EMA/CHMP/572365/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of variations including an extension of indication assessment report

Procedure No. EMEA/H/C/003766/II/0049/G

Invented name: Repatha

International non-proprietary name: evolocumab

Marketing authorisation holder (MAH): Amgen Europe B.V.

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List of abbreviations

Abbreviation or Term	Definition/Explanation
ACC	American College of Cardiology
ADHD	attention deficit hyperactivity disorder
AHA	American Heart Association
AI/pen	autoinjector/pen
AMD	automated mini-doser
AMQ	Amgen MedDRA query
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
BLA	Biologics License Application
CAD	coronary artery disease
CEC	clinical events committee
CHD	coronary heart disease
cIMT	carotid intima-media thickness
CTCAE	Common Terminology Criteria for Adverse Events
CTTC	Cholesterol Treatment Trialists' Collaboration
CVD	cardiovascular disease
EAS	European Atherosclerosis Society
EOS	end-of-study
ESC	European Society of Cardiology
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
FOURIER	Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER)
GVP	Good Pharmacovigilance Practices
HAS	HoFH analysis set
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
hsCRP	high-sensitivity C-reactive protein
iPSP	initial Pediatric Study Plan
LCCA	left common carotid artery

Abbreviation or Term	Definition/Explanation
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LS	least squares
MAA	marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
OLE	open-label extension
PCSK9	proprotein convertase subtilisin/kexin type 9
PIP	Paediatric Investigation Plan
PMR	post-marketing requirement
Q2W	every 2 weeks
QM	once monthly
RCCA	right common carotid artery
RMP	Risk Management Plan
SAP	statistical analysis plan
SC	subcutaneous
SMQ	standard MedDRA query
TIA	transient ischemic attack
UC	ultracentrifugation
URTI	upper respiratory tract infection
US	United States of America
USPI	United States Prescribing Information

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 2 February 2021 an application for a group of variations.

The following variations were requested in the group:

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

C.I.6 (EoI)
Extension of indication to include one new pediatric indication in pediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia as an adjunct to diet, alone or in combination with other lipid-lowering therapy, to reduce LDL-C based on results of study 20120123 (HAUSER-RCT) and of study 20120124 (HAUSER-OLE). It is a randomized, multicenter, placebo-controlled, double-blind, parallel-group, 24 week trial in 158 pediatric patients aged 10 to > 18 years with heterozygous familial hypercholesterolaemia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.0 of the RMP has also been submitted.

C.I.6 (EoI)
Extension of indications to modify the existing indication for treatment of adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies based on interim results from study 20120124 (HAUSER-OLE). It was an open-label, single-arm, multicenter, 80 week trial to evaluate the safety, tolerability and efficacy of Repatha for LDL-C reduction in pediatric patients from aged ≥ 10 to < 18 years of age with homozygous familial hypercholesterolaemia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0105/2018 on the agreement of a paediatric investigation plan (PIP).

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alar Irs

Timetable	Actual dates
Submission date	02 February 2021
Start of procedure:	15 March 2021
CHMP Rapporteur Assessment Report	21 May 2021
CHMP Co-Rapporteur Assessment Report	26 May 2021
PRAC Rapporteur Assessment Report	26 May 2021
PRAC Outcome	10 June 2021
CHMP members comments	15 June 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 June 2021
Request for supplementary information (RSI)	24 June 2021
CHMP Rapporteur Assessment Report	15 September 2021
PRAC Rapporteur Assessment Report	17 September 2021
PRAC Outcome	30 September 2021
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	7 October 2021
Opinion	14 October 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Familial hyperlipidemia is a genetic disorder characterized by elevated serum lipid concentrations. Among the conditions that comprise familial hyperlipidemia, familial hypercholesterolemia (FH) is a more common form of inherited hypercholesterolemia characterized by elevated serum low-density lipoprotein cholesterol (LDL C) and the development of premature cardiovascular disease (CVD).

The study of FH has provided a strong basis of support for the primary role of LDL C in the development of CVD (Rader et al., 2003). The overwhelming majority of culprit mutations manifesting in a diagnosis of FH exist within the low-density lipoprotein receptor (LDLR) (Abifadel et al., 2003; Rader et al., 2003; Goldstein et al., 2001), although contributions from the genes for apolipoprotein B (ApoB) and for proprotein convertase subtilisin/kexin type 9 (PCSK9) have been described.

State the claimed the therapeutic indication

In the current group of variations, a modified indication is proposed by the Applicant to include one new pediatric indication in pediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia based on results of study 20120123 (HAUSER-RCT) and to modify the existing indication for treatment of adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia based on interim results from study 20120124 (HAUSER-OLE).

The **claimed indication** that is now under assessment reads as follows (in bold underlined the proposed extension of the indication):

Hypercholesterolaemia and mixed dyslipidaemia

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

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

Heterozygous familial hypercholesterolaemia

Repatha is indicated in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia as an adjunct to diet, alone or in combination with other lipid-lowering therapy, to reduce LDL-C.

Homozygous familial hypercholesterolaemia

*Repatha is indicated in adults and ~~**adolescents**~~ **paediatric patients** aged ~~**12**~~ **10** years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.*

Established atherosclerotic cardiovascular disease

Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

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

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

In the first assessment round, the CHMP concluded that the wording of the indication should be adjusted, i.e. to combine the adult and the pediatric HeFH populations under the heading "*Hypercholestesrolaemia and mixed dyslipidaemia*", which is in line with other approved lipid-lowering therapies (e.g. Crestor and Lipitor). In the response, the Applicant has adjusted the wording of the indication in accordance with the comments.

The **approved indication** reads as follows (in bold underlined the proposed extension of the indication):

Hypercholesterolaemia and mixed dyslipidaemia

*Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia**, and in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolemia**, as an adjunct to diet:*

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

Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and ~~adolescents~~ paediatric patients aged ~~12~~ 10 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Established atherosclerotic cardiovascular disease

Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

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

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

Epidemiology and biologic features

The true prevalence of FH has recently been estimated as being higher than what has been traditionally thought (up to 1 in 200), but in most countries, it is estimated that fewer than 1% of individuals with FH are diagnosed (Nordestgaard et al., 2013; Marks et al., 2003).

Heterozygous FH (HeFH) accounts for the large majority of FH overall, and is estimated to occur in 1:250 individuals globally (Hu et al., 2020; Wiegman et al., 2015). Untreated LDL-C levels in affected individuals are significantly elevated (270.7 ± 7.7 mg/dL [7.0 ± 0.2 mmol/L]) compared with controls (100.5 ± 3.9 mg/dL [2.6 ± 0.1 mmol/L]) (Raal et al., 2013), and in spite of aggressive statin use, there is still a 2-fold excess of coronary heart disease (CHD) related deaths relative to age-matched controls within this population (Neil et al., 2008).

By comparison, the prevalence of homozygous FH (HoFH) is approximately 1:1,000,000 individuals, and untreated LDL-C levels are 518.2 ± 27.1 mg/dL (13.4 ± 0.7 mmol/L) (Raal et al., 2013). The incidence of major cardiovascular illness among homozygous individuals is even higher than that of HeFH individuals, with events such as myocardial infarction occurring by the second decade of life (Goldstein et al., 2001).

Clinical presentation, diagnosis and stage/prognosis

Familial hypercholesterolemia is associated with increased cardiovascular risk and manifests with premature atherosclerotic cardiovascular morbidity and mortality. Among children with FH, even those who do not have clinically overt presentations have identifiable subclinical manifestations of premature atherosclerotic vascular disease (Kusters et al., 2014; Masoura et al., 2011; Awan et al., 2008; Gidding et al., 1998). It is increasingly recognized that exposure to elevated LDL-C early in life is responsible and that interventions that lower LDL-C can favourably impact the natural history of FH (Wiegman et al., 2015). As such, it is imperative that pediatric subjects with HeFH and HoFH receive early and highly effective intervention to lower LDL-C and improve clinical outcomes later in life.

Management

Statins are currently the standard of care for primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia and have been shown to reduce LDL-C (30% to 40% with standard doses [Grundy et al., 2004]) and cardiovascular events. All statins share a final common pharmacodynamic pathway via competitive inhibition of 3-hydroxy-3-methylglutaryl (HMG) CoA reductase; therefore, these drugs lower intrahepatic cholesterol synthesis, leading to upregulation of LDLR expression with a subsequent reduction in LDL C. Statins also lead to upregulation of PCSK9 expression, potentially explaining diminished LDL-C reduction with higher doses and favoring a synergistic role with PCSK9 (Dubuc et al, 2004).

Non-statin treatment options, including ezetimibe, bile acid sequestering agents (resins), and plant stanols, also lower LDL C, with reductions on the order of 10% to 20% (Rosenson and Underberg, 2013; Zetia® Package Insert, 2013; Laitinen and Gylling, 2012). Often, these secondary treatment options are prescribed in combination with statins to better control LDL C (Agency for Healthcare Research and Quality, 2009).

