21 May 2015
EMA/CHMP/222019/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Repatha

International non-proprietary name: evolocumab

Procedure No. EMEA/H/C/003766/0000

Note

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

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List of abbreviations

AAV	Adeno-associated Virus
ACTH	adrenocorticotropic hormone
ADA	Anti-drug-antibody
AE	adverse event
AI/pen	prefilled autoinjector/pen
ALT	alanine aminotransferase
AMD	automated mini doser (formerly referred to as LVI [larger volume injector] and 3.5 mL personal injector)
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ApoB	Apolipoprotein B
AST	aspartate aminotransferase
ATP	adult treatment panel
AUC	Area under the curve
AUC	area under the concentration time curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration time curve from time 0 to the last quantifiable concentration
AUC_{x-y}	area under the concentration-time curve from time x to time y
$AUEC_{x-y}$	area under the effect curve from time x to time y
BA	bioavailability
BBB	Blood Brain Barrier
BD	Birth day
BE	bioequivalence
BLA	biologics license application
bpm	beats per minute
CAD	coronary artery disease
CAS	completer analysis set
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	confidence interval
CK	creatine kinase
CL	clearance
CL/F	estimated mean apparent clearance
Cmax	Maximum concentration
C_{max}	maximum concentration
CMC	Chemistry, Manufacturing, and Controls
CrCL	creatinine clearance
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVD	cardiovascular disease
DDI	Drug-drug-interactions
DMC	data monitoring committee

EC_{50}	area under the concentration-time curve from week 8 to week 12 required to achieve half-maximal response
ECG	electrocardiogram
E*ff*	effect magnitude
eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ELISA	enzyme-linked immunosorbent assay
EPD	Embryo-foetal and Postnatal Development
EvoMab	evolocumab (AMG 145)
F	bioavailability
FAS	full analysis set
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
GD	Gestation day
GLP	Good Laboratory Practice
GOF	Gain of Function
HbA1c	hemoglobin A1c
HCV	Hepatitis C Virus
HDL C	high density lipoprotein cholesterol
HDL-c	High Density Lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
IDL C	intermediate density lipoprotein cholesterol
IgG	Immunoglobulin type G
IgG2	immunoglobulin G2
IgM	Immunoglobulin type M
IP	investigational product
IV	Intravenous
IV	intravenous(ly)
K_a	absorption rate constant
K_m	concentration of half maximal nonlinear clearance
KO	Knock-out
LDL C	low density lipoprotein cholesterol
LDL	low density lipoprotein
LDL-c	High Density Lipoprotein cholesterol
LDLR	High Density Lipoprotein receptor
LDLR	low density lipoprotein receptor
LLOQ	lower limit of quantification
LOF	Loss of Function
LOF	loss of function

Lp(a)	lipoprotein(a)
LS	least squares
mAb	Monoclonal antibody
NCEP	National Cholesterol Education Program
NDS	new drug submission
NKC	Natural Killer Cells
NOEL	No observed effect level
non HDL C	non high density lipoprotein cholesterol
OLE	open label extension
PCSK9	proprotein convertase subtilisin/kexin type 9
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK / PD	Pharmacokinetics / Pharmacodynamics
PK	pharmacokinetic(s)
PPD	Post partum day
Q2W	Once every two weeks
Q2W	once every 2 weeks
QD	Daily
QD	once daily
QM	Once monthly
QM	once monthly
QTcF	QT interval using Fridericia's correction
QW	Once weekly
RBC	red blood cells
RES	reticuloendothelial system
SC	Subcutaneous
SC	subcutaneous(ly)
SD	standard deviation
SE	standard error
SoC	standard of care
SOC	system organ class
Statin	hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor
TC	total cholesterol
TCR	Tissue Cross Reactivity
TDAR	T-cell dependent antibody response
TG	Triglycerides
TK	Toxicokinetics
Tmax	Time at maximum concentration
t_{max}	time to maximum concentration

UC	Ultracentrifugation
ULN	upper limit of normal
V	volume of distribution
VAS	visual analog pain scale
VLDL C	very low density lipoprotein cholesterol
VLDL-c	Very low density lipoprotein cholesterol
VLDLR	Very low density lipoprotein receptor
V_{max}	nonlinear clearance capacity
Vss	Volume of distribution at steady-state
V_{ss}	mean volume of distribution at steady state
Vz/F	Unbound volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 29 August 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Repatha, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2013.

The applicant applied for the following indications:

Hypercholesterolaemia and mixed dyslipidaemia: Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non- HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG) and lipoprotein(a) (Lp(a)), and to increase (HDL-C) and (ApoA1):

- 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
- alone or in combination with other lipid lowering therapies in patients for whom a statin is not considered clinically appropriate.

Homozygous familial hypercholesterolaemia: Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia to reduce LDL-C, total cholesterol, ApoB, and non-HDL-C in combination with other lipid-lowering therapies.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that evolocumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0127/2013 on the agreement of a paediatric investigation plan (PIP) for the treatment of hypercholesterolaemia and the granting of a waiver for the treatment of mixed dyslipidaemia.

At the time of submission of the application, the PIP (Decision P/0127/2013) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance evolocumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union

Scientific Advice

The applicant received Scientific Advice from the CHMP on 20 September 2012. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

A new application was filed in the following countries: Unites States and Australia.

1.2. Manufacturers

Manufacturers responsible for batch release

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Amgen Technology Ireland
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

1.3. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Alar Irs

- The application was received by the EMA on 29 August 2014.
- The procedure started on 24 September 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2014.
- During the meeting on 9 January 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 22 January 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 January 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 February 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 March 2015.
- During the meeting on 10 April 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 21 April 2015, outstanding issues were addressed by the applicant during an oral explanation before the CHMP. On 23 April 2015, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 28 April 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 8 May 2015.
- Following a written procedure, the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan on 12 May 2015.
- During the meeting on 21 May 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Repatha.

2. Scientific discussion

2.1. Introduction

Primary hypercholesterolemia by definition is any hypercholesterolemia which is caused by a disorder (either familial- or nonfamilial-) in lipid metabolisms and is not caused secondarily by another reason, such as hypothyroidism, or a drug effect.

Hyperlipidemia is the heterogeneous group of disorders characterized by an excess of lipids (ie, cholesterol, phospholipids, triglycerides) in the bloodstream. Hypercholesterolemia, specifically refers to the presence of high levels of cholesterol in the blood. Primary hyperlipidemia is usually due to genetic causes (monogenetic or polygenetic) and environmental factors, such as diet and lifestyle. Primary nonfamilial hyperlipidemia is hyperlipidemia that is not due to a specific genetic disorder, although there are polygenetic influences. **Mixed dyslipidemia** is generally defined as elevated LDL-C and high triglycerides and/or low HDL-C.

Familial Hyperlipidemia is a genetic disorder characterized by elevated serum lipid concentrations. Among the conditions that comprise familial hyperlipidemia, **Familial hypercholesterolemia (FH**) is a form of inherited hypercholesterolemia characterized by elevated serum LDL-C and the development of premature CVD. The overwhelming majority of culprit mutations manifesting in a diagnosis of FH exist within the LDL receptor (LDLR), although contributions from the genes for ApoB and for PCSK9 have been described. The **heterozygous** form of this condition (commonly referred to as heterozygous familial hypercholesterolemia [HeFH]) is estimated to occur between 1:200 and 1:500 individuals globally. LDL-C levels in affected individuals are significantly elevated, and in spite of aggressive statin use, there is still a 2-fold excess of CHD-related deaths relative to age-matched controls within this population. **Homozygous familial hypercholesterolemia** (HoFH) is rare (approximately 1/300 000 – 1/million) inherited disorder in which very high cholesterol values are seen from childhood on, cardiovascular manifestations of CVD appear in early life, and the life expectancy is significantly shortened due to CVD manifestations. Several subtypes of the disorder are known, of which in most cases (approximately 95%) there is a mutation in LDLR gene. In the remaining cases the mutation is either in ApoB (5%) or in in PCSK9 (<0.5%).

A large body of epidemiological evidence exists demonstrating a strong positive correlation and causal relationship between serum low density lipoprotein cholesterol (LDL-C), and the risk of coronary heart disease (CHD). Other clinical manifestations of atherosclerosis also appear linked to plasma LDL-C levels such as cerebrovascular disease (i.e. stroke) or peripheral vascular disease. In addition, clinical trials have shown that LDL lowering therapy with HMG-Co A reductase inhibitors (and possibly ezetimibe) reduces risk for CHD. The relationship between LDL-C levels and CHD risk is present over a broad range of LDL levels. Epidemiologic data indicate a continuous increasing risk from very low to “normal” and high levels of LDL-C.

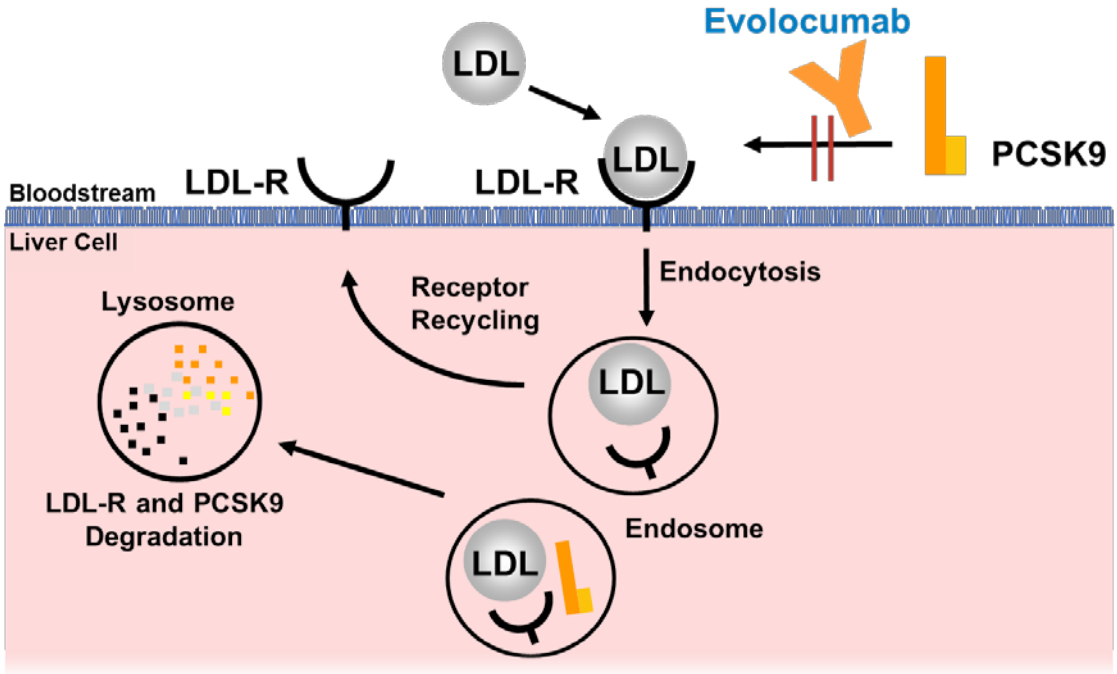
A list of interventions to achieve LDL-C control in patients with elevated LDL-C and with high cardiovascular risk are available, such as statins and other lipid-lowering therapies. Often however these are not sufficiently effective or their use is limited by toxicity. There is an undisputed medical need for new effective and well tolerated treatments of lipid disorders. The primary goal of treating lipid disorders is to prevent cardiovascular morbidity and mortality associated with disturbed lipid levels and ideally this effect should be demonstrated pre-approval. Nevertheless, for medicinal products acting on LDL-C, at least a detrimental effect on mortality and morbidity should be excluded prior to registration (*Guideline on clinical investigation of medicinal products in the treatment of lipid disorders [EMA/CHMP/748108/2013]*).

Recycling of the hepatic cell surface low density lipoprotein receptors (LDLR) plays a critical role in the maintenance of cellular and whole body cholesterol balance by regulating plasma LDL-C levels. It has been shown that PCSK9 plays an important role in the recycling and regulation of LDLR (*Horton et al, 2007; Brown and Goldstein, 2006*). PCSK9 is a member of the subtilisin family of serine proteases and is expressed predominantly in the liver, kidney, and intestine (*Zaid et al, 2008*). Following secretion, it causes post-translational decrease in the expression of hepatic cell surface LDLR by binding it and targeting the LDLR for lysosomal destruction. The reduction in hepatic LDLR leads to increased levels of

circulating LDL-C. Thus, PCSK9 may represent a target for inhibition by novel therapeutics in the indications of (1) primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia and (2) HoFH.

Evolocumab is a first in class fully human monoclonal immunoglobulin G2 directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9). Evolocumab binds selectively and with high affinity to PCSK9 and inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C (see Figure 1 below). In addition to LDL-C, inhibition of PCSK9 by evolocumab reduce total cholesterol, apolipoprotein B (ApoB), non high density lipoprotein cholesterol (non HDL C), very low density lipoprotein cholesterol (VLDL C), triglycerides and lipoprotein(a) (Lp[a]), total cholesterol/HDL C, ApoB/apolipoprotein A1 (ApoA1), and increase HDL C and ApoA1.

Figure 1. Mechanism of action for evolocumab



LDL = low-density lipoprotein; LDL-R = LDL receptor; PCSK9 = proprotein convertase subtilisin/kexin type 9

With its novel mechanism of action, evolocumab could offer an addition to standard of care and available therapies in the reduction of LDL-C and improvements in other lipid parameters as a lipid-lowering agent.

The following indications were approved by the CHMP:

> "*Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:*
>
> *-in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,*
>
> *-alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contra-indicated*
>
> *Homozygous familial hypercholesterolaemia*

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

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

Evolocumab is intended for subcutaneous (SC) administration with either a prefilled syringe (PFS) prefilled autoinjector/pen (AI/pen). The dose is either 140 mg every 2 weeks (Q2W) or 420 mg once monthly (QM).

2.2. Quality aspects

2.2.1. Introduction

The active substance of Repatha, evolucumab, is a recombinant, human monoclonal antibody (mAb; IgG2). Evolocumab specifically binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9) and prevents its interaction with the low density lipoprotein receptor (LDLR). The epitope targeted by evolocumab spans the interaction domain of PCSK9 with repeat A of the epidermal growth factor homology (EGF-A) domain of the LDLR.

PCSK9 is a protein that targets LDL receptors for degradation and thereby reduces the liver's ability to remove low-density lipoprotein cholesterol (LDL-C) from the blood. By binding to PCSK9 evolocumab inhibits PCSK9 from binding to LDL-receptors and prevents PCSK9-mediated LDL-receptor degradation thus resulting in increase of LDL-receptors on the surface of the liver cells and subsequent decreased circulating concentrations of LDL-C.

Evolocumab finished product (140 mg/ml) is formulated in a water for injection solution containing acetic acid, proline, polysorbate 80 and sodium hydroxide as excipients. Evolocumab finished product is provided in pre-filled syringes (PFS) and auto-injector pens (AI/Pen) for subcutaneous administration.

2.2.2. Active Substance

General information

The general information provided on nomenclature, structure and general properties of the active substance, evolocumab, is considered sufficient. The amino acid sequences for the heavy chains (HC) and light chains (LC), glycosylation sites at Asn291 on the HCs, disulphide bonds, molecular formulas and weights were given. Evolocumab does not involve Fc-region effector functions as a part of its mode of action i.e. binding and inhibition of PCSK9. Potentially immunogenic glycans i.e. N-glycoylneuraminic acid (NGNA), non-human sialic acid or terminal α-(1-3) galactose were not detected.

Structure:

Evolocumab is a human monoclonal antibody consisting of 2 heavy chains and 2 light chains of the lambda subclass. Evolocumab contains 36 total cysteine residues involved in both intrachain and interchain disulfide bonds. Each heavy chain contains 441 amino acids with 4 intrachain disulfides. Each light chain contains 215 amino acids with 2 intrachain disulfides. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 291. The theoretical amino acid sequences of evolocumab heavy and light chains are provided.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Manufacturing process

The manufacture of evolocumab active substance represents a conventional monoclonal antibody production process (fermentation, recovery, purification and viral inactivation/removal steps).

The applicant has sufficiently described the outline of the manufacturing process and its control. Flow diagrams for the cell culturing process and purification process have been provided, including information on operational parameters and in process controls, and lifetime of resins and membranes used.

The defined criteria for re-processing of selected process steps can be accepted.

Control of materials

Raw materials

The applicant has provided sufficient information on the compendial and non-compendial materials used in the active substance production process. The qualitative composition of the different cell culture media used during production is provided. No material of animal or human tissue origin is used.

Expression construct and cell banking

The applicant has adequately described the source, history and generation of the cell substrate and cell line development. Upon request the applicant also clarified the origin and history of the cell line.

A two-tiered cell banking system, with a WCB derived from the Master Cell Bank (MCB) has been established. The applicant has adequately described the creation of the MCB and WCB, and the procedure to establish future WCBs. Identity and purity of the MCB and WCB have been evaluated in line with ICH Q5D. No adventitious agents, with the exception of A- and C-type retrovirus-like particles in the MCB, were detected. Genetic stability of MCB, WCB, and cells at the limit of *in vitro* age (LIVCA) was studied. The provided results support stability, and demonstrate that product titre and product quality at the LIVCA is consistent with other lots produced with lower population doubling levels.

Control of critical steps and intermediates

The applicant applied a ranking system from insignificant to severe to assess the criticality of quality attributes. The outcome of the severity ranking, which was based on potential impact on patient safety (toxicology, immunogenicity) and product efficacy (potency, pharmacokinetics (PK)), is in general reasonable. For some quality attributes the applicant provided further justification on request, which was accepted.

Initially, no Critical Quality Attributes (CQAs) as such were identified, which complicated the identification of critical process parameters (CPPs). All quality attributes that were ranked moderate (5), major (7), or severe (9) were classified as CQAs. In addition, criticality assignment of Process Parameters was further addressed. All parameters that had statistical significant and practical important effects on CQAs in the DOE studies were re-evaluated. Criticality was determined based on the magnitude of this effect, which was calculated taken into account the change in the quality attribute caused by the operational parameter and the acceptable limits of the quality attribute. The re-evaluation of process parameter criticality is considered acceptable. Upon request, limits for some critical process parameters were included for some manufacturing steps.

The critical in-process controls (IPCs) were identified by the applicant. Action or rejection limits were set for all IPCs and the actions taken when limits are exceeded were indicated. Upon request, the limits for

some parameters have been tightened. Also, the applicant has provided additional data to demonstrate that product-related impurities, which were identified as the main degradation products of evolocumab, are appropriately controlled.

Upon request, the applicant described how future changes to non-critical and critical Process Parameters and In Process Controls included in the CTD will be handled during the product life cycle. The applicant proposed to report changes to critical PPs and IPCs as Type IB or Type II variation and changes to non-critical operational PPs and IPCs as a Type IA variation. The latter was not accepted by default at D180 because the applicant should comply with the Variation Regulation. In response, the applicant confirmed that changes will be reported in accordance with the Variation Regulation.

Process validation

The validation of the evolocumab active substance commercial manufacturing process has been performed by producing four consecutive commercial scale batches at the Amgen Rhode Island manufacturing site (AML). The process evaluation and verification data demonstrate that the process consistently meets its predefined output parameters and that the purification process is capable to reduce levels of product and process-related impurities. Upon request, also information was provided on operational performance of the process, demonstrating that it is operated within the limits defined in the description of the manufacturing process.

Characterisation

Characterisation of evolocumab active substance manufactured by the commercial Process (ARI) has been performed using state-of-art methods to comprehensively analyse structure, variants and potency. The studies have included analysis of primary structure by specifying amino acid sequence, N- and C-terminal variants, methionine oxidation, asparagine deamidation and hydroxylysine variants. Secondary and tertiary structures were shown to be typical for IgG2 antibodies. Disulfide bond analysis identified three types of disulfide isoforms. Further analysis demonstrated that the biological activities of these isoforms are comparable to that of the active substance. Evaluation of free sulfhydryl content of evolocumab showed low levels of free sulfhydryl typical to antibodies. The charged heterogeneity of evolocumab and carbohydrate structures at the N-linked glycosylation site (HC Asn291) have been thoroughly characterized. The site is almost fully glycosylated. Deglycosylation had no impact on the potency of evolocumab. No O-linked glycosylation was identified, as expected for IgG. Potentially immunogenic glycans i.e. N-glycoylneuraminic acid (NGNA), non-human sialic acid or terminal α-(1-3) galactose were not detected. The charge heterogeneity of evolocumab has been thoroughly characterized, the active substance can be fractioned into three peaks (acidic, main and basic peaks). The further fractioned Acidic peak contained deamidated asparagines at evolocumab CDR region having multiple sites of deamidation with a minor reduction in potency. The basic region was enriched in high molecular weight (HMW) species, methionine oxidation variants, heavy chain C-terminal lysine variants, and light chain N-terminal truncated variants, these fractions were fully potent. The detected variability can be considered common for antibodies.

Size heterogeneity of evolocumab was also analysed and the mAb was shown to exist predominantly monomeric, with low levels of HMW dimeric forms. Low molecular weight (LMW) structures were comprised of LC-LC and LC species. No higher order structures were observed. The antigen specificity of evolocumab i.e. binding to the PCSK9 was demonstrated. The functional mechanism of evolocumab does not involve Fc effector functions considering PCSK9 being a soluble target, furthermore human IgG2 isotype is known to have low affinity to FcγRs and C1q therefore having minimal immune effector functions. However the binding of evolocumab to FcRn receptor was confirmed using cell-based FcRn binding assay.

Specification

After revision during the evaluation procedure, the active substance specifications are considered adequately set and justified.

Analytical methods

The descriptions of analytical methods are in general acceptable.

Data demonstrated proper validation of the assays.

Batch analysis

Batch analytical data are provided for all evolocumab active substance lots used during clinical development through to process validation at the commercial facility. Each lot was tested to the specification in place at the time of lot disposition. The analytical data of active substance manufactured by individual processes was consistent suggesting that the processes were under control.

Reference materials

The applicant has adequately described the reference standards (RS) used. The primary and working RS have been appropriately qualified and characterised with state of art analytical methods. The analysis has included the release testing methods and additional characterisation. The results are within the specifications.

Stability of the reference standards is monitored in the ongoing stability program

Stability

The stability data support the proposed active substance shelf life at the recommended storage temperature. At the recommended storage temperature and at accelerated conditions no trends were observed in any of the parameters tested for the duration of the study.

Post-approval, the applicant commits to continue the ongoing stability studies and to annually add one active substance lot from each manufacturing site to the stability program. The applicant has sufficiently justified the testing program.

Comparability exercise for Active Substance

The applicant has sufficiently described the process changes made during development towards the commercial scale manufacturing Process (ARI).

The applicant evaluated comparability for Process changes. The evaluation consisted of a comparison of lot release testing and biochemical, biophysical and biological characteristics.

Differences were appropriately discussed and give no reason for concern.

Stressed stability studies showed some differences. At the recommended storage temperature and at accelerated conditions no trends were observed in any of the parameters tested.

In conclusion, the provided data do not indicate the presence of meaningful differences between processes, and the nonclinical/clinical data obtained may be used in the benefit risk evaluation.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Composition

Evolocumab finished product is supplied as a 140 mg/mL formulation in a sterile, single-use, preservative-free solution for delivery by subcutaneous injection.

The finished product is supplied in either a prefilled syringe (PFS) or a prefilled Autoinjector pen (AI/pen), which is a disposable, handheld, mechanical (spring-based) injection device that is provided ready-to-use and pre-assembled with the same PFS.

The primary container closure for both presentations consists of a 1 mL Type I glass syringe with a staked-in-place stainless steel needle covered with an elastomeric needle shield. For the PFS, a plastic plunger rod is threaded into the plunger-stopper. The PFS assembled with the AI/pen does not employ the additional outer plastic rigid cover or the plastic plunger rod.

The devices are not CE marked as they are single integral products at the time of product administration, intended exclusively for use in the given combination, and are not reusable.

Table 1: Composition of evolocumab (in 140 mg/mL Formulation)

Component	Grade	Function	Concentration	Quantity (per dose)
Evolocumab	In house [a]	Active ingredient	140 mg/mL	140 mg
Proline	USP, PhEur, JP	Tonicity and viscosity modifier		
Acetic acid, glacial	USP, PhEur, JP	Buffering agent		
Polysorbate 80	NF, PhEur, JP	Surfactant		
Sodium hydroxide [b]	NF, PhEur, JP	Buffer pH adjustment		
Water for injection	USP, PhEur, JP	Aqueous solvent		

qs = quantum sufficit

[a] Tested to internal specifications (3.2.S.4.1, Specification).

[b] Sodium hydroxide may be used to adjust pH. The supplier tests sodium hydroxide pellets to NF, PhEur, and JP standards.

Pharmaceutical development

The active substance protein concentration and excipient composition are not modified during manufacturing of the finished product. The active substance contains 140 mg/mL formulated evolocumab in proline, acetate, polysorbate 80, and is stored at a recommended storage condition of -30°C.

The excipients chosen for the finished product formulation include proline, glacial acetic acid, polysorbate 80, and sodium hydroxide. Proline was added as both as tonicifier and as viscosity reducing agent. A viscosity reducing agent was needed in this formulation due to the high protein concentration, which increases viscosity. Acetate was selected for its buffering capacity at the selected pH. Polysorbate 80 was added to inhibit soluble and insoluble aggregates of evolocumab in a glass PFS.

Development of the evolocumab finished product formulation occurred in two stages; initial clinical studies and late stage development. Finished product developed for initial clinical studies was supplied as a frozen liquid to minimize potential chemical and physical degradation in a 5 mL glass vial consisting of

70 mg/mL evolocumab formulated in acetate, sucrose, polysorbate 20. This formulation has been used throughout the preclinical, phase I, phase II and early phase III clinical studies.

Later stage development targeted a stable, high protein concentration formulation stored as a liquid at 2°C to 8°C. The evolocumab concentration in the formulation was increased from 70 mg/mL to 140 mg/mL in proline, acetate, polysorbate 80, (formulation proposed for Marketing Authorisation)

Device development

To enhance ease of administration, an Autoinjector/Pen (AI/pen) pre-assembled with the same glass PFS, was developed.

Amgen developed the prefilled Autoinjector/Pen 1.0 (AI/Pen 1.0) and subsequently the prefilled Autoinjector/Pen 1.5 (AI/Pen 1.5) on the basis of the existing SureClick® AI/Pen. The AI/Pen version 1.0 is used throughout the phase 3 clinical studies and is regarded as clinically validated. The AI/pen 1.0 differs from the SureClick® autoinjector in colour, plunger spring force (increased for the AI/pen due to the higher viscosity of evolocumab) and syringe carrier material (provides increased impact resistance for the higher spring force). The PFS and AI/Pen are not CE-marked.

The AI/Pen was further modified as a result of observations during human factors studies, clinical trials and design verification studies and designated as AI/pen version 1.5. The final design has been verified and validated, but has not been tested in clinical studies.

The proper functioning of the AI/pen versions 1.0 and 1.5 after long time storage at 2-8 °C has been sufficiently validated. The injection time is comparable for both versions of the AI/pen.

No formula overages are included. The 140 mg/mL PFS is filled to ensure a deliverable volume of 1.0 mL. No novel excipients or excipients of human or animal origin are used in the manufacturing of evolocumab finished product.

Manufacture of the product and process controls

Description of manufacturing process

The finished product manufacturing process has been adequately described. Detailed flow charts and descriptions of each unit operation of the manufacturing process were provided for the PFS. In addition, process flow diagrams for the assembly, labelling, and packaging of the 140 mg/mL prefilled syringe (PFS) and AI/Pen were provided, respectively.

In addition, for the assembly, labelling, and packaging of the 140 mg/mL PFS as well as the assembly of the 140 mg/mL in the AI/pen (rear sub-assembly, front subassembly), the labelling and secondary packaging were sufficiently described.

In-process tests are conducted during the manufacturing process and additional product tests are conducted prior to release. Appropriate controls are in place.

The process validation program included validation of the PFS manufacturing process steps as well as filter validation, aseptic process and sterilization validation, environmental monitoring validation and transportation validation of the PFS and AI/PEN. Three consecutive PFS lots were produced. PFS release specification testing results for the syringe lots were provided and all lots release results passed the proposed commercial specification. In conclusion, validation data demonstrate that the process is controlled and consistent when operated within the defined operating ranges.

Control of excipients

Adequate information has been provided on the control of the excipients.

All excipients used are of Ph. Eur. quality.

Product specification

The finished product specification for the 140 mg/ml PFS and additional specifications for the prefilled AI/pen are presented.

The AI/pen is assembled with the PFS prior to testing, additional test methods and acceptance criteria are used to assure the quality of the 140 mg/mL prefilled AI/pen at release.

The proposed list of finished product release test comprises the same methods as used for the active substance, with some additional tests.

Where necessary specifications were appropriately tightened or justified.

Analytical methods

Summaries of the analytical methods used to assess both evolocumab active substance and finished product were provided and are appropriate. Some analytical methods are specific to either the 140 mg/mL PFS or the 140 mg/ml AI/pen.

In conclusion, the methods proposed for the finished product release testing in addition to the ones for active substance release testing have been sufficiently described and appropriately validated.

Batch analysis

Batch analytical data were provided for all 140 mg/mL PFS lots used during clinical development and for product manufactured at the commercial manufacturing facilities. The data complied with the respective specifications.

Reference materials

The same reference standard(s) are used for both evolocumab active substance and finished product testing (reference is made to the active substance section).

Stability of the product

Finished product stability studies were performed per the ICH Harmonized Tripartite Guidelines Stability Testing of Biotechnological/Biological Products (ICH Q5C) and Stability Testing of New Active substances and Products (ICH Q1A). Stability studies were conducted at the recommended storage condition of 5°C to support expiry and at elevated temperatures to support limited room temperature storage (controlled, 25°C or less) and to support potential temperature deviations during handling and transportation. The finished product is sensitive to light, but shown to be stable during temperature cycling studies.

Stability data compiled to date for the 140 mg/mL PFS and 140 mg/mL AI/pen primary, validation and supporting lots stored at the recommended and accelerated storage conditions of 5°C, 25°C, and 30°C remain within the proposed stability specification acceptance criteria through the latest time points tested. Overall the stability data support the shelf life as claimed in the SmPC.

Comparability exercise for finished medicinal product

Early phase clinical finished product was manufactured at Amgen Thousand Oaks (ATO), using 70 mg/mL active substance. The primary container used during early phase clinical studies was a 5 mL Type I glass vial containing 70 mg/mL evolocumab. The primary container used during late phase clinical development was a 1 mL Type I glass PFS (or prefilled AI/pen version 1.0) containing 140 mg/mL active substance.

For commercial production, the evolocumab finished product process was transferred to the facility at Amgen Manufacturing Limited (AML 1) located in Juncos, Puerto Rico. The comparability of product in the vial (ATO) and PFS (ATO) was discussed. The differences found are not expected to have impact on quality, safety and efficacy.

PFS (ATO), PFS (AML-1), prefilled AI/pen 1.0 (AML-1) and prefilled AI/pen 1.5 (AML-1) finished product were comparable, as demonstrated by the lot release, characterization, and stressed stability data presented.

Adventitious agents

The information provided on non-viral adventitious agents is sufficient. No material of animal origin are used in the manufacturing process of evolocumab. No virus particles were detected in the cell banks, other than A-type and C-type retrovirus-like particles.

Viral clearance studies were performed for the chromatography steps, the viral inactivation step, and the filtration step using appropriate model viruses. Appropriately validated scaled down models were used for the different manufacturing steps.

The results of the virus clearance studies show acceptable reduction of the model virus studied. No significant differences were observed when comparing results for new and used resin. The total (cumulative) estimated XMuLV reduction shows an excess retrovirus clearance.

Virus carry over was assessed with used resin by executing a non-spiked run after cleaning and regeneration of the column. The results gave no reason for concern.

Post Approval Change Management Protocol

The applicant submitted a Post Approval Change Management Protocol (PACMP) for the addition, an alternative manufacturing facility for the formulation and aseptic filling of evolocumab 140 mg/mL prefilled syringes (PFS).

The changes in the manufacturing process were considered to be primarily of GMP concern which would be evaluated at the relevant GMP inspection for the use AML-14. The presented investigational quality results did not reveal any significant impact on quality attributes. Overall the strategy described in the comparability protocol seems suitable. The approach taken by the applicant in determining the equivalence limits is considered acceptable and would be appropriate for the PACMP as well. The proposed post approval change management protocol is considered suitable to support a finished product manufacturing site addition.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant submitted a full dossier for its product Repatha (evolocumab). In summary, the CTD is of appropriate quality and provides an adequate description of the characterisation, manufacture and control of the active substance and finished product. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided demonstrates consistent batch-to-batch production of Repatha achieving a well-defined quality for the active substance and the finished product. No excipients of human or animal origin are used in the product manufacture and there is no risk of contamination with viral or TSE agents by these ingredients.

No major issues were raised during the initial assessment of the dossier; however a number of deficiencies and points for clarification were identified. The main issue concerned the control strategy, including the identification of Critical Quality Attributes (CQAs), criticality assignment of process

parameters (PPs) and in process controls (IPCs), some aspects of the finished product and active substance specifications, and the handling of potential future changes to PPs and IPCs included in the CTD. The applicant applied a ranking system from insignificant to severe to assess the criticality of quality attributes, nevertheless initially did not identify CQAs as such. As this complicated the identification of critical PPs, the applicant was asked to clearly identify and justify the CQAs. In addition, the applicant was asked to re-assess criticality of PPs, focussing on PPs that were shown to have a statistical significant and practical important effect on the identified CQAs and on PPs. Critical IPCs were identified and appropriate action and/or rejection limits were set. Upon request, the applicant confirmed that future changes to non-critical and critical PPs and IPCs included in the CTD will be reported in accordance with the Variation Regulation.

The discussion on active substance and finished product release testing focussed on the inclusion of tests and setting of appropriate release and end of shelf life specifications for some of the quality attributes. The stability data support the proposed shelf life of the active substance and of the finished product as stated in the SmPC.

2.2.5. All issues raised have been adequately addressed by the applicant with two recommendations for future development remaining (see section 2.2.6 below). Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. As only 10 DS batches have been used so far, it is recommended to the applicant to re-assess the finished product specifications after production of 30 commercial scale active substance lots.
2. It is recommended that the first post-approval lot that will come available is put on a stability study which includes the optional short term storage (1 week at 25°C).

2.3. Non-clinical aspects

2.3.1. Introduction

Evolocumab is a fully human monoclonal antibody targeting human proprotein convertase subtilisin/kexin type 9 (PCSK9). When PCSK9 binds to LDLR, the LDLR is targeted for destruction rather than being recycled back to the cell surface, thereby reducing the levels of LDLR available for low-density lipoprotein cholesterol (LDL-c) clearance from the bloodstream.

Evolocumab binds selectively and with high affinity to PCSK9 and inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating

concentrations of LDL-c. The antibody is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Pharmacodynamics at molecular level: Binding affinities of evolocumab to human, cynomolgus monkey, hamster, and mouse PCSK9 were evaluated by KinExA and BIAcore™ solution equilibrium binding assays. The KD values were determined to be approximately 16 pM, 8 pM, 14 pM, and 17000 pM for binding to human, cynomolgus monkey, hamster, and mouse PCSK9, respectively. The capability of anti-PCSK9 antibodies (AMG-145 or 31H4.2) to compete with wildtype (WT) PCSK9 or the gain-of-function (GOF) variant PCSK9-D374Y for binding to LDLR was analysed using an ELISA assay. The evolocumab IC50 values were 1.94 ± 0.32 nM (mean ± SD; n = 3) with WT PCSK9.

Pharmacodynamics *in vitro*: HepG2 cells treated with anti PCSK9 antibodies (AMG-145 or 31H4.2) slightly increase total LDLR levels, which is also reflected on the cell surface for AMG-145. Upon treatment with statins, total LDLR increases more efficiently, which is also reflected in increase in cell surface levels of LDLR. Incubation with statins causes a dose-dependent increase in PCSK9 protein expression in HepG2cells.

The applicant tested the capacity of anti-PCSK9 antibodies to influence uptake of fluorescently labelled LDL by HepG2 cells transfected with LDLR, either the wild-type or the Gain of Function variant harbouring the D374Y mutation. Both tested antibodies, AMG145 and 31H4.2, were able to increase LDL uptake upon incubation of the cells with these antibodies. The effect was more potent in the cells transfected with the gain of function mutant of LDLR. The proposed mechanism is the inhibition of the degradation process of LDLR by inhibition of PCSK9.

Pharmacodynamics *in vivo*: Evolocumab binds to PCSK9 in Hamster and is pharmacologically active as well, lowering cholesterol (both HDL-c and LDL-c). Using Gold Syrian Hamster, pharmacokinetic and pharmacodynamic parameters could be determined for anti PCSK9 antibody evolocumab / AMG 145. Levels of LDL-c, HDL-c and total cholesterol levels were decreased. Hepatic LDLR protein levels were increased. Duration of both effects was dose dependent.

A single subcutaneous injection of evolocumab in Cynomolgous monkey led to a dose dependent decrease in LDL-c and total cholesterol. HDL-c in serum seems not to be affected by evolocumab administration in Cynomolgous monkey. A slight decrease in TG was also observed. In the clinic, slightly decreased TG levels were observed as well, but not regarded to be a risk.

Next to evolocumab / AMG145, the applicant also assessed the effectiveness of other PCSK9 antibodies in mice (after introducing PCSK9 with AAV) and in cynomolgous monkey. Serum concentration of antibody over time and concentration of non HDL in serum were followed. AMG-145 was most potent in decreasing the levels of serum cholesterol.

Secondary pharmacodynamic studies

Consistent with its role in regulating hepatic LDLR, PCSK9 is predominantly expressed in the liver but has also been detected in other organs, including the intestine, kidney, pancreas and brain. Free PCSK9 is also found in the systemic circulation but human plasma concentrations can vary widely. The broad localization of PCSK9 raises the expectation of processes that could be secondarily affected by evolocumab treatment. Several possible processes involving cholesterol have been evaluated by the

applicant performing a thorough literature survey and discussing the potential of evolocumab to influence other processes than the primary pharmacological LDL-c lowering.

From the current understanding from literature as reviewed by the applicant and results from (non-) clinical studies it is strongly suggested that evolocumab is not likely to: have impact on the brain and cognitive function, play a role in hepatitis C infectivity, have impact on insulin resistance and diabetes risk, be involved in mechanistic basis of statin-mediated myopathy.

The potential of PCSK9 to interact with other LDLR family members have been investigated *in vivo* and *in vitro*. PCSK9 has affinity for and interacts with LDLR. Contradictory results are reported in literature for the interaction between PCSK9 with VLDLR and ApoER2. APoER2 is mainly localized to the brain. Antibodies do only minimally cross the blood-brain barrier (BBB), if at all. Since evolocumab is an antibody likely not present in the brain, a possible interaction with this receptor might be of less relevance. The possible binding of PCSK9 to VLDLR might be relevant. Levels of VLDL and triglycerides are decreased upon evolocumab treatment in preclinical studies and clinical trials. Whether this is a direct or indirect effect is not clear, but it does not lead to a risk for the patient.

Safety pharmacology programme

The impact of a single intravenous dose of 300 mg/kg to cynomolgous monkey did not reveal an impact of evolocumab treatment on cardiovascular parameters, respiratory rate and neurobehavioral evaluation. These safety pharmacology parameters were addressed sufficiently in this study and give no reason for further studies.

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions have not been investigated by the applicant. The antibody is designed to bind specifically to PCSK9 and it is very unlikely that it will bind to other human targets. The applicant performed tissue cross-reactivity (TCR) studies to explore the binding of monoclonal antibodies and related antibody-like products to antigenic determinants in tissues from hamster and cynomolgous monkey and human. The CHMP agreed there was no need to perform pharmacodynamics drug interaction studies, apart from the TCR studies.

