)	-68.45 (4.17)
	95% CI	(-76.72, -64.41)	(-74.86, -64.01)	(-69.11, -51.72)	(-76.68, -60.22)
	nominal p-value	<0.001	<0.001	<0.001	<0.001
	adjusted p-value [b]	<0.001		<0.001	

There were two tiers of co-secondary endpoints measured at Week 12 and means at Weeks 10 and 12. The tier one endpoints were change in baseline in LDL-C, percent change from baseline in Non-HDL-C, percent change from baseline in ApoB, percent change from baseline in triglyceride (TC)/HDL-C ratio and percent change from baseline in ApoB/ApoA ratio. Evolocumab 140 Q2W and 420 mg QM in combination with statins resulted in statistically significant changes (p<0.001, multiplicity adjusted) compared with placebo and compared to ezetimibe for the atorvastatin cohorts for all tier 1 co-secondary endpoints. The tier 2 endpoints were percent of subject with LDL-C < 1.8 mmol/L, percent change from baseline in triglycerides, percent change from baseline in VLDL-C and percent change in HDL-C. With the exception of VLDL and triglycerides compared to ezetimibe for the atorvastatin cohorts, statistically significant changes for both dosage regimens of evolocumab compared to placebo for all statin cohorts and were noted.

Study 20110114 (MENDEL 2) This Phase III, multinational, double blind, randomised, double dummy placebo and ezetimibe controlled, parallel group study was designed to evaluate the efficacy, safety, tolerability and pharmacokinetics of evolocumab administered SC as *monotherapy* as 140 mg SC or 420 mg QM by AI/pen for 12 weeks to 614 patients with hyperlipidaemia, in addition to diet and exercise. Eligible subjects were adults, ≤ 80 years old with fasting LDL ≥ 2.6 mmol/L but < 4.9 mmol/L and fasting triglycerides ≤ 4.5 mmol/L. All had NCEP ATP III Framingham risk core[57] of ≤ 10%. Exclusion criteria were similar to Study 20110115 but Type 1 diabetes was not specifically excluded if well controlled. Patients were randomised 2:2:1:1:1 to one of six treatment groups: evolocumab 140 mg SC Q2W + oral placebo daily, 420 mg SC QM+ oral placebo daily, placebo SC Q2W + oral placebo daily, placebo SC QM + oral placebo daily, placebo SC Q2W + 10 mg oral ezetimibe daily and placebo SC QM + 10 mg oral ezetimibe daily. Dose adjustments were not permitted. Major protocol variations occurred in 5% of the patients and were similar across the treatment groups. Six patients (1.0%) had a Framingham score of ≥ 10%. Of the 615 patients randomised, 614 received at least one dose of statin and study drug, approximately 94% of patients completed either the SC or oral treatments and 573 (93.2%) completed both and 598 patients completed the study. Most discontinued early because of withdrawn consent (2.1%) or early enrollment in the extension study prior to the last study visit (1.4%). The study had at least 92% power to detect superiority of both evolocumab treatments over ezetimibe and placebo for the co-primary endpoints. Multiplicity was adjusted for to preserve the family-wise error at 0.05 for the co-primary and co-secondary efficacy endpoints within each (evolocumab or placebo SC) dose frequency.

The study participants were mostly female (66%), White (83.1%) with a mean age of 53.1±12.1 years, and 81.9% were < 65 years of age. The mean BMI was 28.6±6.0 kg/m^2. The mean reflexive LDL-C was 3.7±0.6 mmol/L, and the remainder of the lipid profile was comparable across the treatment arms. The majority (57.2%) were of NCEP CHD risk lower risk, 36.8% moderate risk, 4.9% moderately high risk and high risk in 1.1%. Baseline coronary artery disease was reported for 0.3% and cerebrovascular disease for 0.7%. No patients took statins at baseline.

The co-primary endpoints were percent change from baseline in LDL-C at Week 12 and mean percent change from baseline in LDL-C at Weeks 10 and 12 (Tables 16 and 17).

Table 16: Primary analysis of co-primary endpoint (Week 12) change from baseline in reflexive LDL-C

	EvoMab Q2W vs Ezetimibe QD or Placebo Q2W			EvoMab QM vs Ezetimibe QD or Placebo QM		
	Placebo Q2W + Ezetimibe QD (N=77)	Placebo Q2W + Placebo QD (N=76)	EvoMab 140 mg + Placebo QD (N=153)	Placebo QM + Ezetimibe QD (N=77)	Placebo QM + Placebo QD (N=78)	EvoMab 420 mg + Placebo QD (N=153)
Week 12						
Summary Statistics						
n	70	69	133	69	70	136
Mean	-18.88	-0.29	-58.17	-19.19	-1.30	-56.44
SE	1.48	1.87	1.16	1.63	1.80	0.92
Median	-20.50	-1.55	-59.86	-20.89	-2.05	-57.29
Q1,Q3	(-27.27, -12.80)	(-8.88, 9.29)	(-67.97, -50.99)	(-27.94, -13.08)	(-10.98, 10.40)	(-64.77, -48.34)
Min,Max	(-46.9, 15.8)	(-56.1, 41.4)	(-84.5, -11.8)	(-44.2, 26.3)	(-42.1, 45.8)	(-84.3, -22.0)
LS Mean [a]						
Estimate (SE)	-17.75 (1.67)	0.10 (1.67)	-57.04 (1.23)	-18.57 (1.56)	-1.34 (1.54)	-56.12 (1.12)
95% CI	(-21.03, -14.46)	(-3.19, 3.39)	(-59.45, -54.63)	(-21.63, -15.51)	(-4.38, 1.69)	(-58.33, -53.91)
Treatment difference vs Ezetimibe [b]						
Estimate (SE)	- (-)	- (-)	-39.29 (2.03)	- (-)	- (-)	-37.55 (1.88)
95% CI	(-, -)	(-, -)	(-43.28, -35.31)	(-, -)	(-, -)	(-41.24, -33.86)
p-value	-	-	<0.001	-	-	<0.001
Treatment difference vs Placebo [b]						
Estimate (SE)	- (-)	- (-)	-57.14 (2.03)	- (-)	- (-)	-54.78 (1.87)
95% CI	(-, -)	(-, -)	(-61.14, -53.14)	(-, -)	(-, -)	(-58.46, -51.10)
p-value	-	-	<0.001	-	-	<0.001

[57] The Framingham Risk Score is a gender specific algorithm used to estimate the 10 year cardiovascular risk of an individual.

Table 17: Primary analysis of co-primary endpoint (mean of Weeks 10 and 12) change from baseline in reflexive LDL-C

	EvoMab Q2W vs Ezetimibe QD or Placebo Q2W			EvoMab QM vs Ezetimibe QD or Placebo QM		
	Placebo Q2W + Ezetimibe QD (N=77)	Placebo Q2W + Placebo QD (N=76)	EvoMab 140 mg + Placebo QD (N=153)	Placebo QM + Ezetimibe QD (N=77)	Placebo QM + Placebo QD (N=78)	EvoMab 420 mg + Placebo QD (N=153)
Mean of Weeks 10 and 12 Summary Statistics						
n	75	76	140	72	74	150
Mean	-17.88	-0.72	-57.65	-19.77	-0.97	-59.00
SE	1.27	1.43	1.09	1.43	1.51	0.89
Median	-18.92	-1.24	-60.04	-21.24	-1.17	-60.59
Q1,Q3	(-25.53, -11.00)	(-10.02, 6.78)	(-66.29, -50.00)	(-27.59, -16.72)	(-9.52, 7.05)	(-66.56, -51.36)
Min,Max	(-37.8, 8.9)	(-34.6, 30.9)	(-79.2, -16.4)	(-44.6, 18.4)	(-34.9, 45.8)	(-84.5, -22.0)
LS Mean [a]						
Estimate (SE)	-17.52 (1.46)	-0.43 (1.45)	-56.93 (1.07)	-19.12 (1.39)	-1.41 (1.37)	-58.81 (1.00)
95% CI	(-20.39, -14.65)	(-3.28, 2.42)	(-59.04, -54.81)	(-21.85, -16.38)	(-4.11, 1.30)	(-60.78, -56.84)
Treatment difference vs Ezetimibe [b]						
Estimate (SE)	- (-)	- (-)	-39.41 (1.76)	- (-)	- (-)	-39.69 (1.66)
95% CI	(-, -)	(-, -)	(-42.87, -35.94)	(-, -)	(-, -)	(-42.97, -36.42)
p-value	-	-	<0.001	-	-	<0.001
Treatment difference vs Placebo [b]						
Estimate (SE)	- (-)	- (-)	-56.50 (1.76)	- (-)	- (-)	-57.40 (1.66)
95% CI	(-, -)	(-, -)	(-59.95, -53.04)	(-, -)	(-, -)	(-60.66, -54.14)
p-value	-	-	<0.001	-	-	<0.001

Subgroup analyses adjusted for the covariates of age (<65 year or ≥ 65 years), gender, race, geographical region, baseline LDL-C, BMI, glucose tolerance status, hypertension, smoking (current) baseline CHD risk factors for CHD, family history of premature CHD, PSCK9 level at baseline, triglycerides and NCEP high risk, were consistent with the primary efficacy analysis.

The co-secondary endpoints were at Week 12 and the means at Weeks 10 and 12 in two tiers of endpoints. Tier 1 endpoints were change from baseline in LDL-C, percent of subjects with LDL-C < 1.8 mmol/L, percent change from baseline in non-HDL-C, percent change in baseline in ApoB, percent change from baseline in the total cholesterol/HDL-C ratio, percent change from baseline in ApoB/ApoA 1 ratio. Evolocumab 140 Q2W and 420 mg QM resulted in statistically significant changes (p<0.001, multiplicity adjusted) compared with placebo and to ezetimibe. Tier 2 endpoints were percent change from baseline in Lp(a), percent change from baseline in triglycerides, percent change from baseline in VLDL-C, percent change from baseline in HDL-C. The treatment differences reached statistical significance for comparisons for Lp(a) and HDL-C, for triglycerides when comparing the results for Q2W versus placebo and QM versus ezetimibe, and for evolocumab QM versus ezetimibe for VDL-C.

Study 20110116 (GAUSS 2) This Phase III multinational, multicentre, randomised, double-blind, double-dummy, ezetimibe-controlled, parallel group study in statin intolerant patients with hypercholesterolaemia was designed to assess the efficacy, safety and tolerability of evolocumab 140 mg SC Q2W and 420 mg SC QM given by AI/pen together with diet and exercise, to 306 adults ≤ 80 years. After a 6 week screening and placebo run-in period patients were considered statin intolerant if they had tried at least 2 statins and were unable to tolerate any dose, or an increase in statin dose above a total weekly maximum (atorvastatin 70 mg, simvastatin 140 mg, fluvastatin 280 mg, lovastatin 140 mg, rosuvastatin 35 mg or 7 times the smallest tabled size for any other statins) because of myalgia, myositis or rhabdomyolysis. There were fasting LDL-C entry criteria depending on CHD risk (≥ 2.6 mmol/L if CHD or CHD risk equivalent, ≥ 3.4 mmol/L if no CHD/equivalent and ≥ 2 risk factors for CHD, ≥ 4.1 mmol/L if no CHD/equivalent and 1 risk factor for CHD, ≥ 4.9 mmol/L if no CHD/equivalent and no risk factors). Fasting triglycerides were ≤ 4.5 mmol/L. Exclusion criteria were similar to those for Study 20110115. Eligible patients were randomised 2:2:1:1 to 140 mg SC Q2W and oral placebo, 420 mg SC QM and oral placebo, Q2W placebo and daily 10 mg ezetimibe and QM SC placebo and daily 10 mg ezetimibe. Randomisation was stratified by LDL-C at screening.

Patients were stratified according to baseline LDL-C and statin use (yes/no). A total of 290 patients completed the study but only 88.9% completed treatment with both oral and SC treatments. The study had 92% power to show superiority of both evolocumab dosing regimens over ezetimibe based on a sample size of 300 patients. Major protocol variations were reported in a total of 4.6% of patients, with 5 patients (1.6%) receiving expired or compromised investigational product. The evaluator considered this to be unlikely to have biased the efficacy results. Of the 5.5% that did not complete the study 4.2% completed the 12 week treatment component but were enrolled in the extension study prior to the week 14 interview. The remainder were lost to follow-up or withdrew consent. The patients were 54.1% male, mostly White (93.5%) with a mean age of 61.5±9.8 years and 58.6% were < 65 years of age. The mean BMI was 28.9 ±4.9 kg/m^2. The mean LDL-C at baseline was 5.00±1.52 mmol/L. Patients had mostly baseline coronary artery disease (29.3%) and cerebrovascular or peripheral arterial disease (16%) or were at high risk (56.4%). Baseline metabolic syndrome without diabetes was present in 37.1%.

The co-primary endpoints were percent change from baseline in LDL-C at Week 12 and mean percent change from baseline in LDL-C at Weeks 10 and 12 (Tables 18 and 19).