Some patients, especially those with high LDL-C, are unable to achieve recommended LDL C levels. Not surprisingly, many patients with FH cannot achieve recommended goals despite using maximum doses of statin in combination with ezetimibe, further emphasizing the need for additional treatment options (Pijlman et al, 2010).

2.1.2. About the product

Evolocumab (REPATHA, formerly known as AMG 145) is a fully human monoclonal immunoglobulin G2 (IgG2) that binds specifically to proprotein convertase subtilisin/kexin type 9 (PCSK9), preventing its

interaction with the low-density lipoprotein receptor (LDLR). The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and decreased circulating concentrations of low-density lipoprotein cholesterol (LDL-C).

Evolocumab was approved in the EU on 17 July 2015. In the initial submission, evolocumab has demonstrated a substantial and consistent reduction in LDL-C (a surrogate biomarker for cardiovascular risk reduction) and other lipid parameters alone and on top of existing lipid-lowering therapy (LLT) options including statins and ezetimibe in several groups of patients with hypercholesterolaemia and mixed dyslipidaemia and in patients with homozygous familial hypercholesterolemia. Based on these observations, evolocumab was indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia and in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia. At the time of the initial MA, a statement was included in Section 4.1 of the EU SmPC that the effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined, as the outcome study: 20110118 was ongoing. In 2018, the MAH submitted the results of Study 20110118 (FOURIER study) to extend the indication with the reduction in risk of cardiovascular events in adults with established cardiovascular disease (CVD), in fulfilment of post-authorisation measure MEA 004 (EMEA/H/C/3766/II/017/G).

The **current approved** indication reads as follows:

Hypercholesterolaemia and mixed dyslipidaemia

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

Homozygous familial hypercholesterolaemia

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

Established atherosclerotic cardiovascular disease

Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:
- *in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*

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

Pediatric clinical development plan

An indication for the treatment of elevated cholesterol in pediatric and adult patients with HoFH was approved as part of the original marketing application for Repatha based on Study 20110233 (TESLA) and interim data from Study 20110271 (TAUSSIG).

In Europe, the evolocumab Paediatric Investigation Plan (PIP), initially agreed on 28 May 2013 prior to the original marketing authorisation application (MAA), included 2 clinical measures, pediatric Studies

20120123 (HAUSESR) and 20120124 (HAUSER-OLE), which are the focus of this submission. Similarly, pediatric Studies 20120123 and 20120124, were included and approved in the United States (US) initial Pediatric Study Plan (iPSP) issued on 16 September 2014 and subsequently included as post-marketing requirements (PMR) in the original Biologics License Application (BLA) approval letter issued by FDA on 27 August 2015. These studies focused on expanding the evaluation of evolocumab in children to include pediatric patients with HeFH, another serious genetic lipid disorder placing these young patients at very high risk for CVD, as well as expanding the age range for the approved pediatric HoFH indication to include pediatric patients 10 years and older.

The rationale for including pediatric patients aged 10 years and older in these studies was based on US and European Union (EU) guidelines which recommend pharmacologic treatment for pediatric patients ≥ 10 years of age with elevated LDL-C. Pediatric guidelines in the United States (Daniels and Greer, 2008; McCrindle et al, 2007; Kavey et al., 2006) recommend considering pharmacologic treatment after initial treatment with lifestyle modification has failed in patients ≥ 10 years of age with LDL-C that is:

- ≥ 130 mg/dL (3.4 mmol/L) for the highest risk (e.g., diabetes mellitus)
- ≥ 160 mg/dL (4.1 mmol/L) for intermediate risk (eg, ≥ 2 other CHD risk factors, family history of premature coronary artery disease [CAD])
- ≥ 190 mg/dL (4.9 mmol/L) for the lowest risk (no cardiovascular risk factors)

Similarly, treatment guidelines from the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) (Reiner et al., 2011) and from the National Institute for Health and Clinical Excellence (National Collaborating Centre, 2008) recommend statin treatment in patients who are ≥ 10 years of age and have HeFH or HoFH, and consider pharmacologic treatment for subjects with HoFH at earlier ages (Reiner et al., 2011).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek scientific advice from the EMA.

2.1.4. General comments on compliance with GCP

The comprehensive clinical, nonclinical, and quality program for evolocumab was designed in consideration of the applicable guidance with regard to study design, report preparation, assessment of safety and efficacy, selection of endpoints, and statistical principles. Study 20120123, Study 20120124, and Study 20110271 were conducted in accordance with International Council for Harmonisation Good Clinical Practice and FDA guidances/regulations.

2.2. Clinical aspects

2.2.1. Introduction

GCP

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

The MAH 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.

- Tabular overview of clinical studies

A tabular summary of the studies supporting each indication are presented in the table below.

Table 1. Summary Table of clinical studies contributing to efficacy and safety (generated by assessor)

Study ID	Study Design	Study Population	Primary Endpoint	Dosing
20120123 (completed)	Phase 3, double-blind, randomized, PBO-controlled	Subjects with HeFH On a stable low-fat diet and stable, lipid-lowering therapies at least 4 weeks prior to screening with fasting LDL-C ≥ 130 mg/dL (3.4 mmol/L) Age 10 to 17 years	Percent change from baseline to week 24 in LDL-C	PBO or EvoMab 420 mg SC QM AI/pen
20120124 (ongoing)	Phase 3, open-label extension (80 weeks)	Subjects with HeFH who completed Study 20120123 (and did not experience a treatment - related serious adverse event), or genetic or clinical diagnosis of HoFH. For HoFH, on a stable low-fat diet and stable, lipid-lowering therapies at least 4 weeks prior to screening with LDL-C ≥ 130 mg/dL (3.4 mmol/L) Age 10 to 17 years	Treatment emergent adverse events	PBO or EvoMab 420 mg SC QM AI/pen or AMD
20110271 (completed)	Phase 2/3, open-label, long-term (~5 years)	Completion of a qualifying EvoMab protocol without treatment related SAE that led to investigational product discontinuation and have a diagnosis of HoFH or severe FH (ie, all those not meeting the protocol criteria for HoFH). 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	Treatment emergent adverse events	EvoMab 420 mg SC QM or 420 SC Q2W (if eligible) vial and syringe, AI/pen, or AMD

2.2.2. Pharmacokinetics

The pharmacokinetics of unbound serum evolocumab relevant to the populations supporting this submission are summarized in Section 2.2.2.1. and 2.2.2.2. (Initial Marketing Application) and Section 2.2.2.1. and 2.2.2.4. (this variation, Study 20120123, Study 20120124, and Study 20110271).

2.2.2.1. Summary of pharmacokinetics in primary hyperlipidaemia or mixed dyslipidaemia vs. HeFH - Initial marketing application

In the phase 3 studies provided during the initial MAA, unbound serum evolocumab at week 12 was comparable between patients with HeFH (Study 20110117) and patients with primary hyperlipidaemia and mixed dyslipidaemia when evolocumab 140 mg SC Q2W (**Table 2**) or evolocumab 420 mg SC QM was administered with a statin (Study 20110115) (**Table 3**). 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. 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

In comparing the pharmacokinetics of evolocumab in phase 3 studies with and without background statin therapy, unbound evolocumab trough serum concentrations at week 12 with 140 mg SC Q2W dosing (**Table 2**) and 420 mg SC QM dosing (Table 3) were overlapping between evolocumab monotherapy (Study 20110114) and evolocumab treatment with a statin (Study 20110115), with 55% and 41% lower concentrations, respectively, in patients who were treated with concomitant statins (**Table 2**). However, mean values of unbound serum evolocumab with monotherapy were within the range of values for subjects treated with concomitant statins.

Statins have been shown to increase unbound PCSK9 serum concentrations in patients with primary hyperlipidaemia and mixed dyslipidaemia. Higher unbound PCSK9 serum concentrations would be expected to bind more evolocumab, thereby reducing the serum concentration of unbound evolocumab. Thus, the observed reduction of unbound evolocumab serum concentrations among subjects who received evolocumab treatment with a statin compared with evolocumab monotherapy is consistent with the known effects of statins on unbound PCSK9.

Collectively, these results indicated that HeFH and statin background therapy do not have a clinically meaningful effect on the pharmacokinetic profile of evolocumab at either of the proposed paediatric dosing regimens for HeFH (i.e., 140 mg Q2W or 420 mg QM). While background statin therapy did reduce unbound evolocumab serum concentrations compared with evolocumab monotherapy, values were overlapping and mean values of unbound serum evolocumab with monotherapy were within the range of values for subjects treated with concomitant statins.