2.3.3. Pharmacokinetics

Bio-analytical methods: Unbound serum evolocumab concentration in hamster and cynomolgus monkey serum was determined according to the validated analytical procedure for the determination of evolocumab in cynomolgus monkey serum and hamster. Unbound (free) PCSK9 in cynomolgus monkey serum was measured using a qualified, sensitive and specific enzyme-linked immunosorbent assay (ELISA). The methods were originally developed at Amgen Inc., Seattle, WA. The validation reports for determination of anti-evolocumab antibodies or neutralising antibodies were not included in the dossier.

Analytical Method Validation Report for an Electrochemiluminescence Immunoassay for the Detection of Antibodies Against AMG 145 in Cynomolgus Monkey Serum (MVR-000326): The ECL method validation included establishment of cut-point and lower limit of reliable detection (LLRD), assay sensitivity, specificity, drug tolerance, stability, and intra- and inter-assay variability. The validation was appropriately performed. At high drug serum concentrations drug interference might affect accurate detection of anti-drug antibodies. However, based on the study results the method cam be considered appropriate and sufficient to inform about the cynomolgus monkey toxicity data.

Analytical Method Validation Report for an Electrochemiluminescence Immunoassay for the Detection of Antibodies Against AMG 145 in Hamster Serum (MVR-000365): The ECL method validation included establishment of cut-point and lower limit of reliable detection (LLRD), assay sensitivity, specificity, drug tolerance, stability, and intra- and inter-assay variability. The validation was appropriately performed. The presence of high concentration of evolocumab in the hamster serum at the higher dose levels might interfere with the detection of anti-drug antibodies since the drug levels exceeded the assay tolerance limits. However, as pharmacological activity was demonstrated it can be concluded that interpretation of the hamster toxicity data is not hampered.

Validation of a Receptor Binding Assay for the Detection of a Neutralizing Antibodies Against AMG 145 in Cynomolgus Monkey Serum (MVR-000326): This assay is a receptor-ligand binding assay that detects antibodies present in cynomolgus monkey serum that neutralize the biological activity of evolocumab. Biotinylated human PCSK9-D374Y is used as a ligand that will bind to recombinant human LDL-R coated on the plate. The complex is being detected using streptavidin conjugated ruthenium. Methodology includes a screening phase and a specificity phase. The validation included establishment of cut points, specificity, drug interference, and freeze-thaw stability. The validation was appropriately performed, and the method can be considered appropriate and sufficient for the purpose.

The possibility of interference in measurements with anti-drug-antibodies is not addressed by the company. However, this issue is discussed in the toxicology section of antigenicity.

Absorption: Following SC administration in monkeys; the following pharmacokinetic parameters were determined

- The absolute bioavailability was approximately 82%.
- The mean C_{max} and T_{max} increased with dose, ranging from 1.82 µg/mL to 833 µg/mL and approximately 1 day to 4 days for the 0.2 and 30 mg/kg doses, respectively.
- The C_{max} increased 457-fold increase for a 150-fold increase in dose (0.2 to 30 mg/kg).
- Non-linearity in exposure was also observed based on mean area under the serum evolocumab concentration-time curve from time zero to infinity (AUC_{inf}).
- The values increased greater than dose-proportionally from 0.2 to 30 mg/kg (~3000-fold for an approximate 150-fold increase in dose).
- The mean AUC_{inf} values were approximately dose-proportional (< 2-fold change in AUC when adjusted for dose) from 10 to 30 mg/kg.
- These pharmacokinetic observations were consistent with target-mediated elimination.

Distribution: Following IV administration of 3 mg/kg to cynomolgous monkeys, the estimated unbound mean volume of distribution at steady-state (Vss) value in the serum was 25.3 mL/kg and comparable to plasma volume (45 mL/kg). Following SC administration, the apparent unbound volume of distribution (Vz/F) declined as a function of dose ranging from 64.8 mL/kg at a dose of 0.2 mg/kg to 19.9 mL/kg at a dose of 30 mg/kg. This is consistent with antibodies that exhibit capacity-limited binding.

Metabolism: Evolocumab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Excretion: As a monoclonal antibody, no renal excretion is anticipated due to its molecular size. Therefore, no specific studies to measure excretion of evolocumab were conducted.

PK different formulations: PK and PD from three different formulations were compared. Reference formulation was 70 mg/mL and the two test formulations had evolocumab concentration of 120 or 140 mg/mL. The PK and PD were slightly different. C_{max} and AUC_{0-t} were slightly lower for the two test concentrations compared to the reference formulation of 70 mg/mL.

2.3.4. Toxicology

Single dose toxicity

No formal single-dose toxicity study have been performed which was agreed. Cynomolgus monkey or Hamster did not show acute toxicity after a first dose with evolocumab up to 300 mg/kg.

Repeat dose toxicity

Evolocumab is pharmacological active in human, Cynomolgous monkey and hamster. The latter two were used in toxicology studies, where also the pharmacodynamics parameters were measured. In the repeated dose toxicity studies animals were exposed to evolocumab, up to 300 mg/kg, for max. of 3 months (hamster) and 6 months (monkey). No toxicity was observed upon administration of evolocumab up to 300 mg/kg QW up to 3 months (hamster) and up to 6 months in Cynomolgous monkeys. Only the intended pharmacological effect of decreased serum LDL-c and total cholesterol (up to approximately 85% and 40%, respectively) were observed in these studies and was reversible upon cessation of treatment.

No adverse effects were observed when evolocumab (up to 100 mg/kg Q2W) was dosed in combination with rosuvastatin (5 mg/kg daily [QD], oral) to Cynomolgus monkeys for 3 months. In this combination study, reductions in serum LDL-c and total cholesterol were slightly more pronounced than observed previously with evolocumab alone, and were reversible upon cessation of treatment. However, the lack of pharmacological activity of rosuvastatin needs to be explained.

The Applicant refers to recent publications which describe inconsistent results for statin-mediated effects on LDL-C in the Cynomolgus monkey. The Applicant further clarifies that one explanation for the lack of pharmacological activity may be related to the statin-induced increase in PCSK9 expression. The Applicant further refers to the recent published data on additive effects for another PCSK9 inhibitor monoclonal antibody when administered to Cynomolgus monkeys in combination with atorvastatin.

This may be the case, but as these are hypotheses it is not changing the situation that the data do not enable the evaluation of the additive effects of evolocumab and rosuvastatin on lowering of the cholesterol levels. The low dose (5 mg/kg) may explain the lack of pharmacological activity of rosuvastatin but does not justify the dose selection for the study; according to the publically available data, the therapeutic range seems to be higher than the 5 mg/kg used in the toxicological study.

However, neither drug had significant effect on the PK of the other drug in Cynomolgus monkeys. In addition, the effect of statins, including rosuvastatin, on evolocumab has also been evaluated in clinical studies (leading to a modest decrease in evolocumab exposure that does not affect the pharmacodynamics of LDL-C lowering). Based on these data pharmacokinetic drug-drug interactions were considered not likely.

Thus, the effect of treatment with evolocumab, at exposure levels higher than clinical exposure was limited to the pharmacological effect, which was a reduction in LDL-c, cholesterol and, not consistently,

triglycerides. Apparently, this did not lead to any toxicological effect, suggesting that laboratory animals have excess levels of LDL-c and cholesterol.

Genotoxicity

Evolocumab is a recombinant protein, made up entirely of naturally occurring amino acids. Therefore there were no genotoxicity studies performed which was agreed by the CHMP.

Carcinogenicity

The applicant performed a long term repeated dose toxicity or carcinogenicity study with evolocumab in hamsters. No evolocumab related neoplasm has been found in this study. Evolocumab related effects in this study were also limited to the expected pharmacodynamics effects and further supported the observations that evolocumab does not evoke adverse effect when tested in animals at exposure levels up to 15 times the clinical exposure.

Reproduction Toxicity

The nonclinical reproductive and developmental safety profile of evolocumab was informed by three studies: (1) an enhanced pre-postnatal development study in cynomolgus monkeys, (2) a fertility and early embryonic development study in hamsters and (3) assessment of male and female fertility endpoints in the 6 month cynomolgus monkey study.

Evolocumab treatment did not affect male and female fertility in hamsters (analysed in study 114975) and monkeys (analysed in study 110359). Infant monkeys from mothers treated with 50 mg/kg/dose evolocumab Q2W (which was pharmacological active in mothers) were exposed via transfer of the antibody over the placenta, or via the colostrum. Levels of evolocumab could be measured at birthday 14 (100 µg/ml). This level of antibody in serum evokes a pharmacological effect in adults, however in infants only a minimal reduction in LDL-c and total cholesterol was observed. The serum LDL-C levels were decreased in infants of the mothers that had been treated with evolocumab compared to the infants of the untreated mothers. The LDL-C levels remained lower until the end of the observation period of 6 months. The concern was whether evolocumab treatment during pregnancy could lead to adverse effects in infants that have been exposed to evolocumab in utero. The data (group means) implied that the LDL-C levels of infants of the mothers that had been treated with evolocumab during pregnancy until parturition were consistently lower than in the infants that had not been exposed to evolocumab in utero. Knowing that evolocumab concentrations in infant sera were too low to have pharmacological activity raised a concern of whether in utero exposure to evolocumab might induce some other effects that would lead to sustained reduction in serum LDL-C levels in infants as seen at 6 months (PND180). A newly insightful graphical presentation of the data provided clarification and alleviated the concern. The data were considered sufficient to conclude that *in utero* exposure to evolocumab did not adversely impact the infants up to 6 months of observation.

Three mothers made anti-evolocumab antibodies, of which one had neutralizing antibodies. No anti-evolocumab antibodies were measured in infants. The lack of treatment related findings suggested that infants are not so dependent on cholesterol from maternal circulation, but rather from endogenous production, which is also suggested in literature.

Peadiatric safety:

Evolocumab is being evaluated for the treatment of homozygous familial hypercholesterolemia (HoFH) in patients 12 years and older. No dedicated juvenile animal studies have been performed (and none are planned), but the completed studies provided adequate nonclinical safety support for evaluation of the intended paediatric population.

In accordance with the PIP for evolocumab the applicant provided studies agreed with the PCDO: (1) a 3-months toxicity study with Cynomolgus monkeys between age of 3 and 7 years and (2) an Embryo-foetal and Postnatal Development (EFPD) were infants could be followed. The first of these studies tested evolocumab in Cynomolgus monkeys of 2.5 years and older (in the 6-weeks study), which would generally correspond to human ages of approximately 10 years and older, but for some postnatal events (e.g., immune system development), extrapolation to younger human ages would be appropriate. The supportive EFPD study was age's equivalent to 0 to 2 years in humans as claimed by the applicant. The developmental NOEL was 50 mg/kg Q2W and evolocumab-related effects were limited to expected pharmacology (serum LDL-c and total cholesterol lowering) in the mothers.

No toxicity has been observed, but also the pharmacodynamic effect was less apparent in these animals. In contrast, mature animals exposed at these levels do show a PD effect. Fourteen cases (3 placebo and 11 patients) in the age of 12-18 years old have been treated with evolocumab in the clinical studies. The 6-weeks rather than the EFPD study provided support for the peadiatric indication. The CHMP issued a positive opinion for evolocumab in the treatment adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Toxicokinetic data

Exposure levels in female animals are slightly lower than in male animals. Exposure increases more than dose proportional and C_{max} is increasing dose proportional. These pharmacokinetic observations are consistent with target-mediated elimination.

Local Tolerance

Local tolerance tests with formulations from process 1 (70 mg/mL) and process 2 (140 mg/mL) showed no irritation of injection site reactions and has been sufficiently addressed. In repeat-dose studies, routinely assessed the potential for evolocumab-related injection site reactions and none were observed.

Other toxicity studies

Antigenicity was sufficiently addressed in the repeated dose studies and the pre and post-natal reproduction toxicity study. No antigenic response in the Gold Syrian Hamster against evolocumab has been observed, which was not surprising since the antibody is produced by Hamster cells (CHO). The only species that remained available for testing the antigenic capacity of evolocumab were Cynomolgus monkey. As stated by the applicant, 10% of the monkeys showed antibody development against evolocumab, half of which appeared to be neutralizing antibodies. In some animals, an effect on the pharmacological action of evolocumab was detectable. No neutralizing antibodies have been observed in the clinical development.

Immunotoxicity has been sufficiently addressed in the repeated dose toxicity studies and evolocumab treatment did not show an effect on peripheral blood immunophenotyping, anti-KLH antibody (IgM and

IgG) responses in the TDAR assay or Natural Killer Cell cytotoxicity (NKC) function. Thereby, it was discussed in the secondary pharmacology section.

In the 6 months repeat dose toxicity study, the analysis of T cell dependent antibody responses (TDAR) revealed a statistically significant reduction of anti-KLH IgG response at evolocumab dose levels of 3 and 300 mg/kg, and a statistically significant reduced trend in the secondary IgG response. These data suggested that evolocumab treatment might impair the T cell dependent antibody responses. The Applicant re-analysed the TDAR data after removing the animals with pre-existing anti-KLH antibodies from the analysis. It was acknowledged that removing baseline positive samples reduced the background noise and might increase the informative value of the TDAR analyses. The re-analysed data from selected animals showed no effect on IgG or IgM antibody responses. However, the selection of animals that were removed from the re-analyses seemed inappropriate and unjustified. The Applicant explained and justified their re-analyses. The applicant discussed their approach of selective data analysis, which was not entirely accepted. The CHMP agreed that the data do not indicate that evolocumab treatment would result in immunotoxicity. The re-analysis of available TDAR data was not considered however appropriately justified, and since the full data set had to be taken into consideration, the concern of potential risk of impairment of T cell dependent antibody response at least after long term treatment (3 months) remained. Whether or not the reduced TDAR upon evolocumab treatment in monkey would be a risk in humans, was uncertain and is reflected in section 5.3 of the SmPC.

Tissue Cross Reactivity: A TCR assay with evolocumab has been performed on Human, Hamster and Monkey tissue. In vitro binding of evolocumab to extracellular surface elements in the following normal tissues was observed:- human - striated skeletal muscle, cardiomyocytes, and smooth muscle myocytes in the skin;- Cynomolgous monkey - striated skeletal muscle, cardiomyocytes and smooth muscle myocytes in the eye (iris) and skin; - hamster - striated skeletal muscle; cardiomyocytes; and smooth muscle myocytes in the skin.

However, *in vivo* evaluations of cardiac function and histopathological evaluations of cardiac and skeletal muscle, skin, and eye, revealed no functional or morphological effects of evolocumab on these tissues. The poor specificity of the assay is also recognized by the authorities and reflected in ICH S6(R1). Tissue binding per se does not indicate biological activity *in vivo*. Findings should be evaluated and interpreted in the context of the overall pharmacology and safety assessment package."

The lack of further studies addressing immunotoxicity, dependence potential, metabolites and impurities is agreed.

2.3.5. Ecotoxicity / environmental risk assessment

No ERA have been done, which is agreed seen the nature of the product. Evolocumab is a protein composed of normal amino acids and readily biodegradable. Therefore it does not pose a risk for the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacological, pharmacokinetic and toxicological profiles of evolocumab were studied in HepG2 cells and in Mice, Gold Syrian Hamster and Cynomolous monkey.

Influence of Evolocumab on LDLR levels

The applicant focussed on the *in vivo* increase of LDL receptors (LDLR) in the liver of evolocumab treated Gold Syrian Hamster and a subsequent decrease in LDL-c in serum, the pharmacological effect that was

also noticed in the Cynomolous monkey. PCSK9 antibody targets PCSK9 present in serum. Functioning of LDLR present in other than liver tissues might be also influenced by evolocumab therapy leading to increase of LDLR levels and more efficient LDL-c uptake in that specific tissue. These tissues may thus accumulate LDL-c upon evolocumab treatment. Data on tissue distribution of LDLR, which could be upregulated due to evolocumab treatment, were discussed during current procedure including a discussion on the effect of evolocumab on LDLR other than hepatic and the influence of evolocumab on LDL-c uptake in tissues other than hepatic tissue. Literature data indicated that, unlike the liver, PCSK9 plays a much less important role in regulating LDLR levels in extra-hepatic tissues. There were no signs of cholesterol accumulation in extra-hepatic tissues and no adverse effects in extra-hepatic tissues were observed. Thereby, in case of minor increase of LDL in extra-hepatic tissues, feedback systems are in place within all cells of the body to tightly regulate intracellular cholesterol levels and prevent cholesterol accumulation.

Justification for selection of animals in TDAR analyses

A statistically significant reduction of anti-KLH (anti- Keyhole limpet hemocyanin) IgG response at evolocumab dose levels of 3 and 300 mg/kg, and a statistically significant reduced trend in the secondary IgG response suggesting a potential impairment of the T cell dependent antibody responses (TDAR) was observed in Cynomolgus monkeys. The Applicant re-analysed the TDAR data after removing the animals with pre-existing anti-KLH antibodies. The data set from selected animals showed no effect on IgG or IgM antibody responses. However, the selection of animals that were removed from the re-analyses seems inappropriate and unjustified, and thus the applicant was requested to explain and justify their re-analyses, and re-discuss the overall safety of evolocumab. It was agreed that the data did not indicate that evolocumab treatment would result in immunotoxicity however the re-analysis of available TDAR data was not considered appropriately justified, and since the full data set should be taken into consideration, the concern of potential risk of impairment of T cell dependent antibody response at least after long term treatment (3 months) remained. Whether or not the reduced TDAR upon evolocumab treatment in monkey would be a risk in humans was uncertain and is reflected in section 5.3 of the SmPC.

Immunogenicity anti-drug-antibodies

The occurrence of antidrug antibodies (ADA) was assessed in hamster and Cynomolgous monkey. However, the validation reports for the analytical methods for anti-evolocumab antibody detection in the hamster and in the Cynomolgus monkey, as well as for determination of neutralising antibodies were initially lacking in the dossier and were provided during procedure. In hamster, evolocumab was not immunogenic. In Cynomolgus monkey the incidence of anti-evolocumab antibodies (antidrug antibodies, ADA) was not higher than 10%. In some animals these ADA were neutralising. At high dose levels no ADA were detected, but it could not be excluded that high levels of circulating test article during the dosing phase may have interfered with the detection of ADA. The formation of neutralizing antibodies was included in the RMP as a potential risk. It was found reassuring that neutralising antibodies were not found to be formed in clinical studies.

Assessment of paediatric data on non-clinical aspects

Evolocumab is being evaluated for the treatment of homozygous familial hypercholesterolemia (HoFH) in patients 12 years and older. No dedicated juvenile animal studies have been performed (and none are planned), but the completed studies provided adequate nonclinical safety support for evaluation of the intended paediatric population.

The applicant provided studies: (1) a repeat dose 3-months toxicity study with Cynomolgus monkeys between age of 3 and 7 years and (2) an Embryo-foetal and Postnatal Development (EFPD) were infants

were followed. The first of these studies tested evolocumab in Cynomolgus monkeys that were 2.5 years and older (over 6-weeks). This would generally correspond to human ages of approximately 10 years and older. The supportive EFPD study was age's equivalent to 0 to 2 years in humans. The developmental NOEL was 50 mg/kg Q2W and evolocumab-related effects were limited to expected pharmacology (serum LDL-c and total cholesterol lowering) in the mothers. No toxicity has been observed, but also the pharmacodynamic effect was less apparent in these animals. In contrast, mature animals exposed at these levels do show a PD effect. Fourteen cases (3 placebo and 11 patients) in the age of 12-18 years old have been treated with evolocumab in the clinical studies. The 6-weeks rather than the EFPD study provided support for the peadiatric indication. The CHMP issued a positive opinion for evolocumab in the treatment adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

2.3.7. Conclusion on the non-clinical aspects

A comprehensive pharmacological and toxicological data package was provided to support the application for evolocumab in treatment of adult patients with primary hypercholesterolemia or mixed dyslipidaemia and in adults and adolescents with homozygous familial hypercholesterolemia.

Evolocumab was not carcinogenic in hamsters at exposures much higher than patients receiving evolocumab at 420 mg once monthly. The mutagenic potential of evolocumab has not been evaluated which was agreed. In hamsters and Cynomolgus monkeys at exposures much higher than patients receiving 420 mg evolocumab once monthly, no effect on male or female fertility was observed. In Cynomolgus monkeys at exposures much higher than patients receiving 420 mg evolocumab once monthly, no effects on embryo-foetal or postnatal development (up to 6 months of age) were observed.

Apart from a reduced T-cell Dependent Antibody Response in cynomolgus monkeys immunized with KLH after 3 months of treatment with evolocumab, no adverse effects were observed in hamsters (up to 3 months) and Cynomolgus monkeys (up to 6 months) at exposures much higher than patients receiving evolocumab at 420 mg once monthly. The intended pharmacological effect of decreased serum LDL-C and total cholesterol were observed in these studies and was reversible upon cessation of treatment.

In combination with rosuvastatin for 3 months, no adverse effects were observed in Cynomolgous monkeys at exposures much higher than patients receiving 420 mg evolocumab once monthly. Reductions in serum LDL-C and total cholesterol were more pronounced than observed previously with evolocumab alone, and were reversible upon cessation of treatment.

2.4. Clinical aspects

2.4.1. Introduction

The applicant was seeking approval for the use of evolucumab in a variety of settings:

- Primary Hyperlipidemia and Mixed Dyslipidemia
    - patients on a statin or statin with other lipid-lowering therapies (eg, ezetimibe),
    - patients with statin intolerance, and
    - patients in whom a statin is not clinically appropriate (e.g., patients on fibrates, cyclosporine, certain CYP3A4 inhibitors, such as certain HIV or HCV protease inhibitors, clarithromycin, and itraconazole, and patients with statin hypersensitivity).

– Homozygous Familial Hypercholesterolemia

  - as a combination therapy (with statins or with statin and other lipid-lowering therapies) in adolescents and adults.

The clinical program addresses all these patient groups, the characteristics of the studies are summarised in the tables below.

Table 1. Studies in the MAA by indication / patient group

Therapeutic Settings (Study population/design)	Primary Studies	Supportive Studies
Primary Hyperlipidemia and Mixed Dyslipidemia		
Combination with statin therapy and statin with other lipid-lowering therapies		
(familial and nonfamilial)	20101155 (LAPLACE-1: phase 2) 20110115 (LAPLACE-2: phase 3) 20110109 (DESCARTES: phase 3) 20110110 (OSLER-1: phase 2) 20120138 (OSLER-2: phase 3)	20110231 (YUKAWA-1:phase 2)
(heterozygous familial only)	20090158 (RUTHERFORD-1: phase 2) 20110117 (RUTHERFORD-2: phase 3)	20110271 (TAUSSIG:phase 2/3; severe FH subjects)
Statin-intolerant subjects (familial and nonfamilial)	20090159 (GAUSS-1: phase 2) 20110116 (GAUSS-2: phase 3) 20110110 (OSLER-1: phase 2) 20120138 (OSLER-2: phase 3)	20101154 (MENDEL-1:phase 2) 20110114 (MENDEL-2:phase 3)
Statin use not clinically appropriate (familial and nonfamilial)	20090159 (GAUSS-1: phase 2) 20110116 (GAUSS-2: phase 3) 20110110 (OSLER-1: phase 2) 20120138 (OSLER-2: phase 3)	20101154 (MENDEL-1:phase 2) 20110114 (MENDEL-2:phase 3)
Homozygous Familial Hypercholesterolemia (HoFH)		
Combined with statins and other lipid-lowering therapies	20110233 (TESLA: phase 2/3) 20110271 (TAUSSIG: phase 2/3; HoFH subjects)	

FH = familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia

GCP

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

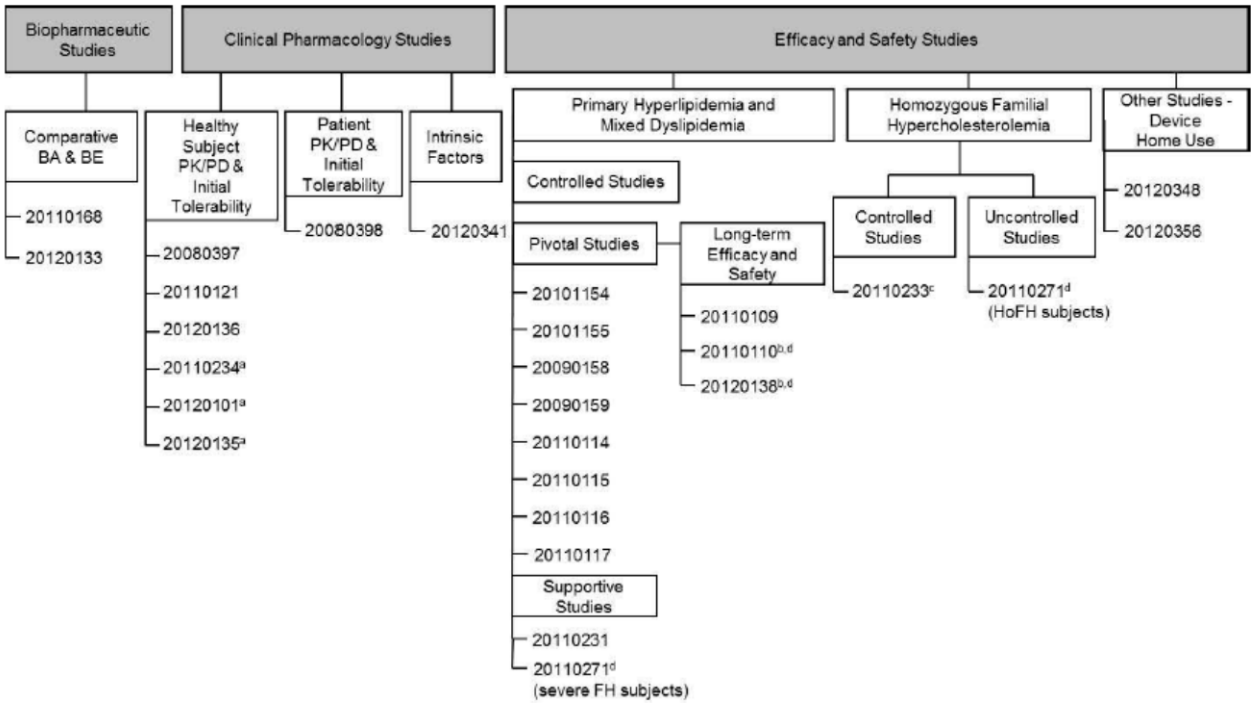
The applicant has provided a statement to the effect that clinical trials conducted outside the community

were carried out in accordance with the ethical standards of Directive 2001/20/EC. No triggers for GCP inspection were identified.

- Overview of clinical studies

The following clinical programme was performed and submitted within current application:

Figure Organization of the Evolocumab Clinical Studies in the Submission



The objectives of the clinical pharmacology program were to characterize the initial safety, tolerability, PK, PD, and exposure-response properties of evolocumab in healthy subjects, patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia, and patients with homozygous familial hypercholesterolemia (HoFH). The PK and PD data in this application were used to:

- support the selection of the dosing regimens for phase 3 studies in the 2 proposed indications;
- assess the relationships between dose and exposure and between exposure and pharmacodynamic response;
- assess the effect of mild to moderate hepatic impairment on the pharmacokinetics and pharmacodynamics of evolocumab (subjects with severe hepatic impairment were not evaluated);
- assess the effect of other patient-specific factors (familial hypercholesterolemia, renal impairment, statin treatment, or demographic covariates such as age, sex, or body weight) on the pharmacokinetics and pharmacodynamics of evolocumab;
- evaluate potential effects of anti-evolocumab antibodies on evolocumab pharmacokinetics and pharmacodynamics.

In Table PK01 the studies are listed in which PK and PD data with rich sampling schemes were collected. In other Phase III studies, limited blood samples were taken for PK purpose. These data are also used for the population PK analysis.

Table PK01. Studies in healthy volunteers for pharmacokinetic and pharmacodynamic characterisation of evolocumab

Study number	Study design	Entry Criteria	Study Objectives	Dose	Number of subjects
Healthy Subject Pharmacokinetics and Initial Tolerability					
20080397 (proof of concept study)	Phase 1, double-blind, randomized, placebo-controlled (ascending single dose)	Healthy men and women	Safety, tolerability, PK, and PD	7, 21, 70, 210, or 420 mg SC; or 21 or 420 mg IV	42/ evolocumab 14/ placebo
20110121	Phase 1, double-blind, randomized, placebo-controlled (ascending single dose)	Healthy men and women; Japanese or white	Safety, tolerability, PK, and PD	Japanese subjects: 70, 210 or 420 mg SC White subjects: 210 mg SC	Japanese subjects: 18/ evolocumab and 6/ placebo White subjects: 6/evolocumab and 2 /placebo
20120136	Phase 1, open-label, crossover (intra-subject variability)	Healthy men and women	Intra subject variability in PK, PD, safety, and tolerability	140 mg SC, 2 doses separated by 56 days	20/evolocumab
20110234	Phase 0, randomized, crossover (tolerability of placebo SC at various infusion rates)	Healthy men and women	Safety, tolerability, and delivery performance	Placebo: each subject received 1.2 mL injection within 5 seconds, 3.5 mL infusion over 1 minute, 3.5 mL infusion over 4 minutes, and 3.5 mL infusion over 10 minutes, in random order on 1 day	48/placebo
20120101	Phase 0, randomized, crossover (tolerability of placebo SC bolus injections with	Healthy men and women	Safety, tolerability, and delivery performance	placebo: each subject received SC bolus injections with 1.2mL of 0.7% CMC placebo, 1.0 mL of 1.1% CMC placebo, and 1.0 mL of 20 mM	36/placebo

	different viscosities)			sodium citrate placebo, in random order on 1 day	
20120135	Phase 0, single-arm (AMD performance using placebo buffer)	Healthy men and women	Safety, tolerability, and delivery performance	Placebo: all subjects received 3 abdominal SC applications of placebo buffer in the AMD on 1 day	100/placebo
Patient Pharmacokinetics and Initial Tolerability					
20080398	Phase 1, double-blind, randomized, placebo-controlled (ascending multiple dose)	Adults with hyperlipidemia taking a statin; or adults with HeFH	Safety, tolerability, PK, and PD	14 or 35 mg SC QWx6; 140 or 280 mg SC Q2Wx3; 420 mg SC QMx2	43/evolocumab
Intrinsic Factor Pharmacokinetics					
20120341	Phase 1, open-label (hepatic impairment)	Adults with mild, moderate, or no hepatic impairment	Safety, tolerability, PK, and PD in hepatic impairment	140 mg SC (single dose)	24/evolocumab

Two clinical PK equivalence studies to bridge the data from phase 3 studies that used the AI/pen presentation containing commercial drug substance (Process 2) to the AMD and PFS presentations containing commercial drug substance:

- **Study 20110168** was an open-label, randomized, parallel study in 292 healthy volunteers that was conducted to demonstrate pharmacokinetic equivalence of 1 AMD (test article) to 3 AI/pens (reference article).
- **Study 20120133** was an open-label, randomized, crossover study in 96 healthy volunteers that was conducted to demonstrate pharmacokinetic equivalence of 1 PFS (test article) to 1 AI/pen (reference article).

2.4.2. Pharmacokinetics

The clinical program consists of ten studies of which 9 studies are performed in healthy subjects and one study in patients with hypercholesterolemia (familial and non-familial). The different studies performed seem appropriate to characterise the PK and PD of evolocumab.

Population Pharmacokinetic/pharmacodynamic Modelling

The applicant performed an extensive Population pharmacokinetic and pharmacokinetic-pharmacodynamic modelling of evolocumab in healthy volunteers and different type of patients. Analyses were based on pooled data from 5474 patients from 11 studies (see Table PK03), including 3414 subjects that received evolocumab and were included in the final population pharmacokinetic analysis: phase 1 Studies 20080397 and 20080398; phase 2 studies 20101154, 20101155, 20090158, and 20090159; and phase 3 studies 20110109, 20110114, 20110115, 20110116, and 20110117. Sparse PK data were collected in the phase 3 studies.

The updated population pharmacokinetic model fit the data adequately, and parameter estimates of the updated model were similar to those from the phase 1+2 model. In the final PK covariate model, body weight, sex (female), statin co-administration, statin + ezetimibe co-administration, and PCSK9 baseline emerged as statistically significant covariates on evolocumab pharmacokinetics. The outcome of the study with respect to the intrinsic variables is discussed under the specific headings.

Absorption and bioequivalence

The relative bioavailability of evolocumab after subcutaneous administration is about 55% compared with the intravenous route of administration.

Study 20110168 showed that the 420 mg dose administered with the AMD presentation at 120 mg/mL with a 3.5 mL fill was pharmacokinetically equivalent to the reference presentation of 3 AI/pens (1 mL each, 140 mg/mL). Study 20120133 showed that the 140 mg dose administered with the PFS presentation at 140 mg/mL with a 1 mL fill was pharmacokinetically equivalent to the reference presentation of 1 AI/Pen (140 mg/mL, 1mL pen).

Bioequivalence between different devices and volumes of administrations has been demonstrated. This application includes 1 mL prefilled syringe and 1 mL AI/pen. The AMD device is not part of this application. For pharmacokinetic analysis, the Applicant included only subjects who had sufficient number of samples for reliable estimation of PK parameters (exclusion criteria - sample missing before or after C_{max}; for AUC missing 2 or more samples or sample before LLOQ missing). These definitions are not in line with the Guideline on Bioequivalence Investigation. A sensitivity analysis including all subjects with calculation of the AUC0-∞ was submitted, to fully characterise also terminal elimination phase. With this parameter bioequivalence was also established.

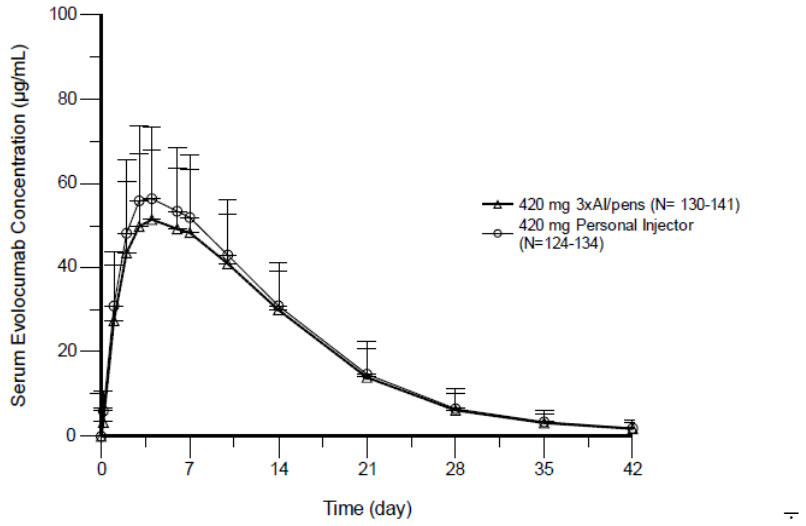
Both bioequivalence studies were conducted using evolocumab manufactured by Process 2. Some phase 1 and 2 studies were conducted using evolocumab manufactured by Process 1. The Applicant did submit comparative data on the pharmacokinetics and pharmacodynamics from the OLE Study 20110110 where subjects transitioned from Process 1 to Process 2 with sufficient evidence of comparability. These data was further supported by comparative data from population PK analysis. Hence, bridging of clinical data between Process 1 and 2 product was considered acceptable.

Distribution

The volume of distribution after iv administration is about 3.3 l. This is considered similar to the plasma volume. The apparent elimination half-life is about 11 to 15 days.

In the figure below a typical concentration-time curve of evolocumab upon subcutaneous administration 420 mg in serum is given.

Figure PK01: Concentration time curve of evolocumab



Metabolism

As evolocumab is a monoclonal antibody, no in vitro permeability, in vitro metabolism, or in vitro metabolic drug-drug interaction studies were conducted. The absence of in vitro and in vivo metabolism studies are considered acceptable as monoclonal antibody are degraded in the body to small peptide molecules by non-specific processes.

Elimination

Evolocumab is eliminated mainly by target mediated binding to PCSK9 at low concentrations. This is a saturable process and causes non-linear pharmacokinetics in the lower concentration range. Evolocumab is also eliminated by non-specific cleavage to small peptides.

Pharmacokinetics in the target population

The C_{max} and AUC_{last} of evolocumab in patients receiving a high-dose statin were slightly lower compared with subjects receiving lower statin doses probably due to higher basal PCSK9 levels. The C_{max} of evolocumab in subjects with HeFH was slightly lower compared with subjects without HeFH on low- to moderate-dose statins receiving the same evolocumab dose regimen (140 mg SC Q2W × 3). However, the AUC_{last} values were comparable.

Pharmacokinetic changes did not result in differences in unbound PCSK9 and LDL-C responses between subjects with and without HeFH (See Pharmacodynamic Assessment).

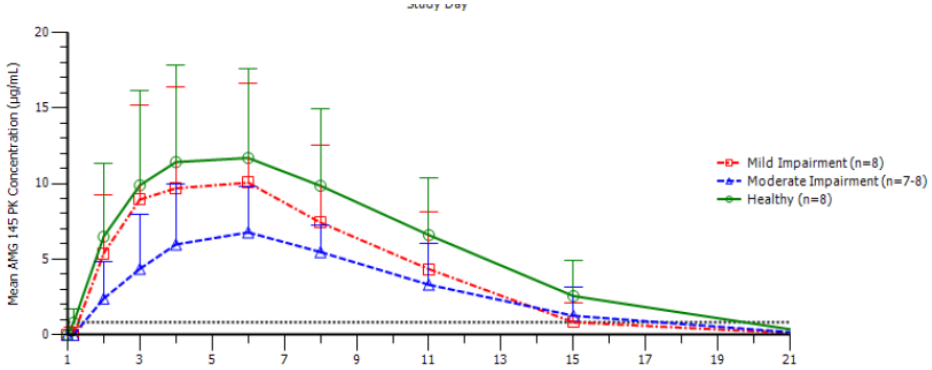
In patients with HoFH the evolocumab concentrations seems lower than in HeFH patients due to the higher basal levels of PCSK9 in this group of patients. However, when evolocumab was used in combination with a statin, with or without other lipid lowering therapy, HoFH did not have a clinically meaningful effect on the observed PK profile for evolocumab compared with non-HoFH populations.

Intrinsic factors

As expected for monoclonal antibodies, renal impairment did not show a clinical significant effect on the clearance of evolocumab.

After a single dose of evolocumab 140 mg SC in patients with mild or moderate hepatic impairment, exposure decreased with increasing hepatic impairment (See Figure below). Median t_{max} was 4.5 or 5.0 days in each group. Compared with healthy subjects, subjects with mild and moderate hepatic impairment had mean AUC_{last} values that were 39% and 47% lower, respectively and mean C_{max} values that were 21% and 34% lower, respectively. The basal PCSK9 levels were similar between the groups investigated.

Figure PK02: Mean (SD) concentration-time curves for evolocumab after single-dose administration of 140 mg SC in hepatic impaired or healthy subjects



As in the SmPC is recommended that no dose adjustment is considered necessary, the clinical relevancy of this diminished exposure in moderate impaired patients is not clear. Therefore, the efficacy in moderate and severe hepatic impaired patients is not warranted. This should be mentioned in the SmPC under 4.4.

The population pharmacokinetic analysis reveal that the gender, race, age, weight did not affect the pharmacokinetics of evolocumab in a clinical significant way.

C_{trough} concentrations tended to be slightly lower in heavier subjects as estimated in population PK/PD analysis, but this did not result in PD differences based on reductions in LDL-C. In subjects with small body weight (40 kg), the model predicted $AUC_{week\ 8\text{-}12}$ was approximately 4-fold higher than is reference subject (male, 84 kg, no co-medications). The Applicant has submitted model predicted and observed evolocumab trough concentrations and LDL-C reductions. These data clearly demonstrates significant impact of body weight on evolocumab PK, but no apparent effect on PD. Therefore, the Applicant has reflected in the SmPC that body weight was significant covariate in pop PK analysis impacting evolocumab trough concentrations (section 5.2).