Table 18: Primary analysis of co-primary endpoint change from baseline in reflexive LDL-C (Week 12)

	EvoMab Q2W vs Ezetimibe QD		EvoMab QM vs Ezetimibe QD	
	Placebo Q2W + Ezetimibe QD (N=51)	EvoMab 140 mg + Placebo QD (N=103)	Placebo QM + Ezetimibe QD (N=51)	EvoMab 420 mg + Placebo QD (N=102)
Week 12				
Summary Statistics				
n	49	98	45	96
Mean	-18.48	-56.25	-17.28	-54.26
SE	1.89	1.82	2.00	1.37
Median	-19.35	-59.50	-18.79	-56.91
Q1,Q3	(-25.15, -13.28)	(-69.48, -49.32)	(-26.96, -5.67)	(-63.80, -46.18)
Min,Max	(-53.9, 10.9)	(-82.9, 10.4)	(-41.4, 10.9)	(-76.2, -12.9)
LS Mean[a]				
Estimate (SE)	-18.08 (2.52)	-56.14 (1.91)	-15.05 (2.13)	-52.60 (1.58)
95% CI	(-23.05, -13.11)	(-59.92, -52.36)	(-19.25, -10.85)	(-55.72, -49.48)
Treatment difference[b]				
Estimate (SE)	- (-)	-38.06 (2.87)	- (-)	-37.55 (2.33)
95% CI	(-, -)	(-43.73, -32.39)	(-, -)	(-42.16, -32.94)
p-value	-	<0.001	-	<0.001

Table 19: Primary analysis of co-primary endpoint percent change from baseline in reflexive LDL-C (mean Weeks 10 and 12)

	EvoMab Q2W vs Ezetimibe QD		EvoMab QM vs Ezetimibe QD	
	Placebo Q2W + Ezetimibe QD (N=51)	EvoMab 140 mg + Placebo QD (N=103)	Placebo QM + Ezetimibe QD (N=51)	EvoMab 420 mg + Placebo QD (N=102)
Mean of Weeks 10 and 12				
Summary Statistics				
n	50	101	49	100
Mean	-19.79	-56.39	-19.23	-56.70
SE	1.71	1.69	1.76	1.32
Median	-20.46	-60.50	-19.93	-59.60
Q1,Q3	(-26.34, -12.23)	(-67.05, -48.36)	(-28.30, -10.53)	(-66.33, -50.35)
Min,Max	(-52.3, 6.2)	(-83.5, 8.9)	(-38.8, 6.4)	(-78.4, -12.4)
LS Mean[a]				
Estimate (SE)	-19.21 (2.40)	-56.11 (1.83)	-16.62 (2.03)	-55.31 (1.53)
95% CI	(-23.94, -14.47)	(-59.73, -52.49)	(-20.63, -12.62)	(-58.33, -52.30)
Treatment difference[b]				
Estimate (SE)	- (-)	-36.90 (2.71)	- (-)	-38.69 (2.21)
95% CI	(-, -)	(-42.26, -31.55)	(-, -)	(-43.06, -34.32)
p-value	-	<0.001	-	<0.001
Least significant p-value[c]	-	<0.001	-	<0.001
Adjusted p-value[d]	-	**<0.001**	-	**<0.001**

Subgroup analyses adjusted for the covariates of age (<65 year or ≥ 65 years), gender, race, geographical region, baseline LDL-C, BMI, glucose tolerance status, hypertension, smoking (current) baseline CHD risk factors for CHD, family history of premature CHD, PSCK9 level at baseline, triglycerides and NCEP high risk, were consistent with the primary efficacy analysis.

The co-secondary endpoints were at Week 12 and the means at Weeks 10 and 12 in two tiers of endpoints that were similar to those in the other Phase III studies. Tier 1 endpoints

were change from baseline in LDL-C, percent of subjects with LDL-C < 1.8 mmol/L, percent change from baseline in non-HDL-C, percent change in baseline in ApoB, percent change from baseline in the total cholesterol/HDL-C ratio, percent change from baseline in ApoB/ApoA 1 ratio. Evolocumab 140 Q2W and 420 mg QM resulted in statistically significant changes (p<0.001, multiplicity adjusted) compared with placebo and compared to ezetimibe for the atorvastatin cohorts for all tier 1 co-secondary endpoints. Tier 2 endpoints only the percent change from baseline in Lp(a), reached statistical significance compared with ezetimibe.

Study 20110117 (RUTHERFORD- 2) This was a Phase III, multinational, multicentre, randomised, double blind, placebo controlled, parallel group study to evaluate the efficacy, safety, tolerability and PK of evolocumab 140 mg SC Q2W or 420 mg SC QM given by AI/pen for 12 weeks in 329 adults ≤ 80 years that met the Simon Broome Register criteria for HeFH (see Table 20 below) on a stable dose of statin and other permitted lipid lowering drugs for at least 4 weeks before screening.

Table 20: Simon Broome Register criteria

Definite familial hypercholesterolaemia is defined as:

a. *Total cholesterol > 6.7 mmol/L or LDL-C > 4.0 mmol/L in a child < 16 years or total cholesterol > 7.5 mmol/L or LDL-C > 4.9 mmol/L in an adult (either pre-treatment or highest levels on treatment)*

b. *PLUS tendon xanthomas in patient or in 1st degree relative (parent, sibling, child) or in 2nd degree relative (grandparent, uncle or aunt) or*

c. *DNA-based evidence of a LDL receptor mutation of familial defective Apo B-100*

Possible familial hypercholesterolaemia is defined as:

Criterion a) above PLUS one of d) or e)

d. *Family history of myocardial infarction: below age of 50 in 2nd degree relative or below age 60 in 1st degree relative*

e. *Family history of raised cholesterols:*

>7.5 mmol/L in adult 1st or 2nd degree relative or >6.7 mmol/L in child or sibling under 16

Eligible patients had a fasting LDL-C of 2.6 mmol/L and fasting triglycerides ≤ 4.5 mmol/L. Exclusion criteria were extensive but included HoFH, LDL or plasma apheresis within 4 months of randomisation, NYHA III or IV heart failure, Type 1 diabetes and poorly controlled and newly diagnosed Type 2 diabetes. The study population was 57.8% male, 90% White, with a mean age of 51.2 ± 12.6 years (85% were aged < 65 years) and mean BMI 27.9 ±4.6 kg/m^2. About 78% had a definite diagnosis of HeFH and 22% had a possible diagnosis. The placebo group contained more low-risk subjects, fewer coronary artery disease subjects and those with fasting glucose > 5.6 mmol/L compared to the evolocumab group. The study had 96% power to test the superiority of each evolocumab dosing regimen over its placebo and 92% power to show the superiority of both evolocumab dosing regimens over placebo. Randomisation was to 1 of 4 treatment groups (evolocumab 140 mg SC Q2W, 420 mg SC QM, placebo SC Q2W, and placebo SC QM), stratified by LDL-C (< or ≥ 4.2 mmol/L) and baseline use of ezetimibe. About 98% of the patients completed study treatment (no discontinuations were due to adverse event). Most (94.3%) completed the study and 3.9% left the study early to enter the open-label extension study. Major protocol violations occurred in 3 patients (5.5%), including 1 patient with Type 1 diabetes, 1 with a negative diagnosis of HeFH and 1 had the study drug dose altered).

The co-primary endpoints were percent change from baseline in reflexive LDL-C and the percent change in mean for Weeks 10 and 12 from baseline in reflexive LDL-C. The results are presented in Tables 21 and 22 below.

Table 21: Primary analysis of co-primary endpoint (Week 12) for percent change from baseline in reflexive LDL-C

	EvoMab Q2W vs Placebo Q2W		EvoMab QM vs Placebo QM	
	Placebo Q2W (N=54)	EvoMab 140 mg (N=110)	Placebo QM (N=55)	EvoMab 420 mg (N=110)
Week 12 Summary Statistics				
n	51	104	46	103
Mean	-1.32	-60.77	4.76	-56.29
SE	3.10	1.51	3.74	2.14
Median	-2.33	-62.69	2.78	-58.79
Q1,Q3	(-11.32, 4.86)	(-71.59, -52.66)	(-7.76, 17.91)	(-68.07, -49.85)
Min,Max	(-41.5, 127.4)	(-89.5, -4.1)	(-45.5, 94.6)	(-85.3, 75.3)
LS Mean [a]				
Estimate (SE)	-2.02 (2.49)	-61.25 (1.77)	5.53 (3.25)	-55.74 (2.25)
95% CI	(-6.93, 2.89)	(-64.74, -57.76)	(-0.88, 11.95)	(-60.18, -51.30)
Treatment difference[b]				
Estimate (SE)	- (-)	-59.23 (2.98)	- (-)	-61.27 (3.91)
95% CI	(-, -)	(-65.11, -53.35)	(-, -)	(-69.00, -53.55)
p value	-	<0.001	-	<0.001

Table 22: Primary analysis of co-primary endpoint (Week 10 and 12) for percent change from baseline in reflexive LDL-C

	EvoMab Q2W vs Placebo Q2W		EvoMab QM vs Placebo QM	
	Placebo Q2W (N=54)	EvoMab 140 mg (N=110)	Placebo QM (N=55)	EvoMab 420 mg (N=110)
Mean of Weeks 10 and 12 Summary Statistics				
n	53	109	54	107
Mean	-0.49	-60.74	2.08	-63.62
SE	3.10	1.35	2.75	1.85
Median	-2.58	-62.46	1.36	-67.09
Q1,Q3	(-9.57, 5.47)	(-70.72, -53.14)	(-8.43, 9.43)	(-75.34, -57.99)
Min,Max	(-41.5, 134.3)	(-87.0, -16.9)	(-45.5, 57.3)	(-89.0, 75.3)
LS Mean [a]				
Estimate (SE)	-1.08 (2.41)	-61.23 (1.71)	2.30 (2.41)	-63.25 (1.70)
95% CI	(-5.84, 3.67)	(-64.61, -57.85)	(-2.46, 7.06)	(-66.61, -59.88)
Treatment difference[b]				
Estimate (SE)	- (-)	-60.15 (2.88)	- (-)	-65.55 (2.90)
95% CI	(-, -)	(-65.83, -54.46)	(-, -)	(-71.27, -59.83)
p-value	-	<0.001	-	<0.001

Sensitivity analysis by type of LDL-C measurement were consistent with the reflexive LDL-C, and analyses that adjusted for screening LDL-C, ezetimibe use at baseline, age, sex, race, region, baseline LDL-C median, baseline BMI, diabetes type 2, metabolic syndrome, glucose tolerance status hypertension current smoker CHD risk factors family history or premature heart disease, PCSK9 baseline, triglyceride baseline, HeFH status, baseline statin usage, NCEP high risk as covariates showed the results to be consistent with the primary analysis.

There were multiple secondary endpoints for other blood lipid parameters. Compared with placebo both doses were statistically significantly different from baseline for each evolocumab group. The percentage of patients with LDL-C < 1.8 mmol/L was 65.09% and 66.31% for the Week 12 and Week 10 to 12 comparisons for evolocumab 140 mg SC Q2W and 60.93% and 78.52% for the same comparisons in the evolocumab 420 mg group.

Study 20110109 (DESCARTES) This Phase III multinational, multicentre, randomised, placebo controlled, double blind, double dummy study was designed to evaluate the long-term tolerability and durability of the efficacy of evolocumab 420 mg SC QM, when added to background lipid lowering therapy, in lowering LDL-C in 905 adult patients aged ≤ 75 years with hypercholesterolaemia. Eligible patients had a LDL-C ≥ 1.9 mmol/L and triglycerides ≤ 4.5 mmol/L and were assigned one of 4 therapies for the 4 week stabilisation period (diet alone, diet plus atorvastatin 10 mg daily, diet plus atorvastatin

80 mg daily and diet plus atorvastatin 80 mg daily plus ezetimibe 10 mg daily) based on NCEP ATP III risk categories. After 4 weeks two up-titrations were permitted in patients with inadequate response and patients on maximal therapy could be down-titrated to single background therapy if the LDL-C was < 1.9 mmol/L. Exclusion criteria were numerous but of note were NYHA class II – IV heart failure, recent cardiovascular event, Type 1 diabetes, recently diagnosed or poorly controlled Type 2 diabetes and patients with CHD or CHD risk equivalent not receiving a statin and with a LDL-C at screening of ≤ 2.6 mmol/L. After the lipid stabilisation period LDL-C had to be ≥ 1.9 mmol/L and < 2.6 mmol/L with CHD or CHD risk equivalent, or ≥ 1.9 and <3.4 mmol/L without CHD or CHD risk equivalents, or ≥ 1.9 mmol/L on maximal statin therapy. Patients were randomised to evolocumab 420 mg SC QM (using a 70 mg/mL concentration and injected at 2 sites, 3 mL per injection site) or placebo in addition to background statin therapy (12.3% diet alone, 42.5% diet + atorvastatin 10 mg, 24.2% diet plus atorvastatin 80 mg and 21.0% diet plus atorvastatin 80mg and ezetimibe 10 mg). Randomisation was stratified by background lipid therapy. Overall patients were mostly White (80.4%), female (52.3%) with a mean age of 56.2 ± 10.6 years and 77.2% were < 65 years old. Among the background lipid lowering therapies groups, more men were on maximal therapy and more women were on diet or low dose atorvastatin. A higher proportion of Asian and Black/African American patients were in the diet group than other groups. There were also differences between the background therapies for baseline CHD risk, use of cigarettes, Type 2 diabetes. About 46% had used lipid lowering therapies pre-screening. Baseline parameters for serum lipids and PCSK9 were similar. The study was had a > 99% power to detect at least 20% reduction in LDL-C compares with placebo. Of the 901 patients that entered the study about 87% of the evolocumab group and 90% of the placebo group completed. About 12% of the evolocumab group and 9.4% of the placebo group discontinued, mostly because of withdrawn consent or subject request (2.6% each) and 2.0% because of adverse events. Major protocol violations occurred in 2.6%, mostly for medication errors.

Primary efficacy outcome was the reduction in UC LDL-C at Week 52, as shown below (Table 23).

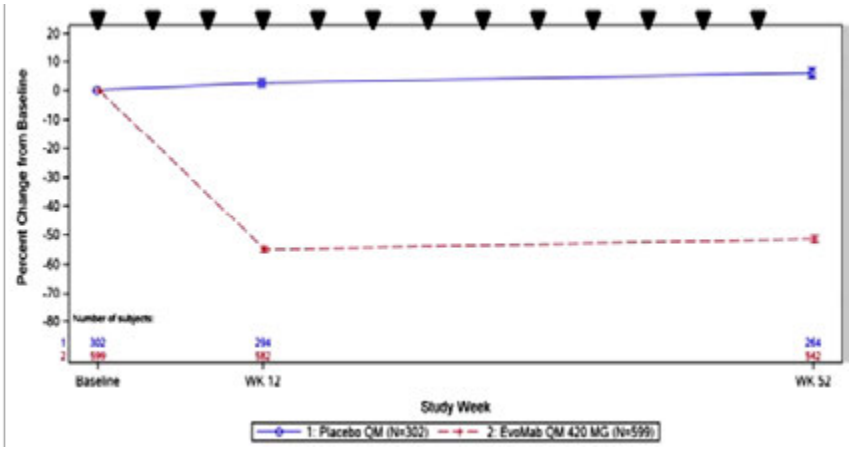
Table 23: Primary analysis of percent change from baseline in UC LDL-C at Week 52

	Placebo QM (N=302)	EvoMab 420 mg QM (N=599)
Summary Statistics		
N	264	542
Mean	6.03	-51.45
SE	1.69	1.20
Median	1.66	-57.63
Q1,Q3	(-9.60, 16.26)	(-68.63, -42.66)
Min,Max	(-91.7, 173.9)	(-95.1, 111.2)
LS Mean [a]		
Estimate	6.83	-50.14
SE	1.75	1.24
95% CI	(3.40, 10.27)	(-52.58, -47.69)
Treatment difference[b]		
Estimate	-	-56.97
SE	-	2.10
95% CI	(-, -)	(-61.08, -52.85)
p-value	-	<0.001
Adjusted p-value[c]	-	**<0.001**

The study included a large number of secondary and tertiary exploratory endpoints.