Table 2. Unbound evolocumab serum concentrations (μg/mL) at week 12: evolocumab 140 mg SC Q2W without a statin in patients with primary hyperlipidaemia and mixed dyslipidaemia (Study 20110114), with a statin in patients with primary hyperlipidaemia and mixed dyslipidaemia (Study 20110115), or heterozygous familial hypercholesterolemia (HeFH, Study 20110117)

	Primary Hyperlipidemia or Mixed Dyslipidaemia Monotherapy (Study 20110114)	Primary Hyperlipidemia or Mixed Dyslipidaemia with a statin (Study 20110115)	HeFH (Study 20110117)
N	112	513	101
Mean	12.0	5.37	5.57
SD	10.1	5.66	7.46
Min	0.00	0.00	0.00
Median	9.97	3.52	3.50
Max	59.8	46.5	56.8
%CV	84.4	105.3	133.8

- %CV = coefficient of variation; max = maximum; min = minimum; Q2W = once every 2 weeks; SC = subcutaneously; SD = standard deviation.

Table 3. Unbound evolocumab serum concentrations (μg/mL) at week 12: evolocumab 420 mg SC QM without a statin in patients with primary hyperlipidaemia and mixed dyslipidaemia (Study 20110114), with a statin in patients with primary hyperlipidaemia and mixed dyslipidaemia (Study 20110115) or heterozygous familial hypercholesterolemia (HeFH, Study 20110117)

	Primary Hyperlipidemia or Mixed Dyslipidaemia Monotherapy (Study 20110114)	Primary Hyperlipidemia or Mixed Dyslipidaemia with a statin (Study 20110115)	HeFH (Study 20110117)
N	133	482	105
Mean	16.4	9.68	8.50
SD	12.6	9.20	7.17
Min	0.866	0.00	0.00
Median	13.1	6.84	6.65
Max	60.8	70.2	37.3
%CV	76.8	95.0	84.3

• %CV = coefficient of variation; max = maximum; min = minimum; QM = once monthly (every 4 weeks); SC = subcutaneously; SD = standard deviation.

2.2.2.2. Summary of pharmacokinetics of primary hyperlipidaemia or mixed dyslipidaemia vs. HoFH - Initial Marketing Application

Mean unbound evolocumab trough serum concentrations at week 12 of evolocumab 420 mg SC QM treatment were comparable between patients with HoFH not on apheresis and patients with primary hyperlipidaemia and mixed dyslipidaemia (**Table 4**).

Furthermore, among 9 paediatric patients aged 13 to < 18 years with HoFH in Study 20110271 who were not on apheresis and had received evolocumab 420 mg SC QM as of the 01 April 2014 interim data cut-off date, unbound evolocumab trough serum concentrations at week 12 ranged from 8.6 to 46.9 μg/mL. These values were within the range of unbound evolocumab concentrations in Study 20110115 in adults with primary hyperlipidaemia and mixed dyslipidaemia on background statin therapy. Collectively, these results indicate that relative to primary hyperlipidaemia and mixed dyslipidaemia, HoFH in adult or paediatric patients does not have a clinically meaningful effect on the pharmacokinetic profile of evolocumab.

More recent data available from the final analysis of Study 20110271 are consistent with these findings. In the final analysis of non-apheresis subjects with HoFH, mean (SD) unbound evolocumab serum concentrations at open-label extension weeks 4, 8, and 12 (ie, *trough* concentrations) were 8.6 (6.7), 12.7 (10.8), and 13.1 (10.8) μg/mL, respectively. Mean (SD) unbound evolocumab serum concentrations in these same subjects at weeks 2, 6, and 10 (ie, *peak* concentrations) were 37.1 (14.9), 34.9 (19.4), and 54.3 (18.4) μg/mL, respectively.

Table 4. Unbound evolocumab serum concentrations (μg/mL) at week 12: evolocumab 420 mg SC QM with a statin (Studies 20110115, 20110233, and 20110271)

	Primary Hyperlipidemia or Mixed Dyslipidaemia (Study 20110115)	HoFH (Study 20110233)	HoFH (Study 20110271)[a]
N	482	30	45
Mean	9.68	10.9	13.1
SD	9.20	7.02	11.5
Min	0.00	0.00	0.00
Median	6.84	10.8	10.4
Max	70.2	32.6	47.9
%CV	95.0	64.5	87.4

- %CV = coefficient of variation; max = maximum; min = minimum; QM = once monthly (every 4 weeks); SC = subcutaneously; SD = standard deviation.
- [a] Interim Analysis Set, data cut-off 01 April 2014; subjects not receiving apheresis.

2.2.2.3. Summary of pharmacokinetics in paediatric HeFH - Study 20120123 and Study 20120124

In Study 20120123, following SC administration of 420 mg evolocumab QM, mean (SD) serum concentrations of evolocumab in paediatric subjects with HeFH were 22.4 (14.7) μg/mL, 64.9 (34.4) μg/mL and 25.8 (19.2) μg/mL over the week 12, week 22, and week 24 time points, respectively, where week 12 and week 24 represent the end of the dosing interval (trough) and week 22 represents the middle of the dosing interval (peak) (**Table 5**).

Table 5. Descriptive statistics of serum evolocumab concentration (ng/mL) after SC administration of 420 mg QM evolocumab to paediatric subjects 10 to 17 years of age with HeFH. Week 12 and week 24:trough, week 22 peak (Study 20120123)

Descriptive Statistics	Study Visit		
	Week 12	Week 22	Week 24
N	99	81	96
Mean	22400	64900	25800
SD	14700	34400	19200
Min	0.00	6230	1440
Median	20600	65100	22100
Max	78100	143000	112000
CV%	65	53	74

QM = once monthly

For paediatric HeFH subjects from Study 20120123 who chose to roll over into Study 20120124, serum evolocumab concentrations remain consistent with those observed in the parent study.
Pharmacokinetic results showed that trough mean (SD) serum evolocumab concentration values in these subjects were 28.9 (21.1) μg/mL and 24.0 (21.6) μg/mL at week 12 and week 80, respectively, of this open-label extension study (**Table 6**).

Table 6. Descriptive statistics of serum evolocumab concentration (ng/mL) after SC administration of 420 mg QM evolocumab to paediatric subjects 10 to 17 years of age with HeFH or HoFH (Study 20120124)

	Heterozygous Familial Hypercholesterolemia (HeFH)		Homozygous Familial Hypercholesterolemia (HoFH)	
Descriptive Statistics	Week 12	Week 80	Week 12	Week 80
N	148	99	12	10
Mean	28 900	24 000	20 300	17 600
SD	21 100	21 600	14 600	28 600
Min	0.00	0.00	3 530	0.00
Median	24 900	20 300	16 600	9 870
Max	107 000	98 500	46 600	97 900
CV%	73	90	72	163

CV = coefficient of variation

Mean serum evolocumab values after 420 mg SC QM dosing in paediatric HeFH subjects in double-blind, placebo-controlled Study 20120123 and open-label extension Study 20120124 were within the range of those observed in adult subjects with primary hyperlipidaemia and mixed dyslipidaemia in Study 20110115 and adult HeFH subjects in Study 20110117 (in Section 2.2.2.1.) These results indicate that, relative to primary hyperlipidaemia and mixed dyslipidaemia and HeFH in adults, HeFH in paediatric patients does not have a clinically meaningful effect on the pharmacokinetic profile of evolocumab.

2.2.2.4. Summary of pharmacokinetics in paediatric HoFH - Study 20120124 and Study 20110271

For de novo paediatric HoFH subjects in open-label Study 20120124, pharmacokinetic analyses showed mean (SD) trough serum evolocumab concentrations after 420 mg QM dosing were 20.3 (14.6) μg/mL and 17.6 (28.6) μg/mL at week 12 and week 80, respectively (Table 6). These values were similar to those observed for all non-apheresis subjects in Study 20110271 who initiated treatment with evolocumab at 420 mg QM; mean (SD) unbound evolocumab serum concentrations at open-label extension weeks 4, 8, and 12 (ie, trough concentrations) were 8.6 (6.7), 12.7 (10.8), and 13.1 (10.8) μg/mL, respectively (Section 2.2.2.2.). Mean (SD) trough serum evolocumab concentrations at week 12, after 420 mg QM dosing in the 10 paediatric non-apheresis subjects in Study 20110271, were 20.9 (15.3) μg/mL with values ranging from 2.1 to 47.9 μg/mL.

Therefore, mean serum evolocumab concentrations for paediatric subjects in both Study 20120124 and Study 20110271 were within the range observed for all subjects with HoFH in Study 20110271 as well as within the range of values observed for subjects with primary hyperlipidaemia and mixed dyslipidaemia in Study 20110115 and HeFH subjects in Study 20110117 (Section 2.2.2.1.).

These results indicate that HoFH in paediatric subjects does not have a clinically meaningful effect on the pharmacokinetic profile of evolocumab.