Dose proportionality and time dependencies

Following a single 420 mg intravenous dose, the mean (SD) systemic clearance was estimated to be 12 (2) mL/hr. In clinical studies with repeated subcutaneous dosing over 12 weeks, dose proportional increases in exposure were observed with dose regimens of 140 mg and greater. An approximate two to three-fold accumulation was observed in trough serum concentrations (C_{min} (SD) 7.21 (6.6)) following

140 mg doses every 2 weeks or following 420 mg doses administered monthly (C_{min} (SD) 11.2 (10.8)), and serum trough concentrations approached steady-state by 12 weeks of dosing.

No time dependent changes were observed in serum concentrations over a period of 124 weeks.

Special populations

Renal impairment

No dose adjustment was considered necessary in patients with mild to moderate renal impairment. Population pharmacokinetic analysis of integrated data from evolocumab clinical trials did not reveal a difference in pharmacokinetics of evolocumab in patients with mild or moderate renal impairment relative to non-renally impaired patients. Evolocumab has not been studied in patients with severe renal impairment and this is reflected in the RMP and SmPC.

Hepatic impairment

No dose adjustment was considered necessary in patients with mild hepatic impairment (Child-Pugh class A). Single 140mg subcutaneous doses of evolocumab were studied in 8 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment and 8 healthy subjects. The exposure to evolocumab was found to be approximately 40-50% lower compared to healthy subjects. However, baseline PCSK9 levels and the degree and time course of PCSK9 neutralisation were found to be similar between patients with mild or moderate hepatic impairment and healthy volunteers. This resulted in similar time course and extent of absolute LDL-C lowering. Evolocumab has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and this is reflected in the RMP and the SmPC.

Body Weight

Body weight was a significant covariate in population PK analysis impacting evolocumab trough concentrations, however there was no impact on LDL-C reduction. The week 12 trough concentration following repeat subcutaneous administration of 140 mg were in patients of 69 kg and 93 kg, 147% higher and 70% lower, respectively, than the trough concentration of the typical 81 kg subject. Less impact from body weight was seen with repeated subcutaneous evolocumab 420 mg monthly doses.

Other special populations

Population pharmacokinetic analyses suggest that no dose adjustments are necessary for age, race or gender. The pharmacokinetics of evolocumab was influenced by body weight without having any notable effect on LDL-C lowering. Therefore, no dose adjustments were considered necessary based on body weight.

	Age 65-74	Age 75-84	Age 85+
PK Trials (N = 577)	9 (1.6%)	0 (0%)	0 (0%)
Controlled Trials (N = 6026)	1556 (25.8%)	223 (3.7%)	0 (0%)
Non Controlled trials (N = 198)	26 (13.1%)	3 (1.5%)	0 (0%)

PK trials = 20090397, 20090398, 20110121, 20110133, 20110168, 20120341, 20120136
Controlled trials = ISS parent studies (20101154, 20101155, 20090158, 20090159, 20110231, 20110109, 20110114, 20110115, 20110116, 20110117, 20120348, 20120356)
Non Controlled trials = 20110271

Pharmacokinetic interaction studies

No *in vitro* interaction studies were performed. This was considered acceptable; no interactions on the level of CYP co-enzymes or transporters were expected as evolocumab is a human monoclonal immunoglobulin.

As evolocumab is not metabolised by specific enzymes, its potential for interaction is low. Only due to target mediated clearance by PCSK9 interaction on the level of PCSK9 concentrations (like statins) are considered of clinical significance.

Statins do decrease the evolocumab exposure is a clinical significant way. Again this may be caused by the higher basal levels of PCSK9 and consequently higher initial clearance of evolocumab. In steady state this effect is diminished.

Unbound levels of PCSK9 are sensitive to the type of lipid lowering agent in the presence of evolocumab. The effect of the increase in unbound PCSK9 is also reflected in lower unbound concentration of evolocumab after administration of the same lipid lowering compound but not on the percent change in LDL-C from baseline.

These effects can be extrapolated to concomitant use with fibrates but as fibrates do have a similar effect on PCSK9 it can be expected that the unbound concentrations of evolocumab will not differ significantly compared to co medication with statins.

2.4.3. Pharmacodynamics

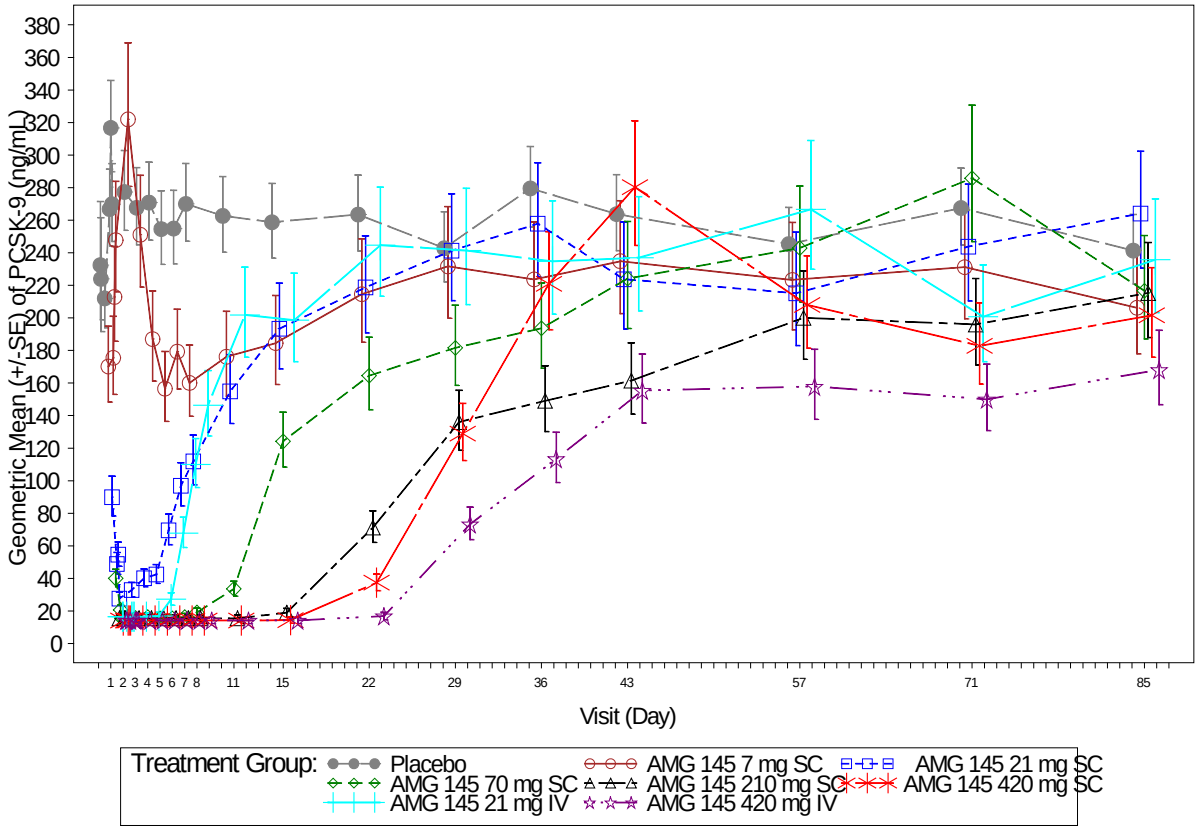
Mechanism of action

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

Primary and Secondary pharmacology

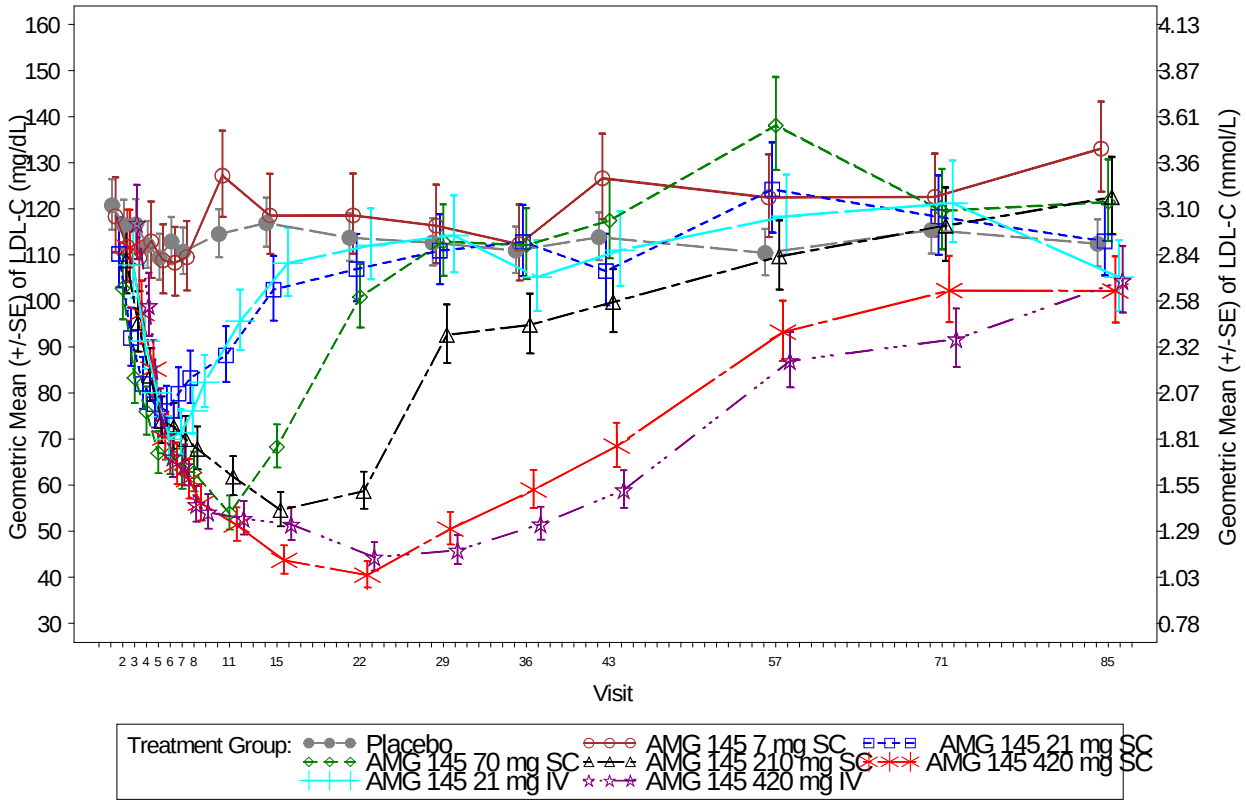
A single SC or IV phase 1 proof-of–concept first in human study conducted in 56 healthy subjects as shown below (Figure PD01 and PD02), showed that the dose response for decrease in unbound PCSK9 over time after dosing correlated well with dose responses for a decrease in LDL-C. Complete suppression of PCSK-9 was found for doses of 70 mg or more with longer suppression found with higher doses. This translated in larger reduction in LDL-C for the higher 210 and 420 mg doses with apparently no difference for the 420 mg SC and 420 mg IV doses.

Figure PD01. Geometric Mean (SE) of Unbound PCSK9 (ng/mL) Over Time (Actual Scale) (Study 20080397)



Note: Values on the x-axis have been shifted slightly for ease of reading and D indicates Day.

Figure PD02. Geometric Mean (SE) of Ultracentrifugation LDL-C Over Time (Study 20080397)



Note: Values on the x-axis have been shifted slightly for ease of reading and D indicates Day.

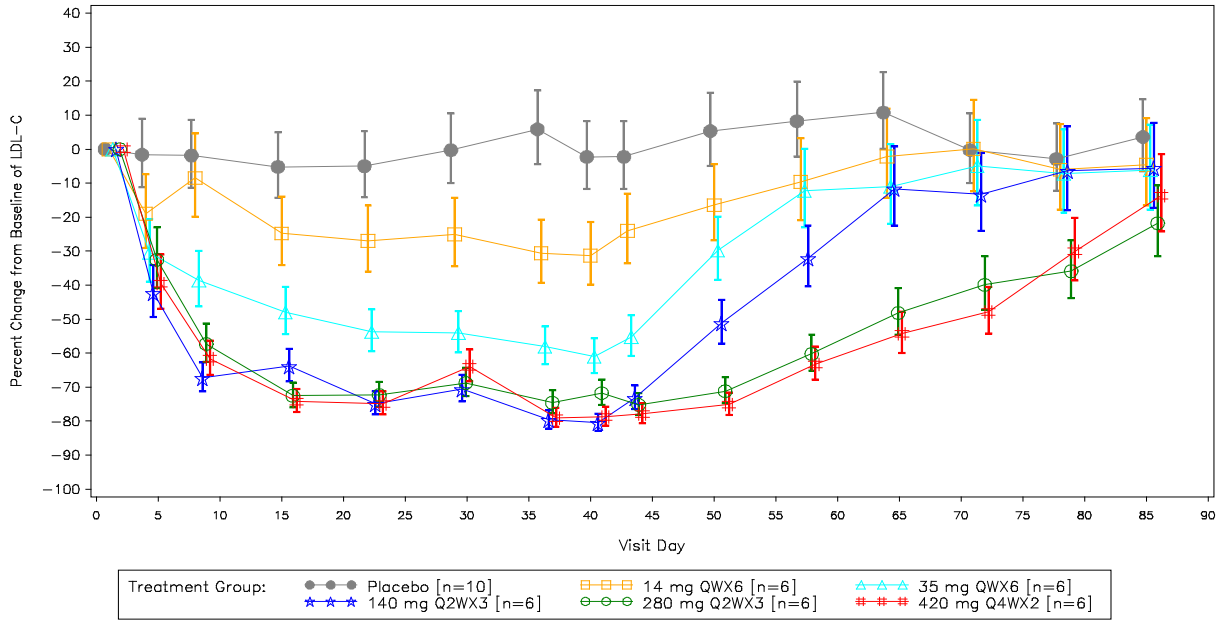
Multiple dosing with evolocumab (see Table PD01 and Figure PD03) resulted in dose-dependent decreases in LDL-C on top of statin treatment. The dose level of statins did not impact the pharmacodynamic response to evolocumab in terms of LDL-C and PCSK9 reduction as these were similar when comparing subjects on low- to moderate-dose statin therapy versus subjects on high-dose statin therapy receiving the same evolocumab dose regimen. Likewise, the diagnosis of HeFH did not impact the pharmacodynamics response to evolocumab following similar comparison.

Table PD01. Dose cohorts (Study 20080398)

Cohort	Patient group	Inclusion Criterion	Evolocumab Dose (mg)	Frequency
1	**Hypercholesterolemia, low- or moderate-dose statin**	rosuvastatin (Crestor®) < 40 mg/day, atorvastatin (Lipitor®) < 80 mg/day, or simvastatin (Zocor®) 20 to 80 mg/day	14	QWx6
2			35	QWx6
3			140	Q2Wx3
4			280	Q2Wx3
5			420	QMx2
6	**Hypercholesterolemia, high dose statin**	rosuvastatin (Crestor®) 40 mg/day or atorvastatin (Lipitor®) 80 mg/day	140	Q2Wx3
7	**HeFH**	diagnosis of HeFH on the basis of a score of ≥ 9 points according to the	140	Q2Wx3

Cohort	Patient group	Inclusion Criterion	Evolocumab Dose (mg)	Frequency
		World Health Organization (WHO) criteria. No statin dose requirement (ie, low- to moderate or high dose)		

Figure PD03. Percent Change From Baseline (± Standard Error) of Ultracentrifugation LDL-C Over Time for Cohorts 1 to 5 on Low- to Moderate-dose Statins (Study 20080398)



Note: Values on the x-axis have been shifted slightly for ease of reading.

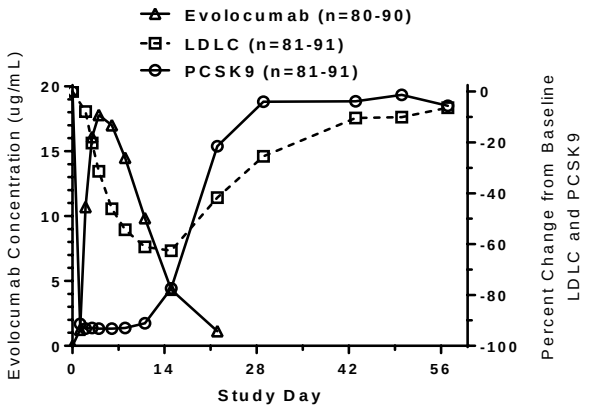
Percentage change is generated by (modeled based ratio to baseline −1) * 100.

Program: /stat/clinpharm/AMG145/20080398/analysis/final/graphs/program/g_pd_pchg_gmean.sas
Output: /stat/clinpharm/AMG145/20080398/analysis/final/graphs/output/f14-037-pd-pchg-gmean-ldl-1to5-l.rtf (Date Generated: 08FEB2012)
Source Data: /stat/clinpharm/AMG145/20080398/analysis/final/statdata/crt/pd.sas7bdat

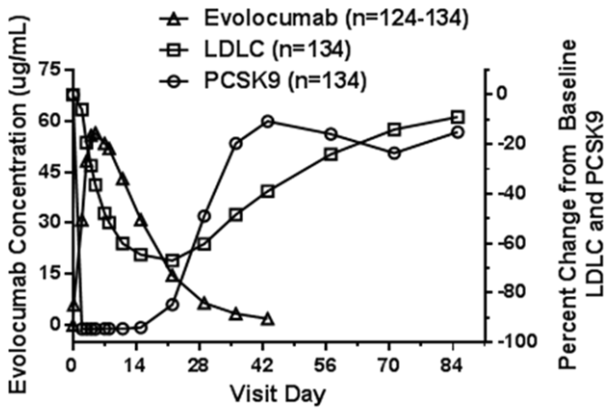
Evolocumab treatment resulted in dose-dependent decreases in LDL-C and unbound PCSK9. After achievement of C_{max} at a median of 3-4 days after a dose, mean unbound evolocumab serum concentrations decrease to the LLOQ 21 and 42 days after a dose of 140 mg and 420 mg, respectively (Figure PD04).

Figure PD04. Mean Unbound Evolocumab Serum Concentrations and Geometric Mean Percent Change From Baseline in Ultracentrifugation LDL-C and Unbound PCSK9 in Healthy Subjects

Single-dose Evolocumab 140 mg SC (Study 20120133)

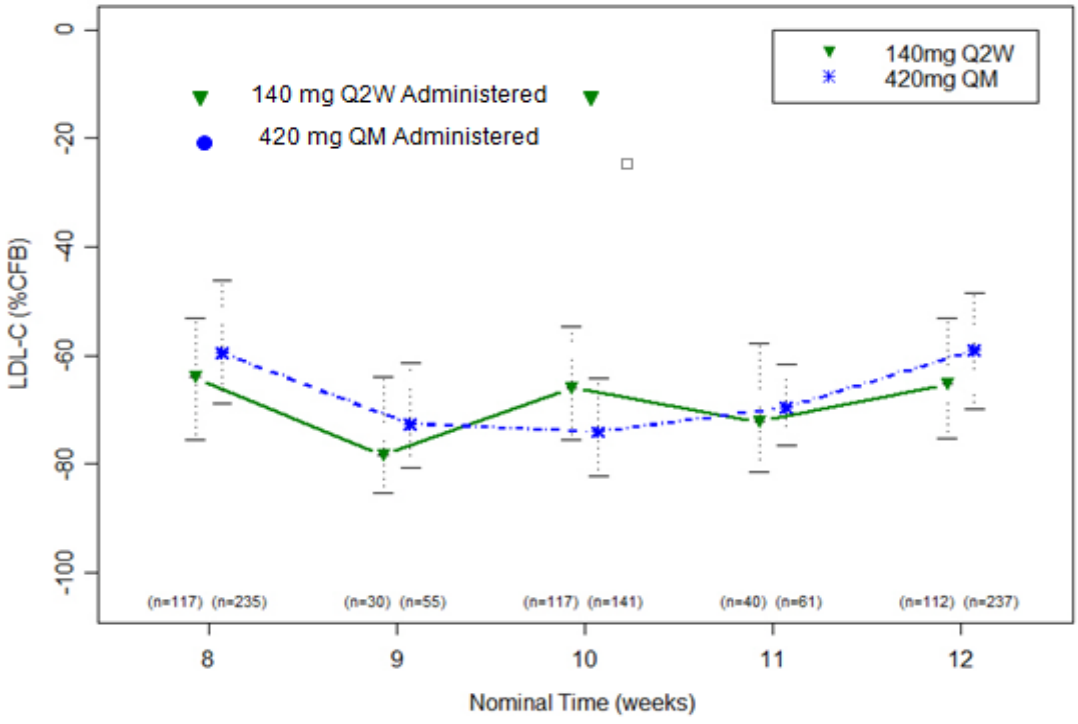


Single-dose Evolocumab 420 mg SC (Study 20110168)



In multiple-dose studies (phase II study 20090158, 20090159, 20101154, and 2010115), temporal changes in LDL-C and unbound PCSK9 serum concentrations were observed in both the Q2W and QM regimens and were characterized by a return toward baseline at the end of the dosing interval. Furthermore, as expected from a regimen with more frequent dosing, the Q2W regimen resulted in less return toward baseline for LDL-C at the end of the dosing interval than the QM regimen (Figure PD05).

Figure PD05. Median Percent Change From Baseline in Calculated LDL-C From Weeks 8 to 12 With Administration of Evolocumab 140 mg SC Q2W or 420 mg SC QM in Patients With Primary Hyperlipidemia and Mixed Dyslipidemia (Studies 20090158, 20090159, 20101154, and 20101155)



2.4.4. Discussion on clinical pharmacology

In study 20080397, evolocumab as a single dose of 21 mg and 420 mg was administered via SC and IV route. Absolute bioavailability after SC administration was approximately 10% and 55%, for 21 mg and for 420 mg dose, respectively. Hence, at clinically relevant doses bioavailability after SC route is approximately 50%, similar to other monoclonal antibodies.

Drug substance for phase 1 and phase 2 clinical studies was initially manufactured by Process 1. Drug substance for the majority of the phase 3 studies was manufactured by Process 2. The commercial drug substance will be manufactured using Process 2. Bioequivalence studies 20110168 and 20120133 were conducted with different devices, but evolocumab in all treatment arms was manufactured by Process 2. Both bioequivalence studies were conducted using evolocumab manufactured by Process 2. Some phase 1 and 2 studies were conducted using evolocumab manufactured by Process 1. The Applicant did submit comparative data on the pharmacokinetics and pharmacodynamics from the OLE Study 20110110 where subjects transitioned from Process 1 to Process 2 with sufficient evidence of comparability. These data were further supported by comparative data from population PK analysis. Hence, bridging of clinical data between Process 1 and 2 products was considered acceptable.

The volume of distribution was 3-4 L indicating that evolocumab is greatly confined to the blood compartment. Evolocumab is eliminated via 2 mechanisms: one mechanism that predominates at low doses (< 140 mg SC) and becomes saturated at higher doses (≥140 mg SC). The saturable target-mediated clearance is likely related to evolocumab binding to PCSK9 and elimination of the antibody-PCSK9 complex. The nonsaturable mechanism of evolocumab elimination is likely nonspecific catabolism in cells of the reticuloendothelial system. The mean clearance for evolocumab 420 mg IV (Study 20080397) was 11.6 mL/hr which is approximately 1.5-fold greater than values reported for natural Ig (clearance of 6.0 to 8.4 mL/hr). This represents both linear (associated with the clearance processes and rates for natural immunoglobulins) and nonlinear (associated with the PCSK9 target) contributions to the total clearance of unbound evolocumab. Population PK model predicted effective half-life for 140 mg SC Q2W was 11.4 days, and the model predictive effective half-life for 420 mg SC QM was 16.8 days.

In population PK analysis multiple SC doses of evolocumab ≥ 140 mg SC Q2W resulted in nearly dose proportional increase in the AUC from week 8 to week 12 (AUCwk8-12), but the PK was higher than dose proportional for fixed doses of 70 to 140 mg SC Q2W.

At repeated administration, evolocumab demonstrated 2 to 3 fold accumulation as evidenced by measured trough and maximal concentrations in phase 2 and 3 studies. Steady state was achieved by week 12 with no apparent differences in the PK between subjects with primary hyperlimidemia/mixed dyslipidemia and subjects with homozygous familial hypercholesterolemia.

In healthy subjects with normal baseline LDL-C evolocumab at single dose of 140 mg SC exhibited highly variable pharmacokinetics as evidenced by intrasubject CV% for Cmax 32% and for AUClast 45%, whereas pharmacodynamic effects were less variable with intrasubject CV% for the reductions in LDL-C 7.5%.

Antibodies have a low potential for pharmacokinetic drug interactions. Therefore no in vitro and in vivo drug interaction studies and they are not are considered necessary at this moment.

In patients on high dose statin, the systemic exposure of evolocumab was slightly lower than in subjects on low-to-moderate dose statin (ratio of AUClast 0.74), but this did not seem to affect PD of evolocumab based on the LS mean LDL-C and PCSK9 AUCs. Slightly lower systemic exposure in patients on high dose statin could be due to statin induced increases in PCSK9.

In line with pharmacokinetics of other IgG type monoclonal antibodies, renal impairment does not affect evolocumab elimination based on population PK analysis.

Interestingly, in subjects with hepatic impairment the systemic exposure of evolocumab was lower than in healthy subjects (ratio of AUClast 0.5 to 0.6 in mild to moderate impairment), most likely due to differences in target-mediated clearance. Differences in the Cmax were smaller (LS mean Cmax values were 21% and 34% lower). This resulted in lower LDL-C reductions (ratio of AUECday1-57 approximately 0.8 in both mild and moderate group). No differences in PCSK9 levels were seen, in line with complete inhibition of target as seen already at lower evolocumab doses.

Gender, race and age had no impact on the PK and PD of evolocumab. Ctrough concentrations tended to be slightly lower in heavier subjects as estimated in population PK/PD analysis, but this did not result in PD differences based on reductions in LDL-C.

No apparent difference in the systemic exposure of evolocumab was seen in patients with HeFH and without HeFH on low-to-moderate dose statin. No apparent differences in LDL-C and PCSK9 reductions were seen between the 140 mg Q2W and 420 mg Q1M, but the duration of action was longer in the higher dose group, supporting less frequent dosing with the higher dose.

The decreases in mean LDL-C values were dose-related. Mean nadirs as low as 40 to 44 mg/dL were reached at approximately study day 22 (in the 420 mg SC group and the 420 mg IV group), with subsequent returns to near baseline by approximately study day 71. In the 210 mg dose group and in the 420 mg groups (SC or IV), mean unbound PCSK9 decreased within hours after dosing to values below the lower limit of quantification (LLOQ) (15 ng/mL), remained below the LLOQ until study day 11, and subsequently returned to or toward baseline. The dose response for decrease in unbound PCSK9 over time after dosing correlated well with the dose responses for decreases in LDL-C.

2.4.5. Conclusions on clinical pharmacology

The proof of concept of evolocumab in inhibition of PCSK9, as measured by a decrease in unbound PCSK9, and the subsequent decrease in LDL-C has sufficiently been demonstrated. Reduction in LDL-C has both been demonstrated in healthy subjects after a single dose of evolocumab as well as in hypercholesterolemia patients on stable statin therapy after multiple dose administration of evolocumab.

No significant difference in LDL-C or PCSK9 reduction was observed when comparing subjects on high-dose statin therapy receiving evolocumab versus subjects on low- to moderate-dose statin therapy receiving the same evolocumab dose regimen at any time point during the study. In addition, heterogenous familial hypercholesterolemia (HeFH) status also had no effect on the evolocumab pharmacokinetic and pharmacodynamic parameters.

In addition to LDL-C reduction, multiple dosing with evolocumab resulted in decreased mean total cholesterol, apolipoprotein B and increased HDL-C and apolipoprotein A-I, while no significant effect in TG levels were observed. Evolocumab was well tolerated by healthy subjects and patients after a single intravenous (IV) or subcutaneous (SC) dose, and after repeated SC doses.

The incidence of anti-evolocumab binding antibodies was low and did not appear to influence the PK and PD of evolocumab. Furthermore, results from population PK and PD analyses support clinical use of the proposed 140 mg SC Q2W or 420 mg SC QM dosing regimens.

2.5. Clinical efficacy

2.5.1. Dose response studies

The following studies were designed to support the selection of dose in different target populations.

- Hypercholesterolaemia and mixed dyslipidaemia

Table E02. Study design of phase 2 studies included in comparison of efficacy in primary hyperlipidemia and mixed dyslipidemia

	Study 20090158 (RUTHERFORD-1)	Study 20090159 (GAUSS-1)	Study 20101154 (MENDEL-1)	Study 20101155 (LAPLACE-1)	Study 20110110 (OSLER-1)	Study 20110231 (YUKAWA-1)
No. of subjects	167	157	406	629	1324	307
Duration	12 wks	12 wks	12 wks	12 wks	Up to 5 yrs	12 wks
Therapeutic Setting	HeFH (familial)	Statin-intolerant (familial and nonfamilial)	Monotherapy (Framingham Risk ≤ 10%) (familial and nonfamilial)	Statin combination (familial and nonfamilial)	Completed phase 2 parent study[a] (familial and nonfamilial)	High-risk/Japanese subjects (familial and nonfamilial)
Fasting LDL-C	≥ 100 mg/dL (2.6 mmol/L)	≥ 100 mg/dL (2.6 mmol/L)	≥ 100 mg/dL (2.6 mmol/L)	≥ 85 mg/dL (2.2 mmol/L)	≥ 85 mg/dL	≥ 115 mg/dL (3.0 mmol/L)
Evolocumab (SC)	350 mg QM or 420 mg QM	280 mg QM or 350 mg QM or 420 mg QM	70 mg Q2W or 105 mg Q2W or 140 mg Q2W or 280 mg QM or 350 mg QM or 420 mg QM	70 mg Q2W or 105 mg Q2W or 140 mg Q2W or 280 mg QM or 350 mg QM or 420 mg QM	420 mg QM	70 mg Q2W or 140 mg Q2W or 280 mg QM or 420 mg QM
Background therapy	Statin (± ezetimibe)	Non-ezetimibe lipid-lowering therapy	None	Statin (± ezetimibe)	SoC	Statin (± ezetimibe)
Control	Placebo SC	Placebo SC + ezetimibe PO QD	Placebo SC or ezetimibe PO QD	Placebo SC	SoC alone	Placebo SC

Study 20101155 (LAPLACE-1)

This was a phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study of evolocumab administered SC for 12 weeks in subjects with primary hyperlipidemia and mixed dyslipidemia. Subjects were randomized into 1 of 8 treatment groups: evolocumab SC Q2W (70 mg, 105 mg, or 140 mg), evolocumab SC QM (280 mg, 350 mg, or 420 mg), placebo Q2W, or placebo QM. The primary objective was to evaluate the effect of 12 weeks of evolocumab SC Q2W or QM, compared with placebo, on percent change from baseline in UC LDL-C when used in addition to a statin with or without ezetimibe in subjects with hyperlipidemia.

Study 20090158 (RUTHERFORD-1)

This was a phase 2, multicenter, double-blind, randomized, placebo-controlled study of evolocumab in subjects with heterozygous familial hypercholesterolemia. Subjects were on a stable dose(s) of statin and other allowed lipid-regulating drugs for at least 4 weeks before LDL-C screening. Subjects were randomized to 1 of 3 treatment groups: evolocumab SC QM (350 mg or 420 mg) or placebo SC QM. The primary objective was to evaluate the effect of 12 weeks of evolocumab SC QM, compared with placebo, on percent change from baseline in UC LDL-C in subjects with HeFH. Secondary objectives were comprised of safety and tolerability, effect on other lipid parameters, and pharmacokinetic evaluation.

Study 20090159 (GAUSS-1)

This was a phase 2, multi center, double-blind (except open-label ezetimibe), randomized, placebo- and ezetimibe-controlled study of evolocumab administered SC for 12 weeks in subjects with primary hyperlipidemia and mixed dyslipidemia who were statin-intolerant. Subjects had tried at least 1 statin and were unable to tolerate any dose or an increase in statin dose above total weekly maximum doses of statins specified in the protocol due to intolerable myopathy. Subjects were randomized into 1 of 5 treatment groups: evolocumab SC QM (280 mg, 350 mg, or 420 mg); evolocumab 420 mg SC QM and ezetimibe 10 mg oral (PO) daily (QD); or placebo SC QM and ezetimibe 10 mg PO QD. The primary objective was to evaluate the effect of 12 weeks of evolocumab SC QM, compared with ezetimibe, on percent change from baseline in UC LDL-C in hypercholesterolemic subjects unable to tolerate an effective dose of a statin. Secondary objectives were comprised of safety and tolerability, effect on other lipid parameters, and pharmacokinetic evaluation.

Study 20101154 (MENDEL-1)

This was a phase 2, multi center, randomized, placebo- and ezetimibe-controlled, dose ranging study of evolocumab in subjects with primary hyperlipidemia and mixed dyslipidemia and a 10-year Framingham risk score of 10% or less. Subjects were randomized into 1 of 9 treatment arms: evolocumab SC Q2W (70 mg, 105 mg, or 140 mg); evolocumab SC QM (280 mg, 350 mg, or 420 mg); ezetimibe 10 mg PO QD; placebo SC (Q2W or QM). The primary objective of this study was to evaluate the effect of 12 weeks of evolocumab SC administered Q2W or QM, compared with placebo, on percent change from baseline in UC LDL-C when used as monotherapy in hyperlipidemic subjects with a 10-year Framingham risk score of 10% or less. Secondary objectives were comprised of safety and tolerability, effect on other lipid parameters, and pharmacokinetic evaluation. The overall study results for phase 2 studies for LDL-C lowering effect of evolocumab are provided in Table E03 below.

Table E03: Summary of efficacy in phase 2 studies with evolocumab in hypercholesterolaemia and mixed dyslipidaemia.

Phase 2	N	Doses used	LDL-C at 12 weeks (%)	Vs Ezetimibe (%)
Primary hyperlipidemia and mixed dyslipidemia				
20101155 LAPLACE-1	A Double-blind, Randomized, Placebo-controlled, Multicenter, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Combination with HMG-CoA Reductase Inhibitors (in Hypercholesterolemic Subjects			
	629	70 mg Q2W	-44	
		105 mg	-63	
		140 mg	-69	
		280 mg QM	-44	
		350 mg	-54	
		420 mg	-54	

Phase 2	N	Doses used	LDL-C at 12 weeks (%)	Vs Ezetimibe (%)
Primary hyperlipidemia and mixed dyslipidemia				
20090158 RUTHERFORD-1	A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Subjects with Heterozygous Familial Hypercholesterolemia			
	167	350 mg QM	-46	
	HeFH	420 mg	-59	
20090159 GAUSS-1	A Randomized, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C, Compared with Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor			
	157	280 mg QM	-26	
	Statin-intolerant	350 mg	-27	
		420 mg	-38	
		420 mg + EZT	NA	
20101154 MENDEL-1	A Randomized, Placebo and Ezetimibe Controlled, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Hypercholesterolemic Subjects With a 10-year Framingham Risk Score of 10% or Less			
	406	70 mg Q2W	-40	-27
		105 mg	-46	-30
		140 mg	-52	-37
		280 mg QM	-45	-25
		350 mg	-50	-30
		420 mg	-57	-34
20110110 OSLER-1	A Multicenter, Controlled, Open-label Extension Study to Assess the Long-term Safety and Efficacy of Evolocumab			
	1324 year 1	420 mg QM		
	937 year 2	Week 12	-59	
	ongoing	Week 52	-54	
		Week 64	-55	
		Week 112	-54	

- Homozygous familial hypercholesterolaemia

Table 9. Main features of the Homozygous Familial Hypercholesterolemia studies

Study ID	Design	Objectives	Subjects	Treatments	Dura-tion	Numbers incl-d/ anal-d
20110233	Part A: phase 2, open-label, single-arm, pilot Part B: phase 3, double-blind, randomized, PBO-controlle	Efficacy (LDL-C and other lipid parameters), safety, tolerability, and PK	Subjects with HoFH on a stable low-fat diet and pre-existing, lipid-lowering therapies at least 4 weeks prior with LDL-C ≥ 130 mg/dL (3.4 mmol/L) Age 12 to 80 years	420 mg SC QM Part B: PBO or EvoMab 420 mg SC QM via vial and syringe or AI/pen	Part A: 12 w Part B: 12 w	Part A: 8/8 Part B: 50/49

Study ID	Design	Objectives	Subjects	Treatments	Dura-tion	Numbers incl-d/ anal-d
	d					
20110271	Phase 2/3, open-label, long-term	Efficacy (LDL-C and other lipid parameters), safety, and tolerability	Completion of a qualifying EvoMab protocol without treatment related SAE that led to IP discontinuation and have a diagnosis of severe FH If *de-novo* subject then must have severe FH and be on background lipid-lowering therapy for ≥ 4 weeks prior LDL-C ≥ 100 mg/dL (2.6 mmol/L) (with CHD or CHD risk equivalent) or ≥ 130 mg/dL (3.4 mmol/L) (no CHD or CHD risk equivalent) Age 12 to 80 years	EvoMab 420 mg SC QM or SC Q2W (if eligible) via vial and syringe, AI/pen, or AMD	~5 y, On-going	238/ 198 incl 96 HoFH

The results of these studies are discussed in the Main studies section of this report.

2.5.2. Main studies

Considering the large number of studies (9 phase 3 studies including 2 home-use device studies) submitted in support of the application, summary tables have been used where possible to describe the study methods.