Key secondary endpoints were analysed in two tiers and allowed adjustment for multiplicity (Figure 3). Approximately 75% of more patients achieved a LDL-C <1.8 mmol/L at Week 52 with evolocumab than placebo. There were improvements in all lipid parameters including triglycerides (reduction of 11.5%) and an improvement in HDL-C of about 5.4%.

Figure 3: Plot of mean change from baseline in UC LDL-C by scheduled visit and investigational product.



Study 20101155 (LAPLACE 1) This Phase II, multinational, multicentre, randomised, placebo controlled, double blind dose ranging study to evaluate the efficacy and safety of 12 weeks of SC evolocumab Q2W or QM, compared to placebo, in combination with a statin in 631 adult patients ≤ 80 years of age with hypercholesterolaemia. Eligible patients had a fasting LDL-C of ≥ 2.2 mmol/L Exclusion criteria included lipid lowering drugs/supplements. Patients were randomised to 1 of 8 treatment groups. There were 3 evolocumab Q2W treatment arms (70 mg, 105 mg and 140 mg), 3 evolocumab QM treatment arms (280 mg, 350 mg and 420 mg) and placebo (Q2W and QM). All evolocumab was administered using 70 mg/mL concentrations solution. The greatest LS mean treatment reductions (evolocumab minus placebo) were in the 140 mg SC Q2W group (66± 3%) and the 420 mg QM group (50±3%).

Study 20101154 (MENDEL 1) This Phase II multinational, multicentre, randomised, placebo and ezetimibe controlled, dose ranging study was designed to evaluate the efficacy (LDL-C reduction) and safety of 12 weeks of evolocumab compared to placebo when administered as monotherapy in 411 adult patients ≤ 75 years of age with hypercholesterolaemia that had not used a lipid-regulating drug in the previous 3 months and had a fasting LDL-C of 2.6 mmol/L and < 4.9 mmol/L and triglycerides < 4.5 mmol/L. Patients were randomised to 1 of 9 treatment groups : 4 QM treatments (280 mg, 350 mg, 420 mg and placebo), 4 Q2W treatments (70 mg , 105 mg, 140 mg and placebo), and ezetimibe (1 group). Compared to placebo all evolocumab groups reduced LDL-C, with the greatest reductions in LDL-C in the 140 mg Q2W group and the 420 mg QM group (47±4% and 53±5%, respectively). In the secondary analyses there were also significant reductions in LDL-C compared to ezetimibe only in the evolocumab groups.

Study 20090159 (GAUSS 1) This Phase II multinational, multicentre, randomised, double blind, placebo and ezetimibe controlled trial was designed to evaluate the tolerability and efficacy of 12 weeks of evolocumab compared to ezetimibe compared to placebo in adult patients ≤ 75 years of age with hypercholesterolaemia unable to tolerate an effective statin dose. Eligible patients were intolerant of at least one statin and unable to tolerate any dose or an increased statin dose above the total weekly limits outlined in the summary of the GAUSS 2 study and were not at the LDL-C goal for their NCEP ATP III risk category, with triglycerides ≤ 4.5 mmol/L and taking no other lipid lowering medications/supplements. They were also excluded if they had NYHA class III or IV heart failure and recent cardiovascular disease (CVD) events. There were 5 treatment groups (evolocumab SC QM 280 mg, 350 mg and 420 mg, evolocumab SC QM 420 mg plus ezetimibe, and SC placebo plus ezetimibe). The reduction in LDL-C at Week 12 was 36±4% for evolocumab 420 mg QM compared to ezetimibe and placebo. The reduction at 12 weeks for evolocumab 420 mg SC with ezetimibe versus placebo and ezetimibe was 47 ± 3%.

Study 20110231 (YUKAWA 1) This Phase II study in 307 Japanese patients aged 20 to < 80 years with hypercholesterolaemia at high risk of cardiovascular events on a stable dose of an approved statin to evaluate the efficacy and safety of 12 weeks treatment with evolocumab 70 mg/mL in one of 6 treatment groups (Q2W 70mg, 140 mg or placebo; QM 280 mg, 420 mg, or placebo). Greatest reductions were seen in the 140 mg SC Q2W and 420 mg SC QM dosage groups.

Study 20090158 (RUTHERFORD 1) This Phase II, multinational, multicentre, randomised, placebo controlled, double blind study in 168 adult patients ≤ 75 years with HeFH, LDL-C of ≥ 2.6 mmol/L and triglycerides ≤ 4.5 mmol/L on a stable dose of statin with or without ezetimibe to evaluate the efficacy and safety of 12 weeks of SC QM evolocumab 350 mg or 420 mg compared to placebo. Dose-dependent reductions in LDL-C were noted (44±4% and 56±4% for 350 mg and 420 mg doses respectively) compared to placebo. The difference between the LDL-C reductions for the 2 evolocumab groups was statistically significant in favour of the 420 mg dose.

Study 20110110 (OSLER 1) This ongoing Phase II multinational multicentre, randomised controlled open label 5 year extension study in 1342 patients that completed a qualifying Phase II study (20090158, 20090159, 20101154, 20101155, 20110231) to assess the long term safety and tolerability of evolocumab 420 mg SC QM. Secondary outcomes included long-term effects on serum lipids. Patients were randomised to evolocumab or standard of care (SoC). In the first 12 weeks of the study LDL-C levels were masked to investigators and no changes in background medication were permitted. In the first year of the study statin continued from the parent Phase II study were to be continued at the same dose. At the end of the first year (Week 52) patients could enter the all evolocumab period (Years 2+) in which patients receive open label evolocumab SC 420 mg QM and statins could be down-titrated if investigators deem this necessary. The interim results for the Year 1 analysis are included below (Table 24).

Table 24: Analysis of percent change form baseline in calculated LDL-C at Week 12 (upper panel) and Week 52 (lower panel)

Week 12

	SoC (N=442)	EvoMab + SoC (N=882)	Treatment Difference
Summary Statistics			
n	421	858	
Mean	-4.40	-58.95	-54.55
SE	0.94	0.68	1.16
Median	-5.02	-61.95	
Q1, Q3	-16.00, 4.76	-72.24, -50.26	
Min, Max	-50.7, 97.4	-96.8, 92.3	
95% CI (mean)	(-6.24, -2.56)	(-60.29, -57.61)	(-56.82, -52.27)
p-value	-	-	<0.001

Week 52

Summary Statistics			
n	342	710	
Mean	-3.12	-54.55	-51.43
SE	1.20	0.89	1.49
Median	-3.73	-59.29	
Q1, Q3	-15.68, 9.79	-69.70, -46.08	
Min, Max	-59.1, 102.6	-93.4, 96.0	
95% CI (mean)	(-5.47, -0.76)	(-56.31, -52.79)	(-54.36, -48.50)
p-value	-	-	<0.001

In the Year 2+ analysis the evolocumab group had a mean reduction of 53.5% and at Week 124 (49.8%). For those switching to evolocumab at Week 52 of the study reductions of 54.3% and 51.4% were observed after 12 and 52 weeks of evolocumab therapy respectively.

Study 20120138 (OSLER-2) This is an ongoing Phase III multinational, multicentre, randomised, controlled (SoC), open label 2 year extension study in patients that completed a qualifying evolocumab protocol (Studies 20110109, 20110114, 20110115, 20110116,

20110117, 20120348 and 20120356) to characterise the safety and tolerability of long-term administration of evolocumab. The secondary objective is to characterise the efficacy of long-term administration of evolocumab using LDL-C, in patients with primary hypercholesterolaemia and mixed dyslipidaemia. Eligible patients were randomised to receive evolocumab 140 mg SC Q2W or 420 mg SC QM plus SoC or SoC alone. At the end of the first year of the extension study all patients entered an evolocumab 140 mg SC Q2W or 420 mg QM open label phase for approximately 1 further year (dosage regimen based on patient preference). The baseline demographics reflected the parent studies. Lipid regulating agents were used in 70.1% of the evolocumab group (66.8% used statins and 11.9% used ezetimibe) and 76.2% of the control group (71.4% and 16.1%). The mean baseline LDL-C was 3.2 ± 1.2 mmol/L and was similar across the treatment groups. An interim analysis was provided from 2784 patients that had reached Week 12, 1904 that had reached Week 24. Only 7 patients had reached Week 48. The results are summarised in Table 25 below.

Table 25: Summary of percent change from parent study baseline in reflexive and calculated LDL-C by scheduled visit in Year 1

	Reflexive LDL-C				Calculated LDL-C			
	Control in Parent Study		EvoMab in Parent Study		Control in Parent Study		EvoMab in Parent Study	
	Control[a] (N = 352)	EvoMab[b] (N = 704)	Control[a] (N = 625)	EvoMab[b] (N = 1247)	Control[a] (N = 352)	EvoMab[b] (N = 704)	Control[a] (N = 625)	EvoMab[b] (N = 1247)
Baseline Value in Parent Study (mg/dL)								
n	352	704	625	1247	352	704	625	1247
Mean	121.0	123.1	125.4	125.9	120.3	122.7	124.6	125.2
SE	2.4	1.7	1.9	1.4	2.4	1.7	1.9	1.4
Percent Change from Baseline to Parent Study End of Study (%)								
n	327	675	601	1210	318	666	587	1195
Mean	-3.41	-3.19	-58.93	-58.62	-2.74	-2.99	-60.76	-60.50
SE	1.5	1.0	0.8	0.5	1.5	1.0	0.9	0.6
Percent Change from Baseline to Extension Study Week 12 (%)								
n	323	676	594	1191	314	670	581	1184
Mean	13.84	-52.23	6.88	-52.97	14.87	-53.46	8.04	-54.38
SE	2.3	1.2	1.5	0.8	2.4	1.3	1.5	0.8
Percent Change from Baseline to Extension Study Week 24 (%)								
n	239	475	388	802	229	469	382	792
Mean	7.94	-50.09	5.34	-51.30	9.66	-50.68	6.74	-52.47
SE	2.7	1.5	1.7	1.0	2.8	1.6	1.7	1.1

[a] standard of care only group; [b] evolocumab plus standard of care group
Data cutoff date 01 APRIL 2014.
EvoMab = evolocumab; LDL-C = low density lipoprotein cholesterol; N = number of subjects randomized in ICOAS in that treatment arm; SE = standard error; SoC = standard of care.
Baseline is defined as the parent study baseline.

Study 20120348 (THOMAS-1): This randomised open-label Phase III study compared the use of PFS or an AI/pen to administer 140 mg SC Q2W in a home setting in 152 patients with primary hypercholesterolaemia or mixed dyslipidaemia over a 6 week period. At Week 4, 96% of patients using the PFS and 92% of patients using the AI/pen fully administered evolocumab in the home-use setting. LDL-C reduction was a secondary endpoint at Week 6 and the LS mean (SE) was 59.7(2.8) % and 63.4 (2.7) % with the PFS and AI/pen, respectively.

Study 20120356 (THOMAS-2): In this randomised open-label Phase III study Patients used evolocumab 420 mg SC delivered by AI/pen or AMD. The sponsor has not requested the automated mini-doser (AMD) as part of this submission. The primary endpoint was subject reported full dose administration using these delivery methods. A secondary outcome was reduction in reflexive LDL-C at the mean of Weeks 10 and 12. The LS mean ± SE reduction was 67.9 ±2.4% and 64.5±2.4% in the AMD and AI/pen groups respectively.

Studies in patients with homozygous familial hypercholesterolaemia

Study 20110233 This was a 2 part Phase II/III, multinational, multicentre study of the safety, tolerability and efficacy of evolocumab in patients with HoFH, conducted in two parts. Part A was a Phase II, 12 week, open label (evolocumab 420 mg SC QM), single arm, multicentre pilot study in 8 patients aged 12 to ≤ 65 years and body weight ≥ 40 kg with a

diagnosis of HoFH by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C of > 13 mmol/L together with either xanthoma before aged 10 or evidence of HeFH in both parents. Eligible patients had a stable low fat diet and lipid lowering therapies but could not have had LDL or plasma apheresis within 8 weeks of enrolment. Exclusion criteria were similar to the other studies but did not include diabetes. Part B was a Phase III, double blind, randomised, placebo controlled study. Inclusion criteria included 50 patients aged 12 to ≤ 80 years but were otherwise the inclusion and exclusion criteria were the same as Part A. Patients were randomised to 420 mg SC QM evolocumab or placebo and randomisation was stratified by screening LDL-C (< 10.9 mmol/L or ≥ 10.9 mmol/L). With 51 patients the study had 81% power to detect a 20% difference between the two treatments to the 0.05 significance level, allowing for a 2% drop-out and treatment attenuation. Of the 49 patients that received study treatment (1 placebo patient not treated) the mean age was 30.9 years, and 10 patients (20.4%) were <18 years. Most patients were White (89.8%), male (51.0%) with a mean BMI of 25.4±5.3 kg/m^2. The mean baseline LDL-C was 8.7±3.8 mmol/L in the placebo group and 9.2±3.5 mmol/L in the evolocumab group (n=33). Three adolescents in the placebo group had LDL-C of 10±4.3mmol/L and 8.4±3.4 mmol/L in the evolocumab group (n=7). Of the total population 42.9% had CHD and 27 patients had 2 or more cardiovascular risk factors. All patients were taking statins (98% high dose statins), 91.8% were taking ezetimibe. LDLR defective genotype (at least 1 LDLR allele with ≥ 5% activity) was the most common genotype (n=28) and the remainder had indeterminate/negative LDLR.