2.2.3. Discussion on clinical pharmacology

The clinical program to evaluate the clinical pharmacology of evolocumab was described in the original evolocumab application and included data on unbound serum evolocumab concentrations from subjects with primary hyperlipidaemia and mixed dyslipidaemia (with evolocumab as both monotherapy or in combination with statins), adult subjects with HeFH, and paediatric and adult subjects with HoFH. Analyses presented in the initial evolocumab marketing application showed that patients with HeFH had unbound serum evolocumab concentrations following treatment comparable to patients with

primary hyperlipidaemia and mixed dyslipidaemia taking background statins and patients with primary hyperlipidaemia and mixed dyslipidaemia treated with evolocumab monotherapy. Analyses also showed that, relative to primary hyperlipidaemia and mixed dyslipidaemia, HoFH did not have a clinically meaningful effect on the pharmacokinetic and pharmacodynamic profiles for unbound evolocumab and unbound PCSK9. Furthermore, mean trough serum evolocumab concentrations at week 12 in paediatric patients with HoFH who were not on apheresis were within the range of those for adults with primary hyperlipidaemia and mixed dyslipidaemia. Collectively, at time of the initial MAA, it was concluded that these results indicate that relative to primary hyperlipidaemia and mixed dyslipidaemia, HeFH and HoFH in adult or paediatric patients do not have a clinically meaningful effect on the pharmacokinetic profile of evolocumab.

Study 20120123 and Study 20120124, provided in support of the new indication in paediatric HeFH patients, used the approved 420 mg QM dosing regimen administered in previous studies of evolocumab in adult subjects with primary hyperlipidaemia and mixed dyslipidaemia, adults with HeFH, and in non-apheresis paediatric and adult subjects with HoFH. Mean serum evolocumab values in paediatric HeFH and HoFH subjects in Study 20120123 and Study 20120124 were within the range of values observed in adult subjects with primary hyperlipidaemia or mixed dyslipidaemia, including HeFH, and within the range of values observed in non-apheresis paediatric subjects with HoFH presented in the initial marketing application.

2.2.4. Conclusions on clinical pharmacology

The PK results provided in this application demonstrate that the PK of evolocumab following a dose of 420 mg QM in paediatric HeFH and HoFH patients aged 10-17 years is similar to the PK in adult HeFH patients and HoFH patient aged 12 years and older. Considering the dose-linear PK as demonstrated in the initial MAA, it is expected that this will also hold for the 140 mg Q2W and the 420 mg SC Q2W dose regimens. Therefore, the PK data provided are in support of the currently proposed dosing regimens for paediatric patients with HeFH aged 10-17 years, being the same as that currently approved for adult patients with HeFH as well as the proposed dosing regimens for paediatric patients with HoFH aged 10-17 years, being the same as that currently approved for adult patients and paediatric patients aged 12-17 years with HoFH.

2.3. Clinical efficacy

2.3.1. Dose response study(ies)

No dose response studies were submitted.

Data relevant to approved dosing from initial evolocumab marketing application

Analyses presented in the initial evolocumab MAA showed that:

- The 140 mg Q2W and 420 mg QM dosing regimens were clinically equivalent as determined by a comparison between the dosing regimens for safety, tolerability, and efficacy.

- Patients with HeFH and patients with primary hyperlipidemia and mixed dyslipidemia had comparable pharmacokinetic profiles. Thus, the doses of 140 mg Q2W and 420 mg QM are also approved in patients with HeFH.

- Relative to primary hyperlipidemia and mixed dyslipidemia, HoFH did not have a clinically meaningful effect on the pharmacokinetic and pharmacodynamic profiles for unbound evolocumab and unbound PCSK9.

- Mean trough serum evolocumab concentrations at week 12 in adolescent patients with HoFH who were not on apheresis were within the range of those for adults with primary hyperlipidemia and mixed dyslipidemia.

-Both the 420 mg QM and 420 mg Q2W dosing regimens of evolocumab were appropriate for use in patients with HoFH. Given the very high baseline PCSK9 levels, severely elevated cholesterol concentrations (despite maximal statin background therapy in a large proportion of subjects), and genetic mutations restricting or ablating the function of the LDLR in patients with HoFH, the highest dose tested in phase 1 and 2 clinical studies of evolocumab (420 mg SC QM) was chosen as the dose for the population of non-apheresis HoFH subjects entering Study 20110233 and the starting dose for this patient population in Study 20110271. However, in recognizing that patients with HoFH may require additional PCSK9 suppression, 420 mg SC Q2W dosing was also evaluated in Study 20110271.

Data relevant to proposed dosing recommendation in pediatric HeFH and HoFH

Pharmacokinetic data from the 2 studies with evolocumab that included adults as well as pediatric subjects age 12 years and older (Studies 20110233 and 20110271) showed that exposure among pediatric subjects is comparable to that seen in adults of similar weight. Further pharmacokinetic modelling to predict the optimal dosing regimen for pediatric subjects 10 to 17 years of age showed that the exposure with monthly administration of 420 mg evolocumab SC in these subjects is expected to fall within the range observed for other studies in the evolocumab development program.

Pharmacokinetic data from Study 20120123 and Study 20120124 confirm that mean evolocumab exposure among pediatric subjects with HeFH and HoFH was within the range of values observed in adult patients with primary hypercholesterolemia or mixed dyslipidemia, including HeFH and within the range of values observed in non-apheresis pediatric subjects with HoFH in Study 20110271 presented in the initial marketing application. Subjects in Study 20120123 randomized to the evolocumab group and all subjects in Study 20120124 received 420 mg QM dosing with evolocumab which is an approved dose per the product labeling. This dose was administered in previous studies of evolocumab in primary hyperlipidemia or mixed dyslipidemia, including adult subjects with HeFH, and in non-apheresis pediatric and adult subjects with HoFH. Pharmacokinetic results in adults and adolescent subjects with HoFH from the final analysis of Study 20110271 are consistent with those provided for this study in the initial marketing application.

Collectively, these results indicate that relative to primary hyperlipidemia and mixed dyslipidemia, HeFH, HoFH, and age do not have a clinically meaningful effect on the pharmacokinetic profile of evolocumab.

As a result, there are no proposed changes to the currently approved evolocumab dosing regimens for each indication in the product labeling:

- The proposed dosing regimens for pediatric patients with HeFH are the same as those currently approved for adult patients with HeFH, ie, 140 mg SC Q2W or 420 mg SC QM.
- The proposed dosing regimens for pediatric patients with HoFH remain the same as those currently approved for pediatric and adult patients with HoFH, 420 mg SC QM and 420 mg SC Q2W (where approved).

The 140 mg subcutaneously (SC) Q2W and 420 mg SC QM regimens are currently approved for adult patients with HeFH; both doses are clinically equivalent. The 420 mg SC QM and 420 mg SC Q2W regimens are currently approved for adults patients and adolescents aged 12 years and over with HoFH. Based on PK data in the initial MAA, the approved 420 QM regimen has been selected for the studies 20120123 and 20120124, which evaluated the efficacy and safety of evolocumab in patients from 10 to < 18 years of age with HeFH or HoFH.

Pharmacokinetic data from Study 20120123 and Study 20120124 confirmed that mean serum evolocumab values of the 420 mg QM regimen in pediatric HeFH and HoFH subjects aged 10-17 years were within the range of values observed in adults with HeFH and non-apheresis pediatric subjects with HoFH presented in the initial marketing application. Additionally, efficacy and safety results of the 420 mg QM regimen observed in these studies were consistent with those found in previous clinical studies in the evolocumab clinical program (see efficacy and safety section). Therefore, no changes to the approved evolocumab dosing regimens were proposed for the populations of pediatric HeFH subjects aged 10-≤17 years and the HoFH subjects aged 10-≤11 years. However, in Study 20120123 and 20120124, only the 420 mg QM regimen has been evaluated, whereas in addition to this regimen also the 140 mg Q2W regimen in pediatric HeFH subjects aged 10-17 years and the 420 mg Q2W regimen in pediatric HoFH subjects 10-11 years are currently proposed (same as those currently stated in the labelling for the approved HoFH and HeFH populations). As such, the efficacy and safety of the 140 mg Q2W dose regimen for pediatric HeFH patients aged 10-≤17 years and the 420 mg Q2W dose regimen for pediatric HoFH patients aged 10-≤11 years have not been evaluated.