- Hypercholesterolaemia and mixed dyslipidaemia

Table E04. Study Design of Phase 3 Studies Included in Evaluation of Efficacy in Primary Hyperlipidemia and Mixed Dyslipidemia

	Study 20110115 (LAPLACE-2)	Study 20110117 (RUTHERFORD-2)	Study 20110116 (GAUSS-2)	Study 20110114 (MENDEL-2)	Study 20110109 (DESCARTES)	Study 20120138 (OSLER-2)	Study 20110271 (TAUSSIG: severe FH only)	Study 20120348 (THOMAS-1)	Study 20120356 (THOMAS-2)
No. of subjects	1896	329	307	614	901	2928	102	149	164
Duration	12 wks	12 wks	12 wks	12 wks	52 wks	Up to 2 yrs	Up to 5 yrs	8 wks	12 wks
Therapeutic Setting	Statin combination (familial and nonfamilial)	HeFH (familial)	Statin-intolerant (familial and nonfamilial)	Monotherapy (familial and nonfamilial)	Range of CV risk (familial and nonfamilial)	Completed phase 3 parent study[a] (familial and nonfamilial)	Severe FH subjects	Home-use of PFS or AI/pen (familial and nonfamilial)	Home-use of AMD or 3 AI/pens (familial and nonfamilial)
Fasting LDL-C	≥ 80 mg/dL (2.1 mmol/L)[b]	≥ 100 mg/dL (2.6 mmol/L)	≥ 100 mg/dL (2.6 mmol/L)	≥ 100 mg/dL (2.6 mmol/L) and < 190 mg/dL (4.9 mmol/L)	≥ 75 mg/dL (1.9 mmol/L)	NA	≥ 100 mg/dL (2.6 mmol/L) for non-apheresis subjects	≥ 85 mg/dL (2.2 mmol/L)	≥ 85 mg/dL (2.2 mmol/L)
Evolocumab (SC) dose	140 mg Q2W or 420 mg QM	140 mg Q2W or 420 mg QM	140 mg Q2W or 420 mg QM	140 mg Q2W or 420 mg QM	420 mg QM	140 mg Q2W or 420 mg QM	420 mg Q2W or 420 mg QM	140 mg Q2W	420 mg QM
Background therapy	Statin (± ezetimibe)[c]	Statin (± ezetimibe)	Non-ezetimibe lipid-lowering therapy[d]	None	Diet ± atorvastatin ± ezetimibe[e]	SoC	stable lipid-lowering therapies	Statin (± ezetimibe)	Statin (± ezetimibe)
Control	Placebo SC and ezetimibe PO QD[f,g]	Placebo SC	Ezetimibe PO QD[f]	Placebo SC and ezetimibe PO QD[f]	Placebo SC	SoC alone	NA	Active control of EvoMab in AI/pen	Active control of EvoMab in AI/pen
Device /process[h]	AI/pens/ process 2	AI/pens/ process 2	AI/pens/ process 2	AI/pens/ process 2	Vial and syringe/ process 1	AI/pens/ process 2	AI/pens/ process 2	AI/pens and PFS/ process 2	AI/pens and AMD/ process 2

- Homozygous Familial Hypercholesterolemia patients

Table E05. Study Design of Phase 2/3 Studies Included in Comparison of Efficacy in HoFH Subjects

	Study 20110233 (TESLA)	Study 20110271 (TAUSSIG)
No. of subjects	Phase 2: 8 Phase 3: 49	198 [a]
Study phase	Phase 2: open-label Phase 3: double-blind	Phase 2/3 (open-label)
Duration	Phase 2: 12 weeks Phase 3: 12 weeks	5 years or until evolocumab becomes commercially available, whichever is earlier
Population	Phase 2 and 3: HoFH	HoFH
Fasting LDL-C	Phase 2 and 3: ≥ 130 mg/dL (3.4 mmol/L)	≥ 100 mg/dL (2.6 mmol/L) for non-apheresis subjects (No LDL-C requirement for apheresis subjects)
Evolocumab (SC)	Phase 2 and 3: 420 mg QM	420 mg QM or 420 mg Q2W
Background therapy	stable lipid-lowering therapies, apheresis not permitted	stable lipid-lowering therapies, apheresis permitted
Control	Phase 2: N/A Phase 3: Placebo SC QM	NA

The company has conducted several studies in different type of patients. Adequate separation between different patients types have been made for evaluation in separate studies. Clinical evaluation has been conducted in controlled studies for 12 weeks. However, patients were subsequently enrolled in long term follow up studies, which were considered adequate to evaluate longer term effects in terms of efficacy and safety.

Methods

Study participants

Studies have been conducted in the following patients groups:

- Primary hyperlipidemia and mixed dyslipidemia
    - In combination with statins
    - In statin intolerant subjects
    - As monotherapy
- Familial Hypercholesterolemia (severe FH and HoFH)

Patient populations were defined in the evolocumab clinical program as follows:

Primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia are defined by elevated LDL-C only (primary hyperlipidemia) or elevated LDL-C along with high triglycerides or low HDL-C (mixed dyslipidemia). Heterozygous familial hypercholesterolemia (HeFH) is defined by the diagnostic criteria outlined by the Simon Broome Register Group (Scientific Steering Committee, 1991). Nonfamilial hypercholesterolemia is the more common form of primary hypercholesterolemia where genes interact with dietary and other lifestyle factors such as physical inactivity, sex, and age.

Additional definitions for primary hyperlipidemia and mixed dyslipidemia populations evaluated include the following:

- Mixed dyslipidemia defined as triglycerides (≥ 150 mg/dL [1.7 mmol/L]), triglycerides (≥ 200 mg/dL [2.3 mmol/L]) or HDL-C (< 40 mg/dL [1.0 mmol/L] in males or < 50 mg/dL [1.3 mmol/L] in females).
- Severe hypercholesterolemia defined as a calculated LDL-C ≥ 160 mg/dL (≥ 4.1 mmol/L) while receiving a statin at screening or ≥ 240 mg/dL (≥ 6.2 mmol/L) without statin therapy.

HoFH was defined as familial or inherited defect leading to severe elevations in cholesterol.

In the placebo-controlled studies, subjects were either on physician optimized background statin therapy (Studies 20101155, 20090158, 20110231, 20110117), randomized background statin therapy per protocol (Study 20110115), or risk-based optimized background lipid-lowering therapy per protocol (Study 20110109).

In the phase 2 Study 20090159, statin intolerance was defined as the inability to tolerate at least 1 statin at any dose, or an increase in statin dose above a total weekly maximum due to intolerable myopathy (ie, myalgia, myopathy, rhabdomyolysis), and having a history of symptom improvement or resolution with statin discontinuation. In phase 3 Study 20110116, the definition of statin intolerance was modified to include a history of being intolerant to at least 2 statins.

Subjects for whom a statin is not considered clinically appropriate (eg, patients on fibrates, cyclosporine, certain CYP3A4 inhibitors, such as certain HIV or hepatitis C virus (HCV) protease inhibitors,

clarithromycin, and itraconazole, and patients with statin hypersensitivity) were not directly evaluated in this program due to small population, the Applicant believes the monotherapy placebo controlled studies to support the efficacy of evolocumab in this population.

Table 3.9. Age ranges included in the Phase 3 studies

Study	Age range
20110114 (MENDEL-2)	18 to 80 years
20110115 (LAPLACE-2)	18 to 80 years
20110116 (GAUSS-2)	18 to 80 years
20110117 (RUTHERFORD-2)	18 to 80 years
20110109 (DESCARTES)	18 to 75 years
20110233 (TESLA: phase 2/3)	12 to 80 years
20110271 (TAUSSIG: phase 2/3)	12 to 80 years

Inclusion criteria seemed generally appropriate with generally fasting LDL-C > 2.6 mmol/L and at CHD risk (for MENDEL-2 this was low CHD risk), this was >4.0 mmol/L in the LAPLACE-2 for patients not taking already a statin, and >2.0 mmol/L in the long term DESCARTES study, in hypercholesterolaemia and mixed dyslipidaemia patients.

For statin-intolerant patients, subjects had a history of statin intolerance as evidenced by both of the following (per subject or physician report):

a. Tried at least 2 statins and was unable to tolerate any dose or increase statin dose above the total weekly maximum doses due to intolerable myopathy, ie, myalgia (muscle pain, ache, or weakness without CK elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation);

b. Symptoms resolved or improved when statin dose was decreased or discontinued.

Patients with HoFH should have been genetic confirmed or a clinical diagnosis based on a history of an untreated LDL cholesterol concentration greater than 13 mmol/L together with either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents, LDL>3.4 mmol/L. For the long term study this was diagnosis of familial hypercholesterolemia and LDL> 2.6 mmol/L (and high CHD risk).

Exclusion criteria were generally poorly controlled or newly diagnosed diabetes; NYHA class III or IV; uncontrolled serious cardiac arrhythmia; uncontrolled hypertension; hypo/hyperthyroidism; severe hepatic impairment; eGFR < 30mL/min/1.73m^2; ALT/AST > 2 x ULN; creatine kinase (CK) > 3 x ULN; myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass, or stroke within 3 months prior to randomization; and malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years.

The studies included a range of patients' representative of the target population and the subject selection was appropriate for the efficacy evaluation. Controlled hypertensive and diabetic patients were allowed to be enrolled. The very elderly were excluded from the studies, which is contrary to the *EMA Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013)* recommendations. The definition of the statin intolerance in the phase 3 study was according to the CHMP Guideline.

Treatments

Hypercholesterolaemia and mixed dyslipidaemia

Efficacy was evaluated in each individual study as well as in a prospective integrated efficacy analysis of the 4 pivotal, 12-week, phase 3 studies in subjects with primary hyperlipidemia and mixed dyslipidemia (Studies 20110114, 20110115, 20110116, and 20110117). The integrated analysis also evaluated efficacy of evolocumab in 4 subpopulations of the primary hyperlipidemia and mixed dyslipidemia indication.

Figure E01. Study Design and Treatment Schema (MENDEL-2: Study 20110114)

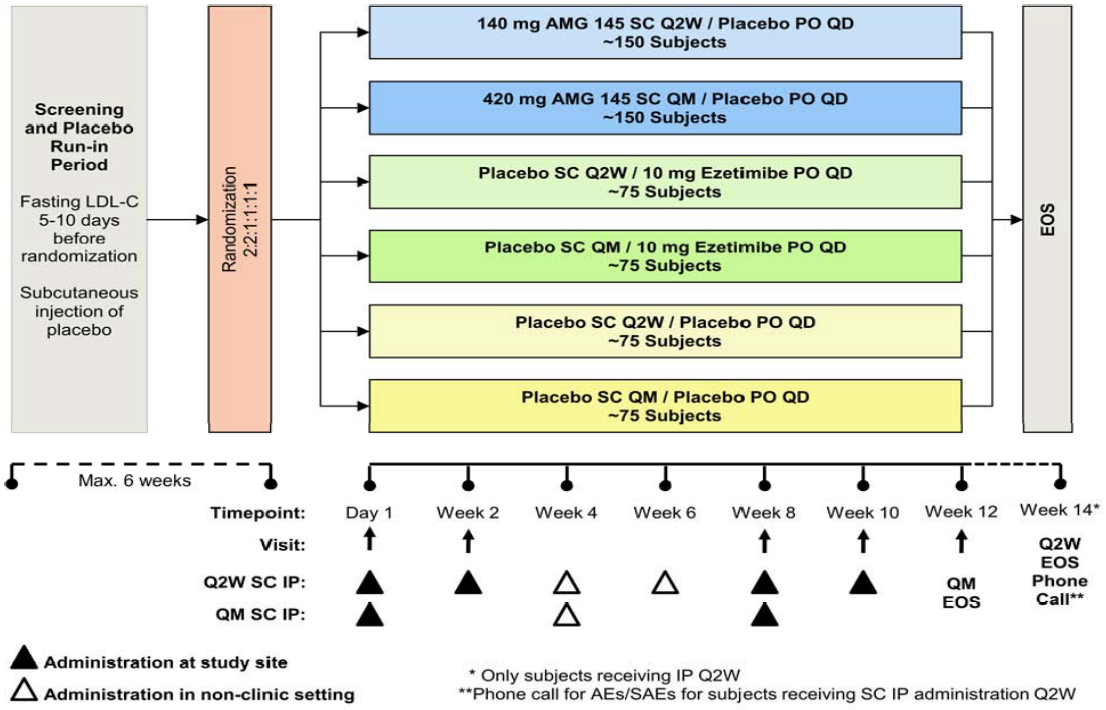
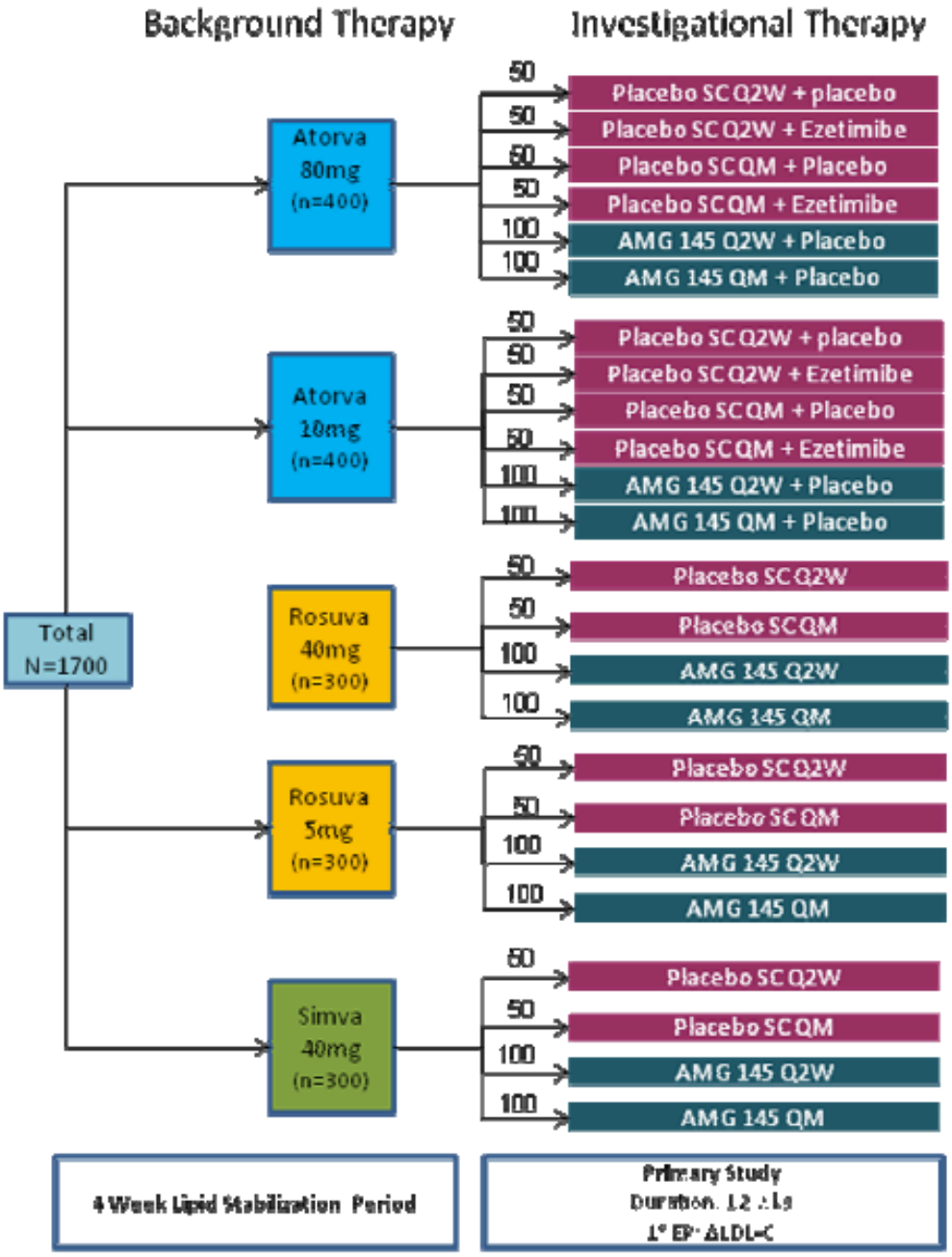
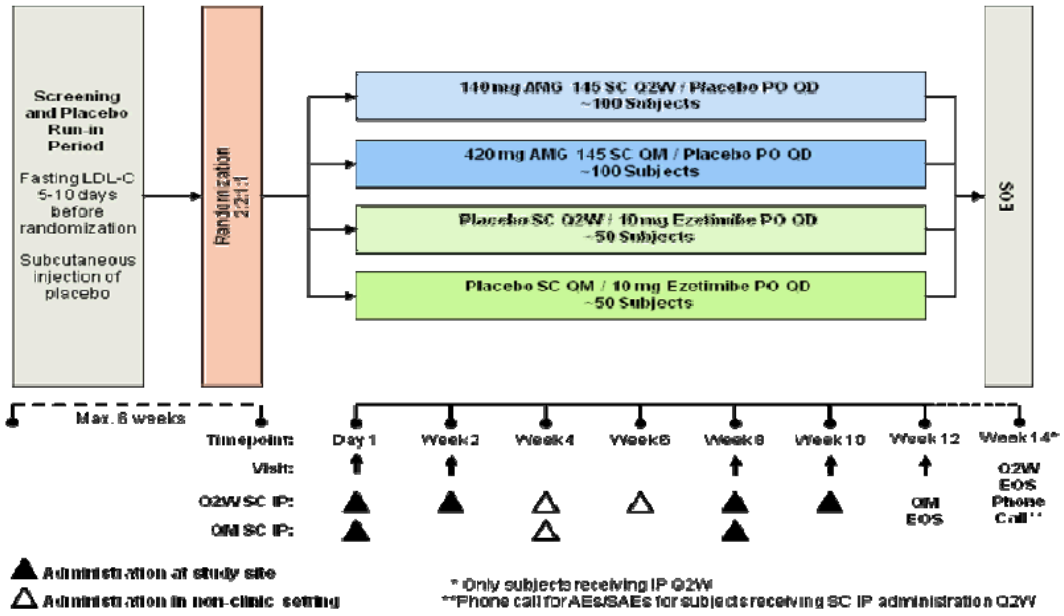


Figure E02. Study Design and Treatment Schema (LAPLACE-2: Study 20110115)



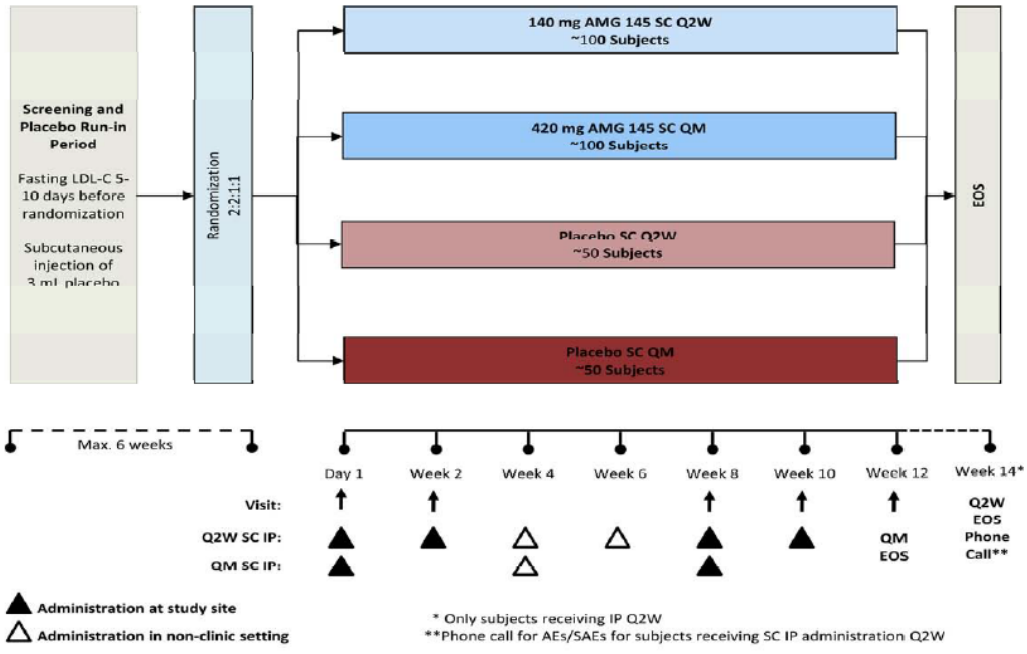
LDL-C = low density lipoprotein cholesterol; Q2W = once every 2 weeks; QM = once monthly; SC = subcutaneous

Figure E03. Study design and Treatment Schema (GAUSS-2: Study 20110116)



EOS = end of study; IP = investigational product; LDL-C = low-density lipoprotein cholesterol; PO = oral; QD = once daily; Q2W = once every 2 weeks; QM = once monthly, SC = subcutaneous

Figure E04. Study design and Treatment Schema (RUTHERFORD-2: Study 20110117)



AE = adverse events; AMG 145 = evolocumab; EOS = end of study; IP = investigational product; LDL-C = low-density lipoprotein cholesterol; Q2W = once every 2 weeks; QM = once monthly; SAEs = serious adverse events; SC = subcutaneous(ly)

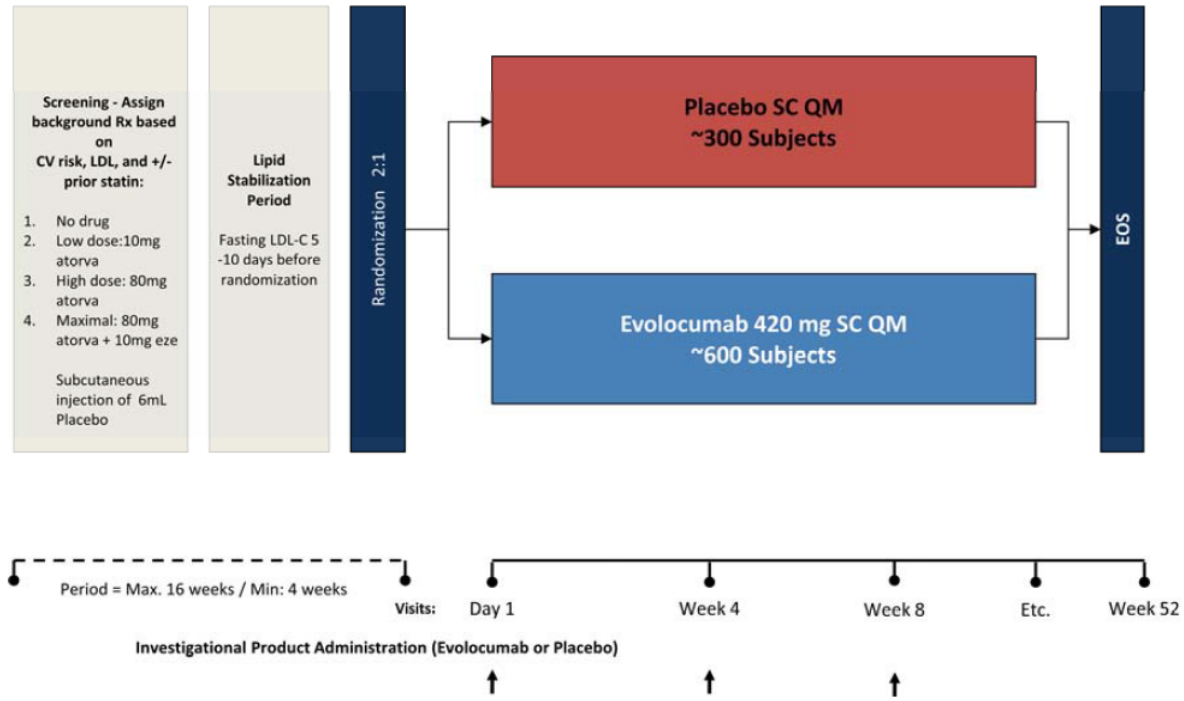
Long term studies

- Study 20110109 (DESCARTES)

- Study 20120138 (OSLER-2)

Study 20110271 (Severe FH Subjects) (TAUSSIG) is discussed below under the HoFH indication, as this study both included severe FH patients and HoFH patients.

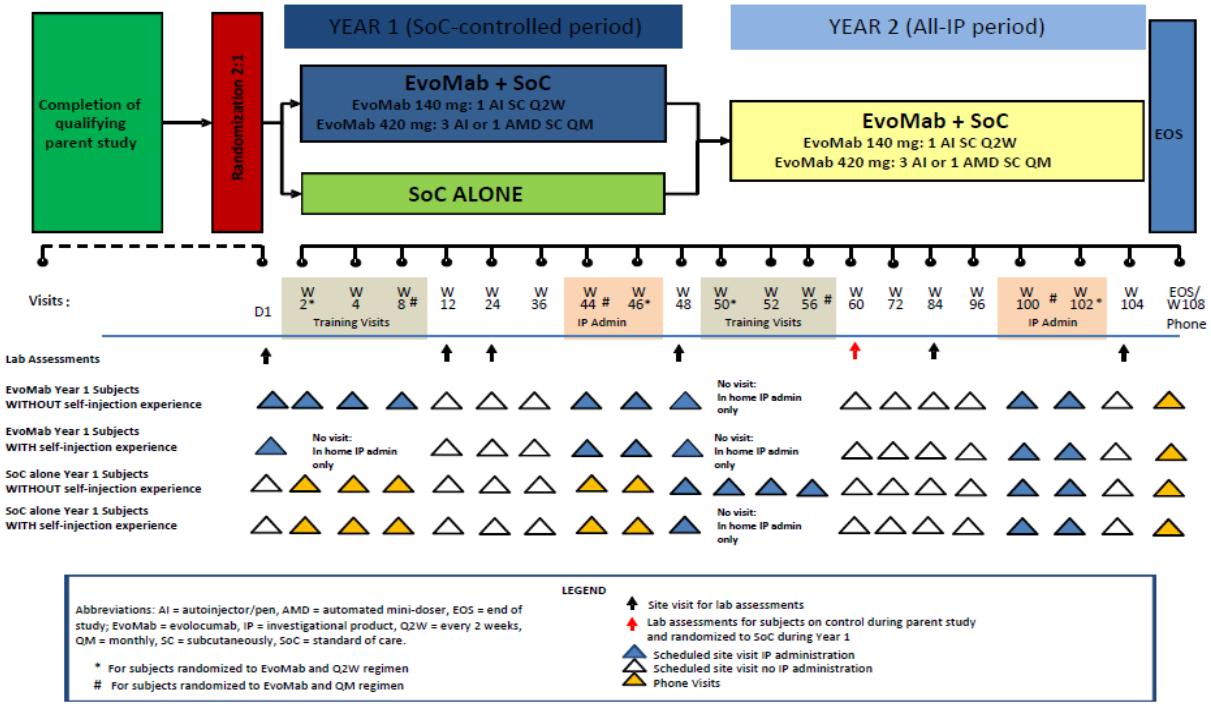
Figure E05. Study Design and Treatment Schema (DESCARTES-2: Study 20110109)



CHD = coronary heart disease; CV = cardiovascular; EOS = end of study; LDL-C = low-density lipoprotein cholesterol; QM = once monthly; SC = subcutaneous

In the study OSLER-2, subjects who completed a qualifying evolocumab protocol and did not discontinue IP in the parent study for any reason, including an adverse event, were eligible for this study. All subjects who entered the study kept the same subject identification number from the parent study. Each site that participated in this study was assigned a different site number from that of the parent study. Subjects were randomized 2:1 after the parent study's end-of-study (EOS) visit to receive either evolocumab and standard of care or standard of care alone. Sites were encouraged to have the day 1 OLE visit occur within 30 days of completion of the parent EOS laboratory visit. If the day 1 OLE visit did not occur within 30 days of completion of the parent EOS laboratory visit, then all end of parent study laboratory procedures had to be repeated prior to OLE study entry in order to confirm eligibility. After week 48 all subjects received open-label evolocumab for approximately 1 year.

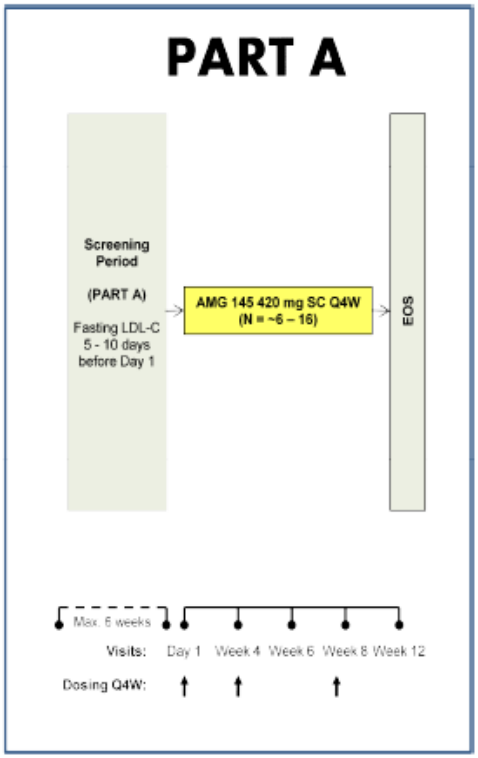
Figure E06. Study Design and Treatment Schema for Open-label Extension (OSLER-2 Study 20120138)



HoFH patients

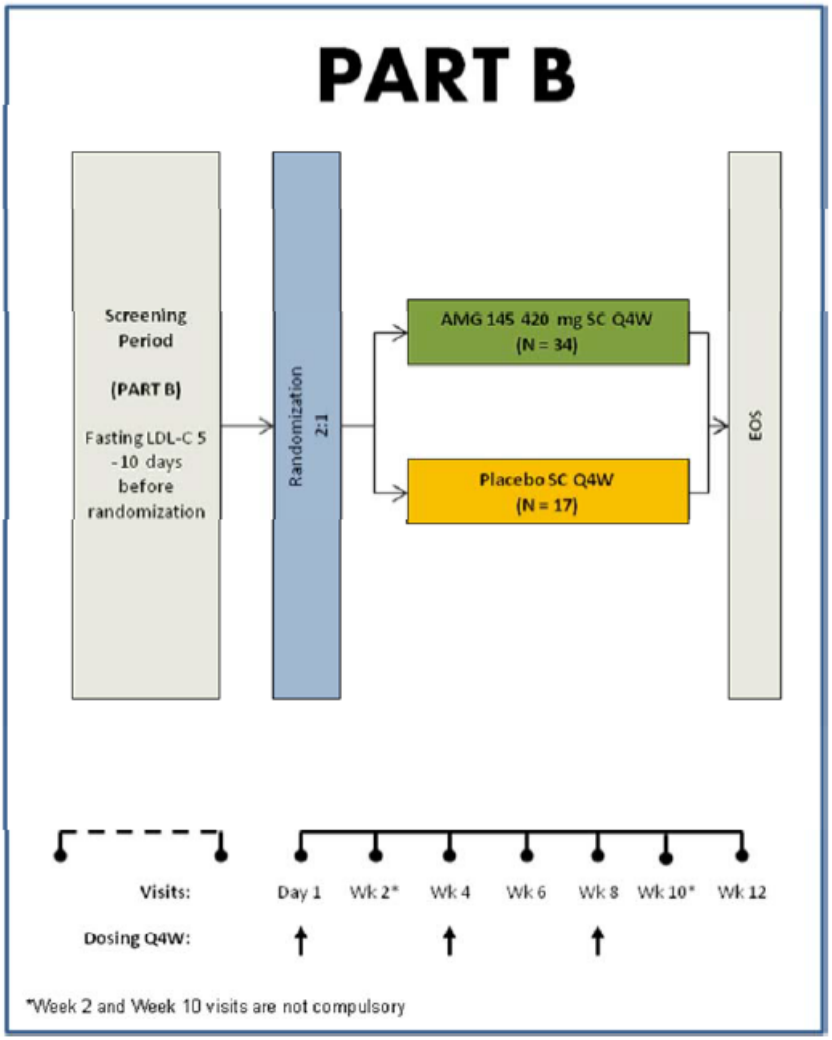
The study design of both: phase 2/3 study 20110233 (TESLA) and phase 3 long term study 20110271 (TAUSSIG) are provided below.

Figure E07. Study Design and Treatment Schema Phase 2 (TESLA : 20110233)



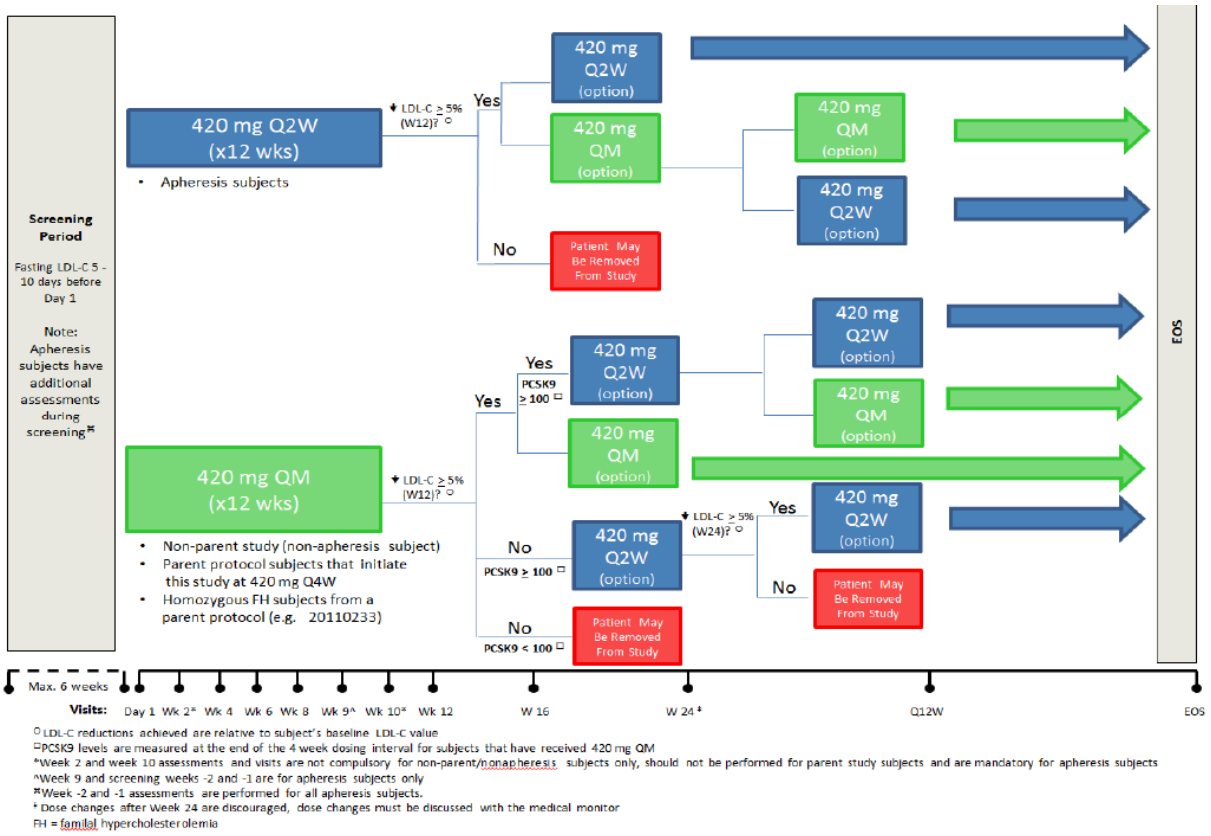
AMG 145 = evolocumab; EOS = end of study; LDL-C = low density lipoprotein cholesterol; Q4W = once monthly (once every 4 weeks); SC = subcutaneously.

Figure E08. Study Design and Treatment Schema Phase 3 (TESLA: 20110233)



AMG 145 = evolocumab; EOS = end of study; LDL-C = low density lipoprotein cholesterol; Q4W = once monthly (once every 4 weeks); SC = subcutaneously.

Figure E09. Study Design and Treatment Schema Phase 3 (TAUSSIG: 20110271)



The designs of the MENDEL-2, GAUSS-2 and RUTHERFORD-2 studies were very similar and were considered appropriate. The run-in period of a maximum of 6 weeks was sufficient to establish a stable run-in cholesterol level and to study the randomized comparison of evolocumab versus placebo or ezetimibe for MENDEL-2 and evolocumab versus ezetimibe in GAUSS-2 and evolocumab versus placebo on a maximum background therapy (statin with or without ezetimibe)(RUTHERFORD-2). A 12 week period with the 2 doses evaluated in the dose findings studies was considered appropriate to provide reasonable results on the LDL-C (and other cholesterol parameters) lowering effect of evolocumab. Two of the six and one of the three dosings for Q2W and QM were in a non-clinical setting, which is acceptable, considering that patients have to be able to administer evolocumab also in a home setting.

For the LAPLACE-2 study a run-in period of 4 weeks was considered appropriate to establish a stable run-in cholesterol level and to evaluate the effect of evolocumab on top of different doses of different statins during 12 weeks of treatment. It was considered essential to study the effect of evolocumab on maximum doses of the most potent statins as has been done in this study.

A 2:1 randomization was used for the controlled studies, which was considered appropriate.

Screening of 4 to 16 weeks in the DESCARTES study of patients with a range of CV risk, LDL level and prior statin therapy were appropriate. The controlled effect of evolocumab for a longer follow up of 52 weeks could be evaluated in this study.

Patients assigned to one of the 4 parent studies could be assigned to be included in the OSLER-2 study to be randomized according to evolocumab treatment of Q2W 140 mg or QM 420 mg and compared to a

background therapy in the first year and open label in the second year. The open-label design was acceptable, considering the long term follow up.

In the HoFH population part A of the TESLA study was appropriate for a first exploratory evaluation of evolocumab in this population. Study TESLA B was 12 weeks placebo controlled, which provided a better understanding of the effect of evolocumab on cholesterol reduction than part A. In the longer term TAUSSIG study patients could be uptitrated according to response to a Q2W dosing scheme on the highest dose instead of QM dosing scheme on the highest dose.

Objectives

Hypercholesterolaemia and mixed dyslipidaemia

Study 20110114 (MENDEL-2)

The primary objective of this study was to evaluate the effect of 12 weeks of evolocumab SC Q2W or QM, compared with placebo and ezetimibe, on percent change from baseline in reflexive LDL-C in hyperlipidemic subjects with a 10-year Framingham risk score of 10% or less. Secondary objectives were comprised of safety and tolerability, effect on other lipid parameters, and LDL-C goal attainment.

Study 20110115 (LAPLACE-2)

The primary objective was to evaluate the effect of 12 weeks of evolocumab SC administered Q2W or QM when used in combination with a statin, on percent change from baseline in reflexive LDL-C compared with placebo and ezetimibe. Secondary objectives were comprised of safety and tolerability, effect on other lipid parameters, and LDL-C goal attainment.

Study 20110116 (GAUSS-2)

The primary objective was to evaluate the effect of 12 weeks of evolocumab SC Q2W and QM, compared with ezetimibe, on percent change from baseline in reflexive LDL-C in hyperlipidemic subjects unable to tolerate an effective dose of a statin. Secondary objectives were comprised of safety and tolerability, effect on other lipid parameters, and LDL-C goal attainment.

Study 20110117 (RUTHERFORD-2)

The primary objective was to evaluate the effect of 12 weeks of evolocumab SC Q2W or QM, compared with placebo, on percent change from baseline in reflexive LDL-C in subjects with HeFH. Secondary objectives were comprised of safety and tolerability, effect on other lipid parameters, and LDL-C goal attainment.

Study 20110109 (DESCARTES)

The primary objective was to evaluate the effect of 52 weeks of evolocumab SC administered QM, compared with placebo, on percent change from baseline in UC LDL-C when added to background lipid-lowering therapy. Secondary objectives were comprised of safety and tolerability, effect on other lipid parameters, and consistency of long-term effect of evolocumab.

Study 20120138 (OSLER-2)

The primary objective was to characterize the safety and tolerability of long-term administration of evolocumab. The secondary objective is to characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C.

Study 20110271 (Severe FH Subjects) (TAUSSIG)

The primary objective is to characterize the safety and tolerability of long-term administration of evolocumab. The secondary objective is to characterize the efficacy of long-term administration of evolocumab as assessed by reflexive LDL-C and other lipid parameters.

HoFH patients

Study 20110233 (TESLA)

The primary objective of the phase 2 portion was to evaluate the effect of 12 weeks of evolocumab SC QM on percent change from baseline in UC and calculated LDL-C in HoFH subjects. Secondary objectives were comprised of safety and tolerability, effect on other lipid parameters, pharmacokinetic, and pharmacodynamic evaluation.

Long-term Efficacy: Study 20110271 (HoFH Subjects) (TAUSSIG)

The primary objective is to characterize the safety and tolerability of long-term administration of evolocumab. The secondary objective is to characterize the efficacy of long-term administration of evolocumab as assessed by reflexive LDL-C and other lipid parameters.

Outcomes/endpoints

"Mean percent change in LDL-C at weeks 10 and 12" and "the percent change in LDL-C at week 12" were used as co-primary endpoints in Phase 3 studies. The mean percent change from baseline at weeks 10 and 12 in LDL-C and other lipid parameters was considered representative of the time-averaged effect and characterized LDL-C reduction and other lipid parameters better than the percent change at week 12 alone.

Analyses of LDL-C in the evolocumab clinical development program utilized 3 different methods: (1) preparative ultracentrifugation (UC) LDL-C, (2) a reflexive approach, and (3) calculated LDL-C. In the phase 2 studies, UC LDL-C values were used for the analysis of the primary endpoint to achieve the most rigorous and accurate LDL-C assessment possible for dose rationale and safety evaluations. Following phase 2, a reflexive testing approach was evaluated in order to assess whether calculated LDL-C concentrations could be used in place of UC LDL-C concentrations in the primary analysis. In this analysis, calculated LDL-C values < 25 mg/dL, < 40 mg/dL, or < 50 mg/dL were replaced with the corresponding UC LDL-C values. Results demonstrated that calculated LDL-C at a cut off value of 40 mg/dL using the reflexive approach was highly correlated with UC LDL-C concentrations.