The primary endpoint was a reduction in LDL-C from baseline at Week 12. Results are shown in Table 26 below.

Table 26: Results for primary efficacy analysis

Analysis Set/ Endpoint	LS Mean (SE)[a] Percent Change From Baseline: Placebo (N = 16)	Evolocumab (N = 33)	Treatment Difference (SE) (95% CI)	p-Value
Primary analysis				
Full analysis set	(N = 16)	(N = 33)		
UC LDL-C, week 12	7.88 (5.26)	-23.05 (3.78)	-30.93 (6.42) (-43.86, -18.00)	<0.001[b]
Calculated LDL-C, week 12	9.02 (5.23)	-23.09 (3.83)	-32.12 (6.42) (-45.05, -19.18)	<0.001[c]

The first assessment at Week 4, after the first dose, showed a reduction in LDL-C in the evolocumab group of approximately 25%. Sensitivity analyses were consistent with the primary analysis. In additional analyses LDLR indeterminate/negative genotypes (n=13) had an attenuated response [mean treatment difference from placebo -16.11% (95% CI: -41.38%, +9.16%) whereas the LDLR defective genotype had a statistically significant response [-35.19% (95% CI: -47.23%, -23.15%)]. Overall the secondary endpoints for reduction of other lipid parameters were met for all except Lp(a).

Adolescent patients (n=7) had a less marked improved in LDL-C compared to placebo, -26.72 (95% CI: -65.67%, +12.22%), and did not demonstrate statistically significant differences compared to placebo for ApoB, Lp(a) and other LDL-C endpoints.

Study 20110271 this Phase II/III multicentre, multinational, open-label, extension study was designed to assess the safety and efficacy of long-term evolocumab 420 mg SC QM or evolocumab 420 mg Q2W in 198 patients with severe familial hypercholesterolaemia (FH) including HoFH for up to 5 years or until commercial availability for the population. Eligible patients were ≥ 12 years and ≤ 80 years, with FH [HoFH (n=96) or severe FH (n=102)], had completed Study 20110233 or another evolocumab study protocol without SAE, met the inclusion criteria for Study 20110233 but were recruited after this study closed, or had genotypes not studied in Study 20110233 (such as gain-of-function mutations of PCSK9). Non-apheresis patients had LDL-C ≥ 2.6 mmol/L with CHD/ risk

equivalent or ≥ 3.4 mmol/L without CHD/risk equivalent. No LDL-C minimum was set for apheresis patients. All had triglycerides < 4.5 mmol/L. Important protocol deviations occurred in 2% of patients and 2% did not meet the eligibility criteria. At baseline the mean age was 44.2±16.9 years and there were 13 patients < 18 years old, all with HoFH, 3 on apheresis. Most were White (88.9%) and male (56.1%), 48.5% had a history of CHD and 56.1% had a family history of premature CHD, 32.8% had a history of hypertension and 49.5% had ≥ 2 cardiovascular risk factors. Baseline statins were used by 94.4%, ezetimibe by 76.3% and 6.6% were using bile acid sequestrants. Patients not on apheresis within 8 weeks of enrolment initiated treatment with 420 mg SC QM and those on apheresis at enrolment had 420 mg Q2W. At Week 12 subjects with a < 5% LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL could discontinue evolocumab at Week 12 or Week 24. If the serum PCSK9 was ≥ 100 ng/mL (maximally suppressed) dosing could be increased to 420 mg Q2W at Week 12. Those on apheresis with a LDL-C reduction of ≥ 5% from baseline at Week 12 and PCSK9 < 100 ng/mL could continue QM treatment. Up-titration of the dose could occur based on PCSK9 levels. Another dose adjustment based on response could occur at Week 24 (either up or down titration) but thereafter was discouraged.

Analyses of reductions in LDL-C for up to 48 weeks were presented for HoFH and severe FH patients separately and summary tables are included below.

Table 27: Change from baseline in UC LDL-C by study visit in patients with HoFH

		OLE Week 4	OLE Week 8	OLE Week 12	OLE Week 16	OLE Week 20	OLE Week 24	OLE Week 36	OLE Week 48
HoFH Interim Analysis Set (N = 96)	n	71	67	68	61	51	45	29	11
	Mean (SE)	-23.84 (3.15)	-21.88 (2.90)	-19.03 (3.04)	-23.71 (2.87)	-22.92 (4.01)	-23.06 (3.62)	-26.19 (4.51)	-19.05 (7.59)
	Median	-21.45	-22.32	-15.61	-22.82	-20.61	-24.14	-27.84	-18.62
	Range	-90.4, 53.7	-90.7, 71.9	-89.1, 47.3	-83.0, 20.8	-83.1, 33.4	-67.8, 43.1	-72.4, 44.9	-62.7, 22.8
Non-apheresis subjects (N = 65)	n	43	43	44	40	35	32	26	9
	Mean (SE)	-27.24 (3.76)	-24.70 (2.99)	-20.37 (3.33)	-26.72 (3.19)	-25.25 (4.44)	-24.50 (4.20)	-27.17 (4.62)	-21.26 (9.16)
	Median	-23.39	-23.97	-18.24	-25.66	-22.13	-23.07	-28.92	-21.74
	Range	-90.4, 53.7	-73.9, 16.9	-80.4, 23.9	-83.0, 15.0	-83.1, 31.5	-67.8, 39.9	-72.4, 44.9	-62.7, 22.8
Apheresis subjects (N = 31)	n	28	24	24	21	16	13	3	2
	Mean (SE)	-18.62 (5.46)	-16.84 (6.02)	-16.59 (6.14)	-17.97 (5.60)	-17.80 (8.39)	-19.51 (7.30)	-17.66 (19.91)	-9.10 (5.12)
	Median	-14.07	-16.34	-14.89	-15.13	-12.02	-24.14	-12.13	-9.10
	Range	-88.3, 31.7	-90.7, 71.9	-89.1, 47.3	-78.2, 20.8	-78.7, 33.4	-59.5, 43.1	-54.6, 13.7	-14.2, -4.0

In the 25 patients that switched from 420 mg QM to 420 mg Q2W for 12 weeks improved all lipid parameters except triglycerides, VDLD-C and HDL-C.

Adolescents had mean reductions in UC LDL-C at Weeks 12, 24 and 36 of 15.0% ± 8.1%, 21.5% ± 8.9%, and 33.3% ± 9.6%, respectively. Three patients on apheresis did not respond - 1 with defective LDLR genotype and 2 genetically homozygous with indeterminate LDLR.

There were no adolescent patients with severe FH, and the numbers of adult patients was small. The following table (Table 28) shows the primary efficacy outcome for the severe FH subgroup.

Table 28: Change from baseline in UC LDL-C by study visit in patients with severe FH

	OLE Week 4	OLE Week 8	OLE Week 12	OLE Week 16	OLE Week 20	OLE Week 24	OLE Week 36	OLE Week 48
Severe FH Interim Analysis Set (N = 102)[a]								
n	45	14	13	12	10	8[b]	4	4
Mean (SE)	-49.40 (2.87)	-44.48 (5.17)	-51.98 (5.65)	-44.92 (5.09)	-45.03 (5.76)	-29.89 (13.88)	-44.73 (6.46)	-51.15 (4.68)
Median	-52.63	-41.40	-52.74	-43.28	-44.72	-44.70	-46.07	-47.66
Range	-78.6, 15.4	-85.3, -15.7	-78.8, -8.8	-71.4, -16.7	-67.2, -1.2	-65.0, 47.7	-58.9, -27.9	-64.8, -44.5

[a] As of the 01 April 2014 data cutoff date, UC LDL-C results in the Severe FH Interim Analysis Set were only available for the non-apheresis subjects.
[b] Of these 8 subjects, 1 subject made changes to background lipid lowering therapy and 1 subject had a late assessment performed at OLE week 24.
FH = familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; OLE = open-label extension; SE = standard error; UC = ultracentrifugation.
N/n = number of evaluable subjects (N) and subjects with observed LDL values at specific visit (n).

Among the secondary endpoints the severe FH patients showed mean improvements in other plasma lipid parameters.

Safety

A total of 5710 subjects (4638 patient years) were exposed to any evolocumab with 5416 exposed for ≥ 3 months, 3350 for ≥ 6 months, 1824 for ≥ 12 months and 614 for ≥ 24 months. Safety data were provided from 4971patients with hypercholesterolaemia and mixed dyslipidaemia and 99 patients with HoFH (including 14 adolescents). Of the patients treated for at least one year 345 had established CVD, 183 had diabetes, 463 were on high intensity statin therapy and 439 were ≥ 65 years of age. Integrated safety data were presented by the sponsor for the parent studies, that is, the Phase II and III studies and the 52 week Study 20110109, Year 1 of the open label extension studies [controlled period, evolocumab plus standard of care (+SoC) versus SoC] and Year 2 and onward (Year 2+) of the open-label extension studies.

Approximately 51% of the patients taking evolocumab experienced an AE versus almost 50% AEs in the control groups in the parent studies. Common events that were more frequent in the evolocumab groups compared with the control groups were nasopharyngitis (5.9% versus 4.8%), upper respiratory tract infection (URTI) (3.2% versus 2.7%), back pain (3.0% versus 2.7%), and nausea (2.1% versus 1.8%). In the Year 1 studies approximately 60% of the evolocumab + SoC and 55% of the SoC reported AEs. The AE profile was similar in the Year 1 and Years 2+ cohorts. Across the entire integrated population nasopharyngitis, URTI, arthralgia and back pain were the most common events.

There were 15 deaths, 9 deaths occurred in patients taking evolocumab: 3 in the parent studies, 3 in the Year 1 studies, 2 in the Year 2+ studies and 1 outside the study period. A total of 11 deaths were adjudicated to be due to cardiovascular events: 8 (0.14%) occurred in patients taking evolocumab and 3 (0.1%) occurred in the controls. SAEs were reported in 2.8% of the evolocumab groups and 2.1% of the controls in the parent studies, in the Year 1 cohort 5.4% evolocumab + SoC and 5.8% SoC and Year 2+ 8.0%. The most commonly reported SAEs in the evolocumab groups (versus control groups) in the parent studies were myocardial infarction (0.2% versus 0%), angina pectoris (0.2% versus 0.2%), unstable angina (0.1% versus 0%), pneumonia 0.1% versus 0%), appendicitis (0.1% versus 0%) and acute pancreatitis (0.1% versus 0%). For the total evolocumab safety set, 12 patients had the SAE of myocardial infarction in the evolocumab groups, 19 had angina or unstable angina, 8 patients had pneumonia.

AEs leading to discontinuations in the parent studies were reported for 1.9% of the evolocumab patients and 3.2% of the control group with most commonly reported events in this cohort were myalgia (0.3% versus 0.5%), nausea (0.2% versus 0.1%), blood CK increased (0.2% versus 0.3%) and dizziness (0 versus 0.2%). In the Year 1 cohort, 2.0% of patients had AE related discontinuations; the most common of which were myalgia (0.2%), arthralgia, fatigue and injection site pain (0.1% each) and in the Year 2+ cohort 1.0% of patients had AE related discontinuations but no single AE was reported for more than one patient.

Analysis of AEs performed by LDL-C concentration in the integrated clinical study safety set for the 826 subjects LDL-C <0.65 mmol/L, 1308 LDL-C < 1.0 mmol/L and the 696 LDL-C ≥ 1.0 mmol/L did not identify a LDL-C concentration at which there was a statistically significant increase in AEs, although the proportion of patients reporting AEs for LDL-C < 0.65 mmol/L and < 1.0 mmol/L were numerically higher than ≥ 1.0 mmol/L for all AEs and SAEs in the Year 2+ and is driven by a higher proportion of patients with cardiac disorders and neoplasms. The most common neoplasm was basal cell carcinoma (BCC). The differences between the groups for AEs did not reach statistical significance

and some of the difference in cardiac events between the groups may be attributable to baseline characteristics. Overall the clinical evaluator was not satisfied that the safety data confirmed there was not a safety signal for the low cholesterol groups.

Overall, neurocognitive events occurred in 0.1% of patients treated with any evolocumab and 0.3% in any control group, 0.6% of the evolocumab plus SoC group versus 1.6% with SoC alone in the initial safety set. In the updated safety set an additional 9 patients were reported in the Year 1 data, giving an overall rate of 0.8% for the year. In the updated data, 2 neurocognitive AEs were reported in the 2+ year exposure group (overall 0.1%). Across the studies the highest proportion of patients with neurocognitive events occurred in the evolocumab and SoC groups.

Five subjects developed angioedema while taking evolocumab. Rash occurred in around 1.5% of evolocumab patients. Between 3.1% and 3.7% of patients taking evolocumab developed injection site reactions compared with 3.0% in any control group.

Injection site reactions were reported in 3% of the control group and 3.3% of evolocumab patients. The majority were mild and there were no SAEs and were mostly pain, erythema or bruising.

Elevations of AST and ALT levels (>3 times ULN) and bilirubin (>2 times ULN) were reported in 3 patients but confounding factors were identified. Elevations of ALT or AST > 5 times ULN were reported in 0.2% to 0.3% of evolocumab patients and similar proportions in the controls. In controlled periods of the parent and extension studies, 1 patient was reported to be hepatitis C antibody positive.

One patient with Type 2 diabetes developed glomerulonephritis and another patient developed an IgA nephropathy but no clear signal for an increased risk of renal injury was demonstrated and no evidence that it increased CK levels or increased the elevation attributable to statins in the trial populations.

There was no signal for QTc prolongation and overall new ECG findings occurred in 6.3% of evolocumab and comparator patients.