PK data have adequately shown that the PK is dose-linear and that relative to primary hyperlipidaemia and mixed dyslipidemia, HeFH, HoFH and age do not have a clinically meaningful effect on the pharmacokinetic profile of evolocumab. As such, the 140 mg Q2W regimen, which is considered clinically equivalent to the 420 mg SC QM regimen proposed for pediatric HeFH patients aged 10-≤17 years, is considered acceptable. However, the 420 mg Q2W regimen proposed for HoFH subjects 10-≤11 years of age concerns a 2-fold higher dose than the 420 mg QM for which the efficacy and safety in the proposed population of pediatric HoFH patients aged 10-11 years is currently unknown. Despite similar PK across different types of FH and age categories, the safety profile of the 420 mg Q2W in the pediatric patients with HoFH aged 10-≤11 years can differ compared to the adult population and the older pediatric HoFH population of 12-≤17 years for which this dose regimen is currently already approved. The efficacy and safety of the 420 mg Q2W dose (together with the 420 mg QM) have only been evaluated in the adult subjects with HoFH or severe FH and in the older pediatric HoFH population of 12-≤17 years in Study 20110271. In this study, dose frequency changes (420 mg QM vs 420 mg Q2W) were permitted if a clinically meaningful response is not achieved. The titration analysis set (TAS), defined as the subset of subjects who were exposed to evolocumab 420 mg QM for at least 12 weeks and then to evolocumab 420 mg Q2W for at least 12 weeks, showed that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W resulted in an additional mean LDL-C reduction of 10.0% corresponding to a mean absolute reduction of 28.3 mg/dL. Considering that in Study 20120124, the median LDL-C reduction was comparable between the HoFH subjects 10 - ≤11 years of age and the overall pediatric HoFH population, it can be anticipated that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W in HoFH subjects 10 - ≤11 years of age results in a comparable additional mean LDL-C reduction of 10%. Previously, secondary prevention LDL-C lowering trials have shown that reduction of 38.7 mg/dL (1 mmol/L) in LDL-C is associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes (Cholesterol Treatment Trialists' Collaboration [CTTC], 2010). Based on above this additional mean absolute reduction of 28.3 mg/dL upon increasing the frequency of the 420 mg dose to Q2W can be considered clinically relevant, particularly in pediatric HoFH subjects which are at high cardiovascular risk.

However, the safety profile of the 420 mg Q2W dose in pediatric HoFH subjects 10-≤11 years of age is still unknown. The Applicant argued that in Study 20120124 and Study 20110271 no unexpected safety concerns has been found. Additionally, none of the adverse events were related to growth, pubertal development, or hormonal status. However, firm conclusion on growth and pubertal development and hormonal status can still not be made due to limited sample size and treatment duration. Moreover, in Study 20120124, only the 420 mg QM regimen has been evaluated, while in Study 20110271 both QM and Q2W regimens has been evaluated but only in HoFH subjects 12-≤17 years of age. In this context, an justification in order to extrapolate these safety results to HoFH subjects aged 10-≤11 years of age receiving the Q2W regimen has not been provided by the Applicant. Nevertheless, it is acknowledged that the benefits of the additional clinically relevant reduction in LDL-C upon increasing the frequency of the 420 mg dose to Q2W in HoFH subjects aged 10-≤11 years who are at very high cardiovascular risk outweigh the adverse events observed in this HoFH population to date.

2.3.2. Main studies

In support of the extension of the indication the MAH submitted the results of 2 studies, i.e. the completed Study 20120123 and its ongoing open-label extension Study 20120124:

Study 20120123 (also referred to as HAUSER-RCT): a double-blind, randomised, multicentre, placebo-controlled, parallel group study to characterise the efficacy, safety, and tolerability of 24 weeks of evolocumab for LDL-C reduction, as add-on to diet and lipid-lowering therapy, in patients from 10 to < 18 years of age with HeFH.

Study 20120124 (also referred to as HAUSER-OLE): an open-label, single-arm, multicentre study to evaluate the safety, tolerability and activity of evolocumab for LDL-C reduction, as add-on to diet and lipid-lowering therapy, in patients from 10 to < 18 years of age with HeFH or HoFH.

Study 20120123 (HAUSER-RCT)(completed):

Methods

Study participants

Eligible subjects were male or female, 10 to 17 years of age at time of randomization, who met the local applicable diagnostic criteria for HeFH. Subjects also had to be on a low-fat diet and optimized background lipid-lowering therapy for ≥ 4 weeks prior to screening as determined by the subject's physician and not requiring up-titration in the opinion of the investigator. Fasting LDL-C had to be ≥ 130 mg/dL (3.4 mmol/L), and fasting triglycerides had to be ≤ 400 mg/dL (4.5 mmol/L) as determined by the central laboratory at screening.

Key inclusion/exclusion criteria are presented in **Table 7**.

Table 7. Key inclusion/exclusion criteria of Study 20120123

Study 20120123
Inclusion Criteria
- Male or female, ≥ 10 to ≤ 17 years of age at time of randomization (includes the year after the subject completes the 17th year after birth but not the day of completing the 18th year after birth).

- Diagnosis of heterozygous familial hypercholesterolemia by local applicable diagnostic criteria for HeFH (ie, criteria outlined by the Simon Broome Register Group [Scientific Steering Committee, 1991], the Dutch Lipid Clinic Network [World Health Organization, 1999], MEDPED [Williams et al, 1993]), or by genetic testing
- On an approved statin with stable dose for ≥ 4 weeks before LDL-C screening and, in the opinion of the investigator, not requiring up-titration.
- Subject must be on a low-fat diet, and if taking any other lipid-lowering therapy (eg, ezetimibe, bile-acid sequestering resin, omega 3 fatty acids or niacin), this therapy must be unchanged for ≥ 4 weeks prior to LDL-C screening; fibrates must be stable for at least 6 weeks prior to screening.
- Fasting LDL-C at screening ≥ 130 mg/dL (3.4 mmol/L) as determined by central laboratory.
- Fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) by central laboratory at screening.
Exclusion Criteria
- Homozygous familial hypercholesterolemia
- Lipid apheresis within the last 12 weeks prior to screening
- Type 1 diabetes or newly diagnosed (within 3 months of randomization) type 2 diabetes, or poorly controlled type 2 diabetes (HbA1c > 8.5%) or newly diagnosed impaired glucose tolerance (within 3 months of randomization).
- Untreated or inadequately treated hyperthyroidism or hypothyroidism as defined by thyroid stimulating hormone (TSH) < lower limit of normal (LLN) or > 1.5 times the upper limit of normal (ULN), respectively, and free thyroxine (T4) levels that are outside normal range at screening.
- Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2 at screening, confirmed by a repeat measurement at least 1 week apart.
- Persistent active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the ULN as determined by central laboratory analysis at screening, confirmed by a repeat measurement at least 1 week apart.
- Creatine kinase (CK) > 3 times the ULN at screening, confirmed by a repeat measurement at least 1 week apart.
- Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction in the judgment of the investigator.
- Unreliability as a study participant based on the investigator's (or designee's) knowledge of the subject (eg, alcohol or other drug abuse in the past year, inability or unwillingness to adhere to the protocol, or psychosis).
- Subject has taken a cholesterylester transfer protein (CETP) inhibitor such as anacetrapib, dalcetrapib or evacetrapib in the last 12 months, or mipomersen or lomitapide in the last 5 months prior to LDL-C screening.
- Subject has previously received evolocumab or any other investigational therapy to inhibit PCSK9.
- Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s). Other investigational procedures or treatments while participating in this study are excluded.

General inclusion criteria seem appropriate to reflect the patients for which an indication is being sought, i.e. pediatric patients with HeFH. HeFH was diagnosed based on genetic testing or in accordance with the clinical Broome criteria, the Dutch Lipid Clinic Network and MEDPED, which is acceptable. The use of optimized background lipid-lowering therapy for ≥ 4 weeks prior to screening was another eligibility criteria. Furthermore, the LDL-C level of ≥ 3.4 mmol/L at screening is in line with the treatment goal for paediatric patients with HeFH recommended in the ESC guidelines for the treatment of dyslipidaemias (2019) and therefore acceptable.

Exclusion criteria can also generally be accepted. Key is that HoFH patients were not to be included.

Treatments

The study included two periods:

- Screening period: Subjects considered for enrollment underwent screening assessments, including laboratory screening by central laboratory and a subcutaneous (SC) administration of placebo to evaluate tolerability of the SC injection via a prefilled autoinjector/pen (AI/pen) prior to randomization. The duration of this pre-treatment phase was maximal 8 weeks.

- Double-blind treatment period: Eligible subjects were randomized in a 2:1 ratio to receive 24 weeks of SC once monthly (QM) evolocumab 420 mg or placebo.