For analyses of the individual phase 3 parent studies and integrated phase 3 data related to LDL-C, unless specified otherwise, a reflexive approach was used, where the calculated LDL-C was employed unless the calculated LDL-C was < 40 mg/dL (1.03 mmol/L) or triglycerides were > 400 mg/dL (4.5 mmol/L), in which case UC LDL-C was determined and utilized. This approach was chosen to provide a robust, conservative, and accurate assessment of LDL-C in the rigorous environment of a controlled clinical

study. In order to provide data to physicians on the efficacy of evolocumab under conditions which will likely be utilized in clinical practice, analysis of the percent change in LDL-C was also evaluated using only calculated LDL-C values.

The absolute and percent change from baseline in ApoB, total cholesterol/HDL-C, total cholesterol, non-HDL-C, Apo B/Apo A1, Lp(a), triglycerides, VLDL-C, HDL-C, and ApoA1 were also incorporated as secondary, tertiary, or exploratory efficacy endpoints.

The percent change from baseline in LDL-C at week 12 was used as the primary efficacy endpoint in the controlled HoFH Study 20110233; however, mean LDL-C reduction at week 6 and 12 was added as a secondary endpoint instead of as a co-primary endpoint. The same other lipid parameters (ApoB, total cholesterol/HDL-C, total cholesterol, non-HDL-C, Apo B/Apo A1, Lp(a), triglycerides, VLDL-C, HDL-C, and ApoA1) were evaluated in this population as well.

The primary endpoints were considered appropriate to establish the LDL-C lowering effect of evolocumab at 12 weeks of treatment and to account for the time dependent effect using the mean of the 10-12 weeks LDL-C lowering effect. The methods of calculated and UC LDL-C were also considered appropriate.

Sample size

Hypercholesterolaemia and mixed dyslipidaemia

Phase 2 and 3 represents a total of total of 6026 patients, who received either any control or evolocumab.

HoFH patients

Phase 2 and 3 represents a total of 96 patients who all received evolocumab.

Severe FH

Phase 3 represents a total of 102 patients who all received evolocumab. For exact sample sizes in the different phase 3 studies see Table S04 and S05.

Randomisation

In phase 3, eligible subjects were assigned to 1 of 2 treatment groups (evolocumab or placebo) on the basis of a computer-generated randomization schedule prepared by the applicant before the start of the study. Randomization could be stratified on the basis of screening LDL-C serum concentration. A site representative used an IVRS to assign a randomization number and group to the subject. A subject was considered randomized into the study after undergoing randomization procedures by IVRS.

Blinding (masking)

Hypercholesterolaemia and mixed dyslipidaemia

All subjects, investigators, and the sponsor investigative staff were blinded to treatment assignments with the exception of ezetimibe therapy, which was provided in tablet form and was self-administered daily by mouth. The sponsor staff members who were involved in randomization and biological sample management were unblinded to treatment assignment information, but they did not have access to subject-level data from the clinical trial database. The ezetimibe treatment group was not blinded because it was provided in tablet form and was self-administered daily by mouth as opposed to SC injection in cases of AMG 145 and placebo groups.

HoFH patients

Phase 2 (Open-label Pilot): Phase 2 of the study was an open-label, single-arm pilot study; blinding was not utilized. Phase 3 (Randomized, Double-blind, Placebo-controlled): To maintain blinding in phase 3, evolocumab and placebo were provided in identical presentations. The site was unblinded to a subject's treatment assignment only when knowledge of the treatment was essential for the subject's safety or for further medical management of the subject. No subject was unblinded to IP assignment. The external independent DMC members and Independent Biostatistical Group had access to unblinded subject data per the DMC charter. Amgen PK scientists and the programmer(s) preparing the population PK/pharmacodynamics (PD) datasets had access to the treatment assignments and limited subject level data. To maintain study integrity, these Amgen staff members were not within the evolocumab study team.

General blinding principles were considered appropriate.

Statistical methods

Hypercholesterolaemia and mixed dyslipidaemia

The statistical methods used are described in the tables below:

Table E08. Statistical Methods for Efficacy Endpoints in the Pivotal and Supportive Studies of Evolocumab for Primary Hyperlipidemia and Mixed Dyslipidemia

Endpoint(s)	Statistical Methods
Co-primary endpoints in Studies 20110114, 20110115, 20110116 and 20110117: • mean percent change from baseline in LDL-C at weeks 10 and 12 • percent change from baseline in LDL-C at week 12 Primary endpoint in Study 20110109: • percent change from baseline in LDL-C at week 52	• A repeated measures linear effects model was used on subjects randomized and receiving at least one dose of IP. • The primary analysis model included terms for treatment group, stratification factor(s), scheduled visit, and the interaction of treatment with scheduled visit, to compare evolocumab with placebo and/or ezetimibe • Multiplicity adjustment method used Hochberg,1988 and the fall back procedure (Wiens, 2003) to control the familywise error rate at 0.05 for the primary (or co-primary) and secondary (or co-secondary) endpoints.
Co-secondary endpoints in Studies 20110114, 20110115, 20110116 and 20110117 – assessed at the mean of weeks 10 and 12 and at week 12: <u>Tier 1 co-secondary endpoints:</u> • change from baseline in LDL-C • achievement of LDL-C < 70 mg/dL (1.8 mmol/L) (Tier 2 for Study 20110115) • percent change from baseline in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio <u>Tier 2 co-secondary endpoints:</u> • percent change from baseline in Lp(a), triglycerides, HDL-C, VLDL-C <u>Additional endpoints:</u> • achievement of LDL-C < 100 mg/dL (2.6 mmol/L) • ≥ 50% reduction in LDL-C from baseline Secondary endpoints in Study 20110109: <u>Tier 1 co-secondary endpoints:</u> • change from baseline in LDL-C at week 52 • percent change from baseline in LDL-C and total cholesterol at week 12 • achievement of LDL-C < 70 mg/dL (1.8 mmol/L) at week 52 • percent change from baseline at week 52 in total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio <u>Tier 2 co-secondary endpoints:</u> • percent change from baseline at week 52 in Lp(a), triglycerides, HDL-C, VLDL-C	• The LDL-C achievement endpoint was analyzed using a CMH test, adjusted for the stratification factor(s). • All other endpoints were analyzed using a repeated measures linear effects model as used in the primary or co-primary endpoints analysis. • Multiplicity adjustment method used Hochberg and the fall back procedure (Wiens, 2003) to control the familywise error rate at 0.05 for the primary (or co-primary) and secondary (or co-secondary) endpoints.

Endpoint(s)	Statistical Methods
Tertiary endpoints in Studies 20110114, 20110115, 20110116 and 20110117: • mean percent change from baseline in ApoA1 at weeks 10 and 12 • percent change from baseline in ApoA1 at week 12 Tertiary endpoint in Study 20110109: percent change from baseline in ApoA1 at week 52	• These endpoints were analyzed using a repeated measures linear effects model as used in the analysis of the primary or co-primary endpoints. • No multiplicity adjustment was used for the tertiary endpoints.

Table E08. Statistical Methods for Efficacy Endpoints in the Pivotal and Supportive Studies of Evolocumab for Primary Hyperlipidemia and Mixed Dyslipidemia

Endpoint(s)	Statistical Methods
Exploratory efficacy endpoints in Studies 20110109, 20110114, 20110115, 20110116 and 20110117: • change and percent change from baseline at each scheduled visit for LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, Lp(a) Additional endpoints for Study 20110109: • change and percent change from baseline at each scheduled visit for hsCRP, HbA1c, PCSK9	• Summary statistics at each scheduled visit were based on observed data with no imputation for missing values.
Primary endpoint in Studies 20090158, 20090159, 20101154, 20101155, and 20110231: • percent change from baseline in LDL-C at week 12	• The primary analysis is the ANCOVA model included treatment group and the stratification factor(s). Repeated measure linear effects model was a pre-specified sensitivity analysis. • Missing data were imputed using the LOCF. • Hierarchical testing procedure compared the highest dose of evolocumab to placebo (or ezetimibe) and continued in descending dose strength until statistical significance was not reached.
Secondary endpoints in Studies 20090158, 20090159, 20101154, 20101155, and 20110231: • change from baseline in LDL-C at week 12 • percent change from baseline non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio at week 12 • LDL-C response at week 12 (Study 20110231)	• The analysis model was similar to the primary analysis of the primary endpoint. • No adjustment was made for multiple comparisons. • LDL-C response was analyzed using logistic regression including terms for treatment group and stratification factor.
Secondary endpoints Study 20110271 (severe FH subjects only) • percent change from baseline in LDL-C, non-HDL-C, Lp(a), ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio at each scheduled visit • response rate of subjects with LDL-C reduction of15% or greater from baseline	• Only descriptive statistics were provided.

Endpoint(s)	Statistical Methods
Exploratory endpoints for Study 20110271 (severe FH subjects only) • Change and percent change from baseline at each scheduled visit in total cholesterol, VLDL-C, HDL-C, ApoA1, triglycerides, PCSK9, hsCRP, and HbA1c Change from baseline at each scheduled visit in LDL-C, non-HDL-C, Lp(a), ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio	• Only descriptive statistics were provided.

HoFH patients

The statistical methods used are described in the tables below:

Table E09. Statistical Methods for Efficacy Endpoints in the Pivotal Studies of Evolocumab for HoFH

Endpoint(s)	Statistical Methods
Primary endpoint for Study 20110233 (part A and B) • percent change from baseline in LDL-C at week 12	Part A • Summary statistics, for all enrolled subjects who received at least 1 dose of IP. Part B • A repeated measures linear effects model was used on subjects randomized and receiving at least one dose of IP. • The primary analysis model included terms for treatment group, stratification factor, scheduled visit, and the interaction of treatment with scheduled visit, to compare evolocumab with placebo
Secondary endpoint for Study 20110233 - Part A • change from baseline in LDL-C at week 12 • percent change from baseline non-HDL-C, ApoB, total cholesterol/HDL-C and ApoB/ApoA1 at week 12 • response rate of subjects with 15% or greater reduction in LDL-C from baseline to Week 12 • change from baseline in PCSK9 at Week 12 Secondary endpoints 20110233 - part B • Mean percent change from baseline in LDL-C, ApoB and Lp(a) at weeks 6 and 12 • Percent change from baseline in ApoB and Lp(a) at week 12	Part A • Only summary statistics were provided. Part B • All secondary endpoints were analyzed using a repeated measures linear effects model as used in the analysis of the primary endpoint. • Multiplicity adjustment method used Hochberg and the fall back procedure (Wiens, 2003) to control the familywise error rate at 0.05 for the primary and secondary endpoints
Exploratory endpoints in Study 20110233 - Part B: • change from baseline in LDL-C at week 12 and mean change at weeks 6 and 12 • percent change from baseline at week 12 and mean percent change at weeks 6 and 12 for non-HDL-C, total cholesterol, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, VLDL-C, triglyceride, HDL-C, and PCSK9 • Response rate of subjects with 15% or greater reduction	• The LDL-C achievement endpoint was analyzed using a CMH test, adjusted for the stratification factor(s). • All other exploratory endpoints were analyzed using a repeated measures linear effects model as used in the analysis of the primary endpoint.

Endpoint(s)	Statistical Methods
in LDL-C at week 12 or in mean LDL-C weeks 6 and 12 compared with baseline LDL-C	
Secondary endpoints for Study 20110271 (HoFH subjects): • percent change from baseline in LDL-C, non-HDL-C, Lp(a), ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio at each scheduled visit • response rate of subjects with LDL-C reduction of 15% or greater from baseline	• Only descriptive statistics were provided.
Exploratory endpoints for Study 20110271 (HoFH subjects) • Change and percent change from baseline at each scheduled visit in total cholesterol, VLDL-C, HDL-C, ApoA1, triglycerides, PCSK9, hsCRP, and HbA1c • Change from baseline at each scheduled visit in LDL-C, non-HDL-C, Lp(a), ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio	• Only descriptive statistics were provided.

Results

Participant flow

3152 subjects from 24 countries in Europe (52.2%), North America (40.4%), and Asia Pacific (7.5%) were randomized in the 4 phase 3 parent studies, and randomization within each country was balanced across treatment groups.

Of the 3152 subjects randomized, 3146 (99.8%) subjects received IP and were included in the FAS:

– 1848 evolocumab (921 evolocumab SC Q2W, 927 evolocumab SC QM)

– 821 placebo (411 placebo SC Q2W, 410 placebo SC QM)

– 477 ezetimibe (240 ezetimibe [placebo SC Q2W], 237 ezetimibe [placebo SC QM])

3005 (95.3%) completed IP, 3026 (96.0%) subjects completed the study and 69 (2.2%) subjects discontinued the study early, not including the 57 (1.8%) subjects who enrolled into extension studies without completing the final follow-up visit in the parent studies.

Table 3.12. Summary Table of Subject Disposition- Phase 3 Parent Studies and Integrated Cohort

Category	Study 20110114 (Monotherapy)	Study 20110115 (Combination Therapy)	Study 20110116 (Statin-Intolerant)	Study 20110117 (HeFH)	Integrated Cohort (Combined parent studies)
Randomized, n	615	1899	307	331	3152
Received IP, n (%)	614 (99.8)	1896 (99.8)	307 (100.0)	329 (99.4)	3146 (99.8)
Completed IP, n (%)	581 (94.5)	1807 (95.2)	293 (95.4)	324 (97.9)	3005 (95.3)
Completed Study, n (%)	598 (97.2)	1826 (96.2)	290 (94.5)	312 (94.3)	3026 (96.0)
Discontinued Study, n (%)	17 (2.8)	73 (3.8)	17 (5.5)	19 (5.7)	126 (4.0)
Withdrawal of consent	3 (0.5)	40 (2.1)	3 (1.0)	6 (1.8)	52 (1.6)
Death	-	1 (0.1)	-	-	1 (0.03)
Decision by sponsor	8 (1.3)	26 (1.4)	13 (4.2)	13 (3.9)	60 (1.9)
For enrollment into extension study	8 (1.3)	23 (1.2)	13 (4.2)	13 (3.9)	57 (1.8)
Lost to follow-up	6 (1.0)	6 (0.3)	1 (0.3)	-	13 (0.4)

The flow of subjects was adequately described and the rates of discontinuation/exclusion from analysis

set have been low in the short term studies. Also in the longer term follow up, the treatment continuation was good.

Recruitment

Hypercholesterolaemia and mixed dyslipidaemia

Patients were recruited from Europe, North America and Asia Pacific, and Japan.

HoFH patients

Phase 3 was conducted at a total of 17 centers.

Conduct of the study

The number of patients with protocol or eligibility deviations was low and not able to significantly influence the results. The handling of the deviations was acceptable.

Baseline data

Major baseline characteristics for the phase 3 parent studies in the primary hyperlipidaemia and mixed dyslipidaemia studies and for the HoFH populations are presented in the tables below.

Table E4: Comparison of Key Baseline Characteristics- Phase 3 Parent Studies and Integrated Cohort

Category Subcategory	Study 20110114 (Monotherapy)	Study 20110115 (Combination Therapy)	Study 20110116 (Statin-Intolerant)	Study 20110117 (HeFH)	Integrated Cohort
N	614	1896	307	329	3146
Female (%)	66%	46%	46%	42%	49%
Age (years)					
Mean (SD)	53 (12)	60 (10)	62 (10)	51 (13)	58 (11)
Coronary artery disease	<1%	23%	29%	31%	20%
Type 2 diabetes mellitus	<1%	16%	20%	7%	12%
Triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L)	29%	29%	52%	27%	31%
Low HDL-C	24%	28%	33%	34%	28%
Current cigarette use	12%	15%	8%	16%	14%
Hypertension	29%	57%	59%	33%	49%
Family history of premature CHD	10%	20%	32%	59%	23%
Risk classification according to ESC/EAS guidelines (%)					
Very high risk	8%	43%	56%	42%	37%
High risk	2%	5%	9%	58%	10%
Moderate risk	57%	43%	29%	0%	40%
Low risk	33%	9%	6%	0%	13%
Statin use at baseline (%)	-	100%	18%	100%	72%
Reflexive LDL-C (mmol/L)					
Mean	3.7	2.8	5.0	4.0	3.3
SD	0.6	1.1	1.5	1.2	1.3
PCSK9 (nmol/L)					
Mean	3.8	4.9	4.0	6.2	4.7
SD	1.2	1.6	1.4	1.9	1.7

Table E5: Summary of Key Baseline Characteristics in the phase 3 HoFH population

Category Subcategory	Placebo (QM) (N = 16) n (%)	EvoMab (420 mg QM) (N = 33) n (%)	Total (N = 49 n (%)
Male	8 (50.0)	17 (51.5)	25 (51.0)
Age (Mean (SD) years)	32.1 (13.8)	30.3 (12.4)	30.9 (12.8)
< 18 years	3 (18.8)	7 (21.2)	10 (20.4)
Coronary artery disease	6 (37.5)	15 (45.5)	21 (42.9)
Type 2 diabetes mellitus	1 (6.3)	2 (6.1)	3 (6.1)
Low HDL-C	13 (81.3)	21 (63.6)	34 (69.4)
Current cigarette use	1 (6.3)	5 (15.2)	6 (12.2)
Hypertension	1 (6.3)	4 (12.1)	5 (10.2)
Family history of premature CHD	12 (75.0)	19 (57.6)	31 (63.3)
Homozygous	8 (50.0)	16 (48.5)	24 (49.0)
Heterozygous	0 (0.0)	1 (3.0)	1 (2.0)
Compound heterozygous	8 (50.0)	16 (48.5)	24 (49.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Gene affected			
LDL Receptor	15 (93.8)	32 (97.0)	47 (95.9)
Apo B	2 (12.5)	0 (0.0)	2 (4.1)
ARH	0 (0.0)	1 (3.0)	1 (2.0)
Calculated LDL-C, Mean (SD) mmol/L	8.7 (3.7)	9.2 (3.5)	9.0 (3.6)
PCSK9, Mean (SD) nmol/L	9.4 (2.5)	8.9 (2.9)	9.0 (2.7)

Numbers analysed

Hypercholesterolaemia and mixed dyslipidaemia

In each parent study, the primary efficacy analyses were performed on the full analysis set (FAS), which included all randomized subjects who had received at least 1 dose of investigational product. Of the 3152 subjects randomized, 3146 (99.8%) subjects received IP (investigational product) and were included in the FAS:

• 1848 evolocumab (921 evolocumab SC Q2W, 927 evolocumab SC QM)

• 821 placebo (411 placebo SC Q2W, 410 placebo SC QM)

• 477 ezetimibe (240 ezetimibe [placebo SC Q2W], 237 ezetimibe [placebo SC QM])

HoFH patients

Thirty three patients in the placebo controlled study and 99 patients in the long term HoFH study were analysed.

Outcomes and estimation

LDL-C reduction of approximately 55% to 75% was achieved with evolocumab as early as week 1 and maintained during long-term therapy. Maximal response was generally achieved within 1 to 2 weeks after dosing with 140 mg every 2 weeks and 420 mg once monthly.

Evolocumab reduced LDL-C, non-HDL-C, Apo B, TC, Lp(a), VLDL-C, TG, TC/HDL-C, and ApoB/ApoA1and increased HDL-C in patients with mixed dyslipidaemia. Evolocumab was superior to ezetimibe in reducing LDL-C, TC, ApoB, non-HDL-C, Lp(a), TC/HDL-C, and ApoB/ApoA1.

The clinical relevance, including the long-term safety, of sustained very low levels of LDL C (i.e., < 0.65 mmol/L [< 25 mg/dL]) have not yet been established.

Hypercholesterolaemia and mixed dyslipidaemia

- *Combination with a statin and statin with other lipid-lowering therapies*

LAPLACE-2: Evolocumab significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with placebo for the rosuvastatin and simvastatin groups and compared with placebo and ezetimibe for the atorvastatin group ($p < 0.001$).

RUTHERFORD-2: Evolocumab significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with placebo ($p < 0.001$).

- *Statin intolerant patients*

GAUSS-2: Evolocumab significantly reduced LDL-C compared with ezetimibe ($p < 0.001$).

- *Treatment in the absence of a statin*

MENDEL-2: Repatha significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with both placebo and ezetimibe ($p < 0.001$).

Figure. Treatment Differences for Percent Change From Baseline in Calculated LDL-C in the Phase 3 Evolocumab Program

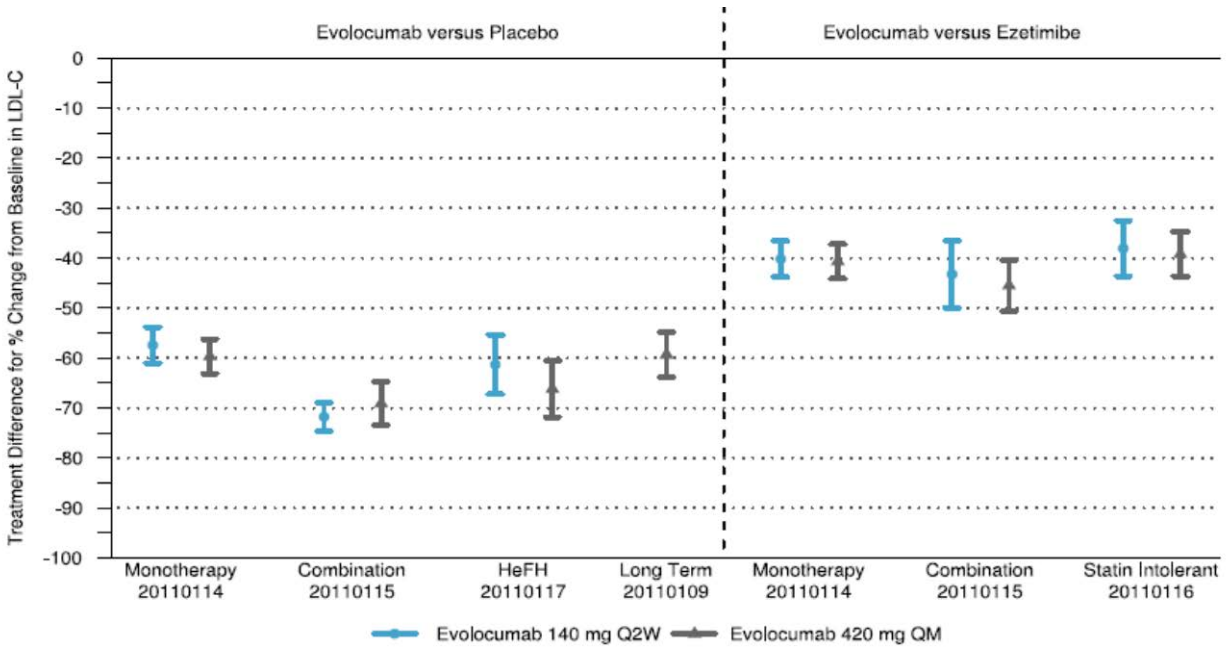


Table. Summary of Treatment Differences Compared With Placebo and Ezetimibe in Co-primary and Co-secondary Endpoints Integrated Phase 3 Parent Studies Cohort (Full Analysis Set)

	EvoMab 140 mg Q2W vs Placebo Q2W	EvoMab 420 mg QM vs Placebo QM	EvoMab 140 mg Q2W vs Ezetimibe QD	EvoMab 420 mg QM vs Ezetimibe QD
ApoB				
% change[a] at week 12 (95% CI)	-54.04 (-57.96, -50.13)	-49.87 (-51.97, -47.78)	-34.32 (-36.79, -31.84)	-33.54 (-36.01, -31.06)
Adjusted p-value	<0.001	<0.001	<0.001	<0.001
Total cholesterol				
% change[a] at week 12 (95% CI)	-40.63 (-43.44, -37.82)	-37.00 (-39.00, -35.01)	-24.71 (-26.73, -22.69)	-23.94 (-25.79, -22.10)
Adjusted p-value	<0.001	<0.001	<0.001	<0.001
Non-HDL-C				
% change[a] at week 12 (95% CI)	-58.51 (-63.06, -53.95)	-54.24 (-56.86, -51.62)	-34.88 (-37.36, -32.41)	-33.70 (-36.00, -31.39)
Adjusted p-value	<0.001	<0.001	<0.001	<0.001
Triglycerides				
% change[a] at week 12 (95% CI)	-15.03 (-20.45, -9.61)	-19.90 (-25.53, -14.27)	-3.33 (-8.34, 1.68)	-6.44 (-13.72, 0.85)
Adjusted p-value	<0.001	<0.001	0.77	0.33
VLDL-C				
% change[a] at week 12 (95% CI)	-15.80 (-22.04, -9.56)	-19.68 (-26.64, -12.73)	-1.96 (-6.67, 2.76)	-4.18 (-12.04, 3.67)
Adjusted p-value	<0.001	<0.001	0.83	0.59
HDL-C				
% change[a] at week 12 (95% CI)	6.17 (4.51, 7.83)	8.02 (6.26, 9.77)	6.71 (4.50, 8.93)	5.47 (3.27, 7.68)
Adjusted p-value	<0.001	<0.001	<0.001	<0.001

- *Long term effect*

Evolocumab demonstrates a long-term reduction in LDL-C as expressed in the figures below for the different phase 2/phase 3 open label long term ongoing studies.

DESCARTES: Evolocumab 420 mg once monthly significantly reduced LDL-C from baseline at 52 weeks compared with placebo ($p < 0.001$). Treatment effects were sustained over 1 year as demonstrated by reduction in LDL-C from week 12 to week 52(-59% LDL-C reduction with the 420 mg QM dose at 52 weeks versus standard of care) . Reduction in LDL-C from baseline at week 52 compared with placebo was consistent across background lipid-lowering therapies optimised for LDL-C and cardiovascular risk. Evolocumab significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and increased HDL-C and ApoA1 at week 52 compared with placebo ($p < 0.001$).

OSLER and OSLER-2 are two ongoing, randomised, controlled, open-label extension studies to assess the long-term safety and efficacy of evolocumab in patients who completed treatment in a 'parent' study. A total of 1324 patients enrolled in OSLER. Evolocumab 420 mg once monthly significantly reduced LDL-C from baseline at week 12 and week 52 compared with control (nominal $p < 0.001$). Treatment effects were maintained over 124 weeks as demonstrated by reduction in LDL-C from week 12 in the parent study to week 112 in the open-label extension. A total of 2928 patients enrolled in OSLER-2. Evolocumab significantly reduced LDL-C from baseline at week 12 compared with control (nominal $p < 0.001$). Treatment effects were maintained as demonstrated by reduction in LDL-C from week 12 to week 24 in the open-label extension. Evolocumab significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C,

ApoB/ApoA1, VLDL-C, TG and Lp(a) , and increased HDL-C and ApoA1 from baseline to week 52 in OSLER and to week 24 in OSLER-2 compared with control (nominal p < 0.001). LDL-C and other lipid parameters returned to baseline within 12 weeks after discontinuation of evolocumab at the beginning of OSLER or OSLER-2 without evidence of rebound.

Figure E2: Plot of Mean Percent Change from Baseline in Reflexive LDL-C by Scheduled Visit and Treatment Group Study OSLER 1; 20110110 phase-2 (Interim SoC-Controlled Period Analysis Set and Interim All-IP Period Analysis Set)

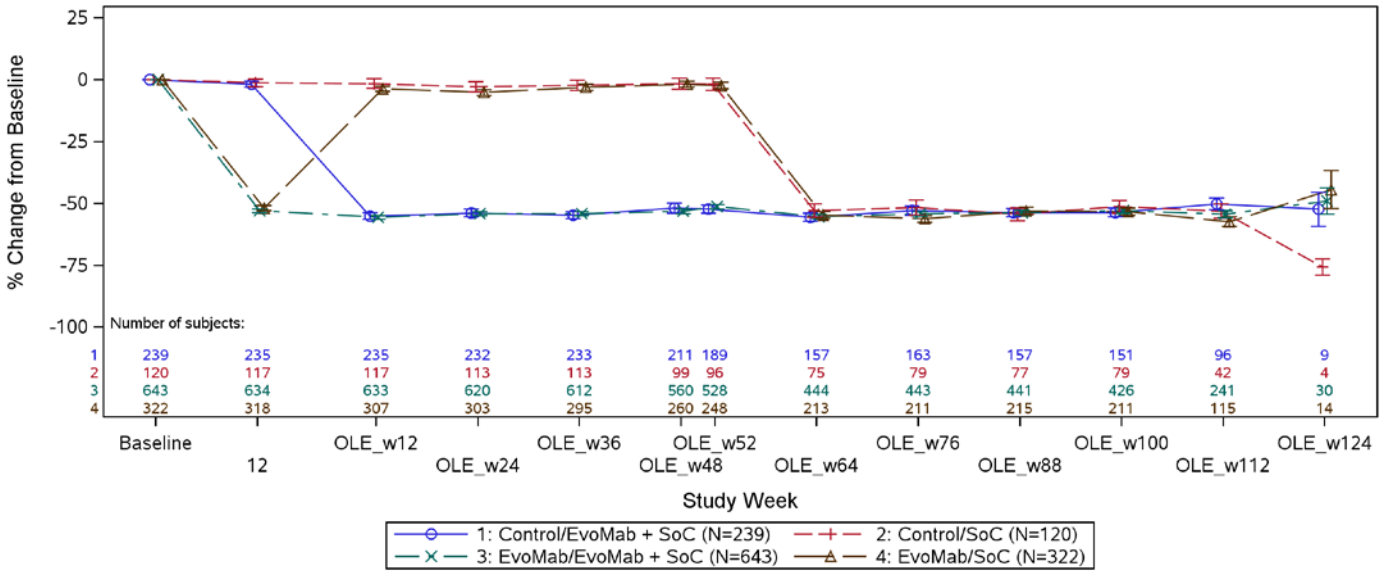
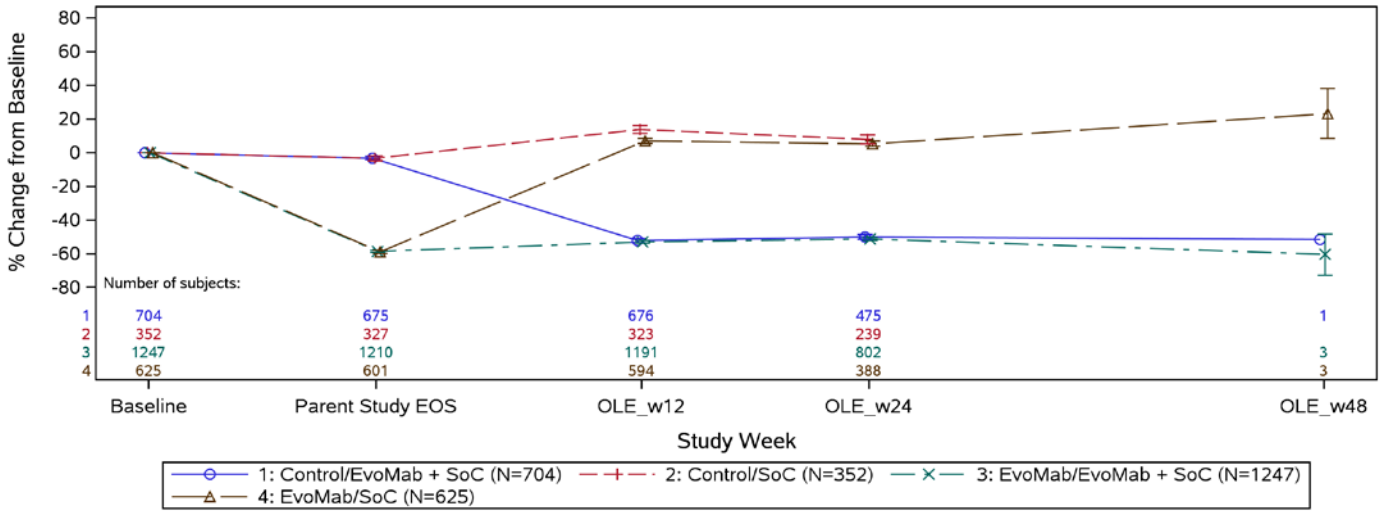


Figure E3: Plot of Mean Percent Change from Baseline in LDL-C by Scheduled Visit and Treatment Group Study OSLER 2; 20120138 phase-3 (Interim SoC-Controlled Period Analysis Set and Interim All-IP Period Analysis Set)



<u>Severe familial hypercholesterolaemia, including homozygous familial hypercholesterolaemia.</u>

TAUSSIG is an ongoing multicentre, open-label, 5-year extension study to assess the long-term safety and efficacy of Repatha, as an adjunct to other lipid lowering therapies, in patients with severe familial

hypercholesterolaemia, including homozygous familial hypercholesterolaemia. A total of 102 severe familial hypercholesterolaemia patients and 96 homozygous familial hypercholesterolaemia patients enrolled in TAUSSIG. Patients could be uptitrated after 12 weeks according to response to a Q2W dosing scheme on the highest dose instead of QM dosing scheme on the highest dose and could be downtitrated during the study as well. Long-term use of evolocumab demonstrated a sustained treatment effect as evidenced by reduction of LDL-C in patients with severe familial hypercholesterolaemia. Patients on apheresis showed slightly less effect. The highest Q2W dose showed slightly increased effect compared to the QM dose. The limited number of adolescent patients showed similar effect as the overall adult population.

Homozygous familial hypercholesterolaemia

TESLA: Evolocumab 420 mg once monthly, as an adjunct to other lipid-lowering therapies (e.g., statins, bile-acid sequestrants), significantly reduced LDL C and ApoB at week 12 compared with placebo ($p < 0.001$).

In TAUSSIG, long-term use of evolocumab demonstrated a sustained treatment effect as evidenced by reduction of LDL-C of approximately 20% to 30% in patients with homozygous familial hypercholesterolaemia not on apheresis and approximately 15% to 25% in patients with homozygous familial hypercholesterolaemia on apheresis.

Table E 7: Percent Change in Lipid Parameters from Baseline with Long-term Evolocumab Treatment in HoFH subjects

Percent change (Mean [SE]) from baseline[a] to OLE (open label extension) week 24	Overall HoFH (N = 46)	Apheresis (N = 13)	Non-apheresis (N = 33)	EvoMab 420 mg Titration[b] (Non-apheresis) QM (N=25)	Q2W	Age < 18 (N = 8)
UC LDL-C	-23.1 (3.6)	-19.5 (7.3)	-24.5 (4.2)	-15.5 (3.9)	-21.7 (4.3)	-21.5 (8.9)
Responders with ≥ 15% reduction in UC LDL-C, n (%)	29 (64.4)	9 (69.2)	20 (61.0)	13 (52.0)	16 (64.0)	5 (62.5)
Calculated LDL-C	-23.0 (3.7)	-20.3 (7.5)	-24.1 (4.3)	-15.2 (4.1)	-21.4 (4.3)	-19.8 (9.0)
Non-HDL-C	-21.1 (3.4)	-17.6 (7.0)	-22.5 (4.0)	-14.5 (4.0)	-20.6 (4.1)	-18.5 (8.6)
ApoB	-19.2 (2.9)	-15.3 (5.8)	-20.7 (3.4)	-10.8 (3.5)	-18.8 (3.5)	-16.0 (8.1)
TC/HDL-C ratio	-19.2 (3.8)	-12.5 (9.1)	-21.9 (3.9)	-20.8 (3.8)	-22.2 (3.5)	-17.2 (7.0)
ApoB/ApoA1 ratio	-21.6 (3.5)	-15.4 (8.2)	-24.1 (3.7)	-13.6 (3.3)	-24.5 (3.2)	-20.5 (8.1)
Lp(a)	-12.6 (3.8)	-10.7 (9.4)	-13.37 (4.0)	-4.5 (4.3)	-10.1 (3.8)	-9.5 (8.9)

Summary of main studies

Table E2: Summary of efficacy for the pivotal trials in the Hypercholesterolaemia and mixed dyslipidaemia population

Phase 3	**Hypercholesterolaemia and mixed dyslipidaemia**					
Study	**N**	**Baseline LDL-C (mmol/l)**		**Doses used**	**Vs PLB at 12 weeks (%)**	**Vs EZT at 12 weeks (%)**
20110114 MENDEL-2	A Double-blind, Randomized, Placebo and Ezetimibe-controlled, Multicenter Study to Evaluate Safety and Efficacy of Lipid Lowering Monotherapy With AMG 145 in Subjects With a 10-Year Framingham Risk Score of 10% or Less					

Phase 3	**Hypercholesterolaemia and mixed dyslipidaemia**					
Study	**N**	**Baseline LDL-C (mmol/l)**		**Doses used**	**Vs PLB at 12 weeks (%)**	**Vs EZT at 12 weeks (%)**
	615	3.7 (0.6)	Versus placebo + ezetimibe	140 mg Q2W	-57	-39
				420 mg QM	-55	-38
20110115 LAPLACE-2	A Double-blind, Randomized, Placebo and Ezetimibe Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-C in Combination With Statin Therapy in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia					
	1899	2.8 (1.1)	On top of ator, rosu or simva	140 mg Q2W (ator10)	-74	-44
			Vs placebo and ezetimibe	420 mg QM (ator10)	-61	-43
				140 mg Q2W (ator80)	-80	-50
				420 mg QM (ator80)	-74	-41
				140 mg Q2W (rosu5)	-71	
				420 mg QM (rosu5)	-66	
				140 mg Q2W (rosu40)	-71	
				420 mg QM (rosu40)	-59	
				140 mg Q2W (simva40)	-71	
				420 mg QM (simva40)	-62	
20110116 GAUSS-2	A Double-blind, Randomized, Multicenter Study to Evaluate Safety and Efficacy of AMG 145, Compared With Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor					
	307	5.0 (1.5)	Vs ezetimibe	140 mg Q2W		-39
	Statin intolerant			420 mg QM		-38
20110117 RUTHERFORD-2	A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of evolocumab on LDL-C in Subjects With Heterozygous Familial Hypercholesterolemia					
	331	4.0 (1.2)	Vs placebo	140 mg Q2W	-61	
	HeFH			420 mg QM	-60	
20110109 DESCARTES	A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Long-term Tolerability and Durable Efficacy of AMG 145 on LDL-C in Hyperlipidemic Subjects					
	901	2.7 (0.6)	Long-term vs placebo	420 mg QM Week 52	-59	
20120138 OSLER-2	A Multicenter, Controlled, Open-label Extension Study to Assess the Long-term Safety and Efficacy of AMG-145					
	2928	3.2 (1.2)	Open label extension 2 years vs SoC	Original 140 mg Q2W or 420 mg QM		
			ongoing	Week 12	-54	
				Week 24	-53	
20110271 TAUSSIG (severe HeFH)	A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia (Severe FH)					
	102	184.1 (61.5) mg/dL	Open label long term 5 years	420 Q2W or 402 mg QM		
			ongoing	Week 12	-52	
				Week 24	-34	
20120348 THOMAS-1	149	3.0 (0.7)	Change from baseline week 6	140 mg Q2W PFS	-61	

Phase 3	Hypercholesterolaemia and mixed dyslipidaemia					
Study	**N**	**Baseline LDL-C (mmol/l)**		**Doses used**	**Vs PLB at 12 weeks (%)**	**Vs EZT at 12 weeks (%)**
	Home use device			140 mf Q2W A/pen	-64	
20120356 THOMAS-2	164	3.0 (0.7)	Change from baseline mean week 10 and 12	420 mg QM AMD	-69	
	Home use device			420 mg QM A/pen	-67	

Table E3: Summary of efficacy for the pivotal trials in the HoFH population

Phase 3	N	Baseline LDL-C (mmol/L) Mean(sd)		Doses used	Vs PLB	Vs EZT
20110233 TESLA	A 2-Part, Phase 2/3 Study to Assess the Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial Hypercholesterolemia. Part A - Open-label, Single-arm, Multicenter Pilot Study to Evaluate Safety, Tolerability, and Efficacy of AMG 145 in Subjects With Homozygous Familial Hypercholesterolemia. Part B - Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 in Subjects With Homozygous Familial Hypercholesterolemia					
Part A phase 2	HoFH (n=8)	11.4 (2.9)	Change from baseline	420 mg QM	-17	
Part B phase 3	HoFH (n=49)	9.0 (3.5)	Vs placebo	420 mg QM	-32	
20110271 TAUSSIG	A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia					
	98	8.3 (3.4)	Open label long term 5 years	420 mg Q2W Week 24	-21	
	HoFH		ongoing	420 mg QM Week 24	-15	

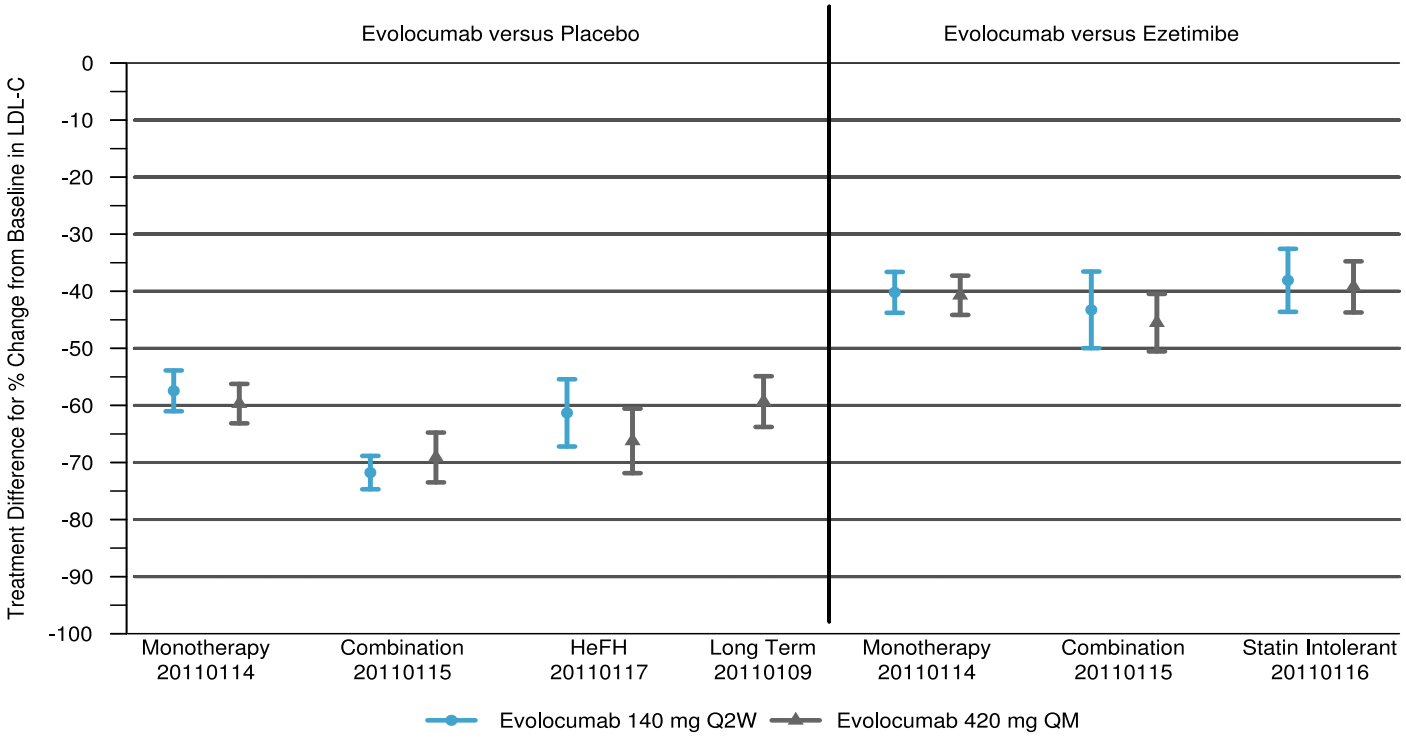
Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy on LDL-C reduction was substantial for the pivotal trials according to Q2W and QM dose, as presented below, for both components of the primary endpoint, the mean LDL-C reduction from week 10 and 12, and the LDL-C reduction at week 12. Reflexive LDL-C is a combination of calculated LDL-C and UC measurement when LDL-C drops below 40 mg/dL. The method of measurements seems to be approximately similar. In addition, the data were supported by other lipid parameters in both study groups.