In two separate studies analyses of steroid hormones after up to 1 year of exposure did not reveal any differences between the evolocumab 420 mg SC QM and SoC. LDL-C subgroups including those with LDL-C < 1.0 mmol/L, <0.6 mmol/L and ≥ 1.0mmol/L showed consistent results. There was also no observed effect on vitamin E levels.

For the whole patient safety set, 6 patients reported 7 events of pancreatitis, with 6 of those events occurring in patients taking evolocumab. One of the events was due to gall stones, 4 had other confounding factors, and for 2 the aetiology was unknown. Cholelithiasis or cholecystitis was reported for 8 evolocumab patients and 2 control patients across all studies.

The incidence of anti-evolocumab binding antibodies was low in the integrated analysis from 14 Phase II and III studies (0.1% of subjects [7/4846]) (Integrated Immunogenicity Report). None of the 7 anti-evolocumab antibody positive subjects tested positive for neutralising antibodies but a 0.3% incidence was observed among the comparator groups, suggesting cross-reactivity with other proteins.

The 102 patients with severe FH and HoFH did not demonstrate a different safety profile from the other patients with hyperlipidaemia and mixed dyslipidaemia. There were no increased safety concerns in patients aged ≥ 65 years, and ≥ 75 years. No safety signals were detected among the adolescents but the numbers were very small. Patients with moderate to severe hepatic disease and patients with eGFR < 30 ml/min/1.73 m^2 were specifically excluded from the studies. No specific drug-drug or drug-food interactions were conducted. No studies were conducted in pregnancy and lactation. Seven maternal and 9 paternal exposures were reported without adverse event.

Risk management plan

The TGA has accepted the EU Risk Management Plan for Repatha (evolocumab) version 1.2 dated 28 April 2015 and Australian Specific Annex version 2.0 dated 21 June 2015.

The following was an outstanding matter and should be followed up with TGA in the sponsor's Pre-ACPM response:

- The sponsor should correct the part of the RMP where relative exposures have been calculated for a 420 QM dose rather than the maximum proposed dose of 420 mg Q2W.

Risk-benefit analysis

Delegate's considerations

Efficacy

The efficacy of evolocumab in reducing LDL-C was assessed in four adequately designed double blind randomised placebo or ezetimibe- controlled trials of 12 weeks duration and one 52 week placebo controlled trials. The four 12 week trials assessed evolocumab in 4 different settings:

1. in combination with statins (n=1896),
2. monotherapy in a population of low cardiovascular risk (n=614),
3. in statin-intolerant patients (n=307) and in HeFH (n=329).

In the four 12 week studies 92% of the patients were White, from Europe (52%) or North America (40%) and 30% were aged ≥ 65 years. About 29% of patients had a prior diagnosis of coronary artery disease and 10% had cerebrovascular disease or peripheral arterial disease. About 10% had had a myocardial infarction at baseline but only about 2% had had a stroke. About 12 % had Type 2 diabetes, 49% had hypertension and 1370 participants were moderate-high or high risk of CVD at baseline and 72% were taking a statin. Of the 1848 randomised to evolocumab, 921 received Q2W dosing and 927 received QM dosing. In these four different settings evolocumab was shown to reduce LDL-C by between 60 and 77% versus placebo and 38 to 40% versus ezetimibe. One year extension data demonstrated sustained efficacy between 12 and 52 weeks and there is limited longer term efficacy data.

Two studies assessed the efficacy of evolocumab in addition to statin therapy in 99 patients with characteristics of HoFH. Patients were overall younger, with higher baseline LDL-C than in the studies in primary hypercholesterolaemia and mixed dyslipidaemia. In Study 20110233 that did not allow lipid apheresis as part of treatment and showed a 23% reduction in LDL-C from baseline. In the open label extension Study 20110271 lipid apheresis was permitted. Evolocumab reduced UC LDL-C by 19% at Week 12 and 23% at Week 24 in the HoFH analysis set. Increasing the dose frequency from 420 mg QM to 420 mg Q2W in HoFH patients further reduced the LDL-C by about 6%. The non-apheresis patients had a reduction of about 25% whereas the apheresis patients had a reduction of about 20%. This rare disorder carries a very high risk of cardiovascular disease at an early age and early mortality. Although modest compared with the LDL-C reduction demonstrated in primary hypercholesterolaemia, the LDL-C when taken with statins compared with statins alone improvement is of similar magnitude to that observed in clinical trials with statins and ezetimibe in this population. It also improved LDL-C in addition to LDL-C apheresis, although the treatment effect was more modest. Adolescents from Study 20110233 did not achieve statistically significant differences from placebo for

the primary and secondary endpoints but only 7 patients received evolocumab and the confidence intervals around the estimates of effect are large.

All the clinical studies in this submission used a reduction in LDL-C as the primary efficacy endpoint and as a surrogate for reduced cardiovascular morbidity or mortality. While there is no safety signal for increased cardiovascular risk an improvement in cardiovascular outcomes has not been established. The TGA adopted EU guideline on lipid lowering medication states that a relative reduction in LDL-C is acceptable as a primary efficacy endpoint in patients with primary hypercholesterolaemia. LDL-C reduction has been accepted in the past for lipid reduction therapy, for example ezetimibe. In response to questions the sponsor has provided an analysis of evolocumab plus SoC versus SoC alone from the Year 1 SoC-controlled periods of Studies 20110110 and 20120138 with a median exposure time of about 10 months that shows an overall Hazard Ratio (HR) 0.5 (95% CI: 0.29, 0.86) in favour of evolocumab and the Kaplan-Meier curve from the same analysis shows divergence of the incidence of cardiovascular events over the Year 1 period between these two groups. Although these data suggest a possible reduction in cardiovascular risk, or at least no increased risk of CVS events, however the numbers of patients are relatively small, the duration of exposure is relatively short and no firm conclusion can be reached. It is also noted there is a definitive cardiovascular outcomes (the Fourier study, Study 20110118) is ongoing. An update about this study will be requested from the sponsor. The sponsor has not proposed to claim a beneficial effect for evolocumab on cardiovascular morbidity and mortality.

A similar drug, alirocumab is approved in the US for the treatment of adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C as an adjunct to diet and maximally tolerated statin therapy. Investigators of this drug have included a post hoc analysis of cardiovascular outcomes in their publication of a study conducted over 78 weeks comparing alirocumab and statin with statin alone that found a lower risk of cardiovascular outcomes in patients that were at high risk for cardiovascular events at the pre specified primary endpoint (at Week 24 of therapy).

Safety and RMP

The exposure of a total of 5710 subjects for evolocumab was sufficient to detect common events however the chance of observing rare AEs was low and the less than three year exposure time limits the opportunity to observe AEs that occur because of prolonged exposure. There are also limitations to the data by age (very few adolescents were included in the safety data set) and race (majority of subjects were white and the specific study conducted in Japanese patients was small). Overall evolocumab was well tolerated in the development program to date and the overall adverse event rate was low. The most common adverse events are nasopharyngitis and URTI across all studies, immunological events were infrequent and injection site reactions were not a major feature of the adverse effect profile. There were no signals for renal or hepatic events. Adverse event profiles were similar for 140 mg Q2W and 420 QM dosing. There were limited safety data in diabetic patients mostly because Type 1 diabetes, poorly controlled and newly diagnosed Type 2 diabetes were exclusion criteria in the majority of the studies. The risk of new onset diabetes has not been quantified although this has been considered by the sponsor and there is no apparent safety signal at this time.

Neurocognitive effects have been identified, and although numbers are small they increased in the last safety update in patients with longer exposure. Evolocumab, as a circulating antibody is likely to have limited distribution to the CNS with an intact blood brain barrier. PCSK9 knockout mice showed no increase in brain LDLR levels. The sponsor suggests that this suggests that PCKS9 does not regulate LDLR in the brain. It does not indicate however if there are other functions of PCSK9 in the brain. The sponsor has also noted two studies in older people, one showing no reduction in cognitive performance in

patients with reduced serum cholesterol and another showing no association between PCSK9 sequence variants and dementia. Although there is no clear signal at present there are insufficient data to provide assurances that there is no safety concern.

No signals were detected for an increased incidence of hepatitis C virus (HCV). HCV modulates lipid metabolism in infected hepatocytes to attain intracellular enrichment of lipids necessary for viral propagation. LDLR activity is suspected to be involved in HCV entry into the hepatocyte and stable expression of PCSK9 has been found to reduce CD81, a major HCV receptor. It has been reported that HCV induces down regulation of PSCK9 to prevent LDLR degradation which enhances lipid uptake in HCV-infected cells.[58] A broader population is likely to be exposed to evolocumab than the clinical trial population. At this time HCV reactivation or more severe infection is a potential concern.

Small numbers of patients reported pancreatitis and biliary tree related events were reported in similar numbers to the SoC groups. The nonclinical evaluator has raised a concern about the consequences of an increased hepatic uptake of cholesterol. The sponsor will be requested to comment.

Large animal studies provided limited data about the safety of evolocumab in pregnancy. The data are very limited in human pregnancy exposure. The ACPM will be requested to comment on whether there are potential safety concerns in this regard.

Dose

The two different dosage regimens for use in primary hypercholesterolaemia and mixed dyslipidaemia were designed to offer patients choice in the dosage regimen rather than to allow titration of the dose. Integrated data from four Phase II studies showed 140 mg SC Q2W and 420 mg QM provided the greatest effects on LDL-C and other lipid parameters while maintaining safety and tolerability. This was supported by the PK/PD modelling in which these dosing regimens were predicted to achieve approximately 80% of the model-predicted maximum reduction in LDL-C at Weeks 10 and 12. The sponsor has provided evidence to support the proposed dosage regimen of 140 mg Q2W or 420 mg QM. There are incrementally greater improvements in some lipid parameters with twice monthly dosing regimen in some studies although these were not consistent and are not likely to be clinically meaningful. There is limited evidence to support the use of 420 mg Q2W in patients with HoFH. There is no evidence to suggest a dose reduction is warranted in adolescents or the elderly, and with mild renal or hepatic disease. The medication is delivered by pre-filled syringe or by auto-injector pen and evidence of the usability and tolerability has been provided.

Indication

The sponsor was requested to amend the wording of the indication by the clinical evaluator to refer to hypercholesterolaemia rather than hyperlipidaemia. It is noted that the European indication and US have further refinements on the indication. The ACPM has been requested to provide advice on the wording of the indication.

Data deficiencies

There are limited data in adolescents, and the implications for growth, neuropsychiatric development and fertility are unknown, and there is limited information available from animal models. In the RMP the sponsor has indicated there will be additional studies in adolescents, although each is short term. There is no direct evidence of an improvement in cardiovascular outcomes with the use evolocumab. A reduction in cardiovascular risk has been noted for similar populations with the use of statins and patients with a non-sense mutation of the PCSK9 gene are noted to have a low incidence of cardiovascular disease.

[58]Syed GH et al Hepatitis C Virus Stimulates Low-Density Lipoprotein Receptor Expression To Facilitate Viral Propagation J Virol March 2014, 88(5):22519-2529

The absence of long term efficacy and safety data from clinical trials has been previously noted and evolocumab has recently been approved for use in Europe and the US so post-market data are very limited.

Conditions of registration

The following are proposed as conditions of registration if evolocumab is approved.

1. Implement EU-RMP version 1.2 dated 28 April 2015 with Australian Specific Annex version 2.0 dated 21 June 2015 and any future updates.
2. Studies 20130295 the LTE from Fourier, and Study 20130385 (neurocognitive outcomes) and 20150162 (pregnancy)
3. Study 20120123 in adolescents with HeFH
4. Study 20120124 in adolescents with HeFH or HoFH
5. The interim and final study reports for Study 20120332 in patients unable to tolerate an effective dose of HMG-CoA reductase inhibitor because of muscle related side effects
6. Study 20110118 to assess the impact of additional LDL-C reduction on major cardiovascular events when evolocumab is used in combination with statin therapy in patients with clinically evident cardiovascular disease

Questions for the sponsor

1. Please comment on any common factors identified among non-responders to evolocumab in the Phase III pivotal trials in primary hypercholesterolaemia and mixed dyslipidaemia.
2. In Study 20110233, in the evolocumab group the PCSK9 percentage reduction was greater at Week 6 (90.1%) than in Week 12 (26.6%). Please comment on the possibility of reduced efficacy of evolocumab over time in this patient group.
3. The efficacy outcomes differed between adult and adolescent patients in Study 20110233. Please comment on the factors that may have contributed.
4. The non-clinical evaluator has noted an absence of data on the homeostatic mechanisms in response to the increased hepatic uptake of cholesterol including the potential for drug interactions based on bile transporters. Please indicate how the sponsor has or is planning to address this.
5. The sponsor provided updated safety information with a data-lock of 1 July 2014 in the response to questions during the evaluation. Please provide a summary of any safety information beyond 1 July 2014 if available. Please include a separate account of hypersensitivity events, neurocognitive events, new onset diabetes and pancreatitis.
6. Please provide an update on progress of the Fourier study (Study 20110118), including an indication of when interim analyses will be made available for evaluation.

Summary of issues

The primary issues with the submission are as follows:

1. The primary endpoint of the pivotal studies in the submission was LDL-C reduction. There were no endpoints in these studies relating to the reduction in cardiovascular mortality or morbidity.
2. There are no long-term safety data.

3. The risks of reducing LDL-C below 1.8 mmol/L are not well quantified.
4. The role of PCSK9 is not fully characterised. Effects on other organ systems of inhibiting PCSK9 are difficult to predict.