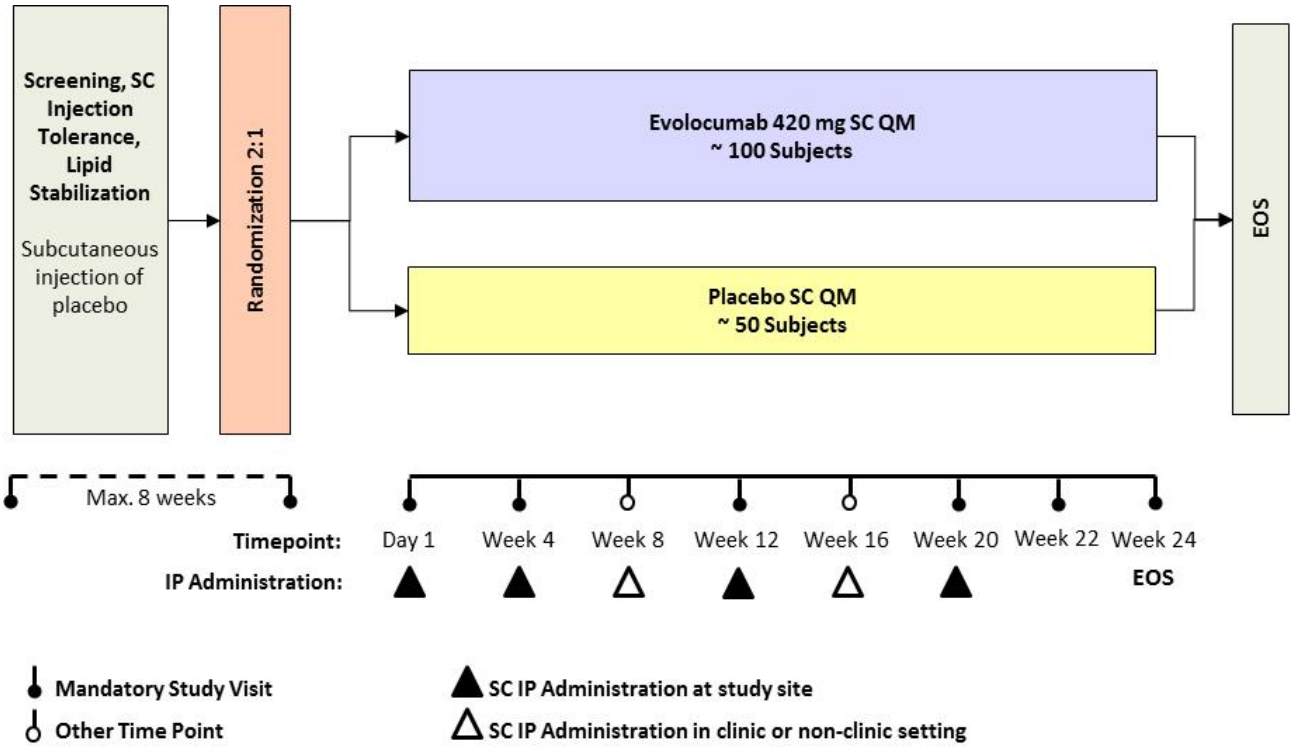
  Subjects visited the study site for assessments at weeks 4, 12, 20, 22, and 24 (end-of-study [EOS]). Investigational product administration at week 8 and week 16 could be at the study

site (optional visit) or at a non-clinic location (e.g., at home). The subject (or caregiver, if not a qualified healthcare professional) had to demonstrate competency at the administration of SC injections before self-administration was permitted, and the first self-administered dose by the subject (or designee) had to be administered at the site under the supervision of a healthcare provider. The last administration of investigational product occurred at week 20. The EOS visit occurred at week 24.

After completion of study 20120123, subjects were offered to participate in an extension study where they will receive open-label evolocumab.

The study design is presented in **Figure 1** below.

Figure 1. Study design and treatment schema for Study 20120123



Investigational products

Evolocumab and placebo were manufactured and packaged by Amgen Inc. and distributed using Amgen clinical investigational product distribution procedures. Evolocumab 420 mg was presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical prefilled AI/Pen for fixed dose, SC injection. Each AI/pen contained a 1.0 mL deliverable volume of 140 mg/mL evolocumab or 1.0 mL deliverable volume of placebo. Each QM administration of investigational product consisted of 3 injections of 140 mg evolocumab or placebo in 1.0 mL (administration by 3 AI/Pens) for a total of 3.0 mL (placebo or 420 mg evolocumab) administered.

The multicentre international double-blinded placebo-controlled design of the study is appropriate to achieve the primary objective of the study. The duration of the screening period of a maximum of 8 weeks should be sufficient to establish a stable run-in cholesterol level. The 24-week double-blind treatment period is considered appropriate to provide reasonable results on the LDL-C (and other cholesterol parameters) lowering effect of evolocumab. After completing study 20120123, subjects

were offered to participate in an extension study where they will receive open-label evolocumab (Study 20120124, discussed hereafter).

A 2:1 randomization was used in this study, which is considered appropriate.

The approved formulation and dose of evolocumab (420 mg SC QM) for adult patients with HeFH and for adults and adolescents aged 12 years and over with HoFH has been used in the study (see also "dose response studies" section). Each QM administration of investigational product (IP) consisted of 3 injections of 140 mg evolocumab (420 mg) or placebo in 1.0 mL (administration by 3 AI/Pens).

Objectives/endpoints

The objectives/endpoint of Study 20120123 are presented in **Table 8**.

Table 8. Objectives and endpoints of Study 20120123

Objectives	Endpoints
Primary	
• to evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab compared with placebo, when added to standard of care, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in pediatric subjects 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH).	• percent change from baseline to week 24 in LDL-C
Secondary	
• to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on mean percent change from baseline to weeks 22 and 24 and change from baseline to week 24 in LDL-C, and on percent change from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio, in pediatric subjects 10 to 17 years of age with HeFH	• mean percent change from baseline to weeks 22 and 24 in LDL-C • change from baseline to week 24 in LDL-C • percent change from baseline to week 24 in the following: - non-HDL-C - ApoB - total cholesterol/HDL-C ratio - ApoB/apoA1 ratio
• to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH	• subject incidence of treatment emergent adverse events • safety laboratory values and vital signs at each scheduled assessment • incidence of anti-evolocumab antibody (binding and neutralizing) formation
• to characterize pharmacokinetic (PK) exposure	• serum concentration of evolocumab at each scheduled assessment
Exploratory	
• to describe the effects over time of SC evolocumab, compared with placebo, on change from baseline in proprotein convertase subtilisin/kexin type 9 (PCSK9) levels and on change from baseline and percent change from baseline of LDL-C, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, total cholesterol, VLDL-C, HDL-C, ApoA1, triglycerides, and Lp(a) in pediatric subjects 10 to 17 years of age with HeFH	• change and percent change from baseline at each scheduled assessment in the following: - LDL-C - Non-HDL-C - ApoB - total cholesterol/HDL-C ratio - ApoB/ApoA1 ratio - total cholesterol - VLDL-C - HDL-C - ApoA1 - Triglycerides - Lp(a) - PCSK9 change from baseline at each scheduled assessment

	• Subject incidence of adjudicated events: - death by any cause - cardiovascular death - myocardial infarction - hospitalization for unstable angina - coronary revascularization - stroke - hospitalization for heart failure - transient ischemic attack (TIA) • Subject incidence of non-coronary revascularization
Other Safety Endpoints	
	• Change from baseline score in the components of the Cogstate battery at each scheduled administration

The primary endpoint of percent change from baseline to week 24 in LDL-C is considered appropriate to establish the LDL-C lowering effect of evolocumab. Secondary endpoints are considered acceptable to provide further insight on and confirmation of the primary objective.

Sample size

This study was designed to evaluate evolocumab in approximately 150 paediatric subjects. Based on the treatment effect from the global phase 3 study in adult subjects with HeFH, evolocumab reduced LDL-C by approximately 55% compared with placebo (Raal et al, 2015). A planned total sample size of 150 paediatric subjects (100 randomized to evolocumab 420 mg QM and 50 randomized to placebo QM) provided approximately 99% power in testing the superiority of evolocumab 420 mg QM over placebo to reduce LDL-C using a two-sided t-test with a 0.05 significance level and assuming a treatment effect of 40% reduction in LDL-C, a common standard deviation (SD) of 20%, and 20% of subjects discontinuing investigational product prior to completion of the study.

The sample size was calculated with sufficient power to detect a relevant difference, using realistic assumptions, including a 20% withdrawal and is in agreement with the PIP (EMEA-001268-PIP01-12) and is acceptable.

Randomisation

Randomization to evolocumab or placebo (2:1 ratio) was stratified by screening LDL-C (< 160 mg/dL [4.1 mmol/L] vs ≥ 160 mg/dL) and age (< 14 years vs ≥ 14 years).

The randomisation procedure is considered acceptable. Stratification factors are limited to screening LDL-C level and age, which is also acceptable.

Blinding (masking)

Evolocumab and placebo in the study were identical in appearance. Each was administered via an identical AI/pen.

Since some laboratory results may inadvertently unblind investigators to treatment assignment to evolocumab, central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), fasting vitamins A, D, E, and K, PCSK9, and evolocumab were not available to the investigator (or study personnel) post-screening. Investigators were instructed not to perform non-protocol (ie, local laboratory) testing of these analytes during a subject's study participation from first administration of investigational product until at least 12 weeks after last investigational product administration, or the subject's end of study, whichever is later. A subject's treatment assignment was only to be unblinded when knowledge of the

treatment was essential for the further management of the subject. Unblinding at the study site for any other reason was considered a protocol deviation. The investigator was strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment.