Table E 9: Comparison of Treatment Differences in the Co-primary Endpoints Using Reflexive or Calculated LDL-C Concentrations between Phase 3 Parent Studies and Integrated Cohort

		Treatment Differences in Percent Change of LDL-C from Baseline (%)									
		Study 20110115 (Combination Therapy)		Study 20110117 (HeFH)		Study 20110116 (Statin-Intolerant)		Study 20110114 (Monotherapy)		Integrated Cohort	
Co-primary Endpoint	Analysis Method	EvoMab Q2W	EvoMab QM	EvoMab Q2W	EvoMab QM	EvoMab Q2W	EvoMab QM	EvoMab Q2W	EvoMab QM	EvoMab Q2W	EvoMab QM
Evolocumab vs Placebo											
Mean of weeks 10 &12	Reflexive LDL-C[a]	-69	-67	-60	-66	-	-	-57	-57	-66	-65
	Calculated LDL-C	-72	-69	-61	-66	-	-	-57	-60	-68	-67
Week 12	Reflexive LDL-C[a]	-71	-62	-59	-61	-	-	-57	-55	-67	-60
	Calculated LDL-C	-73	-64	-61	-60	-	-	-59	-57	-69	-62
Evolocumab vs Ezetimibe											
Mean of weeks 10 &12	Reflexive LDL-C[a]	-40	-44	-	-	-37	-39	-39	-40	-39	-40
	Calculated LDL-C	-43	-46	-	-	-38	-39	-40	-41	-40	-42
Week 12	Reflexive LDL-C[a]	-42	-40	-	-	-38	-38	-39	-38	-40	-38
	Calculated LDL-C	-43	-42	-	-	-39	-38	-40	-38	-41	-39

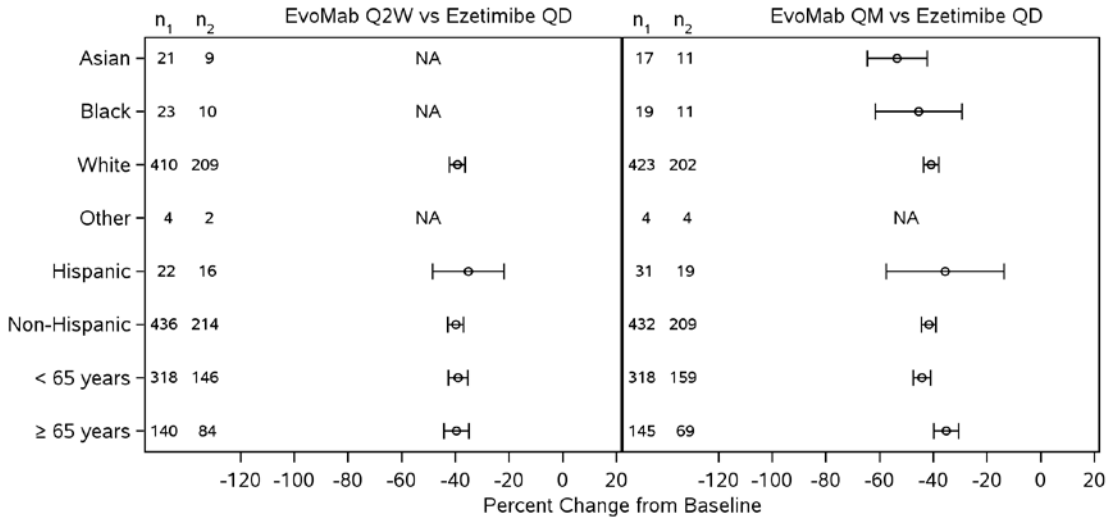
Figure E 6: Treatment Differences for Percent Change From Baseline in Calculated LDL-C in the Phase 3 Evolocumab Program



Clinical studies in special populations

No differences in effect according to subgroups have been identified both in comparison against placebo as in comparison to ezetimibe (see figure below).

Figure E 5: Subgroup Analysis of Percent Change from Baseline Compared with Ezetimibe in LDL-C at the Mean of Week 10 and Week 12 Integrated Phase 3 Parent Studies Cohort (Full Analysis Set)



1779 (29.5%) of patients >65 years of age have been included. 223 (3.7%) of patients age 75-84 have been included. For subjects ≥ 75 years old, LDL-C reductions were similar to those observed for the integrated phase 3 parent cohort.

Table E8: LDL-C change for the subgroup of patients aged 75 years or over in the phase 3 studies.

	Placebo			Ezetimibe			EvoMab		
	Q2W (N = 20)	QM (N = 18)	Overall (N = 38)	Placebo Q2W + Ezetimibe QD (N = 7)	Placebo QM + Ezetimibe QD (N = 6)	Overall (N = 13)	140 mg Q2W (N = 33)	420 mg QM (N = 47)	Overall (N = 80)
Percent change from baseline to week 12 (%)									
n	19	17	36	7	5	12	32	45	77
Mean	5.30	6.53	5.88	-26.11	-21.99	-24.39	-66.15	-57.96	-61.36
SD	25.04	37.14	30.88	3.75	5.22	4.70	12.80	14.24	14.17
SE	5.75	9.01	5.15	1.42	2.34	1.36	2.26	2.12	1.61
Median	-2.42	0.00	-1.70	-25.68	-23.15	-24.02	-66.26	-58.16	-61.40
Q1, Q3	-12.26, 11.93	-5.34, 5.31	-9.59, 8.61	-28.81, -22.27	-23.34, -22.58	-27.86, -22.43	-75.01, -58.30	-64.93, -48.57	-70.27, -52.84
Min, Max	-17.4, 81.1	-32.8, 142.4	-32.8, 142.4	-31.8, -21.3	-27.5, -13.3	-31.8, -13.3	-90.8, -39.0	-88.4, -31.3	-90.8, -31.3

Supportive studies

Study YUKAWA-1

This was a phase 2, multicenter, double-blind, randomized, placebo-controlled study of evolocumab in Japanese subjects with primary hyperlipidemia and mixed dyslipidemia and high cardiovascular risk. Subjects were randomized into 1 of 6 treatment groups: evolocumab SC Q2W (70 mg or 140 mg); evolocumab SC QM (280 mg or 420 mg); or placebo SC (Q2W or QM) to evaluate the effect of 12 weeks of SC evolocumab administered Q2W or QM, compared with placebo, on percent change from baseline in UC LDL-C when used in addition to statin therapy. Mean (SD) serum concentration of UC LDL-C at baseline was 141.8 (20.9) mg/dL (3.7 [0.5] mmol/L). Compared with placebo, evolocumab resulted in statistically significant reductions in LDL-C at week 12 when administered Q2W (-57 to -72%) and QM (-60% to -66%). Evolocumab Q2W and QM also showed statistically significant improvement in secondary lipid endpoints.

Other Studies – Home- Use Setting

Study THOMAS-1

This was a phase 3, multicenter, randomized, study designed to assess subjects' ability to administer a full dose of evolocumab SC in a home-use setting using either a PFS or an AI/pen. Eligible subjects with primary hyperlipidemia and mixed dyslipidemia on statin therapy with or without ezetimibe were randomized to receive evolocumab 140 mg SC Q2W for 4 weeks (day 1, week 2, and week 4) for a total of 3 administrations (the first performed in the clinic and 2 subsequent self-administrations performed at home) via PFS or AI/pen. The percent reduction in LDL-C from baseline to week 6 was clinically equivalent between the PFS and AI/pen groups. Treatment emergent adverse events were reported in 29.3% and 27.0% of subjects in the PFS and AI/pen groups, respectively. Overall, 3 (2.0%) subjects discontinued IP due to adverse events, including 2 (2.7%) in the PFS group and 1 (1.4%) in the AI/pen group. No subject tested positive for anti-evolocumab antibodies.

Study THOMAS-2

This was a phase 3, multicenter, randomized, study designed to assess subjects' ability to administer a full dose of evolocumab in a home-use setting using either an AMD or 3 AI/pens. Eligible subjects with primary hyperlipidemia and mixed dyslipidemia on statin therapy with or without ezetimibe were randomized to receive evolocumab 420 mg SC QM for 8 weeks (day 1, week 4, and week 8) for a total of 3 administrations (the first performed in the clinic and 2 subsequent self-administrations performed at home) via AMD or 3 AI/pens. The percent reduction in LDL-C from baseline at the mean of weeks 10 and 12 was clinically equivalent between the AMD and AI/pen groups. Treatment emergent adverse events

were reported in 25.6% and 32.9% of subjects in the AMD and AI/pen groups, respectively. One (1.2%) subject in the AI/pen group discontinued IP due to an adverse event.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

General

The company has conducted several studies in different type of patients. The objectives of the presented studies were considered in line with the claimed indications. Studies are conducted in patients with hypercholesterolaemia and mixed dyslipidaemia on top of maximum statin therapy, statin intolerant patients, and patients also using ezetimibe. The criteria applied to identify statin intolerant patients were considered sufficiently rigorous with patients who had to try at least 2 statins and be unable to tolerate them based on adverse events which resolved or improved when statin dose was decreased or discontinued. Clinical evaluation has been conducted in controlled studies for 12 weeks. The primary endpoints were considered appropriate to establish the LDL-C lowering effect of evolocumab at 12 weeks of treatment and to account for the time dependent effect using the mean of the 10-12 weeks LDL-C lowering effect. Patients were subsequently enrolled in long term follow up studies, partly in a controlled fashion, which seems adequate to evaluate longer term effects in terms of efficacy and safety.

Analyses of LDL-C in the evolocumab clinical development program utilized 3 different methods: (1) preparative ultracentrifugation (UC) LDL-C, (2) a reflexive approach, and (3) calculated LDL-C. The methods used to analyse the LDL-C were considered appropriate. The randomisation and the general blinding principals were considered appropriate. Ezetimibe and the 2QW and QM differentiation in dosing have not been blinded, but this was considered unfeasible, as ezetimibe is a tablet and the dosing interval cannot be mimicked. Appropriate secure blinding principles of measurements and evaluation were applied for assessment of laboratory values by an independent laboratory and an external independent monitoring committee to review the safety data to avoid a possible increased risk. The statistical methods used were considered appropriate. The objective to also evaluate other lipid parameters was agreed to be supportive and provided a good understanding of the evolocumab effect. An important limitation of the presented data was the lack of clinical outcome data and these were agreed to be provided postauthorisation. Although LDL-C reduction was considered an established surrogate marker for cardiovascular risk reduction, this is primarily been demonstrated for statin therapy and not for newer therapies such as evolocumab treatment.

Hypercholesterolaemia and mixed dyslipidaemia

The designs of the MENDEL-2, GAUSS-2 and RUTHERFORD-2 studies were similar and were considered appropriate. The run-in period of a maximum of 6 weeks was sufficient to establish a stable run-in cholesterol level and to study the randomized comparison of evolocumab versus placebo or ezetimibe for MENDEL-2 and evolocumab versus ezetimibe in GAUSS-2 and evolocumab versus placebo on a maximum background therapy (statin with or without ezetimibe)(RUTHERFORD-2). A 12 week period with the 2 doses evaluated in the dose findings studies was sufficient to provide data regarding the LDL-C (and other cholesterol parameters) lowering effect of evolocumab. Two of the six and one of the three doses for Q2W and QM were tested outside the clinical settings, which were acceptable, considering that patients have to be able to administer evolocumab also in a home setting. For the LAPLACE-2 study a run-in period of 4 weeks was considered appropriate to establish a stable run-in cholesterol level and to evaluate the effect of evolocumab on top of different doses of different statins during 12 weeks of treatment. It was considered essential to study the effect of evolocumab on maximum doses of the most potent statins as has been done in this study. A 2:1 randomization was used for the controlled studies, which was

considered appropriate. Screening of 4 to 16 weeks in the DESCARTES study of patients with a range of CV risk, LDL level and prior statin therapy was considered appropriate. The controlled effect of evolocumab for a longer follow up of 52 weeks was evaluated in this study. This period was agreed to be minimal for a intended life-long treatment. Patients assigned to one of the 4 parent studies were afterwards included in the OSLER-2 long term study where they were randomized according to evolocumab treatment of Q2W 140 mg or QM 420 mg and compared to a background therapy in the first year and studied open label in the second year. The open-label design was considered acceptable, given the long term follow up.

HoFH population

Studies were presented with the objective to demonstrate controlled as well as long term effect of evolocumab in patients with HoFH. Due to the small number of patients available, hard outcome studies were less feasible, but outcome data derived from other studies may provide indication of the predicted effect in this HoFH population. Part A of the TESLA study was considered appropriate for a first exploratory evaluation of evolocumab in this population. Study TESLA B was 12 weeks placebo controlled, which provided a better understanding of the effect of evolocumab on cholesterol reduction than part A. In the longer term TAUSSIG study patients could be up-titrated and back-titrated according to response to a Q2W dosing scheme on the highest dose instead of QM dosing scheme on the highest dose.

Efficacy data and additional analyses

Phase 2 dose evaluation

In the phase 2 evaluation several doses have been investigated in different patient populations. In all studies a dose dependent effect was observed for the treatment of evolocumab for both the Q2W dosing and the QM dosing in comparison to the control group. In those studies where both the Q2W and the QM dosing were tested, the LAPLACE study on top of statin therapy showed a slightly better efficacy for the Q2W dosing when comparing the 140 Q2W dose with the 420 QM dose, while in MENDEL-1 versus placebo, the 420 mg QM was slightly more effective except on top of ezetimibe where the Q2W demonstrated higher efficacy. In the other studies only QM dosing was tested and a dose dependent effect was demonstrated.

Hypercholesterolaemia and mixed dyslipidaemia

In the studies including hypercholesterolaemia and mixed dyslipidaemia patients, there was a high proportion of patients (around 95%) completing these studies. An acceptably low number of patients was lost to follow-up or discontinued the study due to withdrawal of consent or other reasons. The “parent” studies were multicenter and recruited patients across the globe, which was also judged to be sufficiently representative for the European population. Overall baseline data for the hypercholesterolaemia and mixed dyslipidaemia patients was sufficiently well distributed across the different treatment groups, with some slight imbalances for some of the characteristics. For instance, LDL-C levels were slightly higher in the evolocumab treatment arms in comparison to placebo and slightly lower in comparison to the ezetimibe randomised patients. This could have slightly influenced the results. All studies included substantial number of patients with high cardiovascular risk, except the monotherapy study due to ethical reasons.

Evolocumab demonstrated a substantial reduction in the co primary endpoint of: “mean percent change in LDL-C at weeks 10 and 12” and “the percent change in LDL-C at week 12” for both the Q2W 140 mg dose and the 420 mg QM dose in a consistent fashion across all of the pivotal phase 3 studies evaluating different patients including high risk CV patients, HeFH patients, and patients at low CV risk. On top of placebo or on top of standard of treatment a reduction of between 60 and 70 percent was demonstrated.

Compared to patients who were treated with ezetimibe, evolocumab demonstrated a less reduction of around 40% across the 3 pivotal studies on top of SoC, statin intolerant patients, and on top of placebo.

Primary endpoint analyses were supported by the secondary cholesterol profile evaluations showing significant reductions in e.g. ApoB, total cholesterol, non-HDL-C and triglycerides and increase in HDL-C. In addition, the effect of LDL-C reduction was maintained as compared to SoC up to 48 to 64 weeks of treatment and in an open label single-arm fashion up to 124 weeks, although the studies are still ongoing and limited data have been evaluated for this long time frame. For the severe FH population, reduction of approximately 40% in LDL-C was sustained during 48 weeks of treatment in the interim analysis. These data were generally supported by beneficial effects in the secondary cholesterol parameters.

The pooled analyses demonstrate a substantial and comparable efficacy between the 140 mg Q2W dosing and the 420 QM dosing both in terms of LDL-C reduction over time (mean Week 10 and 12) as well as LDL-C reduction at the week 12 endpoint. This was similar for both comparisons: against placebo as well as against ezetimibe. The used method of reflexive LDL-C measurement seems not substantially differ from the calculated LDL-C measurement method when the overall data are considered.

The applicant presented the data of the number of patients older than 65 and 75 in the safety information. A substantial proportion of patients was older than 65. This subgroup does not show a difference in efficacy compared to younger patients. However, patients over 75 of age were underrepresented, although similar efficacy was demonstrated in this subgroup as well. Other subgroup analyses also demonstrated no major differences in effect.

The study in a Japanese patients also demonstrate efficacy in this patient population. In addition, both the study THOMAS-1 and THOMAS-2 demonstrated a comparable efficacy for different administration formulations of AMD, PFS, and the AI/pen in a home setting. Therefore it was considered acceptable to combine results from studies using different formulation in performed analyses.

Assessment of paediatric data on clinical efficacy

HoFH patients

A high proportion of patients completed TESLA phase 3 study. Currently, an acceptable high proportion of patients are on study drug (approximately 90%) in the long term study (TAUSSING) with a slightly smaller proportion of patients who are on study drug and on apheresis and for paediatric patients (approximately 83%). Most discontinuations were due to physician decision. Although the number of patients with HoFH included in the studies is limited, distribution across the treatment group and placebo group appears to be acceptable. Despite baseline values for LDL-C and PCSK9 were slightly different between the treatment and the placebo groups, this was still considered acceptable. Similar differences also appeared in the long term follow-up studies across the categories of apheresis, non-apheresis and patients <18 years, however, patients were not randomised across these categories. Approximately half of the patients had a HoFH mutation and half were compound HeFH (with a different mutation in each allele). The number of patients with HeFH remained very limited in the controlled phase 3 study. The applicant made a distinction between patients with a defective LDL receptor and with a negative or undetermined LDL-R receptor in HoFH population. Efficacy in the defective LDL-R population was weaker as compared to the negative or undetermined LDL-R population. In the small group of patients with HoFH younger than 18 years of age (n=14) evolocumab showed approximately similar efficacy as compared to adult patients.

2.5.4. Conclusions on the clinical efficacy

In conclusion, evolocumab demonstrated efficacy as measured by substantial and consistent reduction in LDL-C and other lipid parameters on top of existing therapy options for both patient groups: (1) of hypercholesterolaemia and mixed dyslipidaemia, and subgroups of those, and (2) for patients with homozygous familial hypercholesterolemia. In addition, limited data have been provided for adolescents showing consistent results. Ongoing long term studies provide data regarding maintenance of effect in the long term.

2.6. Clinical safety

Patient exposure

The clinical safety profile includes data from 16 phase 2 and phase 3 studies: 12 studies that were ~12 weeks in duration and 4 studies that were long term studies (a 52 week completed study [20110109] and 3 ongoing extension studies [20110110, 20120138 and 20110271). Some of the data have been updated from safety data of 01 April 2014 to 01 July 2014.

Three integrated analysis sets are used to describe the data from the primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia studies:

- The Integrated Parent Analysis Set (IPAS) comprises integrated data from the phase 2 and phase 3 parent studies, all being controlled blinded studies, *i.e.* the 12 week studies 20101154, 20101155, 20090158, 20090159, 20110114, 20110115, 20110116, 20110117, 20120348, 20120356, and 20110231 and the 52 weeks study 20110109.
- The Integrated Extension Standard of Care (SoC) Controlled Period Analysis Set (IECAS) comprises integrated data from year 1 (the controlled period) of the open label extension (OLE) studies 20110110 and 20120138.
- The Integrated Extension All Investigational Product (IP) Period Analysis Set (IEAAS) comprises integrated data from year 2+ (the all IP period) of the open label extension studies 20110110 and 20120138.

Exposure data are presented below for both the primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia studies, as well as the more limited data of the HoFH population.

Table S01. Overall Summary of Exposure (Phase 1,2,3)

	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

As of the data cutoff date 01 July 2014, the total of 6026 primary hyperlipidaemia and mixed dyslipidaemia subjects remained constant while the total exposure increased from 6165 subject years to 7235 subject years. Cumulative exposure to evolocumab increased to 5246 patient years and the cumulative number of subjects exposed to evolocumab for ≥ 6, ≥ 12, ≥ 18, ≥ 24, and ≥ 30 months increased to 3549, 2458, 1124, 709, and 491 subjects, respectively.

Table S02. Summary of exposure in severe HeFH patients

	Control		EvoMab		
	Any Placebo	Any Control[a]	EvoMab 140 mg Q2W or 420 mg QM or 420mg Q2W [b]	Any EvoMab	All Unique Subjects
Severe Familial Hypercholesterolemia					
Number of Subjects	0	0	102	102	102
Total pt-year exposure	0	0	18	18	18
Number of Subjects					
< 3 months	0	0	85	85	85
≥ 3 months	0	0	17	17	17
≥ 6 months	0	0	8	8	8
≥ 12 months	0	0	4	4	4
≥ 18 months	0	0	3	3	3
≥ 24 months	0	0	0	0	0

Table S03. Summary of exposure in HoFH patients

	20110233 HoFH Parent Study Rollover			20110271 HoFH Non-Parent / Other Parent Study Rollover			
	Part A EvoMab (N = 8)	Part B EvoMab (N = 30)	Part B Placebo (N = 16)	Apheresis at Enrollment (N = 31)	Non-apheresis at Enrollment (N = 11)	Total (N = 42)	Total (N = 96)
Number of subjects exposed to at least one IP dose, n (%)	8 (100.0)	30 (100.0)	16 (100.0)	31 (100.0)	11 (100.0)	42 (100.0)	96 (100.0)
≥ 4 weeks	8 (100.0)	29 (96.7)	16 (100.0)	29 (93.5)	6 (54.5)	35 (83.3)	88 (91.7)
≥ 8 weeks	8 (100.0)	29 (96.7)	14 (87.5)	27 (87.1)	6 (54.5)	33 (78.6)	84 (87.5)
≥ 12 weeks	8 (100.0)	22 (73.3)	11 (68.8)	24 (77.4)	4 (36.4)	28 (66.7)	69 (71.9)
≥ 24 weeks	8 (100.0)	15 (50.0)	8 (50.0)	13 (41.9)	3 (27.3)	16 (38.1)	47 (49.0)

Adverse events

All reported adverse events in the controlled blinded period are provided below. Patients in the control group were taking placebo injections. A comparison is provided for the 140 mg Q2W and the 420 mg QM doses.

Table S04: Reported adverse events in the pivotal controlled blinded studies for evolocumab treated patients and for placebo and ezetimibe treated patients according to dose.

	Control			EvoMab			
Preferred Term	Placebo SC Q2W (N = 586) n (%)	Placebo SC QM (N = 940) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N = 1245) n (%)	420 mg QM (N = 1956) n (%)	420 mg QM + Ezetimibe QD (N = 30) n (%)
Number of subjects reporting adverse events	240 (41.0)	513 (54.6)	278 (50.2)	397 (55.5)	543 (43.6)	1056 (54.0)	20 (66.7)
Nasopharyngitis	23 (3.9)	54 (5.7)	22 (4.0)	74 (10.3)	40 (3.2)	114 (5.8)	3 (10.0)
Upper Respiratory Tract Infection	15 (2.6)	28 (3.0)	13 (2.3)	21 (2.9)	22 (1.8)	81 (4.1)	3 (10.0)
Back Pain	8 (1.4)	36 (3.8)	13 (2.3)	15 (2.1)	29 (2.3)	70 (3.6)	3 (10.0)
Headache	19 (3.2)	27 (2.9)	20 (3.6)	16 (2.2)	32 (2.6)	66 (3.4)	6 (20.0)
Influenza	3 (0.5)	29 (3.1)	9 (1.6)	9 (1.3)	17 (1.4)	56 (2.9)	1 (3.3)
Myalgia	5 (0.9)	23 (2.4)	27 (4.9)	22 (3.1)	21 (1.7)	49 (2.5)	6 (20.0)
Arthralgia	8 (1.4)	25 (2.7)	12 (2.2)	18 (2.5)	25 (2.0)	47 (2.4)	1 (3.3)
Nausea	6 (1.0)	19 (2.0)	12 (2.2)	13 (1.8)	21 (1.7)	47 (2.4)	0 (0.0)
Pain In Extremity	8 (1.4)	25 (2.7)	6 (1.1)	7 (1.0)	17 (1.4)	46 (2.4)	3 (10.0)
Cough	1 (0.2)	19 (2.0)	6 (1.1)	21 (2.9)	13 (1.0)	43 (2.2)	1 (3.3)
Urinary Tract Infection	7 (1.2)	19 (2.0)	8 (1.4)	3 (0.4)	14 (1.1)	43 (2.2)	0 (0.0)
Diarrhoea	10 (1.7)	26 (2.8)	14 (2.5)	15 (2.1)	21 (1.7)	42 (2.1)	1 (3.3)
Dizziness	8 (1.4)	15 (1.6)	11 (2.0)	9 (1.3)	13 (1.0)	41 (2.1)	2 (6.7)
Fatigue	7 (1.2)	14 (1.5)	19 (3.4)	11 (1.5)	20 (1.6)	40 (2.0)	0 (0.0)
Muscle Spasms	7 (1.2)	16 (1.7)	14 (2.5)	12 (1.7)	17 (1.4)	39 (2.0)	0 (0.0)
Bronchitis	6 (1.0)	21 (2.2)	2 (0.4)	8 (1.1)	19 (1.5)	36 (1.8)	1 (3.3)
Gastroenteritis	5 (0.9)	9 (1.0)	2 (0.4)	5 (0.7)	8 (0.6)	25 (1.3)	1 (3.3)
Injection Site Erythema	0 (0.0)	13 (1.4)	6 (1.1)	7 (1.0)	9 (0.7)	21 (1.1)	1 (3.3)
Injection Site Bruising	2 (0.3)	11 (1.2)	5 (0.9)	7 (1.0)	0 (0.0)	18 (0.9)	1 (3.3)
Abdominal Pain	4 (0.7)	5 (0.5)	6 (1.1)	3 (0.4)	9 (0.7)	16 (0.8)	1 (3.3)
Cystitis	5 (0.9)	5 (0.5)	5 (0.9)	5 (0.7)	6 (0.5)	16 (0.8)	2 (6.7)
Constipation	10 (1.7)	4 (0.4)	3 (0.5)	5 (0.7)	16 (1.3)	14 (0.7)	3 (10.0)
Epistaxis	1 (0.2)	2 (0.2)	1 (0.2)	2 (0.3)	4 (0.3)	10 (0.5)	1 (3.3)
Gout	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.3)	2 (0.2)	10 (0.5)	1 (3.3)
Abdominal Distension	0 (0.0)	6 (0.6)	3 (0.5)	1 (0.1)	11 (0.9)	9 (0.5)	1 (3.3)
Gastroenteritis Viral	1 (0.2)	3 (0.3)	2 (0.4)	2 (0.3)	3 (0.2)	9 (0.5)	1 (3.3)
Flatulence	1 (0.2)	3 (0.3)	3 (0.5)	7 (1.0)	2 (0.2)	8 (0.4)	1 (3.3)
Asthenia	0 (0.0)	4 (0.4)	0 (0.0)	4 (0.6)	2 (0.2)	7 (0.4)	1 (3.3)
Decreased Appetite	1 (0.2)	0 (0.0)	1 (0.2)	3 (0.4)	3 (0.2)	7 (0.4)	1 (3.3)
Injection Site Swelling	0 (0.0)	2 (0.2)	2 (0.4)	1 (0.1)	1 (0.1)	7 (0.4)	1 (3.3)
Excoriation	1 (0.2)	1 (0.1)	1 (0.2)	3 (0.4)	2 (0.2)	5 (0.3)	1 (3.3)
Oral Herpes	1 (0.2)	3 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	5 (0.3)	1 (3.3)
Hyperhidrosis	1 (0.2)	4 (0.4)	2 (0.4)	0 (0.0)	2 (0.2)	4 (0.2)	1 (3.3)
Malaise	0 (0.0)	3 (0.3)	2 (0.4)	3 (0.4)	4 (0.3)	4 (0.2)	1 (3.3)
Helicobacter Infection	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	1 (3.3)
Inguinal Hernia	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)	1 (3.3)
Road Traffic Accident	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.2)	1 (3.3)
Wound	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.2)	1 (3.3)
Limb Injury	0 (0.0)	4 (0.4)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)	1 (3.3)
Night Sweats	0 (0.0)	1 (0.1)	2 (0.4)	0 (0.0)	1 (0.1)	2 (0.1)	1 (3.3)
Face Oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (3.3)
Corneal Erosion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Glucose Tolerance Impaired	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (3.3)
Humerus Fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (3.3)
Injection Site Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Joint Stiffness	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Localised Oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Miliaria	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (3.3)
Scab	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Spontaneous Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (3.3)
Vestibular Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)

Table S05: Adverse events across therapeutic settings

	Monotherapy (Studies 20101154, 20110114, and sußbjects in 20110109 in the diet-alone background therapy stratum)			**Combination Therapy With Statins (Studies 20101155, 20110115, 20110231, 20120348, 20120356, 20090158, 20110117, and subjects in 20110109 in the low, high, or maximal background drug therapy cohorts)**			**Statin Intolerant (Studies 20090159 and 20110116)**		**Entire Integrated Population**		
Controlled Blinded Studies											
N	EvoMab: 651	Control: 480	Placebo	EvoMab 2965	Control: 1466	Placebo	EvoMab 330	Control: 134	EvoMab: 3946	Control: 2080	Placebo
All AEs	324 (49.8%)	236 (49.2%)	140 (49.8%)	1479 (49.9%)	702 (47.9%)	613 (49.2%)	213 (64.5%)	93 (69.4%)	2016 (51.1%)	1031 (49.6%)	753 (49.3%)
SAEs	9 (1.4%)	5 (1.0%)	4 (1.4%)	90 (3.0%)	34 (2.3%)	32 (2.6%)	11 (3.3%)	4 (3.0%)	110 (2.8%)	43 (2.1%)	36 (2.4%)
AEs leading to discontinuation	8 (1.2%)	13 (2.7%)	8 (2.8%)	46 (1.6%)	20 (1.4%)	16 (1.3%)	21 (6.4%)	15 (11.2%)	75 (1.9%)	48 (2.3%)	24 (1.6%)
Most common AEs (EvoMab vs control)											
myalagia							9.1%	14.2%	2.5%	2.6%	
nasopharyngitis	4.3%	4.0%		6.3%	4.9%		4.5%	5.0%	5.9%	4.8%	
upper respiratory tract infection	4.3%	5.2%		3.1%	2.1%				3.2%	2.7%	
diarrhea	3.2%	2.9%									
headache	3.2%	3.1%		2.6%	2.9%		7.0%	6.7%	3.0%	3.2%	
back pain	2.55	2.5%		2.9%	2.9%		4.5%	2.2%	3.0%	2.7%	
pain in extremity							5.8%	1.5%			
muscle spasms							5.2%	5.2%			
arthralgia				2.4%	2.0%						
influenza				2.4%	2.1%						
cough				2.0%	1.1%						
	all others ≤ 2% in any EvoMab group			all others < 2% in any EvoMab group			all others < 4% in any EvoMab group				

Year 1 SoC-controlled Period								
N	EvoMab+SoC: 485	SoC alone: 264	EvoMab+SoC: 2101	SoC alone: 1028	EvoMab+SoC: 247	SoC alone: 127	EvoMab+SoC: 2833	SoC alone: 1419
All AEs	314 (64.7%)	155 (58.7%)	1216 (57.9%)	538 (52.3%)	178 (72.1%)	88 (69.3%)	1708 (60.3%)	781 (55.0%)
SAEs	26 (5.4%)	9 (3.4%)	110 (5.2%)	60 (5.8%)	17 (6.9%)	13 (10.2%)	153 (5.4%)	82 (5.8%)
AEs leading to discontinuation of IP	13 (2.7%)	0%	36 (1.7%)	0%	9 (3.6%)	0%	58 (2.0%)	0 (0%)
Most common AEs (EvoMab+SoC and SoC alone)								
myalagia					8.5%	7.9%		
nasopharyngitis	7.0%	4.2%	8.7%	8.2%	10.1%	13.4%	8.5%	7.9%
upper respiratory tract infection	6.8%	5.3%	3.6%	3.8%	4.5%	3.1%	4.2%	4.0%
diarrhea	3.1%	2.3%						
headache								
back pain			3.3%	2.1%			3.1%	2.5%
pain in extremity					4.5%	2.4%		
muscle spasms								
arthralgia	3.5%	3.8%	3.4%	2.1%			3.4%	2.5%
influenza					4.9%	4.7%		
cough	3.9%	2.7%						
urinary tract infection	4.3%	2.7%						
hypertension	3.5%	1.9%	3.0%	2.9%			3.1%	2.7%
bronchitis	3.5%	5.3%			4.0%	7.1%		
Sinusitis					4.5%	4.7%		
	all others < 3% in any EvoMab+SoC group		all others < 3% in any EvoMab+SoC group		all others < 4% in any EvoMab+SoC group			

Year 2+ OLE Period				
N	Total: 258	Total: 585	Total: 111	Total: 954
All AEs	Total: 196 (76.0%)	Total: 439 (75.0%)	Total: 78 (70.3%)	713 (74.7%)
SAEs	Total: 9 (3.5%)	Total: 56 (9.6%)	Total: 11 (9.9%)	76 (8.0%)
AEs leading to discontinuation of IP	Total: 5 (1.9%)	Total: 3 (0.5%)	Total: 2 (1.8%)	10 (1.0%)
myalagia				
nasopharyngitis	8.1%	13.2%	12.6%	11.7%
upper respiratory tract infection	12.0%	6.7%		7.7%
diarrhea			5.4%	
headache				
back pain		7.4%	8.1%	6.6%
pain in extremity			8.1%	
muscle spasms				
arthralgia	7.8%	5.6%	9.9%	6.7%
influenza	7.0%			
cough	6.6%	5.1%		
urinary tract infection	5.8%			
hypertension	5.0%	5.6%	5.4%	
bronchitis	7.4%	5.0%		
Sinusitis	9.3%		6.3%	
	all others < 4% in any evomab+soc group	all others < 5% in any total group	all others < 5% in total group	

Specific attention has been given to patients achieving **very low levels of LDL-C**. In addition to the tables below, specific attention has been given to **neurocognitive adverse events**, **vitamin E levels** and **steroid analytes** as further discussed below.