Request for ACPM advice

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

1. Whether the evidence provided is sufficient to support the proposed indications?
2. Whether the potential risks with the concomitant use of statins have been sufficiently well characterised?
3. Whether the uncertainty about the long-term safety of evolocumab, including possible neurocognitive effects, the possibility of Hepatitis C virus reactivation or enhanced infectivity, and a possible signal for pancreatitis is acceptable given evolocumab's efficacy?
4. Whether there is/are subgroup(s) of patients for whom the benefits do not outweigh the risks/uncertainties?
5. Whether the indication should be restricted to patients with familial hypercholesterolaemias (heterozygous and homozygous hypercholesterolaemia)?
6. Whether the indication should be modified to restrict the use of evolocumab to patients that failed to achieve LDL-C goals with maximum statin therapy, who are statin-intolerant or for whom statins are contraindicated?
7. Whether there is sufficient evidence to support evolocumab as monotherapy?
8. Whether there is a there specific cause for concern if there is exposure during pregnancy given IgG antibodies that are of a similar size to evolocumab cross the placental barrier?
9. Whether the PI should include instructions for monitoring serum lipids. If so, how frequently should this monitoring occur?
10. Whether the Dosage and Administration section should contain instructions about stopping therapy if there is not initial response?

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.

Proposed action

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

Response from sponsor

The sponsor has accepted the TGA recommendation to include 'adolescents aged 12 and over' in the homozygous familial hypercholesterolaemia indication.

Section A: Questions raised for the ACPM regarding proposed indication

The Delegate proposed 10 questions to the ACPM, 5 of which (1 and 4 to 7) are relevant to the proposed indication. The sponsor believes that indication statement as proposed is appropriate and should not be limited with respect to the questions from the Delegate.

Question 1. Whether the evidence provided is sufficient to support the proposed indications?

Question 4. Whether there is/are subgroup(s) of patients for whom the benefits do not outweigh the risks/uncertainties?

Question 5. Whether the indication should be restricted to patients with familial hypercholesterolaemias (heterozygous and homozygous hypercholesterolaemia)?

Question 6. Whether the indication should be modified to restrict the use of evolocumab to patients that failed to achieve LDLC goals with maximum statin therapy, who are statin intolerant or for whom statins are contraindicated?

Question 7. Whether there is sufficient evidence to support evolocumab as monotherapy?

The sponsor believes that evolocumab as an adjunct to statin therapy is an important therapeutic option for physicians to have for their patients who require additional LDL-C reduction. LDL-C is a major modifiable risk factor for cardiovascular disease and is one of the best validated surrogates in medicine. Though statins are effective and well tolerated, there also remain key groups of patients who still require an additional option for lipid lowering that is both highly effective and safe because either their clinical risk is high, their LDL-C remains high, or both. In addition, there are patients who appear unable to tolerate statins at all or can only tolerate low doses and, thus, are in need of some other type of potent LDL-C reduction. Therefore, there is a clear unmet medical need for patients who need additional robust LDL-C reduction after statins.

Evolocumab has demonstrated consistent and significant reduction in LDL-C with favourable effects on other lipid parameters and the adverse event profile with evolocumab is similar to comparators with no major safety issues identified, including in subjects achieving very low LDL-C levels. Thus, The sponsor believes that evolocumab should be an additional therapeutic option to reduce LDL-C for all patients with primary hypercholesterolaemia and mixed dyslipidaemia (PHMD) and to patients with HoFH.

A robust, comprehensive clinical development programme of 26 clinical studies evaluated the safety, tolerability and efficacy of evolocumab in the intended populations. Sixteen of the 26 studies were Phase II and Phase III studies that directly support the proposed lipid-lowering indications; 14 studies enrolled subjects primarily to support the proposed PHMD indication, and 2 studies enrolled subjects primarily to support the proposed HoFH indication. These 16 studies used various background therapies including diet alone, statins at various doses and intensities and ezetimibe. Eleven of the studies included a placebo and/or ezetimibe control group. Three of the studies were open label extension studies, including 2 studies that used a standard-of-care control (active control) for the first year. Two of the studies were randomised, device-controlled, home-use studies.

An analysis of efficacy across the Phase III studies of PHMD supports the following key conclusions:

- Evolocumab 140 mg Q2W and 420 mg QM resulted in consistent and equivalent LDL-C reduction of approximately 55% to 75% compared with placebo and 35% to 45% compared to ezetimibe in PHMD subjects.
- This effect was observed early and maintained with long-term therapy
- These 2 dosing regimens were effective in all subgroups relative to placebo and ezetimibe, with no notable differences observed between subgroups, such as age, race, gender, region, body mass index, National Cholesterol Education Program risk, statin dose and intensity, current smoking status, baseline coronary heart disease (CHD) risk factors, family history of premature CHD, glucose tolerance status (diabetes mellitus Type 2, metabolic syndrome, or neither), hypertension, unbound baseline PCSK9, baseline LDL-C and baseline triglycerides.

Overall analysis of efficacy in the HoFH studies show the following:

- Evolocumab 420 mg QM reduced LDL by 31% compared to placebo with the 420 mg Q2W dosing regimen providing an additional 6% reduction, akin to doubling of a statin effect in a non-homozygous FH patient.
- No overall difference in efficacy of evolocumab was observed between adolescent and adult subjects with HoFH.

A total of 6026 subjects were exposed to study treatment (any evolocumab or any control) in the Phase II and Phase III studies for the proposed PHMD indication; the cumulative exposure to study treatment was 7235 patient-years and 3669 and 1156 subjects were dosed for ≥ 1 and ≥ 2 years, respectively. Extensive analyses across the PHMD and HoFH populations have not identified major safety issues, including for low LDL-C. Thus, the benefit: risk of evolocumab is favourable and can address the clear unmet medical need for patients who require additional LDL-C reduction beyond what they can achieve with statins and other currently available lipid-lowering therapies.

No subgroup of patients evaluated in the clinical development programme has been identified in which the benefits of evolocumab do not outweigh the risks or uncertainties. Across the Phase III studies of PHMD, evolocumab was effective in all subgroups relative to placebo and ezetimibe. In addition, there were no differences in safety across the populations in the Phase III studies including those patients who were statin intolerant, unable to take statins or unable to take effective doses of statins as well as in any special patient populations assessed (such as geriatric patients, paediatric patients with HoFH).

The proposed indication positions evolocumab as a combination therapy with statins or as second-line therapy in subjects with PHMD and as a combination therapy in subjects with HoFH. In support of evolocumab used as monotherapy, data from a Phase III double blind, randomised, double dummy, placebo and ezetimibe controlled study in 614 subjects with PHMD demonstrated that evolocumab is superior to placebo and ezetimibe in reducing LDL-C and improving other lipid parameters, with no safety risk. In addition, data from another Phase III, multi center, double-blind, randomised, double dummy, ezetimibe controlled Study in 307 statin intolerant subjects demonstrated that evolocumab is superior to ezetimibe in reducing LDL-C and improving other lipid parameters, with no safety risk.

There is unmet need for the treatment of hypercholesterolaemia in patients who, despite statin therapy, are unable to control their LDL-C. The proposed indication positions evolocumab as a combination or second-line LDL-C reduction therapy in these patients with PHMD who require additional LDL-C reduction on top of statins, who have tried and cannot tolerate a statin, or who need a statin, but have a contraindication. The benefit from additional LDL-C reduction extends to all patients in these categories, not just those at the highest levels of cardiovascular risk (eg, those with familial hypercholesterolaemias).

Section B: Other questions raised for the ACPM

The sponsor's position on the other 5 questions from the Delegate to the ACPM (2, 3, and 8 to 10) is provided below.

Question 2. Whether the potential risks with the concomitant use of statins have been sufficiently well characterised?

The sponsor believes that the potential risks with concomitant use of evolocumab with statins have been well characterised. There were no adverse effects (including a detailed assessment of immune function) in a 3 month Cynomolgus monkey study in which evolocumab (at exposure levels up to 21 times higher than patients receiving evolocumab at 420 mg QM) was administered in combination with rosuvastatin. The potential risks of concomitant statin use were also characterised in a total of 4431 subjects (2965 evolocumab, 1466 control) across 8 Phase II and III studies. In particular, the potential

risk of combination therapy with intensive statins was assessed in one of the Phase III studies (N = 329) and also by statin type and intensity in another of the Phase III studies (N = 1896). Overall, the results of these evaluations demonstrated that evolocumab had an acceptable safety profile in all populations and with a broad range of background statin therapy, with no clinically relevant differences observed between the evolocumab and control treatment groups for the varying statin types and intensities. Adverse events were mild or moderate in severity and serious adverse events and adverse events leading to discontinuation of investigational product were infrequently reported. Furthermore, no relevant differences between the evolocumab and control (placebo or ezetimibe) treatment groups were observed in reactions associated with other lipid-lowering therapies (diabetes, liver and muscle events), and no safety risks were associated with low LDL-C levels. Evolocumab combination therapy did not have a different safety profile compared with evolocumab monotherapy.

Question 3. Whether the uncertainty about the long term safety of evolocumab, including possible neurocognitive effects, the possibility of Hepatitis C virus reactivation or enhanced infectivity and a possible signal for pancreatitis is acceptable given evolocumab's efficacy?

The sponsor has not identified a safety risk for neurocognitive events, Hepatitis C virus infection, or pancreatitis, even with long-term use of evolocumab, based on the data from the evolocumab clinical development programme.

Most of the neurocognitive events were non-serious and mild or moderate in severity. No overall pattern related to time to onset or outcome was identified, regardless of whether the subject continued or discontinued evolocumab therapy and most subjects had confounding factors. Subjects with risk factors for hepatitis-C were tested for hepatitis-C antibodies across the evolocumab programme and a limited number of subjects (9 in total) were diagnosed with hepatitis-C. Most subjects had undetectable virus levels, and all had either stable or mildly elevated (1 subject) liver function tests throughout the studies. Additionally, the weight of evidence from literature supports that evolocumab mediated PCSK9 inhibition would not increase neurocognitive or Hepatitis C virus infection risks (viral entry or replication). These evaluations were presented in detail in responses to previous questions raised by the TGA.

Based on comprehensive reviews of nonclinical and clinical data, including evaluations of the 01 July 2014 dataset, no safety risk was identified for pancreatitis. Nonclinical data generated by The sponsor (for example, no evidence of gallstones in studies up to lifetime exposure and preliminary research data showing no change in hepatic cholesterol level, gall bladder bile acid composition or bile acid excretion rate) together with published data in PCSK9 knockout mice[59] are consistent with the ability of the liver to accommodate an increase in lipoprotein delivery following PCSK9 inhibition without any adverse consequences, which supports the conclusion that evolocumab would not increase the risk for pancreatitis. In the integrated Phase II and III clinical studies, the overall incidence of pancreatitis was low (≤ 0.1%) for evolocumab and control treatment groups in the PHMD population, and individual cases were found to have alternative explanations or confounding factors, including alcohol use or gallstones. Incidence rates fell with accumulating data within the range seen in similar populations, based on epidemiologic data. No pancreatitis adverse events were reported in the HoFH population.

Therefore, the sponsor believes that the safety risk for neurocognitive events, Hepatitis C virus infection, and pancreatitis is acceptable given lack of an observed safety signal and the established benefits of evolocumab. The sponsor will continue to monitor long-term safety, including these events, in clinical trials and in the postmarketing setting as part of routine pharmacovigilance.

[59]Parker RA, Garcia R, Ryan CS, et al. Bile acid and sterol metabolism with combined HMG CoA reductase and PCSK9 suppression. *J Lipid Res*. 2013;54:2400-2409.

Question 8. Whether there is a specific cause for concern if there is exposure during pregnancy given IgG antibodies that are of a similar size to evolocumab cross the placental barrier?

The clinical data for evolocumab use in human pregnancy is very limited. However, the potential risk to embryo-fetal and neonatal development was extensively assessed in the Cynomolgus monkey, a biologically relevant model for human pregnancy, both in terms of placental transfer kinetics and infant cholesterol metabolism.[60, 61] No adverse effects were observed in pregnant monkeys dosed with evolocumab throughout gestation or in the newborn infants who were studied closely for a 6 month postnatal period. Measurable evolocumab serum concentrations were observed in infant monkeys at birth at comparable levels to maternal serum, indicating that evolocumab, like other monoclonal antibodies, crosses the placental barrier. However, placental transfer of monoclonal antibodies during organogenesis, generally regarded as the most sensitive period of embryo-fetal development, is known to be low. [60]

Evolocumab produced the expected pharmacological effect in pregnant female monkeys throughout the dosing phase, although there was a lack of pharmacological effect in infants, irrespective of exposure level. While the fetus requires cholesterol for normal development during pregnancy, the fetus synthesises at least 80% of its own cholesterol rather than deriving it from maternal circulation.[62, 63] Consistent with its mechanism of action, there are no data indicating that evolocumab impacts cholesterol synthesis and, therefore, evolocumab would not be expected to disrupt fetal cholesterol synthesis. Furthermore, a recent report showed that in humans, PCSK9 levels in newborn infants were significantly lower than their mothers.[64] Although PCSK9 levels were not measured in the Cynomolgus monkey study, the postnatal pharmacokinetics would be consistent with reduced target-mediated clearance of evolocumab in infants compared to their mothers. These differences, coupled to the age-specific differences in cholesterol homeostatic control in newborns, suggest that PCSK9 plays a less important role in the regulation of serum LDL-C levels in infants compared to later life stages and support the conclusion that exposure of human infants to evolocumab would result in a similar lack of effect on LDL-C.

Question 9. Whether the PI should include instructions for monitoring serum lipids. If so, how frequently should this monitoring occur?

The sponsor considers that additional lipid monitoring beyond that recommended in current lipid management guidelines (for example, Guidelines for the Management of Absolute Cardiovascular Disease Risk by the Australian National Vascular Disease Prevention Alliance [NVDPA, 2012]) is not required, based on available clinical literature and nonclinical and clinical data from the evolocumab clinical development programme. Collectively, these data show that the response to evolocumab is predictable and consistent across multiple patient types and that there was no evidence of harm associated with very low LDL-C concentrations observed with evolocumab administration. Therefore, the routine monitoring of patients according to lipid management guidelines

[60]Moffat GJ, Retter MW, Kwon G et al. Placental transfer of a fully human IgG2 monoclonal antibody in the cynomolgus monkey, rat and rabbit: a comparative assessment from during organogenesis to late gestation. *Birth Defects Res Part* B. 2014; 101:178-188.
[61]Dietschy JM, Turley SD. Cholesterol metabolism in the central nervous system during early development and in the mature animal. *J Lipids Res*. 2004;45:1375-1397.
[62]Bartels A, O'Donoghue K. Cholesterol in pregnancy: a review of knowns and unknowns. *Obstetric Medicine* 2011; 4:147-151.
[63]Woollett LA. Maternal cholesterol in fetal development: transport of cholesterol from the maternal to the fetal circulation. *Am J Clin Nutr*. 2005;82:1155-1161.
[64]Peticca P, Raymond A, Gruslin A, et al. Human serum PCSK9 Is elevated at parturition in comparison to nonpregnant subjects while serum PCSK9 from umbilical cord blood is lower compared to maternal blood. *ISRN Endocrinol*. 2013, 341632.

and the physician's judgment will be sufficient for all patients who receive evolocumab and additional monitoring instructions would not be necessary or appropriate for inclusion in the PI.