General blinding principals seem appropriate.

Statistical methods

Analysis sets

The final analysis was conducted when all subjects had either completed all scheduled study visits or had early terminated from the study. Unless otherwise specified, efficacy and safety analyses were performed on the FAS and data were summarized by randomized treatment group.

Subject disposition, demographics, baseline characteristics, and exposure to investigational product were summarized by treatment group and overall using descriptive statistics.

Statistics

Summary statistics for continuous variables included the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage were summarized.

Methods of handling missing data for efficacy endpoints are described below. Missing data were not imputed for safety endpoints.

Efficacy Analyses

The superiority of evolocumab to placebo was assessed for all efficacy endpoints. For all analyses related to LDL-C, unless specified otherwise, a reflexive approach was used, where the calculated LDL-C based on the Friedewald equation was employed unless the calculated LDL-C was < 40 mg/dL (1.0 mmol/L) or triglycerides were > 400 mg/dL (4.5 mmol/L), in which case preparative ultracentrifugation (UC) LDL-C was determined and utilized.

Primary Efficacy Analyses

The estimand of primary interest was the difference in mean percent change from baseline in reflexive LDL-C at week 24 regardless of treatment adherence for subjects in the FAS. A repeated measures linear effects model (Littell et al, 2000) was used to compare the efficacy of evolocumab with placebo. The repeated measures model included terms for treatment group, stratification factors (as appropriate), scheduled visit and the interaction of treatment with scheduled visit. To account for the repeated LDL-C measurements within a subject across the visits, the repeated measures linear effects model used an unstructured covariance. Missing values were not imputed when the repeated measures linear effects model was used. The analysis used LDL-C values measured, regardless of treatment adherence.

Sensitivity Analyses of the Primary Endpoint

To evaluate the robustness of the analysis results, sensitivity analyses were performed as follows:

- The primary analysis was repeated using the CAS.
- Non-parametric analyses (Quade test) were carried out.
- To evaluate the impact of missing data,

- A sensitivity analysis under the assumption that subjects that discontinued investigational product and had missing endpoint data had a mean zero percent change from baseline was conducted using multiple imputation.
- If there were at least 25 subjects who discontinued investigational product but had non-missing week 24 endpoint data, the primary analysis model was repeated using FAS with missing values imputed for subjects who discontinued investigational product. Missing values were imputed using non-missing data from subjects who discontinued investigational products within the same treatment group.

Subgroup analyses of the primary and secondary LDL-C efficacy endpoint

Treatment effect differences among subgroups, which represent subgroup by treatment interactions, were estimated and tested based on statistics from the subgroup repeated measures models.

For subgroup analyses, the stratification factors from the eCRF were used. Differences in stratum assignment between data collection via IVRS and eCRF were tabulated.

Secondary, Tertiary, and Exploratory Efficacy Endpoint Analyses

The statistical model and testing of the secondary and tertiary efficacy endpoints were similar to the primary analysis of the primary endpoint.

Exploratory endpoints related to lipid parameters and PCSK9 were summarized by randomized treatment group and by scheduled visit using descriptive statistics.

Death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure were adjudicated by an independent CEC. Non-coronary revascularizations were collected on the eCRF and were not adjudicated. Subject incidence of adjudicated endpoints and non-coronary revascularizations were summarized.

Multiplicity Adjustment Method

In order to preserve the familywise error rate at 0.05, multiplicity adjustment for the multiple endpoints (primary efficacy endpoint: percent change from baseline to week 24 in LDL-C and secondary efficacy endpoints: mean percent change from baseline to weeks 22 and 24 in LDL-C, change from baseline to week 24 in LDL-C and percent change from baseline to week 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio) was performed using sequential gatekeeping and Hochberg procedures (Hochberg, 1988) as follows:

1. If the treatment effect from the primary analysis of the primary endpoint was significant at a significance level of 0.05, statistical testing of the mean percent change from baseline to weeks 22 and 24 in LDL-C and change from baseline to week 24 in LDL-C proceeded using the sequential procedure with a significance level of 0.05 (i.e., change from baseline to week 24 in LDL-C was tested only if mean percent change from baseline to weeks 22 and 24 in LDL-C was statistically significant at 0.05 significance level).

2. If the treatment effect from change from baseline to week 24 in LDL-C was significant at a significance level of 0.05, statistical testing of the percent change from baseline to week 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio followed the Hochberg procedure at a significance level of 0.05.

Unless specified otherwise, all other hypothesis testing was 2-sided with a significance level of 0.05.

The definition of the analysis population is considered standard and acceptable. The primary and secondary analyses will be performed with a linear effects model, and missing values are not imputed. This is in line with the PIP (EMEA-001268-PIP01-12) and thus acceptable.

Results

Participant flow

A total of 202 subjects were screened for the study; 158 subjects (105 evolocumab, 53 placebo) were enrolled and randomized.

One subject in the evolocumab group did not receive any investigational product. Overall, 153 (96.8%) subjects completed investigational product in the study. Four subjects (all in the evolocumab group) discontinued investigational product; 2 at the subject's request, 1 subject due to an adverse event, and 1 subject due to "other" (subject missed the week 20 visit; the final dose of investigational product was administered at week 16). Overall, 157 (99.4%) subjects completed the study with 1 subject in the evolocumab group discontinuing the study by withdrawing consent (**Table 9**).

One hundred fifty-seven subjects received at least 1 dose of investigational product and were included in the FAS. The completer analysis set (CAS) included 136 (86.1%) subjects who completed IP and who have observed values for the primary endpoints. Of the 22 subjects excluded from the CAS, 5 missed doses of investigational product and 18 were missing the primary endpoint.

Table 9. Subject disposition with discontinuation reason- Study 20120123 (all randomized subjects)

	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 105) n (%)	Total (N = 158) n (%)
Investigational product accounting			
Subjects who never received IP	0 (0.0)	1 (1.0)	1 (0.6)
Subjects who received IP	53 (100.0)	104 (99.0)	157 (99.4)
Subjects who completed IP	53 (100.0)	100 (95.2)	153 (96.8)
Subjects who discontinued IP	0 (0.0)	4 (3.8)	4 (2.5)
Adverse event	0 (0.0)	1 (1.0)	1 (0.6)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Subject request	0 (0.0)	2 (1.9)	2 (1.3)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.0)	1 (0.6)
Study completion accounting			
Subjects who completed study	53 (100.0)	104 (99.0)	157 (99.4)
Subjects who discontinued study	0 (0.0)	1 (1.0)	1 (0.6)
Withdrawal of consent from study	0 (0.0)	1 (1.0)	1 (0.6)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)

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N = Number of subjects randomized; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous); IP = Investigational Product
Number of subjects screened: 202; First subject enrolled: 24MAR2016; Last subject completed study: 25NOV2019.

In Study 20120123, 158 subjects (105 evolocumab, 53 placebo) were enrolled and randomized. The disposition data generally appear acceptable. A high proportion of subjects completed the study (99.0% for the evolocumab group and 100.0% for the placebo group). Similarly, a high proportion of subjects completed IP (95.2% vs 100%, respectively); In the evolocumab group 4 subject discontinued IP due to subject request (n=2), adverse event (n=1) or "other" (n=1).

Protocol deviations

Important protocol deviations (IPD's) are summarized in **Table 10**.

Overall, 11 (7.0%) subjects (8 [7.6%] subjects evolocumab; 3 [5.7%] subjects placebo) had at least 1 IPD. Five (3.2%) subjects had IPD's reported as 'other'; these consisted of 3 evolocumab subjects who did not have a pregnancy test during screening, 1 evolocumab subject who did not have a CK measurement at screening (the results of CK at day 1 was normal), and 1 placebo subject who stopped statin background therapy for approximately 30 days during the study due to adverse events of jaundice and abdominal pain which subsequently resolved.

A total of 5 subjects had eligibility deviations (n=1 in placebo group with no informed consent; n=4 in evolocumab group with 1 had no legally acceptable representative consent and 3 missing eligibility labs).

Table 10. Summary of important protocol deviations - Study 20120123 (all randomized subjects)

	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 105) n (%)	Total (N = 158) n (%)
Number of subjects with at least one important protocol deviation	3 (5.7)	8 (7.6)	11 (7.0)
Important protocol deviations	3 (5.7)	8 (7.6)	11 (7.0)
Missing eligibility labs	0 (0.0)	1 (1.0)	1 (0.6)
No informed consent or subject assent[a]	1 (1.9)	0 (0.0)	1 (0.6)
No legally acceptable representative consent[b]	0 (0.0)	1 (1.0)	1 (0.6)
Other	1 (1.9)	4 (3.8)	5 (3.2)
Received expired or compromised IP	1 (1.9)	3 (2.9)	4 (2.5)
Received prohibited lipid regulating medications	0 (0.0)	1 (1.0)	1 (0.6)
Received wrong IP box	0 (0.0)	1 (1.0)	1 (0.6)

N = number of subjects randomized; EvoMab = Evolocumab (AMG 145); IP = Investigational Product; QM = monthly (subcutaneous)
Note: Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.
[a] Subject assent was not collected at screening, but was completed at the next visit.
[b] Both parents were present at screening, but only mother signed consent form. Father signed later.