Table S06: Adverse events in the achieved LDL-C subgroups

	LDL-C < 25 mg/dL (< 0.6 mmol/L)		**LDL-C < 40 mg/dL (< 1.0 mmol/dL)**		**LDL C ≥ 40 mg/dL (≥ 1.0 mmol/L)**		**Entire Integrated Population**	
Controlled Blinded Studies								
N	EvoMab: 1609	Control: 6	EvoMab: 2565	Control: 30	EvoMab: 1339	Control: 2038	EvoMab: 3946	Control : 2080
All AEs	826 (51.3%)	4 (66.7%)	1308 (51.0%)	12 (40.0%)	696 (52.0%)	1018 (50.0%)	2016 (51.1%)	1031 (49.6%)
SAEs	47 (2.9%)	1 (16.7%)	70 (2.7%)	2 (6.7%)	35 (2.6%)	41 (2.0%)	110 (2.8%)	43 (2.1%)
Most common AEs (any EvoMab and any control)								
nasopharyngitis	6.5%	33.3%	6.6%	10.0%	4.6%	4.7%	5.9%	4.8%
upper respiratory tract infection	4.0%	0%	3.6%	0%	2.6%	2.7%	3.2%	2.7%
back pain	3.5%	0%	3.2%	0%	2.5%	2.8%	3.0%	2.7%
arthralgia	2.7%	0%	2.4%	0%	2.2%	2.2%		
influenza	2.6%	0%	2.3%	0%				
headache	2.6%	0%	2.7%	0%	3.6%	3.2%	3.0%	3.2%
cough	2.3%	0%	2.5%	0%				
myalgia	2.2%	0%			3.6%	2.7%	2.5%	2.6
diarrhea	2.1%	0%	2.0%	3.3%	2.0%	2.0%		
dizziness	2.1%	0%						
nausea					2.4%	1.8%		
fatigue					2.0%	2.4%		
	all others < 2% in any total group		all others < 2% in any total group		all others < 2% in any total group			

	LDL-C < 25 mg/dL (< 0.6 mmol/L)		LDL-C < 40 mg/dL (< 1.0 mmol/dL)		LDL C ≥ 40 mg/dL (≥ 1.0 mmol/L)		Entire Integrated Population	
Year 1 SoC-controlled Period								
N	EvoMab+SoC: 666	SoC alone: 4	EvoMab+SoC: 1369	SoC alone: 12	EvoMab+SoC: 1427	SoC alone: 1380	EvoMab+SoC: 2833	SoC alone: 1419
All AEs	394 (59.2%)	0%	814 (59.5%)	4 (33.3%)	882 (61.8%)	774 (56.1%)	1708 (60.3%)	781 (55.0%)
SAEs	34 (5.1%)	0 (0%)	68 (5.0%)	0 (0%)	85 (6.0%)	80 (5.8%)	153 (5.4%)	82 (5.8%)
Most common AEs (EvoMab+SoC and SoC alone)								
nasopharyngitis	10.2%	0%	9.2%	8.3%	8.1%	8.0%	8.5%	7.9%
upper respiratory tract infection	4.4%	0%	3.9%	0%	4.6%	4.1%	4.2%	4.0%
back pain	4.2%	0%	3.7%	0%			3.1%	2.5%
arthralgia	3.8%	0%	4.2%	0%			3.4%	2.5%
hypertension	3.5%	0%	3.7%	0%			3.1%	2.7%
diarrhoea	3.3%	0%						
cough	3.3%	0%						
influenza					3.8%	2.7%		
headache					3.2%	1.7%		
	all others <3% in any total group		all others <3% in any total group					

	LDL-C < 25 mg/dL (< 0.6 mmol/L)	LDL-C < 40 mg/dL (< 1.0 mmol/dL)	LDL C ≥ 40 mg/dL (≥ 1.0 mmol/L)	Entire Integrated Population
Year 2+ OLE Period				
N	Total: 193	Total: 419	Total: 518	Total: 954
All AEs	Total: 159 (82.4%)	Total: 324 (77.3%)	Total: 386 (74.5%)	Total: 713 (74.7%)
SAEs	Total: 25 (13.0%)	Total: 37 (8.8%)	Total: 39 (7.5%)	Total: 76 (8.0%)
Most common AEs (Total)				
nasopharyngitis		12.2%	11.8%	11.7%
upper respiratory tract infection	11.9%	9.3%	6.6%	7.7%
back pain	7.8%	6.2%	7.1%	6.6%
arthralgia		5.3%	7.9%	6.7%
hypertension	7.8%	5.7%		
bronchitis	5.2%		6.6%	
cough	5.2%		6.4%	
	all others < 5% in any EvoMab+SoC group	all others < 5% in any total group	all others < 6% in any total group	

Neurocognitive adverse events

Neurocognitive adverse events analyses were performed for the LDL-C subgroups. In the LDL C < 25 mg/dL (< 0.6 mmol/L) subgroup, 2 evolocumab subjects reported amnesia. In the LDL-C < 40 mg/dL (< 1.0 mmol/L) subgroup, 3 subjects reported amnesia, 1 subject reported disorientation, 1 subject reported mental impairment, and 4 subjects reported memory impairment; all 9 subjects were in an evolocumab treatment group. However, there was no overall difference in neurocognitive adverse events with the LDL-C < 25mg/dL and LDL-C<40 mg/dL subgroups compared with LDL-C≥ 40 mg/dL.

Vitamin E

Analyses of vitamin E in the long-term studies (20110109, 20110110, 20120138) were performed by LDL C subgroups (< 25 mg/dL [< 0.6 mmol/L], < 40 mg/dL [< 1.0 mmol/L], or ≥ 40 mg/dL [≥ 1.0 mmol/L]). The analyses were overall consistent across the LDL-C subgroups.

Steroid Analytes

Analyses of steroid analytes were performed by LDL-C subgroups (< 25 mg/dL [< 0.6 mmol/L], < 40 mg/dL [< 1.0 mmol/L], or ≥ 40 mg/dL [≥ 1.0 mmol/L]). The analyses were overall consistent across the LDL C subgroups (data not shown).

Adverse events of special interest

Muscle adverse events

Given the concerns with statins, muscle events were monitored throughout the evolocumab clinical program. In the controlled blinded studies, adverse events for the Musculoskeletal and Connective Tissue Disorders system organ class were reported in 581 (14.7%) subjects in the any evolocumab group and 284 (13.7%) subjects in the any control group, of which the most common adverse events in the any evolocumab group and any control group were back pain (3.0% and 2.7%), myalgia (2.5% and 2.6%), and arthralgia (2.3% and 2.2%). Serious events in this system organ class were reported in 9 (0.2%) and in 2 (0.1%) subjects in the any evolocumab and any control group, respectively. Back pain was the only serious adverse event in this system organ class to be reported in > 1 subject during the parent studies (3 subjects in the any evolocumab group).

To examine cases of CK elevation most likely to represent clinically meaningful muscle events, subjects were identified who had normal baseline CK levels, a post baseline CK elevation > 5 x ULN, and a concurrent muscle related adverse event. There were 51 subjects with CK elevation > 5 x ULN (normal at baseline) and 613 subjects with an adverse event from the HLGT “Muscle Disorders.” Of those identified subjects, 6 subjects had both a muscle adverse event and an elevated CK. Four of these 6 subjects were on evolocumab treatment (2 myalgia, 1 muscle spasms, and 1 myositis) and 2 were on SoC (2 muscle spasms). Of the 4 cases occurring during treatment with evolocumab, evolocumab was continued in all but 1 subject, who was participating in the statin intolerance study (20090159). In 5 of the 6 cases for which post peak CK values were available, serum CK rapidly improved. For the other subject (on statin only), the final reported CK level was the peak CK. Creatinine was normal for all 6 subjects at the time of and post CK elevation. One of the 6 events was reported by the site as likely due to hard physical labor preceding the CK elevation (subject on evolocumab only), and in 2 other subjects the adverse event duration did not overlap the CK elevation (1 subject on evolocumab plus statin and 1 on statin only). Of the other 3 subjects, 2 were treated with statins.

Hepatic adverse events

In the controlled blinded studies, adverse events for the hepatobiliary disorders system organ class were reported in 13 (0.3%) subjects in the any evolocumab group and 9 (0.4%) subjects in the any control group, of which the most common adverse events in the any evolocumab group and any control group

were cholelithiasis (0.1% and 0.2%), hepatic steatosis (0.1% and < 0.1%), and biliary colic (0.1% and 0%). Serious adverse events for this system organ class were reported in 4 (0.1%) subjects in the any evolocumab group (cholecystitis, cholelithiasis, and biliary tract disorder) and 2 (0.1%) subjects in the any control group (cholecystitis acute, drug-induced liver injury).

In the year 1 SoC controlled period, 15 (0.5%) subjects and 8 (0.6%) subjects reported an adverse event for this system organ class in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were hepatic steatosis (0.2% in both groups), cholelithiasis (0.1% and 0.2%), and hepatic function abnormal (0.1% and 0%). Three (0.1%) subjects and 1 (0.1%) subject reported a serious adverse event in the evolocumab plus SoC group (cholelithiasis, hepatic function abnormal, and hepatotoxicity) and SoC alone group (bile duct stone and cholecystitis chronic), respectively. In the year 2+ OLE period, 9 (0.9%) subjects reported an adverse event, of which most common adverse event was cholelithiasis (0.3%). Five (0.5%) subjects reported a serious adverse event, including biliary dyskinesia, cholecystitis, and cholecystits acute. No HoFH subjects in Studies 20110233 or 20110271 reported an adverse event in the hepatobiliary disorders system organ class.

Diabetes

Since diabetes related adverse events have been observed with statins, broad and narrow search strategies were used to assess safety risks with evolocumab therapy. The incidence of diabetes events was low in the controlled blinded studies (any evolocumab: 0.9%; any control 0.8%), the year 1 SoC-controlled period (evolocumab plus SoC: 2.1%; SoC alone: 1.6%), and the year 2+ OLE period (1.8%). Additional analyses were performed to evaluate adverse events, HbA1c levels, fasting blood glucose levels, and proteinuria in subjects with type 2 diabetes mellitus, metabolic syndrome, or neither type 2 diabetes nor metabolic syndrome at baseline.

Changes in HbA1c and fasting blood glucose in the controlled blinded and the extension studies were similar and were also comparable across treatment groups within the analysis periods.

There were no differences in adverse events, HbA1c levels, fasting blood glucose levels, and proteinuria in subjects with type 2 diabetes mellitus, metabolic syndrome, or neither type 2 diabetes nor metabolic syndrome at baseline.

Renal adverse events

In the controlled blinded studies, adverse events for the Renal and Urinary Disorders system organ class were reported in 58 (1.5%) subjects in the any evolocumab group and 24 (1.2%) subjects in the any control group, of which the most common adverse events in the any evolocumab group and any control group were hematuria (0.3% and 0.3%), nephrolithiasis (0.3% and 0.1%), and pollakiuria (0.2% and 0.1%). Serious adverse events for this system organ class were reported in 4 (0.1%) subjects in the any evolocumab group (glomerulonephritis acute, glomerulonephritis minimal lesion, iga nephropathy, and renal failure acute) and no subjects in the any control group.

In the year 1 SoC-controlled period, 47 (1.7%) subjects and 29 (2.0%) subjects reported an adverse event in the evolocumab plus SoC group and the SoC alone group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were hematuria (0.4% and 0.2%) and nephrolithiasis (0.2% and 0.4%). Six (0.2%) subjects and 1 (0.1%) subjects reported a serious adverse event in the evolocumab plus SoC group (nephrolithiasis, urinary incontinence, Calculus Ureteric, and renal failure acute) and SoC alone group (renal failure acute), respectively. In the year 2+OLE period, 22 (2.3%) subjects reported an adverse event, and the most common adverse event was nephrolithiasis (0.7%). Two (0.2%) subjects reported a serious adverse event (nephrolithiasis).

For HoFH in study 20110271, 3 (3.1%) HoFH subjects reported adverse events. Hematuria was the only adverse event reported in > 1 subject; and in 1 of the 2 subjects who reported it, the adverse event of hematuria was reported as serious.

Treatment related adverse events

Treatment related AEs in the parent studies are provided below. No evolocumab related adverse event was reported in > 1% of subjects in the any evolocumab group. Myalgia was the only adverse event reported in > 1% of subjects in the any control group (33 [0.8%] any evolocumab, 22 [1.1%] subjects any control. No trends in the incidences of adverse events related to IP were observed between the any evolocumab and any control groups.

Table S07: Summary of Subject Incidence of Adverse Events During the Integrated Parent Studies (IPAS)

	Any Placebo (N = 1526) n (%)	Any Control (N = 2080) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N = 3201) n (%)	Any EvoMab (N = 3946) n (%)
All adverse events	753 (49.3)	1031 (49.6)	1599 (50.0)	2016 (51.1)
Serious adverse events	36 (2.4)	43 (2.1)	95 (3.0)	110 (2.8)
Leading to discontinuation of IP	24 (1.6)	48 (2.3)	71 (2.2)	75 (1.9)
All adverse events related to IP	115 (7.5)	181 (8.7)	278 (8.7)	361 (9.1)
Serious adverse events	4 (0.3)	4 (0.2)	10 (0.3)	10 (0.3)
Leading to discontinuation of IP	7 (0.5)	16 (0.8)	27 (0.8)	30 (0.8)

For the extension controlled period, the treatment related AEs were substantially higher for evolocumab vs control (n=283 (9.5%) vs 4 (0.3%)), which could be exposure related, as the subjects randomised to SoC did not receive evolocumab in the first year. In the 2 years extension period 4.2% of treatment related AEs were observed.

Device Related Adverse Events

Data from clinical studies demonstrate that all 3 subcutaneous (SC) presentations (ie, prefilled syringe [PFS], autoinjector/pen [AI/pen] and automated mini doser [AMD]) evaluated during the evolocumab clinical development program exhibited device related adverse events that were uncommon, mostly grade 1, and generally limited to injection site reactions.

The AI/pen was used in the phase 3 parent studies. Across the controlled blinded phase 3 device studies, fewer than 3% of subjects reported a device related adverse event. The overall incidence of device related adverse events across treatment groups were 1.5% in evolocumab 140 mg Q2W; 2.8% in evolocumab 420 mg QM, 0.8% in placebo Q2W, and 2.6% in placebo QM. The large majority of device related adverse events were related to the injection site (i.e., injection site bruising, injection site erythema, and injection site pain). Most devices related adverse events were grade 1 in severity. Furthermore, there were no serious or unexpected device related adverse events reported in clinical studies of evolocumab.

In the year 1 SoC-controlled period, thirty seven (1.9%) subjects reported device related adverse events in the evolocumab plus SoC group. All 37 subjects were in the evolocumab group because subjects assigned to SoC alone did not receive any placebo injections. Most devices related adverse events were grade 1 in severity.

During the year 2+ OLE period, 17 subjects received evolocumab via AI/pen in study 20120138, and no device related adverse events were reported.

Two phase 3, evolocumab clinical home-use studies (20120348 and 20120356) assessed the effective administration of evolocumab by subjects or caregivers in the home use setting (self-administration) using the 3 different SC presentations (PFS, AI/pen, and AMD) and showed consistent results with the safety profile across the evolocumab program.

Serious adverse event / deaths / other significant events

Serious adverse events

In the controlled blinded studies, serious adverse events were reported in 110 (2.8%) subjects in the any evolocumab group and 43 (2.1%) subjects in the any control group (Table S08). The incidence of serious adverse events between the evolocumab 140 mg Q2W group (36 [2.9%] subjects) and the 420 mg QM group (59 [3.0%] subjects) was similar. In the year 1 SoC controlled period, serious adverse events were reported in 153 (5.4%) subjects in the evolocumab plus SoC group and 82 (5.8%) subjects in the SoC alone group (Table S09). In addition, serious adverse events were reported in 76 (8.0%) subjects in the year 2+ OLE period (Table S10).

Table S08: Serious Adverse Events During the Controlled Blinded Studies by Preferred Term in Descending Order of Frequency Reported by 2 or More Subjects in Any Treatment Group.

	Control			EvoMab			
Preferred Term	Placebo SC Q2W (N = 586) n (%)	Placebo SC QM (N = 940) n (%)	Ezetimibe QD (N = 554) n (%)	Other EvoMab Dose (N = 715) n (%)	140 mg Q2W (N = 1245) n (%)	420 mg QM (N = 1956) n (%)	420 mg QM + Ezetimibe QD (N = 30) n (%)
Number of subjects reporting serious adverse events	12 (2.0)	24 (2.6)	7 (1.3)	15 (2.1)	36 (2.9)	59 (3.0)	0 (0.0)
Angina Pectoris	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.2)	0 (0.0)
Angina Unstable	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)
Back Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)
Myocardial Infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	2 (0.1)	0 (0.0)
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Pancreatitis Acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)	0 (0.0)
Pulmonary Embolism	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Ventricular Extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Vertigo Positional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Acute Myocardial Infarction	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)
Hepatic Enzyme Increased	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Transient Ischaemic Attack	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

N = number of subjects randomized in the integrated parent analysis set (IPAS); EvoMab = Evolocumab (AMG 145); QD = once a day; Q2W = every 2 weeks; QM = monthly; SC = subcutaneous
Includes the following studies: 20090158, 20090159, 20101154, 20101155, 20110109, 20110114, 20110115, 20110116, 20110117, 20110231, 20120348, 20120356. Coded using MedDRA version 17.0.

Table S09: Serious Adverse Events During the Year 1 SoC Controlled Period by Preferred Term in Descending Order of Frequency Reported by 2 or More Subjects in Any Treatment Group

	Control in Parent Study		EvoMab in Parent Study		All	
Preferred Term	SoC (N = 472) n (%)	EvoMab + SoC (N = 943) n (%)	SoC (N = 947) n (%)	EvoMab + SoC (N = 1890) n (%)	SoC (N = 1419) n (%)	EvoMab + SoC (N = 2833) n (%)
Number of subjects reporting serious adverse events	24 (5.1)	48 (5.1)	58 (6.1)	105 (5.6)	82 (5.8)	153 (5.4)
Osteoarthritis	1 (0.2)	1 (0.1)	1 (0.1)	8 (0.4)	2 (0.1)	9 (0.3)
Angina Pectoris	0 (0.0)	2 (0.2)	2 (0.2)	5 (0.3)	2 (0.1)	7 (0.2)
Myocardial Infarction	1 (0.2)	1 (0.1)	2 (0.2)	4 (0.2)	3 (0.2)	5 (0.2)
Non-Cardiac Chest Pain	2 (0.4)	1 (0.1)	0 (0.0)	4 (0.2)	2 (0.1)	5 (0.2)
Appendicitis	1 (0.2)	2 (0.2)	0 (0.0)	2 (0.1)	1 (0.1)	4 (0.1)
Chest Pain	2 (0.4)	0 (0.0)	1 (0.1)	4 (0.2)	3 (0.2)	4 (0.1)
Coronary Artery Disease	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.2)	0 (0.0)	4 (0.1)
Acute Myocardial Infarction	2 (0.4)	1 (0.1)	0 (0.0)	2 (0.1)	2 (0.1)	3 (0.1)
Angina Unstable	1 (0.2)	0 (0.0)	6 (0.6)	3 (0.2)	7 (0.5)	3 (0.1)
Pneumonia	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)	1 (0.1)	3 (0.1)
Syncope	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	1 (0.1)	3 (0.1)
Accelerated Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Aortic Stenosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Carotid Artery Stenosis	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	1 (0.1)	2 (0.1)
Cerebrovascular Accident	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Chest Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Contrast Media Allergy	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Diabetes Mellitus	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Hypertension	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	1 (0.1)	2 (0.1)
Intraductal Proliferative Breast Lesion	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Meniscus Injury	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Nephrolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Pleurisy	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Prostate Cancer	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	2 (0.1)	2 (0.1)
Transient Ischaemic Attack	0 (0.0)	1 (0.1)	3 (0.3)	1 (0.1)	3 (0.2)	2 (0.1)
Ventricular Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Atrial Fibrillation	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	2 (0.1)	1 (0.0)
Pulmonary Embolism	3 (0.6)	0 (0.0)	2 (0.2)	1 (0.1)	5 (0.4)	1 (0.0)
Breast Cancer	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	3 (0.2)	0 (0.0)

Table S10: Serious Adverse Events During the Year 2+ OLE Period by Preferred Term in Descending Order of Frequency Reported by 2 or More Subjects in Any Treatment Group

	SoC in SoC-Controlled period	EvoMab + SoC in SoC-Controlled Period	
Preferred Term	EvoMab + SoC (N = 312) n (%)	EvoMab + SoC (N = 642) n (%)	Total (N = 954) n (%)
Number of subjects reporting serious adverse events	18 (5.8)	58 (9.0)	76 (8.0)
Non-Cardiac Chest Pain	0 (0.0)	4 (0.6)	4 (0.4)
Pneumonia	1 (0.3)	3 (0.5)	4 (0.4)
Angina Pectoris	0 (0.0)	3 (0.5)	3 (0.3)
Cardiac Failure	1 (0.3)	2 (0.3)	3 (0.3)
Chest Pain	1 (0.3)	2 (0.3)	3 (0.3)
Myocardial Infarction	0 (0.0)	3 (0.5)	3 (0.3)
Abdominal Pain	0 (0.0)	2 (0.3)	2 (0.2)
Angina Unstable	0 (0.0)	2 (0.3)	2 (0.2)
B-Cell Lymphoma	1 (0.3)	1 (0.2)	2 (0.2)
Bursitis Infective	0 (0.0)	2 (0.3)	2 (0.2)
Cerebrovascular Accident	1 (0.3)	1 (0.2)	2 (0.2)
Chronic Obstructive Pulmonary Disease	0 (0.0)	2 (0.3)	2 (0.2)
Inguinal Hernia	2 (0.6)	0 (0.0)	2 (0.2)
Nephrolithiasis	0 (0.0)	2 (0.3)	2 (0.2)
Pyelonephritis	0 (0.0)	2 (0.3)	2 (0.2)
Rib Fracture	1 (0.3)	1 (0.2)	2 (0.2)
Transient Ischaemic Attack	0 (0.0)	2 (0.3)	2 (0.2)
Wrist Fracture	1 (0.3)	1 (0.2)	2 (0.2)

N = number of subjects randomized and in the integrated extension all-IP period analysis set (IECAS); EvoMab = Evolocumab (AMG 145); SoC = Standard of Care; IP = investigational product.
Includes the following studies: 20110110, 20120138.
Coded using MedDRA version 17.0.

For the HoFH studies, there were no serious adverse events in part A or part B of study 20110233. Seven (7.3%) subjects reported a serious adverse event in study 20110271, of which six occurred after enrolment from the parent study (Table S11). Additionally, for the severe FH subjects, one subject (1.0%) a serious adverse event (uterine prolapse).

Table S11 Serious Adverse Events by Preferred Term in Descending Order of Frequency Study 20110271 (HoFH Interim Analysis Set)

	20110233 HoFH Parent Study Rollover			20110271 HoFH Non-Parent / Other Parent Study Rollover			
Preferred Term	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B Placebo (N = 16) n (%)	Apheresis at Enrollment (N = 31) n (%)	Non-apheresis at Enrollment (N = 11) n (%)	Total (N = 42) n (%)	Total (N = 96) n (%)
Number of subjects reporting treatment-emergent adverse	2 (25.0)	3 (10.0)	1 (6.3)	1 (3.2)	0 (0.0)	1 (2.4)	7 (7.3)

events							
Angina Pectoris	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Aortic Stenosis	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Aortic Valve Disease	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Chest Pain	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Coronary Artery Disease	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Coronary Artery Occlusion	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Haematuria	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	1 (2.4)	1 (1.0)
Non-Cardiac Chest Pain	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

N = number of HoFH subjects enrolled and dosed in Study 20110271; HoFH=Homozygous Familial Hypercholesterolemia; EvoMab=Evolocumab (AMG 145).
Data cutoff date 01APR2014.
Coded using MedDRA version 17.0.
Adverse event summaries do not include positively adjudicated clinical endpoints.

At the time of the MAA (data cutoff date 01 April 2014), 87 cardiovascular events were adjudicated in the completed primary hyperlipidaemia and mixed dyslipidaemia parent studies (N = 34) and in year 1 (N= 41) and year 2+ (N = 12) of the ongoing OLE Studies 20110110 and 20120138. From 01 April 2014 to 01 July 2014, an additional 16 positively adjudicated cardiovascular events occurred.

Table S12: Subject incidence of positively adjudicated cardiovascular events and noncoronary revascularizations

	Data cutoff date 01 April 2014		Data cutoff date 01 July 2014 (cumulative data since 01 April 2014)		
	Integrated Parent Studies[a] (placebo and active-controlled)		Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)		Year 2+ OLE Period (year 2+ of OSLER1 and OSLER2)
	Any Control (N = 2080) n (%)	Any EvoMab (N = 3946) n (%)	SoC (N = 1489) n (%)	EvoMab + SoC (N=2976) n (%)	EvoMab + SoC (N = 1675) n (%)
Number of subjects with any positively adjudicated clinical event (includes events recorded before or after study period)	9 (0.4)	25 (0.6)	26 (1.7)	26 (0.9)	17 (1.0)
Death	2 (0.1)	4 (0.1)	4 (0.3)	3 (0.1)	3 (0.2)
Cardiovascular	2 (0.1)	4 (0.1)	1 (0.1)	3 (0.1)	2 (0.1)
Non-cardiovascular	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	1 (0.1)
Undetermined	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Myocardial infarction (fatal and non-fatal)	2 (0.1)	8 (0.2)	5 (0.3)	8 (0.3)	3 (0.2)
Fatal	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal	1 (0.0)	8 (0.2)	5 (0.3)	8 (0.3)	3 (0.2)
Hospitalisation for unstable angina	0 (0.0)	2 (0.1)	2 (0.1)	3 (0.1)	1 (0.1)
Coronary Revascularisation	5 (0.2)	11 (0.3)	14 (0.9)	12 (0.4)	8 (0.5)
PCI	3 (0.1)	9 (0.2)	13 (0.9)	7 (0.2)	5 (0.3)
Surgical	2 (0.1)	2 (0.1)	1 (0.1)	5 (0.2)	3 (0.2)

	Data cutoff date 01 April 2014		Data cutoff date 01 July 2014 (cumulative data since 01 April 2014)		
	Integrated Parent Studies[a] (placebo and active-controlled)		Year 1 SoC-controlled Period[b] (year 1 of OSLER1 and OSLER2)		Year 2+ OLE Period (year 2+ of OSLER1 and OSLER2)
	Any Control (N = 2080) n (%)	Any EvoMab (N = 3946) n (%)	SoC (N = 1489) n (%)	EvoMab + SoC (N=2976) n (%)	EvoMab + SoC (N = 1675) n (%)
Cerebrovascular Event	3 (0.1)	5 (0.1)	7 (0.5)	3 (0.1)	5 (0.3)
Transient ischemic attack	0 (0.0)	2 (0.1)	5 (0.3)	1 (0.0)	2 (0.1)
Stroke (fatal and non-fatal)	3 (0.1)	3 (0.1)	2 (0.1)	2 (0.1)	3 (0.2)
Fatal	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischemic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischemic with hemorrhagic conversion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhagic stroke	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Type undetermined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal	2 (0.1)	3 (0.1)	2 (0.1)	2 (0.1)	3 (0.2)
Ischemic	2 (0.1)	3 (0.1)	0 (0.0)	1 (0.0)	2 (0.1)
Ischemic with hemorrhagic conversion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhagic stroke	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.0)	1 (0.1)
Type undetermined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart failure event	0 (0.0)	3 (0.1)	1 (0.1)	1 (0.0)	2 (0.1)
Heart failure hospitalisation	0 (0.0)	3 (0.1)	1 (0.1)	1 (0.0)	2 (0.1)
Urgent heart failure visit	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-coronary revascularisation	1 (0.0)	1 (0.0)	3 (0.2)	7 (0.2)	4 (0.2)
Percutaneous	0 (0.0)	1 (0.0)	2 (0.1)	3 (0.1)	3 (0.2)
Surgical	1 (0.0)	0 (0.0)	1 (0.1)	4 (0.1)	1 (0.1)

The data showed a reduction in the cumulative incidence and relative risk of all cause death, myocardial infarction, hospitalisation for unstable angina, coronary revascularisation, stroke or transient ischemic attack, or hospitalisation for heart failure with evolocumab, and excludes evidence of cardiovascular harm with an observed hazard ratio (95% CIs) of 0.50 (0.29, 0.86). The median exposure in this analysis was approximately 11 months and number of cardiovascular events was 52.

Deaths

Overall, 15 deaths were reported (n=12 in subjects who ever received evolocumab and n= 3 in subjects who received placebo and/or SoC). Six deaths occurred during the controlled blinded studies (n=4 (0.1%) for evolocumab and n=2 (0.1%) in SoC; 2 deaths occurred after the end of the parent study), 7 deaths occurred during the year 1 SoC controlled period (n=3 (0.1%) for evolocumab and n=4 (0.3%) in SoC), 2 deaths occurred during the year 2+ OLE period. All deaths were reviewed and adjudicated by the Clinical Endpoint Committee and as cardiovascular or non-cardiovascular deaths. A total of 11 deaths were deemed to be cardiovascular. Only 1 death in a 69 year old subject (11521012010 of Study 20120138) was reported by the investigator as related to IP. The investigator reported the cause as unknown, but presumed it to be myocardial infarction.

There were no deaths reported in the HoFH studies, including severe FH subjects.

Laboratory findings

Liver and renal function laboratory findings were balanced between treatment groups within the 3 analysis periods. Changes in HbA1c and fasting blood glucose in the integrated parent and the integrated extension studies were similar and were also comparable across treatment groups within the analysis periods. The incidence of potential hepatitis C was low in the year 1 SoC-controlled period (evolocumab plus SoC: 0%; SoC alone: 0.1%) and the year 2+ OLE period (0.1%). Of the 94 subjects identified at risk for HCV and tested for HCV antibody, 9 subjects had confirmed positive antibody tests. In those 9 subjects, LFTs were all < 2 x ULN. A total of 3 subjects had measurable HCV RNA on day 1 or subsequent visits: two of them transaminase levels remained < 2 x ULN; the third subject (10966402015) had mildly elevated LFTs from day 1. No HCV infection events were noted for any HoFH subject. Concentrations of overall vitamin E and vitamin E normalized to total cholesterol were evaluated in the long-term study (20110109), the phase 2 OLE study (20110110), and the phase 3 OLE study (20120138, only when UC LDL-C was < 25 mg/dL [< 0.6 mmol/L]). The serum total vitamin E decreased in the evolocumab group compared with control. This decrease in serum total vitamin E reflected the evolocumab-mediated decrease in total cholesterol, which is responsible for the transport of vitamin E. When serum total vitamin E was normalized by total cholesterol, the normalized serum total vitamin E was unchanged.

Safety in special populations

Table S13: Analyses of adverse events in the ≥ 65 years and ≥ 75 years subgroups

	≥ 65 Years Subgroup		≥ 75 Years Subgroup		Entire Integrated Population	
Controlled Blinded Studies						
N	EvoMab: 1193	Control: 586	EvoMab: 158	Control: 65	EvoMab: 3946	Control: 2080
Overall incidence of AEs in subgroup	619 (51.9%)	282 (48.1%)	69 (43.7%)	30 (46.2%)	2016 (51.1%)	1031 (49.6%)
Most common AEs with subject incidence (any EvoMab and any control)						
nasopharyngitis	5.7%	4.2%	5.1%	3.1%	5.9%	4.8%
myalgia	3.1%	2.4%			2.5%	2.6%
headache	3.1%	2.9%			3.0%	3.2%
fatigue			3.2%	1.5%		
hypertension			3.2%	1.5%		
arthralgia			3.2%	3.1%		
upper respiratory tract infection					3.2%	2.7%
back pain					3.0%	2.7%
	all others < 3% in any EvoMab group		all others < 3% in any EvoMab group			
Year 1 SoC-controlled Period						
N	EvoMab+SoC: 852	SoC alone: 449	EvoMab+SoC: 105	SoC alone: 58	EvoMab+SoC: 2833	SoC alone: 1419
Overall incidence	543 (63.7%)	260 (57.9%)	69 (65.7%)	36 (62.1%)	1708 (60.3%)	781 (55.0%)

	≥ 65 Years Subgroup		≥ 75 Years Subgroup		Entire Integrated Population	
of AEs in subgroup						
Most common AEs with subject incidence (EvoMab+SoC and SoC alone)						
nasopharyngitis	9.2%	7.8%	5.7%	3.4%	8.5%	7.9%
hypertension	4.1%	2.4%	4.8%	0%	3.1%	2.5%
arthralgia	3.5%	1.8%			3.4%	2.5%
osteoarthritis	3.2%	1.8%				
headache	3.1%	1.1%				
urinary tract infection			6.7%	5.2%		
fatigue			5.7%	1.7%		
bronchitis			4.8%	1.7%		
cough			3.8%	3.4%		
upper respiratory tract infection					4.2%	4.0%
back pain					3.1%	2.5%
	all others < 3% in EvoMab+SoC group		all others < 3% in any EvoMab+SoC group			
	≥ 65 Years Subgroup		≥ 75 Years Subgroup		Entire Integrated Population	
Year 2+ OLE Period						
N	Total: 258		Total: 23		Total: 954	
Overall subject incidence of AEs in subgroup (total)	Total: 192 (74.4%)		Total: 20 (87.0%)		Total: 713 (74.7%)	
Most common AEs with subject incidence						
back pain	7.4%				6.6%	
hypertension	5.4%					
cough	5.0%		13.0%			
oedema peripheral	3.9%		8.7%			
cystitis	3.5%		8.7%			
procedural pain	3.5%					
myalgia	3.5%					
pain in extremity	3.5%					
pneumonia	3.1%					
insomnia	3.1%		13.0%			
contusion			13.0%			
rhinitis			8.7%			
upper respiratory tract infection			8.7%		7.7%	
arthralgia			8.7%		6.7%	
dizziness			8.7%			
nausea			8.7%			
fall			8.7%			

	≥ 65 Years Subgroup	≥ 75 Years Subgroup	Entire Integrated Population
angina pectoris		8.7%	
sciatica		8.7%	
syncope		8.7%	
		all others < 2 subjects in total group	

Pediatric HoFH Subjects

A total of 14 adolescent subjects (≥ 12 to < 18 years), all of whom were HoFH, were enrolled into 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 enrolled into Study 20110271 as well.

Analyses of adverse events were performed according age ≥ 12 to < 18 years (**Table S14**) or ≥ 18 years. While the number of HoFH subjects precludes detailed analyses, the overall pattern of adverse events in HoFH adolescents is consistent with that seen in adult HoFH subjects and subjects with primary hyperlipidemia and mixed dyslipidemia. In the subgroup of adolescent subjects, adverse events were reported in 3 (42.9%) subjects in the evolocumab group and 2 (66.7%) subjects in the placebo group, and no preferred term was reported for > 1 adolescent subject in either treatment group.

Table S14 Analysis of Adverse Events for Subjects ≥ 12 Years to < 18 Years of Age study 20110233 Part B

	Placebo	EvoMab
SYSTEM ORGAN CLASS Preferred Term	QM (N = 3) n (%)	420 mg QM (N = 7) n (%)
Number of subjects reporting treatment emergent adverse events	2 (66.7)	3 (42.9)
GASTROINTESTINAL DISORDERS	1 (33.3)	1 (14.3)
Abdominal Pain	1 (33.3)	1 (14.3)
Nausea	1 (33.3)	0 (0.0)
GENERAL DISORDERS and ADMINISTRATION SITE CONDITIONS	1 (33.3)	0 (0.0)
Injection Site Pain	1 (33.3)	0 (0.0)
INFECTIONS and INFESTATIONS	0 (0.0)	3 (42.9)
Gastroenteritis	0 (0.0)	1 (14.3)
Influenza	0 (0.0)	1 (14.3)
Nasopharyngitis	0 (0.0)	1 (14.3)
Upper Respiratory Tract Infection	0 (0.0)	1 (14.3)
INVESTIGATIONS	1 (33.3)	0 (0.0)
Weight Decreased	1 (33.3)	0 (0.0)
MUSCULOSKELETAL and CONNECTIVE TISSUE DISORDERS	0 (0.0)	1 (14.3)
Tendonitis	0 (0.0)	1 (14.3)

SYSTEM ORGAN CLASS Preferred Term	Placebo QM (N = 3) n (%)	EvoMab 420 mg QM (N = 7) n (%)
REPRODUCTIVE SYSTEM and BREAST DISORDERS	1 (33.3)	0 (0.0)
Dysmenorrhoea	1 (33.3)	0 (0.0)
RESPIRATORY, THORACIC and MEDIASTINAL DISORDERS	0 (0.0)	1 (14.3)
Asthma	0 (0.0)	1 (14.3)

Table S15: Analysis of adverse events in the elderly

	≥ 65 Years Subgroup		≥ 75 Years Subgroup		Entire Integrated Population	
Controlled Blinded Studies						
N	EvoMab: 1193	Control: 586	EvoMab: 158	Control: 65	EvoMab: 3946	Control: 2080
Overall incidence of AEs in subgroup	619 (51.9%)	282 (48.1%)	69 (43.7%)	30 (46.2%)	2016 (51.1%)	1031 (49.6%)
Most common AEs with subject incidence (any EvoMab and any control)						
nasopharyngitis	5.7%	4.2%	5.1%	3.1%	5.9%	4.8%
myalgia	3.1%	2.4%			2.5%	2.6%
headache	3.1%	2.9%			3.0%	3.2%
fatigue			3.2%	1.5%		
hypertension			3.2%	1.5%		
arthralgia			3.2%	3.1%		
upper respiratory tract infection					3.2%	2.7%
back pain					3.0%	2.7%
	all others < 3% in any EvoMab group		all others < 3% in any EvoMab group			
Year 1 SoC-controlled Period						
N	EvoMab+SoC: 852	SoC alone: 449	EvoMab+SoC: 105	SoC alone: 58	EvoMab+SoC: 2833	SoC alone: 1419
Overall incidence of AEs in subgroup	543 (63.7%)	260 (57.9%)	69 (65.7%)	36 (62.1%)	1708 (60.3%)	781 (55.0%)
Most common AEs with subject incidence (EvoMab+SoC and SoC alone)						
nasopharyngitis	9.2%	7.8%	5.7%	3.4%	8.5%	7.9%
hypertension	4.1%	2.4%	4.8%	0%	3.1%	2.5%
arthralgia	3.5%	1.8%			3.4%	2.5%
osteoarthritis	3.2%	1.8%				
headache	3.1%	1.1%				
urinary tract infection			6.7%	5.2%		
fatigue			5.7%	1.7%		

bronchitis			4.8%	1.7%		
cough			3.8%	3.4%		
upper respiratory tract infection					4.2%	4.0%
back pain					3.1%	2.5%
	all others < 3% in EvoMab+SoC group		all others < 3% in any EvoMab+SoC group			
	≥ 65 Years Subgroup		≥ 75 Years Subgroup		Entire Integrated Population	
Year 2+ OLE Period						
N	Total: 258		Total: 23		Total: 954	
Overall subject incidence of AEs in subgroup (total)	Total: 192 (74.4%)		Total: 20 (87.0%)		Total: 713 (74.7%)	
Most common AEs with subject incidence						
back pain	7.4%				6.6%	
hypertension	5.4%					
cough	5.0%		13.0%			
oedema peripheral	3.9%		8.7%			
cystitis	3.5%		8.7%			
procedural pain	3.5%					
myalgia	3.5%					
pain in extremity	3.5%					
pneumonia	3.1%					
insomnia	3.1%		13.0%			
contusion			13.0%			
rhinitis			8.7%			
upper respiratory tract infection			8.7%		7.7%	
arthralgia			8.7%		6.7%	
dizziness			8.7%			
nausea			8.7%			
fall			8.7%			
angina pectoris			8.7%			
sciatica			8.7%			
syncope			8.7%			
			all others < 2 subjects in total group			

Immunological events

General findings

In the controlled blinded studies, adverse events for the Immune System Disorders system organ class were reported in 20 (0.5%) subjects in the any evolocumab group and 14 (0.7%) subjects in the any control group. The most common adverse events in the any evolocumab group and any control group were seasonal allergy (0.4% and 0.5%) and hypersensitivity (0.1% and 0.1%). In the year 1 SoC-controlled period, 31 (1.1%) subjects and 12 (0.8%) subjects reported an adverse event for the Immune System Disorders system organ class in the evolocumab plus SoC group and the SoC alone

group, respectively. The most common adverse events in the evolocumab plus SoC group and the SoC alone group were seasonal allergy (0.7% and 0.5%) and hypersensitivity (0.2% in both groups). In the year 2+ OLE period, 22 (2.3%) subjects reported an adverse event in this system organ class, and the most common adverse event was seasonal allergy (1.6%). For HoFH, no subjects in study 20110233 reported an adverse event in the Immune System Disorders system organ class In study 20110271, 1 (2.4%) HoFH subject (who did not participate in the 20110233 parent study) reported a non-serious adverse event of seasonal allergy in this system organ class.