Question 10. Whether the Dosage and Administration section should contain instructions about stopping therapy if there is not initial response?

The sponsor does not believe that instructions about stopping evolocumab therapy in the absence of an initial response is necessary or appropriate for the PI since the management of evolocumab treatment, as for any lipid-lowering therapeutic, would be based on the physician's assessment of benefit: risk according to the individual patient's needs and current lipid management guidelines (for example, NVDPA's Guidelines for the Management of Absolute Cardiovascular Disease Risk).

Section C: Outstanding questions for the sponsor

Question 1. Please comment on any common factors identified among non-responders to evolocumab in the Phase III pivotal trials in primary hypercholesterolaemia and mixed dyslipidaemia.

Non-responders to evolocumab were rare in the Phase III clinical program and no common factors were identified among such subjects.

For the purposes of this question, 'non-responder to evolocumab' was defined as a subject who did not have a low-density lipoprotein cholesterol (LDL-C) response (did not have an LDL-C reduction of ≥ 15% from baseline) at any point in the respective study despite detectable serum evolocumab levels. Overall, 5/6026 (0.08%) subjects met this definition. Three subjects were identified during the initial parent studies (2 subjects from Study 20110116 and 1 subject from Study 20110115) and 2 additional subjects were identified during long-term open-label extension Study 20120138 (1 from parent Study 20110116 and 1 from parent Study 20110115). Overall, none of the 5 subjects tested positive for anti-evolocumab antibodies and all had LDL-C values at baseline that were consistent with a diagnosis of heterozygous familial hypercholesterolemia (HeFH).

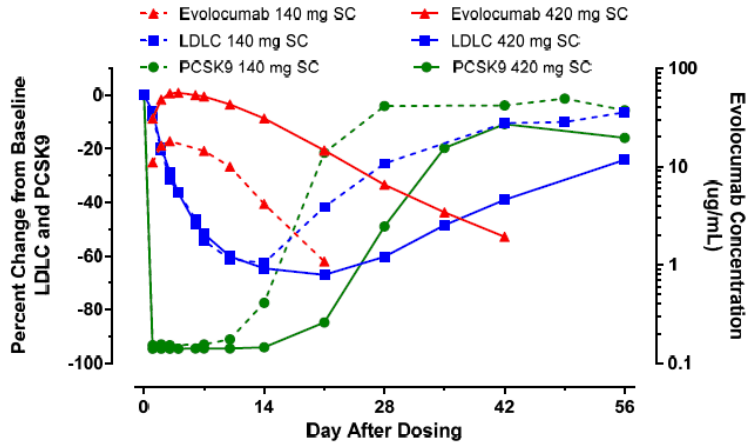
Three subjects (Study 20110116) had a genetic diagnosis of HeFH and 2 had the same LDL receptor genotype of C143X; however, others with this genotype have been shown to respond to evolocumab (Study 20110271).

Question 2.In Study 20110233, in the evolocumab group the PCSK9 percentage reduction was greater at Week 6 (90.1%) than in Week 12 (26.6%). Please comment on the possibility of reduced efficacy of evolocumab over time in this patient group.

The greater magnitude of PCSK9 reduction at Week 6 (halfway through the dosing interval) compared to Week 12 (at the end of the dosing interval, or trough) among subjects receiving evolocumab in Study 20110233 is consistent with the known pharmacokinetics of the 420 mg once monthly dose of evolocumab. The observed difference in LDL-C reduction at Week 6 is due to the Week 6 time point occurring at the mid-point of the dosing cycle (peak) rather than immediately pre dose (trough) as is seen at Week 12.

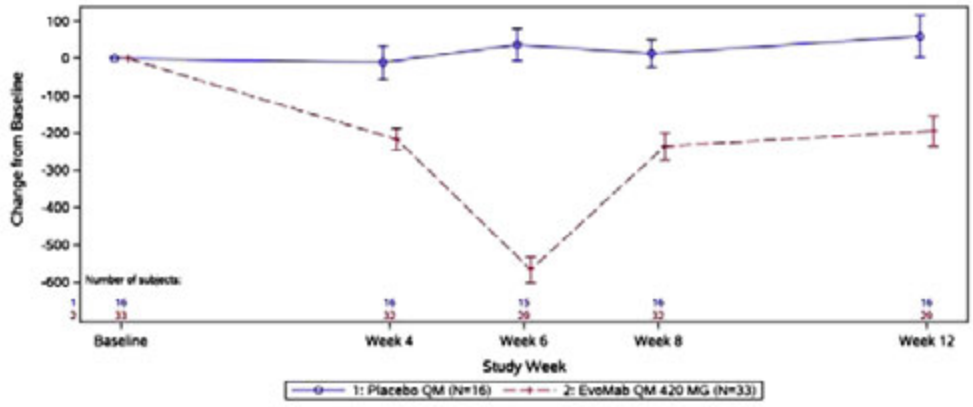
In Study 20110233, all subjects were to receive investigational product (evolocumab 420 mg or matching placebo) every 4 weeks (Day 1, Week 4 and Week 8). As noted, the mean percent reduction from baseline was greater at Week 6 (90.1%) than in Week 12 (26.6%). This is expected, as PCSK9 levels are known to start increasing toward the end of the dosing interval (Figure 4). The percent reductions from baseline at Weeks 4 and 8 (32.1% and 33.3%, respectively; Figure 5), which are also trough time points, are comparable to that seen at Week 12, consistent with a stable effect of evolocumab on PCSK9 over time despite a cyclic effect over the course of a dosing interval.

Figure 4: Mean Unbound Evolocumab Serum Concentrations and Mean Percent Change From Baseline in Ultracentrifugation LDL-C and Unbound PCSK9 After a Single Dose in Healthy Subjects



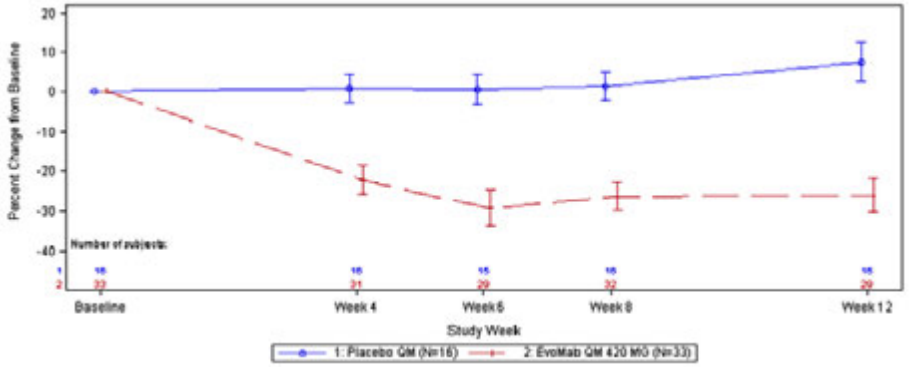
LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SC =subcutaneous. Dashed lines = 140 mg dose, Solid lines = 420 mg dose. Red symbols = unbound evolocumab concentrations, green symbols = unbound PCSK9, blue symbols = LDL-cholesterol

Figure 5: Plot of Mean Change From Baseline in PCSK9 in ng/mL by Scheduled Visit and Treatment Group Study 20110233 Phase III (Full Analysis Set)



N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly; PCSK9 = Proprotein convertase subtilisin/kexin type 9 Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.

Figure 6: Plot of Mean Percent Change From Baseline in Calculated LDL-C by Scheduled Visit and Treatment Group Study 20110233 Phase III (Full Analysis Set)



LDL-C = low-density lipoprotein cholesterol; N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.

In conclusion, the observed difference in percentage reduction in PCSK9 levels among patients receiving evolocumab in Study 20110233 at Week 6 and Week 12 is due to expected cyclic variation over the dosing interval. This observation is consistent with the known pharmacokinetics of evolocumab, and does not indicate reduced efficacy over time.

Question 3.The efficacy outcomes differed between adult and adolescent patients in Study 20110233. Please comment on the factors that may have contributed.

Study 20110233 evaluated evolocumab therapy in adults (age 18 to 80 years) and adolescents (age 12 to < 18 years) with HoFH. Results at Week 12 for the primary efficacy endpoint (low-density lipoprotein cholesterol [LDL-C]) and the secondary efficacy endpoints (apolipoprotein B [ApoB] and Lp(a)) in Study 20110233 Phase III are summarised by age group in Table 29. Despite the comparatively small number of subjects in each age group and the known increased variability of efficacy in HoFH subjects, the reduction in LDL-C and ApoB was comparable between the adult and adolescent populations, both for least square mean (LSM) changes and for observed mean changes from baseline to Week 12. Additionally, the observed mean changes in Lp(a) among adolescents were comparable to the LSM and observed mean changes in adults.

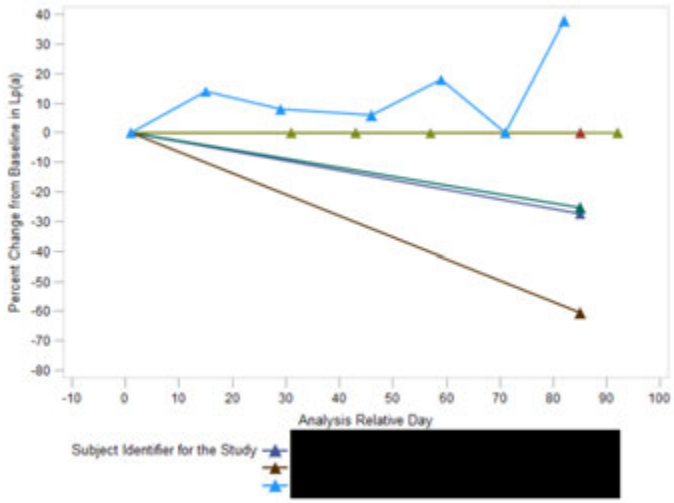
The LSM change from baseline in Lp(a) at Week 12 among adolescents was discrepant with the observed mean change from baseline. This was due to a combination of a comparatively small sample size, particularly for time-points between baseline and Week 12 when data were available for only 3 subjects, affecting the model, and large inter-subject variability as evidenced by large standard errors. Review of individual subject results showed that they were better represented by the observed mean than by the LSM result. Of the 7 adolescents in the evolocumab group, all had stable or decreased Lp(a) values at Week 12 except for 1 subject with low-density lipoprotein receptor (LDLR) negative phenotype recorded at baseline (Figure 7). No adult subjects in the evolocumab group had LDLR negative phenotype. For the aforementioned reasons, this subject's Lp(a) data had a substantial effect on the model estimates for LSM changes and the discrepancy between the LSM change and the observed mean change from baseline. Because of these factors, the observed discrepancy in LSM values for Lp(a) appears to represent the limitations of the modelled LSM in a small and variable group, rather than a true difference in efficacy between adults and adolescents, making the observed mean change from baseline a more appropriate statistic to describe the cohort characteristics in this particular case.

Table 29: Percent Change from Baseline to Week 12 for Primary and Secondary Lipid Parameters among Adults and Adolescents in Study 20110233 Phase III

	Adults (18 to 80 years)				Adolescents (12 to < 18 years)			
	Placebo (N = 13)	Evolocumab 420 mg QM (N = 26)	Treatment Difference (SE)	p	Placebo (N = 3)	Evolocumab 420 mg QM (N = 7)	Treatment Difference (SE)	p
UC LDL-C								
LS Mean	10%	-23%	-33 (7)%	<0.001	1%	-26%	-27 (16)%	0.14
Observed Mean	6%	-25%	-	-	5%	-31%	-	-
ApoB								
LS Mean	3%	-18%	-21 (7)%	0.003	3%	-13%	-16 (17)%	0.39
Observed Mean	2%	-19%	-	-	7%	-26%	-	-
Lp(a)								
LS Mean	3%	-9%	-12 (7)%	0.090	-9%[a]	8%[a]	17 (22)%[a]	0.47
Observed Mean	2%	-10%	-	-	-1%	-15%	-	-

ApoB = apolipoprotein B; Lp(a) = lipoprotein(a); LS = least square; QM = once monthly; UC LDL-C = ultracentrifugation low-density lipoprotein cholesterol; SE = standard error. [a]Least squares mean is from the repeated measures model, which includes treatment group, stratification factor(s), scheduled visit, and the interaction of treatment with scheduled visit as covariates, as well as unstructured covariance matrix. For Lp(a) data among adolescents, due to small sample size, the mixed model did not converge and an alternate model with compound symmetry was used.

Figure 7: Line Plot of Lp(a) for Adolescents in the Evolocumab Treatment Group of Study 20110233 Phase III



Note: Data points overlapped for Subjects [information redacted] (no post-baseline assessment), and [information redacted] (only post-baseline visit on Day 85).

Question 4.The nonclinical evaluator has noted an absence of data on the homeostatic mechanisms in response to the increased hepatic uptake of cholesterol including the potential for drug interactions based on bile transporters. Please indicate how the sponsor has, or is planning to address this.

In the response provided to the nonclinical evaluator in May 2015, the sponsor presented additional data to address the above concern. These data included preliminary research with an evolocumab homologue indicating that increased hepatic cholesterol trafficking as a result of PCSK9 inhibition does not disrupt hepatic lipid/bile acid homeostasis.