Anti-evolocumab antibody formation

Across 6026 subjects of the evolocumab clinical program of primary hyperlipidemia and mixed, 15 subjects (from all subjects tested and including pre-existing antibodies) tested positive for binding antibodies (Table S16).

No HoFH subject (0 out of 80) developed anti-evolocumab antibodies after receiving at least 1 dose of evolocumab. Two HoFH subjects tested positive for pre-existing anti-evolocumab binding antibodies at baseline (prior to receiving evolocumab).

Based on a review of adverse events for the subjects with binding antibodies, there were no adverse events (ie, hypersensitivity) determined to be due to the presence of a binding antibody. No serious adverse events were temporally associated with a positive antibody result.

Table S16: Adverse events that correlate temporally with a positive binding antibody result

Study Period	Treatment	Visit Day	Additional Results	Reported AEs
Parent Study	EvoMab 420 mg QM	day 1	(parent) day 85 to (OLE) day 87 were negative	None
Parent Study	EvoMab 420 mg QM	day 87 day 253	(parent) day 365 (EOS visit) was negative	day 193 grade 1 folliculitis day 255 & 277 grade 1/2 influenza day 325 grade 1 back pain day 330 grade 1 sinusitis
Parent Study	EvoMab 420 mg QM	day 1	(parent) day 86 to (OLE) day 167 were negative	none
Parent Study	EvoMab 140 mg Q2W	day 1	(parent) day 88 was negative	day 53 grade 1 cystitis
Parent Study	EvoMab 420 mg QM	day 1 day 92	(parent) no further results after day 92	day 14 grade 1 rhinitis, grade 1 laryngitis
Parent Study	EvoMab 420 mg QM	day 1	(parent) day 85 was negative	day 35 grade 1 joint swelling that was resolved on day 85 without change of evolocumab dose
Parent Study	EvoMab 105 mg Q2W	day 29	(parent) day 99 to (OLE) day 364 were negative	day 26 grade 1 abdominal pain
Parent Study	Placebo SC QM	day 86	(OLE) day 28 to day 708 were negative	none
Parent Study	SoC only	day 29	(OLE) day 85 to day 350 were negative	none
Year 1 SoC-Controlled	SoC only	day 27	(OLE) day 84 to day 365 were negative	none
Year 1 SoC -Controlled	EvoMab + SOC	day 1	(OLE) day 85 was negative	none
Year 1 SoC -Controlled	EvoMab + SoC	day 36 day 85 day 337	(OLE) day 169 and day 253 negative	day 36 grade 1 contusion day 85 grade 2 worsening diabetes mellitus
Parent Study Year 1 SoC -Controlled	Placebo SC QM EvoMab + SoC	day 86 day 1	(OLE) day 29 and day 85 were negative	day 44 grade 1 myalgia
Year 1	EvoMab 140 mg	day 92	(OLE) day 85 and day162	day 75 grade 1 influenza

Study Period	Treatment	Visit Day	Additional Results	Reported AEs
SoC -Controlled	Q2W		were negative	day 77 grade 1 back pain day 85 grade 1 malaise
Parent Study	EvoMab 420 mg QM	day 183	(OLE) day 89, day 91 were negative	None

Safety related to drug-drug interactions and other interactions

No studies on potential drug-drug or drug-food interactions were conducted with evolocumab due to the fact that no PK drug-drug interactions are expected with evolocumab.

Discontinuation due to adverse events

In the controlled blinded period, adverse events leading to discontinuation of IP were reported in 75 (1.9%) subjects in the any evolocumab group and 48 (2.3%) subjects in the any control group. The only adverse events leading to discontinuation of IP (any evolocumab and any control groups, respectively) occurring in ⩾ 0.2% subjects in the any evolocumab group or the any control group were myalgia (0.3% and 0.5%), nausea (0.2% and 0.1%), and dizziness (0% and 0.2%). In the year 1 SoC-controlled period, 58 (2.0%) subjects in the evolocumab plus SoC group reported an adverse event leading to discontinuation. During this period, the only adverse events leading to discontinuation of IP occurring in ⩾ 0.2% subjects in the evolocumab plus SoC group was myalgia (0.2%). In the year 2+ OLE period, 10 (1.0%) subjects reported an adverse event leading to discontinuation of evolocumab, while no adverse events leading to discontinuation of IP occurred in ⩾ 0.2% subjects.

In the HoFH studies, 1 (2.4%) HoFH subject discontinued study treatment due to a grade 3 adverse event of rash.

2.6.1. Discussion on clinical safety

A substantial number of **6026 subjects were exposed** to any dose of evolocumab representing 5246 patient-years of exposure, with 3549 evolocumab dosed subjects for at least 6 months, 2458 for at least 12 months, and 1124 evolocumab for 2 years or more. This was mainly attributable to patients with primary hyperlipidaemia (heterozygous familial and non-familial) and mixed dyslipidemia. In terms of numbers this was sufficient according to guideline recommendations and considering that evolocumab may be used as a life-long treatment. In addition, sufficient number of patients treated with evolocumab (compared to subjects on placebo or standard of care) was evaluated to be able to identify evolocumab related safety effects, observed in the controlled pivotal studies and in 1 year controlled follow-up. However, safety data **in patients with HoFH** were far more limited due to the rarity of the condition, with 8 subjects with a mean exposure of 18 months, 33 patients included in the 12 weeks phase 3 study and 99 patients included in the still ongoing long term study. This resulted in 81 HoFH subjects who received evolocumab for at least 3 months and 56 HoFH subjects for at least 6 months.

Overall, evolocumab displays a **safety profile** similar to that of the control treated (51.1% vs 49.6%) groups. The most common adverse events were: nasopharyngitis, upper respiratory tract infection, headache and back pain, which occurred at approximately similar incidence in both evolocumab and control treatment groups (5.9% vs 4.8%, 3.2% vs 2.7%, 3.0% vs 3.2% and 3.0% vs 2.5% in the controlled studies, respectively). The frequency was only slightly different when separated according to placebo controlled data, evolocumab treatment on top of statins, or for statin-intolerant patients. Also, treatment related AEs in the “parent” studies were approximately similar. For the extension controlled period, the treatment related AEs were substantially higher for evolocumab vs control (n=283 (9.5%) vs 4 (0.3%)), however the CHMP agreed with the applicant that this could be exposure related, as the

subjects randomised to control did not receive evolocumab in the first year. **For HoFH patients**, an approximately similar safety profile was observed with nasopharyngitis, headache, and influenza being the most prominent adverse events observed. As expected in a population with very high cardiovascular risk, a high incidence of 4.2% of angina pectoris was reported. Incidence of adverse events in subjects on apheresis were comparable with subjects not on apheresis (76.5% vs 75%, respectively).

When considering longer treatment, overall frequency of adverse events increased slightly (51.1% for the controlled blinded studies, 60.3% during first year, and 74.7% during 2 years) with also a slightly higher incidence in the evolocumab group compared to the standard of care (60.3% vs 55.0% during first year). However, for the overall population, the annualized adverse event rate was comparable between the evolocumab and control groups in each period and the rates decreased over long-term treatment: integrated "parent" studies (any evolocumab: 90.8%; any control 89.7%), the year 1 standard of care-controlled period (evolocumab plus SoC: 77.6%; SoC alone: 71.6%), and the year 2+ open extension period (75.8%). The most common serious adverse events were myocardial infarction, angina pectoris, pneumonia, osteoarthritis, and non-cardiac chest pain.

Cardiovascular events and deaths were of major interest, as a harmful effect should at least be excluded prior to approval of medicinal products from the new pharmacological class according to the *EMA Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013)*. Overall the number of cardiovascular events was limited (n=103), although this was only slightly lower than the expected number of events to occur. A relative risk analysis based on the 1 year data of all cause death, myocardial infarction, hospitalisation for unstable angina, coronary revascularisation, stroke or transient ischemic attack, or hospitalisation for heart failure with evolocumab, excluded evidence of cardiovascular harm with an observed hazard ratio (95% CIs) of 0.50 (0.29, 0.86). Therefore, these limited data cannot identify any possible harmful effect of evolocumab with respect to cardiovascular events. There were 15 deaths reported with the data cut off of 1 April 2014, of which 12 in the evolocumab treated patients. This seemed imbalanced; however, evolocumab was randomized in a 2:1 ratio versus placebo. Furthermore, in the pivotal studies, the incidences of deaths were similar in the evolocumab group versus control (0.1% each), and in the 1 year data, less deaths in the evolocumab group (0.1%) versus SoC (0.3%) were observed. Also, exposure to evolocumab was longer due to the open-label 2 years extension. Moreover, from the detailed descriptions of each death case, one cannot exclude that the underlying condition may have importantly contributed to death. Therefore, overall the data were reassuring and did not indicate any higher incidence of death that could be attributed to evolocumab treatment, although no firm conclusions could be made due to the limited number of deaths observed and the lack of long-term experience.

Hardly any **discontinuations** during the studies were observed (1.9% vs 2.3% in the controlled blinded studies), with even more limited number of patients discontinuing due to adverse events (myalgia (0.3% and 0.5%), nausea (0.2% and 0.1%), and dizziness (0% and 0.2%), 2.0% during first year, and 1.0% (n=10) during 2 years).

Specific attention was given to safety of **different doses** proposed for registration. The incidence in adverse events in 420 mg QM dose group was slightly higher compared with 140 mg Q2W group however, a similar pattern was also observed in Q2W and QM placebo groups. This could be mainly attributed to the longer term DESCARTES study using only the 420 mg QM dose. The **prefilled autoinjector/pen (AI/pen) and prefilled syringe (PFS)** were proposed for approval within this MAA. In phase 2 studies most of the subjects received the investigational product (IP) via vial and syringe and in the phase 3 studies all subjects received IP via the AI/Pen (with the exception of the long term controlled DESCARTES study where subjects were exposed to the vial and syringe). A PK study showed that the 140 mg dose administered with the PFS was equivalent to evolocumab administered with the AI/pen from PK and clinical point of view. Device related adverse events were uncommon, mostly not severe, and generally limited to injection site reactions (injection site bruising, erythema and pain).

Of particular interest was whether patients achieving **very low levels of LDL-C** would display a different safety profile to patients with less low LDL-C levels achieved, in particular, as very low levels of LDL-C have been associated with increased risk of cancer, hemorrhagic stroke, non-cardiovascular death and neurocognitive abnormalities and could affect steroid production. Specific interest has been given to neurocognitive adverse events, vitamin E and steroid analytes in this respect. Overall, similar incidence of AEs was observed across each of the groups of subjects who achieved: LDL-C < 25mg/dL, LDL-C<40 mg/dL or LDL-C ≥ 40 mg/dL during the controlled blinded studies as well as during 1 year treatment period. However the incidence of AEs was slightly higher in subjects who achieved LDL-C < 25mg/dL and LDL-C<40 mg/dL (82.4% and 77.3%), compared to subjects who achieved LDL-C ≥ 40 mg/dL (74.5%) in the 2 years treatment period. Some differences were found in the type of most frequently observed adverse events within each group of LDL-C achieved level, however without any clear pattern. No safety signal was identified regarding vitamin E and steroid analytes and these remained within the normal levels. Several neurocognitive adverse events in the < 25mg/dL and < 40mg/dL patients were reported, all in the evolocumab treatment group. However, the data cannot be considered controlled, as hardly any patients in the control group achieved these LDL-C levels, and thus meaningful comparisons to the control groups could not be made.

Since evolocumab is a human monoclonal immunoglobulin, specific attention was given to anti-evolocumab antibodies. These were infrequent (n=15) and not associated with clinically relevant adverse events. In addition, no neutralizing antibodies were detected in any subject.

Specific attention was given to musculoskeletal and connective tissue disorders, hepatic disorders, renal disorders, and diabetes, as these are known to be associated with treatment with several lipid lowering agents. Evolocumab treatment did not show any effect on **musculoskeletal disorders**. A slightly higher incidences of musculoskeletal and connective tissue disorders was observed and was increasing over time (evolocumab vs control 14.7% vs 13.7% in controlled blinded studies, 19.1% vs 15.2% in 1 year and 28.1% in 2 years). From the 51 subjects with CK elevation > 5x ULN and 613 subjects with a muscle related adverse event, 6 subjects had both a muscle adverse event and an elevated CK. Four of these 6 subjects were on evolocumab treatment (2 myalgias, 1 muscle spasms and 1 myositis) and 2 were on standard of care (2 muscle spasms). However, no clear pattern could be identified among the type of adverse events observed. Moreover, such events could also likely to be related to the background statin therapy. Serious events related to musculoskeletal and connective tissue disorders were uncommon. In addition, no safety signal concerning creatine kinase has been identified in the HoFH subjects. No clear effect was observed with evolocumab concerning **hepatic disorders or liver function tests**, with a low and comparable incidence versus control: 0.9% vs 0.8% in controlled blinded studies, 1.1% vs 1.2% during 1 year and 1.4% during 2 years. Also, a specific phase 1 study in subjects with mild or moderate hepatic impairment did not indicate any issues related to PK, PD, safety, and tolerability of evolocumab, as expected, as evolocumab is not metabolised by the liver. Overall, any evolocumab effect on **renal disorders** was limited with low and comparable to control adverse effects, which can be expected since evolocumab is not cleared by the kidneys. Some higher incidences for evolocumab were found in statin intolerant and diabetes patients; however, these could be confounded or explained by baseline differences. No effect on the incidence of **diabetes** or HbA1C was observed with evolocumab or in patients with diabetes or metabolic syndrome. Also no patterns indicative of clinically important treatment related laboratory abnormalities in vitamin E, and steroid analytes were observed.

Changes from baseline for systolic and diastolic blood pressure and heart rate did not reveal clinically important differences among treatment groups.

Safety according to age was also assessed, displaying more adverse events for longer term in the >75 years age group in comparison to the overall population, although the numbers were small which made firm conclusion difficult.

The diagnosis of HeFH did not affect the safety profile of evolocumab.

There is limited amount of data from the use of evolocumab in pregnant women and in women who are breast-feeding. As a result, as proposed by the applicant in the SmPC, evolocumab should not be used during pregnancy or during breast-feeding.

Assessment of paediatric data on clinical safety

Fourteen adolescent patients were included in the studies of whom 8 patients were HoFH patients. A similar safety profile was observed in these patients, although number of patients was limited. To be more specific, adverse events were reported in 3 (42.9%) subjects in the evolocumab group and 2 (66.7%) subjects in the placebo group, and no preferred term was reported for > 1 adolescent subject in either treatment group.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Evolocumab displayed an acceptable safety profile comparable to that of the comparator therapy (placebo or standard of care), with very limited patients discontinuing treatment or showing serious adverse events. Any signs of a harmful effect on cardiovascular morbidity or mortality could not be clearly identified, while data on this were limited and were agreed to be provided in the post-authorisation phase. Safety in patients achieving very low LDL-C levels, mainly focused on neurocognitive adverse events, vitamin E and steroid analytes and was similar to patients who did not achieve very low LDL-C levels. Any antibody formation was very rare and not of any concern. Any substantial effects on known safety issues identified with known lipid lowering therapy such as liver disorders, renal disorders, diabetes and musculoskeletal disorders were not observed with evolocumab treatment. A limited number of adolescents was included in the study and displayed a similar safety profile. Similarly, HoFH patients also displayed a similar safety profile, although data were far more limited. Slightly more adverse events was observed in elderly patients (>75 age) although data was limited. Any safety differences between the Q2W and QM dosing were considered to be only marginal.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

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

The PRAC considered that the Risk Management Plan version 1.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

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-Pugh class C) use in patients with hepatitis-C use in patients with type 1 diabetes use in patients with HIV long-term use including effects of LDL-C < 40mg/dL (< 1.03 mmol/L)

LDL-C = low density lipoprotein-C

Pharmacovigilance plan

Study/Activity Title and category (1 - 3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20110271 Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of Evolocumab (AMG 145) on LDL-C in Subjects with Severe Familial Hypercholesterolaemia (including HoFH) Category 3	• To characterize the safety and tolerability of long-term administration of evolocumab among subjects with severe familial hypercholesterolaemia (including HoFH) • To characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C and non-HDL-C, Lp(a), ApoB, total cholesterol/HDL-C ratio, ApoB/ ApoA1 ratio, and response of LDL-C reduction (15% or greater) in subjects with severe familial hypercholesterolaemia (including HoFH)	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Ongoing	Q4 2020
20120138 A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of Evolocumab (AMG 145) Category 3	• To characterize the safety and tolerability of long-term administration of evolocumab • To characterize efficacy of long-term administration of evolocumab as assessed by LDL-C in subjects with primary hyperlipidaemia and subjects with mixed dyslipidaemia	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Ongoing	Q4 2018

Study/Activity Title and category (1 - 3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20120153 A Double-blind, Randomized, Multi-center, Placebo-controlled, Parallel Group Study to Determine the Effects of Evolocumab (AMG 145) Treatment on Atherosclerotic Disease Burden As Measured By Intravascular Ultrasound in Subjects Undergoing Coronary Catheterization Category 3	• To evaluate the effect of evolocumab on the change in burden of coronary atherosclerosis as measured by percent atheroma volume in subjects with coronary artery disease requiring angiography for a clinical indication who are taking statins. • To evaluate the effect of evolocumab on the change in normalized total atheroma volume and the percentage of subjects who demonstrate regression of coronary atherosclerosis.	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Ongoing	Q1 2017
20120332 A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Evolocumab (AMG 145), Compared With Ezetimibe, in Hypercholesterolaemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects (Part C only) Category 3	• To evaluate the long-term safety and efficacy of AMG 145 in statin-intolerant subjects (Part C).	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Ongoing	Part C: Q2 2018

Study/Activity Title and category (1 - 3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20130385 A Double-blind, Placebo controlled, Multicenter Study to Assess the Effect of Evolocumab on Cognitive Function in Patients with Clinically Evident Cardiovascular Disease and Receiving Statin Background Lipid Lowering Therapy: A Study for Subjects Enrolled in the FOURIER (Study 20110118) Trial Category 3	• To evaluate change over time in executive function, as assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) strategy index of executive function, in subjects receiving statin therapy in combination with evolocumab, compared with subjects receiving statin therapy in combination with placebo.	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Ongoing	No later than Q2 2018[a]
20150162 A Multi-national Observational Study to Evaluate the Safety of Repatha® in Pregnancy Category 3	• To evaluate outcomes of pregnancy in females diagnosed with FH, exposed to Repatha® during pregnancy.	Use in pregnant women	Study initiation Q2 2016	Periodic updates with each PSUR Feasibility Report: Q3 2019 Final Report: Q2 2027

Study/Activity Title and category (1 - 3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20130295 A Multicenter, Open-label Extension Study to Assess Long-Term Safety and Efficacy of Evolocumab Therapy in Patients with Clinically Evident Cardiovascular Disease (FOURIER-OLE) Category 3	• To characterize the safety and tolerability of extended long-term administration of evolocumab in subjects having received evolocumab or placebo in the completed FOURIER trial	Long term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Study initiation Q3 2017	Q2 2023
20130286 A Double Blind, Randomized, Placebo Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab in HIV Positive Patients with Hyperlipidemia and Mixed Dyslipidemia Category 3	• Evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in HIV positive subjects with hyperlipidemia or mixed dyslipidemia	Use in patients with HIV	Study initiation Q3 2016	Q3 2019

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks: not applicable		
Important Potential Risks		
Hypersensitivity	SmPC: • Section 4.3, Contraindications • Section 4.8, Undesirable effects PIL: What you need to know before you use evolocumab	None
Immunogenicity	SmPC: • Section 4.8, Undesirable effects	None
Missing Information		
Use in pregnant/lactating women	SmPC: • 4.6 Fertility, pregnancy and lactation PIL: • Pregnancy and breastfeeding	None
Use in paediatric patients	SmPC: • Section 4.2, Posology and method of administration (Special Populations: Paediatric Population) PIL: • Children and adolescents	None
Use in elderly patients ≥ 75 years old	SmPC: • Section 4.2, Posology and method of administration (Special Populations: Elderly Population) • Section 4.8, Undesirable effects.	None
Use in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2)	SmPC: • Section 4.2, Posology and method of administration (Special Populations: Renal Impairment Population) • Section 4.4, Special Warnings and Precautions for Use.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Missing Information		
Use in patients with severe hepatic impairment (Child-Pugh class C)	SmPC: • Section 4.2, Posology and method of administration (Special Populations: Hepatic Impairment Population) • Section 4.4, Special Warnings and Precautions for Use.	None
Use in patients with Hepatitis-C	None	
Use in patients with type 1 diabetes	None	
Use in patients with HIV	None	
Long-term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	SmPC: • Section 5.1, Pharmacodynamic Properties	None

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Evolocumab is a first in class fully human monoclonal immunoglobulin G2 directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9), which inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. This leads to LDL-C reduction. The pharmacokinetics of evolocumab is similar to other human monoclonal antibodies. At low concentrations the elimination is target mediated by PCSK9 and at higher concentration by non-specific processes. The proposed indication for evolocumab includes patients with hypercholesterolaemia and mixed dyslipidaemia, and patients with homozygous familial hypercholesterolemia (HoFH), including treatment of adolescents.

Benefits

Beneficial effects

Hypercholesterolaemia and mixed dyslipidaemia

Evolocumab demonstrated a substantial reduction of 60-70% versus placebo or on top of statins (including maximal doses of atorvastatin and rosuvastatin) and of approximately 40% versus ezetimibe in the co-primary endpoints of: "mean percent **change in LDL-C** at weeks 10 and 12" and "the percent change in LDL-C at week 12" in patients with baseline LDL-C levels between 2.8-5.0 mmol/L. Efficacy was supported by significant and beneficial changes in **other parameters of the cholesterol profile**, i.e. triglycerides (- 15-20%), HDL-C (+ 6-8%) and also ApoB, total cholesterol/HDL-C ratio, total cholesterol, non-HDL-C, and ApoB/ApoA1 ratio, Lp(a), and VLDL-C (with no significant reductions in TG and VLDL-C vs ezetimibe). This efficacy in terms of reduction of LDL-C and other lipid parameters was **consistent across the phase 2** (n=1359) **and phase 3** studies (n=3146) (phase 3: LAPLACE-2, RUTHERFORD-2, GAUSS-2, and MENDEL-2) including high CV risk patients (47% across the different studies), heterozygous familial hypercholesterolaemia (HeFH) patients (n=331 in phase 3), and statin intolerant patients (n=307 in phase 3).

The criteria applied to identify **statin intolerant patients** in GAUSS-2 study were rigorous as patients had to have tried at least 2 statins and be unable to tolerate statins based on adverse events which resolved or improved when statin dose was decreased or discontinued. A consistent effect on LDL-C reduction (of 38-39%) has been demonstrated versus ezetimibe therapy in these patients.

Efficacy was found to be similar for the intended doses of 140 mg Q2W and 420 mg QM dose. The LDL-C effect of evolocumab was **consistent in all subgroups**, i.e. race, ethnicity, age, gender, region, glucose tolerance status, CV risk, statin intensity at baseline, and HDL-C. A comparable efficacy was found when the medicinal product was administered with different devices of automated mini-doser (AMD), prefilled syringe (PFS), prefilled autoinjector/pen (AI/pen) in a home setting as separately analysed in two small studies (THOMAS-1 and THOMAS-2).

A sustained effect of LDL-C reduction has been demonstrated up to 52-68 weeks in the **ongoing long term studies** [OSLER-1, OSLER-2, DESCARTES (completed)] including patients from the controlled blinded studies but also unique patients, with 1 year of controlled data. For the **severe FH population**, a reduction of approximately 40% in LDL-C was sustained during 48 weeks of treatment in the interim analysis.

Homozygous familial hypercholesterolemia (HoFH) population

Evolocumab demonstrated an overall significant **LDL-C reduction** of 15-32% on top of standard of care in the co-primary endpoint of LDL-C reduction after 12 weeks or the mean of 10 to 12 weeks compared to standard of care in patients with baseline LDL-C levels of 8.3-11.4 mmol/L. The efficacy was supported by improvement in **other lipid parameters** (total cholesterol, ApoB, non-HDL-C, total cholesterol/HDL-C, and ApoB/ApoA1). The LDL-C reduction was **sustained** during 28 weeks of treatment for both patients on apheresis and not on apheresis, with evolocumab being slightly less effective in apheresis patients. The limited number of **14 adolescent** HoFH subjects (age 12 to< 18 years) showed similar reductions in LDL-C (-21.5%) and changes in other lipid parameters compared with adult patients. Patients up titrated to the Q2W 420 mg dose demonstrated an additional decrease in lipid parameters compared to the QM dose (approximately 5%).

Uncertainty in the knowledge about the beneficial effects

Hypercholesterolaemia and mixed dyslipidemia

Efficacy has been demonstrated based on the reduction in LDL-C level, an **established surrogate** marker for CV disease but the **outcome data were not available**. The number of cardiac events was very low and no meta-analytic approach could be used to analyse the data in terms of CV outcome.

Although similar efficacy of evolocumab was demonstrated in **patients over 75 years** of age, patients in this subgroup were underrepresented.

HoFH population

Efficacy data in the HoFH patients was based on only **96 patients** included in the long term study, which may be considered limited, however, HoFH patients are rare. Also in this population, hard clinical **outcome data are missing**. The applicant distinguishes between patients with a defective LDL receptor and patients with a negative or undetermined LDL-R receptor for HoFH. It was confirmed that for patients with undetermined or negative LDLR some efficacy could be observed, although **less than for patients with defective LDLR**, since evolocumab has its mechanism of action through the LDLR receptor.

Risks

Unfavourable effects

Hypercholesterolaemia and mixed dyslipidemia

Sufficient number of patients was evaluated for safety according to *ICH guideline on the extent of population* ***exposure to assess clinical safety*** *for drugs intended for long-term treatment of non-life-threatening conditions (ICH E1)*, including 6026 evolocumab dosed subjects for at least 6 months, 2458 for at least 12 months, and 1124 evolocumab for 2 years or more. These were mainly patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

Evolocumab displayed a **safety profile approximately similar to that of the control**, (i.e. placebo, ezetimibe, or maximum statin therapy with or without ezetimibe). The incidence of AEs reported in the controlled blinded studies was 51.1% and 49.6% in the evolocumab and control treated group, respectively. Also, treatment related AEs in the “parent” studies were approximately similar. For the extension controlled period, the treatment related AEs were substantially higher for evolocumab vs control (n=283 (9.5%) vs 4 (0.3%)), however it was agreed with the applicant that this could be exposure related, as the subjects randomised to control did not receive evolocumab in the first year.The most common adverse events were nasopharyngitis, upper respiratory tract infection, headache and back pain, which occurred at approximately similar incidence in both evolocumab and control treatment groups (5.9% vs 4.8%, 3.2% vs 2.7%, 3.0% vs 3.2% and 3.0% vs 2.5%, respectively). The frequency of adverse events was only slightly different when separated according to the different therapeutic settings, *i.e.* placebo controlled data, evolocumab treatment on top of statins, or for statin-intolerant patients. In statin intolerant patients, type and incidence of adverse events were comparable between evolocumab and control groups, with even slightly higher incidence of myalgia in control group patients during the controlled blinded period. The safety profile in severe HeFH patients is similar as for the whole population investigated.

Evolocumab was well tolerated with very low number of **discontinuations** during the studies (1.9% in evolocumab vs 2.3% in controls in the controlled blinded studies). Even less patients discontinued due to adverse events (1.8%). This included myalgia (0.3% and 0.5%), nausea (0.2% and 0.1%), and dizziness (0% and 0.2%). An incidence of discontinuations of 2.0% and 1.0% during the first and 2 years of treatment were reported, respectively.

A slightly higher **incidence in adverse events in 420 mg QM** (54.0%) compared with 140 mg Q2W (43.6%) of evolocumab was found; a pattern also observed in QM and Q2W dosing in placebo groups (54.6% and 41.0%). This was mainly attributed to the long term DESCARTES study where only the 420 mg QM dose was used.

No safety signal was identified regarding changes from baseline for **systolic and diastolic blood pressure and heart rate** did not reveal clinically important differences among treatment groups.

Overall, a similar incidence of AEs was found across each of the subgroups of subjects who achieved very low levels of LDL-C (LDL-C < 25mg/dL, LDL-C<40 mg/dL) compared to the groups with normal levels (LDL-C ≥ 40 mg/dL) during the controlled blinded studies as well as during the 1 year treatment period. However, this was slightly higher (82.4% and 77.3% compared to 74.5%) in the 2 years treatment period. The incidence of **neurocognitive adverse event, vitamin E and steroid analytes** was consistent across patients reaching very low LDL-C levels (LDL-C < 25mg/dL, LDL-C<40 mg/dL) compared to normal levels (LDL-C ≥ 40 mg/dL), with vitamin E and steroid analytes remaining within normal levels.

Evolocumab treatment was not associated with any apparent **musculoskeletal AEs,** adverse events known to be associated with existing lipid lowering therapies. Although, a slightly higher incidences of musculoskeletal and connective tissue disorders were observed over time (evolocumab vs control 14.7% vs 13.7% in the controlled blinded studies, 19.1% vs 15.2% in 1 year and 28.1% in 2 years), no clear pattern could be identified among the type of adverse events observed in the different safety analysis sets and events were also likely to be related to the background statin therapy and heavy physical activity. In addition, the incidence of CK elevation was comparable across the different treatment groups within the controlled blinded period and the 1 year treatment period. Serious events related to musculoskeletal and connective tissue disorders were uncommon.

Specific attention has also been given to **hepatic disorders** as such adverse events were also associated with the existing lipid lowering therapies. The incidence of hepatic disorders observed during the treatment with evolocumab was low and comparable with control patients (0.9% vs 0.8% in the controlled blinded studies, 1.1% vs 1.2% during 1 year and 1.4% during 2 years). A specific phase 1 study in subjects with mild or moderate hepatic impairment did not indicate any safety issues, which was expected as evolocumab is not metabolized by the liver.

No effect on **incidence of diabetes or HbA1C**, suggested to be associated with statin therapy, was found for evolocumab. Also, no patterns indicate clinically important treatment related laboratory abnormalities in vitamin E, and steroid analytes.

Since evolocumab is a human monoclonal immunoglobulin, specific attention was paid to the possibility of developing **anti-evolocumab antibodies**. The number of patient who developed anti-evolocumab antibodies was low (n=15) and his finding was not associated with clinically relevant adverse events. In addition, no neutralizing antibodies have been detected in any subject.

Device related adverse events were uncommon, mostly not severe, and generally limited to injection site reactions (injection site: bruising, erythema and pain).

HoFH patients

An approximately **similar safety profile** compared to primary hyperlipidemia and mixed dyslipidemia studies was observed in HoFH subjects with nasopharyngitis, headache, and influenza being the most prominent adverse events observed. A similar safety profile as for adults was observed for the fourteen **adolescent patients** of whom 10 patients were included in the controlled 12 week HoFH study. Adverse events were reported in 3 (42.9%) HoFH subjects in the evolocumab group and 2 (66.7%) in the placebo group.

Uncertainty in the knowledge about the unfavourable effects

The number of cardiovascular events was 103 in 6026 patients, which was considered relatively low, but only slightly lower as compared to what may be expected. In the pivotal studies, a slightly higher

percentage of subjects had positively adjudicated cardiovascular events of death (CV or non CV), MI, UA, and coronary revascularisation in the evolocumab group (25, 0.6%) compared with control (9, 0.4%), while in the year 1 controlled data this was 22[0.8%] versus 19[1.3%]. A relative risk analysis based on the 1 year data of these (extended) MACE events with evolocumab excludes evidence of cardiovascular harm with an observed hazard ratio (95% CIs) of 0.50 (0.29, 0.86).

During the clinical development program, 15 deaths have been reported (with a cutoff date of 1 April 2014), of which 12 were reported in the evolocumab treated patients. This seemed imbalanced, however, evolocumab was randomized in a ratio 2:1 versus placebo. Furthermore, in the pivotal studies, the incidence of death was similar in the evolocumab group versus control group (0.1% each), and in the 1 year data less deaths in the evolocumab group (0.1%) versus standard of care (0.3%) were observed. Also, exposure to evolocumab was longer due to the open-label 2 years extension. Moreover, from the detailed descriptions of each death case, it appeared that the underlying condition may have importantly contributed to death. Therefore, overall data were reassuring and did not indicate a higher incidence of death that could be attributed to evolocumab treatment.

Although, any evolocumab effect on **renal function** was considered limited and comparable to the renal adverse effects in the control group, a higher incidence in proteinuria in statin intolerant and diabetes subjects was noticed, however, it was agreed that these could be confounded or clarified by baseline differences.

More adverse events were observed in the long term treatment of **patients above 75 years** of age (not for the controlled blinded data) in comparison to the overall population, although the numbers were small (n=23) which made firm conclusion difficult.

Benefit-risk balance

Importance of favourable and unfavourable effects

Evolocumab has demonstrated a substantial and consistent reduction in LDL-C and other lipid parameters alone and on top of existing therapy options including statins and ezetimibe in several groups of patients with hypercholesterolaemia and mixed dyslipidaemia and in patients with homozygous familial hypercholesterolemia. These were considered to be clinically relevant effects as reduction in the LDL-cholesterol is an important surrogate marker with potential benefits in terms of cardiovascular outcome. MACE analyses did not indicate any trend towards cardiovascular harm. However, the actual impact of the long-term lipid reduction with evolocumab in terms of improved cardiovascular outcome was still missing and need to be addressed in the post-authorisation phase.

Regarding safety, evolocumab displayed an acceptable safety profile with a comparable or slightly higher incidence of adverse events to that of the comparator therapy (placebo or standard of care), with very limited patients discontinuing treatment or showing serious adverse events. In addition, evolocumab treatment did not cause any major effects on known safety problems associated with existing lipid lowering therapies such as liver disorders, renal disorders, diabetes and musculoskeletal disorders.

The long term studies provided data indicating maintenance of efficacy and safety, although the period was considered limited taking into account that intended evolocumab treatment could be lifelong. Cardiovascular events have been reported, but did not give rise to specific concern but also did not allow for any conclusions due to the limited numbers and limited duration of treatment.

The method of administration of evolocumab (injections) did not give a rise to any safety issue and could be done in a home setting. A comparable efficacy was found across different devices, including the prefilled syringe (PFS) and prefilled autoinjector/pen (AI/pen) in a home setting, of which the autoinjector was largely been used in the phase 3 studies.

Benefit-risk balance

Evolocumab demonstrated a consistent and substantial beneficial effect on LDL-C in several patient's groups (including patients at low cardiovascular risk, patients on maximum statin therapy, patients intolerant to statins and heterozygous familial hypercholesterolemia [HeFH] patients) with hypercholesterolaemia and mixed dyslipidemia, as well as for homozygous familial hypercholesterolemia (HoFH) patients on top of currently available therapies for LDL-C reduction. Evolocumab administered every 2 weeks or every month has an acceptable safety profile and is well tolerated, which is considered important for an intended life-long treatment. Thus, the benefit/risk balance is considered positive regarding the LDL-C lowering effect. However, duration of treatment was still limited and further data to be provided post-authorisation are considered necessary to assess long term safety and the occurrence of unexpected events. One major uncertainty remained on whether the substantial LDL-C reduction translates into cardiovascular mortality/morbidity benefit. An outcome study to address this issue post-authorisation is already ongoing.

Discussion on the benefit-risk balance

The applicant conducted studies in patients in need for further LDL-C reduction based on their increased cardiovascular risk profile including patients on maximum statin therapy, patients intolerant for statins and HeFH/HoFH patients. Most of these patients have been well characterised. In particular, patients with statin intolerance were well defined. Across the different studies efficacy was found to be similar for the proposed doses of 140 mg Q2W and 420 mg QM.

The increased cardiovascular risk was considered obvious in HeFH and HoFH patients due to the highly elevated LDL-C levels from early age that remained elevated throughout their lifetime even with aggressive available lipid lowering therapy. These patients are difficult to treat and available treatment options are limited (in particular for HoFH). They often require apheresis that is available in some specialised clinics only, time consuming and burdensome to the patient. Therefore, there was still an unmet medical need in these types of patients from an early age, which justifies that some adolescent patients were included in the current clinical development program.

Also, for the limited number of HoFH patients investigated, evolocumab showed a consistent reduction in lipid levels, although less than in the population of patients with hypercholesterolaemia and mixed dyslipidemia, but still significantly beyond what could be achieved with current lipid lowering therapy options. This was also found in the 14 adolescent HoFH patients with a similar safety profile as in adults, justifying the approval of indication in these patients.

Generally, included patients achieved LDL-C levels close to the recommended in the European clinical practice guideline (*2011 ESC/EAS Guideline for the management of dyslipidaemias)* and sometimes even lower. There is an ongoing discussion in the clinical community regarding the optimal treatment target and the concept of "the lower, the better". In general, the opinion is shifting in the direction of treating patients to LDL-C levels as low as possible (*2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults*), but the question of whether a so-called J-shaped curve may exist remained open. Clearly, with evolocumab very low levels of LDL-C (<40 mg/L) could be achieved in some patients. Although data did not indicate a higher incidence of adverse events compared to LDL-C ≥ 40 mg/dL in the 2 years treatment period, more data need to be collected on this important issue, in particular from the ongoing CV outcome study. This is also reflected in the agreed version of the RMP. In the past, with statins, concerns were raised of assumed increased risk when cholesterol would be lowered too much, including an increased risk for cancer, hemorrhagic stroke, non-cardiovascular death, neurocognitive abnormalities and alterations in steroid production, but these concerns have never been confirmed.

As already concluded above, with regards to the safety profile of evolocumab, the CHMP did not identify any substantial safety issues and the incidence of adverse events in evolocumab-treated patients as compared to different background therapies was similar or slightly increased. Adverse events specifically known to be associated with existing lipid lowering therapy, including muscle related events, hepatic events, renal events and diabetes risk, have been closely monitored throughout the evolocumab development program, and did mostly not give rise to specific concerns. These issues certainly need to be investigated further in the post-authorisation programme as agreed within the RMP.

Finally, an important limitation of the dossier is the lack of cardiovascular outcome data. Although reduction in LDL-C was considered to be a strong surrogate for cardiovascular risk reduction, this was mainly based on outcome data obtained with statins. The results of the recent IMPROVE-IT trial (with ezetimibe, a lipid lowering agent different from statins) strengthen the value of LDL-C as a surrogate marker. Still the value of the LDL-C in terms of CV outcomes will need further confirmation with evolocumab and other novel therapies. The limited data that are currently available, are reassuring, but do not exclude long-term harm in this respect. The cardiovascular outcome trial (FOURIER study) is already ongoing and the final results are expected in 2017. Given new mechanism of action of evolocumab and the lack of long-term experience the use of evolocumab was restricted to second line therapy in patients not sufficiently controlled by a maximum tolerated dose of a statin or who are intolerant to statins. The indication included both groups of patients: with hypercholesterolemia and with mixed hyperlipidemia (including patients with diabetes mellitus), as both may be at increased cardiovascular risk and in need for further lowering of (LDL-)cholesterol as also specified by the current clinical practice guidelines. For homozygous familial hypercholesterolemia patients a CV outcome study was considered not feasible due to the limited number of patients available, but reassurance on the surrogate effect could be extrapolated from the clinical event data of the aforementioned FOURIER study.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Repatha in the following indication is favourable:

Hypercholesterolaemia and mixed dyslipidaemia

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

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

Homozygous familial hypercholesterolaemia

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

The effect of Repatha on cardiovascular morbidity and mortality has not yet been determined. And therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that evolocumab is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (Decision P/0127/2013) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.