These results are consistent with previously published research in PCSK9 knockout mice which showed that in the absence of PCSK9, expression of bile acid transporter proteins was unaffected.[65] These data would suggest that in the presence of a PCSK9 inhibitor like evolocumab, the pharmacokinetic/pharmacodynamic profile of drugs that may utilise

[65]Parker RA, Garcia R, Ryan CS, et al. Bile acid and sterol metabolism with combined HMG CoA reductase and PCSK9 suppression. *J Lipid Res*. 2013;54:2400-2409.

these transport mechanisms such as statins would also be unaffected. This hypothesis was supported by nonclinical and clinical data generated with evolocumab which showed no effect on the disposition of rosuvastatin, a known substrate for bile transporters. In summary, these additional data provided evidence that the increased hepatic cholesterol trafficking induced by evolocumab does not disrupt biliary homeostasis or affect the expression of bile acid transporter proteins thus removing any potential concern for possible drug interactions. Further detail is provided below.

There are several well characterised feedback control mechanisms that tightly regulate hepatic cholesterol and bile acid homeostasis including reduction in endogenous cholesterol biosynthesis[66], excretion directly into the bile as free cholesterol (via ABCG5/G8 transporters;[67]) or conversion of cholesterol into bile acids (regulated by CYP7A1) and excretion into bile.[68] These mechanisms have been shown to compensate for increased hepatic LDLR activity in PCSK9 knockout (KO) mice, where liver triglyceride, cholesterol, and bile acid content was equivalent to wild-type mice[69] even following treatment with a statin[59].

Preliminary data from the sponsor indicate similar results in the presence of an anti-PCSK9 monoclonal antibody. Single administration of an evolocumab homologue (26H5) to hamsters reduced serum non-HDL-C by approximately 80% compared to baseline and was associated with no changes in gall bladder bile acid composition with respect to the ratio of cholesterol to phospholipids and bile acids at study termination (6 days following the administration of anti-PCSK9 antibody). The level of liver cholesterol, cholesterol ester, and triglyceride in 26H5 treated animals were not significantly different compared to control animals. Further, there was no increase in the fecal bile acid excretion rate.

Published results in PCSK9 KO mice confirmed and extended these data further by also examining bile acid transporter expression.[59] These investigators studied the effect of PCSK9 deficiency by comparing PCSK9 KO mice with their wild type background strain, with or without atorvastatin over a 12 week period. In this study, the hepatic gene expression of a number of bile acid transporters (Asbt, Bsep, Ntcp and Oatp) showed no statistically significant changes, regardless of genotype (PCSK9 KO vs wild type) or treatment (+/- atorvastatin). It is also reasonable to conclude that other bile acid transporters not assessed in this study such as Mrp3 and Mrp4 were unaffected.

Increased Mrp3 and/or Mrp4 expression would be expected to result in increased plasma levels of bile acids but there was no difference in plasma bile acid or liver bile acid and cholesterol levels, regardless of genotype or treatment. Consistent with the data described above for evolocumab and its homologue 26H5, the authors concluded that 'the liver handles its responsibilities very well even when faced with the profound LDL lowering action of the combined PCSK9-statin mechanism'.[59]

Further evidence that the potential for drug-drug interactions with evolocumab is considered low was demonstrated in a study with nonhuman primates. Unbound evolocumab serum and total rosuvastatin plasma concentrations were measured in a combination toxicology study where Cynomolgus monkeys received rosuvastatin alone or in combination with evolocumab. These data demonstrated that evolocumab had no effect on rosuvastatin concentrations and that rosuvastatin did not alter unbound evolocumab serum concentrations in Cynomolgus monkeys. Rosuvastatin is a known substrate for the

[66]Espenshade PJ, Hughes AL. Regulation of sterol synthesis in eukaryotes. *Annu Rev Genet*. 2007;41:401-427.
[67] Wu JE, Basso F, Shamburek RD, et al. Hepatic ABCG5 and ABCG8 overexpression increases hepatobiliary sterol transport but does not alter aortic atherosclerosis in transgenic mice. *J Biol Chem*. 2004;279:22913-22925.
[68] Russell DW. The enzymes, regulation, and genetics of bile acid synthesis. *Annu Rev Biochem*. 2003;72:137-174.
[69] Rashid S, Curtis DE, Garuti R, et al. Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9. *Proc Natl Acad Sci USA.* 2005;102:5374-5379.

organic anion transporter polypeptides (OATP1B1, 1B2, 1B3 and 1A2) and the sodium taurocholate co-transporting polypeptide (NTCP)[70,71] which are all expressed in the Cynomolgus monkey (NIH HomoloGene). Since evolocumab did not alter the disposition of rosuvastatin in non-human primates, then it is unlikely that evolocumab altered the expression or function of these or other bile acid transporters.

Clinical data lends further support to this conclusion. A Phase Ib study (Study 20080398), examined the effect of evolocumab (dosed at 140 mg Q2W) on the steady state concentrations of rosuvastatin. In subjects (n=7) receiving 40 mg of rosuvastatin upon study entry, no changes in the mean rosuvastatin concentrations were observed over a 12 week period suggesting that evolocumab had no effect on the clearance of rosuvastatin at an evolocumab dose that produced maximum PCSK9 and LDL-C lowering.

Together, these data support the conclusion that evolocumab does not affect the expression of bile acid transporter proteins thus removing any potential concern for possible drug interactions.

Question 5.The sponsor provided updated safety information with a data lock of 1 July 2014 in the response to questions during the evaluation. Please provide a summary of any safety information beyond 1 July 2014 if available. Please include a separate account of hypersensitivity events, neurocognitive events, new onset diabetes and pancreatitis.

The sponsor's Summary of Clinical Safety in the original marketing application (MA) for evolocumab included data from 16 Phase II and Phase III studies through a data cut-off date of 01 April 2014. The safety of evolocumab has been further evaluated using a more recent dataset, which included cumulative safety data with a data cut-off date of 01 July 2014 from the 3 ongoing extension studies (Studies 20110110, 20120138 and 20110271). No notable differences were observed in the types and incidences of serious adverse events, adverse events leading to discontinuation of investigational product, adverse events of special interest or device related treatment emergent adverse events using data from the 01 July 2014 dataset compared with those reported in the original MA (01 April 2014 dataset) and the findings did not change the conclusions of the initial MA. Additionally, in the Year 1 standard of care (SoC) controlled period, the cumulative incidence and severity of adverse events were similar in the 01 July 2014 dataset compared with the original MA. No new safety risks were identified and evolocumab continues to have a favourable safety profile based on these updated data. No additional data cuts to support a full safety analysis have been completed since the 01 July 2014 data cut.

Regarding the events specified in this question, please note that a comprehensive safety evaluation of neurocognitive events, hypersensitivity events and diabetes related events based on the 01 July 2014 dataset was previously provided. No safety risks were identified for neurocognitive events, hypersensitivity events, or diabetes related events with evolocumab use.

Additionally, as described in the sponsor's comment on evaluations Section B Question 3, based on comprehensive reviews of nonclinical and clinical data (using the 01 July 2014 dataset); no safety risk was identified for pancreatitis with evolocumab use.

The sponsor will continue to conduct comprehensive safety surveillance through routine pharmacovigilance activities both in clinical trials and in the postmarketing setting.

[70]Ho RH, Tirona RG, Leake BJ et al. Drug and bile acid transporters in rosuvastatin hepatic uptake: function, expression and pharmacogenetics. *Gastroenterology* 2006;130:1793-1806

[71]Niemi M, Pasanen MK, Neuvonen PJ. Organic Anion Transporting Polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacological Reviews* 2011;63:157-181

Question 6

Please provide an update on progress of the Fourier study (Study 20110118), including an indication of when interim analyses will be made available for evaluation.

The cardiovascular outcomes Study 20110118 (FOURIER) is event driven. As a result, the projected dates are based on estimates of when the cardiovascular events specified in the protocol will be achieved. Current estimates for the study's progress are as follows:

- Last Patient Enrolled: June 2015
- Estimated Trial Completion: September 2017
- Final Report Submission: June 2018

The Data Monitoring Committee regularly reviews the study data on an unblinded basis and can provide advice to the sponsor regarding changes to the conduct of the study.

To date, no Data Monitoring Committee intervention has required changes to the study. No interim analyses are planned for this study.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Repatha solution for injection containing 140 mg/mL 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***
>
> *Adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD) in combination with a statin or statin with other lipid lowering therapies, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant.*
>
> ***Homozygous familial hypercholesterolemia (HoFH)***
>
> *In combination with other lipid lowering therapies in adults and adolescents aged 12 years and over.*
>
> *The effect of Repatha on cardiovascular morbidity and mortality has not been determined.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

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

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the statements included in the section *Specific Advice* below.

Specific Advice

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

1. *Whether the evidence provided is sufficient to support the proposed indications?*

The ACPM considered the evidence submitted was sufficient to support the proposed modified indications.

2. *Whether the potential risks with the concomitant use of statins have been sufficiently well characterised?*

The ACPM advised there is sufficient evidence of support for use with statins providing the PI states;

- The limitations of outcome data; the PRECAUTIONS section should include a statement that treatment with REPATHA may lead to very low serum cholesterol levels (that is, LDL-C < 0.65 mmol/L) where safety has not yet been established.
- The very limited data in adolescents and
- The need for long term monitoring of unanticipated effects and sequelae of very low LDL.

3. *Whether the uncertainty about the long-term safety of evolocumab, including possible neurocognitive effects, the possibility of Hepatitis C virus reactivation or enhanced infectivity, and a possible signal for pancreatitis is acceptable given evolocumab's efficacy?*

The ACPM advised on the need for more long term data, but little or no evidence of harm has been reported to date. The ACPM considered whether this represented the absence of evidence rather than evidence of absence of harm. While there is the hint of a safety signal for neurocognitive effects and pancreatitis the rate of reported AEs is non-significant and the number of patients evaluated in the safety gives reassurance. The RMP is considered adequate. However, along with reactivation of Hepatitis C these events should be monitored and reported.

4. *Whether there is/are subgroup(s) of patients for whom the benefits do not outweigh the risks/uncertainties?*

The lack of data in adolescents suggests this population should be excluded (other than for HoFH) until more is known about the effects on growth and maturation.

5. *Whether the indication should be restricted to patients with familial hypercholesterolaemias (heterozygous and homozygous hypercholesterolaemia)?*

The ACPM advised that the lack of evidence of safety in particular, limits widespread use and the restriction to patients with familial hypercholesterolaemias is necessary.

6. *Whether the indication should be modified to restrict the use of evolocumab to patients that failed to achieve LDL-C goals with maximum statin therapy, who are statin-intolerant or for whom statins are contraindicated?*

The ACPM was of the view that the restriction to patients that failed to achieve LDL-C goals with maximum statin therapy or who are statin-intolerant is warranted until there is more understanding of the long term effects of very low serum cholesterol levels. The ACPM was concerned for patients '.for whom statins are contraindicated' (in pregnancy; in active liver disease/unexplained elevations of LFTs, and most are contraindicated with concomitant use with fusidic acid) as there is little or no evidence of safety or efficacy in these patient groups for Repatha.

7. *Whether there is sufficient evidence to support evolocumab as monotherapy?*

The ACPM advised that despite 2 short term studies of monotherapy there is a lack of long term data for monotherapy. Guidelines suggest a 1 year duration of studies, while the studies submitted are only of 12 weeks duration. The lack of outcome data and of long term safety data, as well as the excellent alternative treatments available means the use of this agent as monotherapy is not currently supported.

8. *Whether there is a there specific cause for concern if there is exposure during pregnancy given IgG antibodies that are of a similar size to evolocumab cross the placental barrier?*

There are few pregnancy data in humans. Statins have a Pregnancy classification of D with pregnancy listed as a contraindication. The ACPM advised caution, given the animal data and the limited potential access to the developing brain by large molecules, the proposed Pregnancy Category B1 seems appropriate. The lack of data on very low cholesterol levels would indicate caution is definitely warranted.

9. *Whether the PI should include instructions for monitoring serum lipids. If so, how frequently should this monitoring occur?*

The ACPM advised that monitoring of cholesterol may be left as a clinical decision, particularly given that there is no up-titration of dose available.

Notwithstanding this view, the ACPM advised that only monitoring and notification of very low LDL will answer questions concerning safety at <0.6 mmol/L. A possible scenario could be at least yearly monitoring with notification of all individuals with LDL < 0.6 mmol/L. This may require a specific registry.

10. *Whether the dosage and administration section should contain instructions about stopping therapy if there is not initial response?*

The data suggest that non responders appear to be limited to HoFH patients with 2 LDL-R negative alleles and treatment in these patients could be discontinued.

The ACPM 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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Repatha evolocumab (rch) 140 mg/mL injection solution syringe and Repatha evolocumab (rch) 140 mg/mL injection solution syringe within a pen injector for SC administration, indicated for:

> *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.*

Specific conditions of registration applying to these goods

1. The evolocumab EU-Risk Management Plan (RMP), version 1.2, dated 28 April 2015 with Australian Specific Annex version 2.0 dated 21 June 2015, included with

submission PM-2014-03144-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia

2. You [the sponsor] are to provide the clinical study reports for the following studies to the TGA for evaluation as Category 1 submission when available:
   - Study 20120332 in patients unable to tolerate an effective dose of HMGCoA reductase due to muscle related side effects
   - Study 20120123 in adolescents with heterozygous familial hypercholesterolaemia
   - Study 20120124 in adolescents with heterozygous or homozygous familial hypercholesterolaemia
   - Study 20110118 (the Fourier study)
   - Study 20130385 investigating neurocognitive outcomes
   - Study 20130295, the long term extension study to assess long term safety in patients with clinically evident cardiovascular disease
   - Study 20150162 in pregnant patients
3. You [the sponsor] will continue to investigate and monitor for neurocognitive adverse events.
4. Batch Release testing by OLSS: It is a condition of registration that, as a minimum, the first five independent batches of:
   a. Repatha evolocumab (rch) 140 mg/mL injection solution syringe
   b. Repatha evolocumab (rch) 140 mg/mL injection solution syringe within a pen injector imported into Australia are not released for sale until samples and/or
   c. The manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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