The percentage of clinically important protocol deviations were relatively low (7.0%), however slightly higher in the evolocumab group compared with the placebo group (7.6% vs 5.7%, respectively). Nevertheless, these deviations were not considered to impact data interpretation.

Recruitment

This study was conducted at 47 centers in 23 countries in the regions of Asia Pacific (3.8%), Europe (65.8%), Latin America (16.5%), and North America (13.9%).

The first subject was enrolled on 24 March 2016 and the last subject completed their last visit on 25 November 2019.

This study was a multicentre study (n=47). Considering that more than half of the subjects (65.8%) were from Europe, the population is sufficiently representative of Europe.

Conduct of the study

The original protocol was finalized on 09 December 2014 (0 subjects enrolled between this date and the date of the first amendment). Subsequently, there were 2 amendments (**Table 11**)

Table 11. Protocol amendment summary

Amendment	Major Changes
Original Protocol 09 December 2014 (0 subjects enrolled between this date and the date of the first amendment)	–
Amendment 1 20 May 2015 (0 subjects enrolled between this date and the date of the next amendment)	• added hematology, urinalysis, and anti-evolocumab antibody assessments at week 12 • added exclusion of apheresis subjects to synopsis • added documentation of historical lipid therapies • added assessments of cognitive function to schedule of assessments and as an exploratory endpoint • clarification that the calculation of sample size accounts for 20% of randomized subjects discontinuing investigational product prior to completion of the study • deleted the exploratory endpoint of "categorical change from baseline in high sensitivity C-reactive protein"
Amendment 2 01 September 2015 (158 subject enrolled under this amendment)	• added explicit exclusion of homozygous familial hypercholesterolemia subjects • added adverse device effects (ADE) and disease-related events (DRE) as safety assessments • removed cogstate neurocognitive battery as an exploratory endpoint and added it as another safety endpoint. • added low-fat diet as background therapy to be maintained throughout the study • added explicit exclusion subjects receiving lipid apheresis • added definition of product complaints to the schedule of assessments • added the primary estimand • added statistical methodology for reporting vital signs, antibody data, and pharmacokinetic data

No amendments were made that would compromise the endpoints or outcomes of the study. The amendments are considered valuable and are therefore acceptable. Moreover, all subjects were enrolled under the last amendment.

Baseline data

Overall, 56.1% of subjects in Study 20120123 were female, the majority (84.7%) were white, and 8.3% were of Hispanic/Latino ethnicity. The mean (SD) age at time of enrolment was 13.7 (2.4) years with the range of 10 to 17 years of age. Thirty-nine (24.7%) subjects were children 10-≤11 years of age and 119 (75.3%) subjects were adolescents 12 -≤17 years of age. Baseline demographic characteristics are summarized in the **Table 12**.

Table 12. Baseline demographics

	Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)	Total (N = 157)
Sex - n (%)			
Male	26 (49.1)	43 (41.3)	69 (43.9)
Female	27 (50.9)	61 (58.7)	88 (56.1)
Ethnicity - n (%)			
Hispanic/Latino	7 (13.2)	6 (5.8)	13 (8.3)
Not Hispanic/Latino	46 (86.8)	98 (94.2)	144 (91.7)
Race - n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	2 (1.9)	2 (1.3)
Black (or African American)	0 (0.0)	2 (1.9)	2 (1.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	44 (83.0)	89 (85.6)	133 (84.7)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Other	9 (17.0)	11 (10.6)	20 (12.7)
Age (years)			
n	53	104	157
Mean	13.7	13.7	13.7
SD	2.5	2.3	2.4
Median	14.0	14.0	14.0
Q1, Q3	11.0, 15.0	12.0, 16.0	12.0, 16.0
Min, Max	10, 17	10, 17	10, 17
Age group - n (%)			
< 14 years	25 (47.2)	48 (46.2)	73 (46.5)
≥ 14 years	28 (52.8)	56 (53.8)	84 (53.5)

Systolic blood pressure (mmHg)			
n	53	104	157
Mean	112.0	110.8	111.2
SD	12.1	11.5	11.7
Median	110.0	110.0	110.0
Q1, Q3	105.0, 120.0	101.5, 118.0	103.0, 120.0
Min, Max	90, 140	86, 144	86, 144
Diastolic blood pressure (mmHg)			
n	53	104	157
Mean	67.2	66.3	66.6
SD	8.7	7.7	8.1
Median	68.0	66.0	67.0
Q1, Q3	62.0, 71.0	60.0, 70.0	61.0, 70.0
Min, Max	49, 89	47, 89	47, 89
Heart rate (beats/min)			
n	53	104	157
Mean	74.3	74.5	74.4
SD	11.7	11.1	11.2
Median	76.0	75.0	75.0
Q1, Q3	65.0, 82.0	66.0, 80.0	66.0, 80.0
Min, Max	53, 96	55, 127	53, 127
Height (cm)			
n	53	104	157
Mean	158.6	160.2	159.6
SD	12.8	11.5	11.9
Median	158.5	161.5	160.3
Q1, Q3	148.0, 165.5	152.0, 168.0	151.0, 168.0
Min, Max	130, 191	133, 191	130, 191
Weight (kg)			
n	53	104	157
Mean	54.5	58.7	57.3
SD	16.3	17.5	17.2
Median	53.3	55.3	54.8
Q1, Q3	42.4, 61.0	48.0, 68.8	46.8, 67.0
Min, Max	26, 95	26, 128	26, 128
Body mass index (kg/m^2)			
n	53	104	157
Mean	21.3	22.6	22.1
SD	4.2	5.5	5.1
Median	20.4	21.1	21.0
Q1, Q3	18.6, 23.5	19.0, 24.9	18.8, 24.6
Min, Max	14, 33	14, 46	14, 46
Waist circumference (cm)			
n	50	103	153
Mean	75.9	76.5	76.3
SD	12.2	13.0	12.7
Median	72.5	75.0	74.0
Q1, Q3	68.0, 84.8	66.0, 84.0	67.0, 84.0
Min, Max	54, 105	54, 116	54, 116

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N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145);

Baseline lipid and other parameters

Lipid parameters, high-sensitivity C-reactive protein (hsCRP), fasting vitamin concentrations, and PCSK9 levels at baseline were generally similar across treatment groups. Overall mean (SD) LDL-C at baseline was 184.3 (45.6) mg/dL, total cholesterol was 249.6 (47.7) mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) was 202.6 (47.5) mg/dL, and PCSK9 was 283.1 (95.4) ng/mL.

Mean (SD) hsCRP at baseline was 0.94 (1.29) mg/L and mean concentrations of vitamins A, D, E, and K were within normal reference ranges (Table 13).

Table 13. Baseline Lipid Parameters, hsCRP, Fasting vitamins A/D/E/K and PCSK9 of Study 20120123 (full analysis set).

	Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)	Total (N = 157)
LDL-C [a] (mg/dL)			
n	53	104	157
Mean	183.0	185.0	184.3
SD	47.2	45.0	45.6
Median	173.0	172.8	173.0
Q1, Q3	148.0, 208.5	155.0, 207.5	154.0, 208.0
Min, Max	122, 326	118, 368	118, 368
LDL-C, calculated (mg/dL)			
n	53	104	157
Mean	182.9	184.8	184.2
SD	47.2	44.9	45.6
Median	173.0	172.8	173.0
Q1, Q3	148.0, 208.5	155.0, 207.5	154.0, 208.0
Min, Max	122, 326	118, 368	118, 368
Total cholesterol (mg/dL)			
n	53	104	157
Mean	247.3	250.7	249.6
SD	49.5	47.0	47.7
Median	239.5	237.8	238.0
Q1, Q3	210.5, 275.0	221.0, 272.5	216.5, 274.0
Min, Max	181, 392	173, 445	173, 445
HDL-C (mg/dL)			
n	53	104	157
Mean	47.2	46.8	46.9
SD	11.9	12.0	11.9
Median	45.0	45.3	45.0
Q1, Q3	39.5, 51.5	38.5, 54.5	38.5, 54.0
Min, Max	26, 89	26, 82	26, 89

Triglycerides (mg/dL)			
n	53	104	157
Mean	86.6	95.0	92.2
SD	32.7	41.9	39.2
Median	78.0	86.8	84.0
Q1, Q3	62.5, 101.0	63.8, 117.0	63.0, 108.0
Min, Max	47, 220	44, 281	44, 281
VLDL-C [a] (mg/dL)			
n	53	104	157
Mean	17.2	19.0	18.4
SD	6.6	8.4	7.8
Median	15.5	17.3	16.5
Q1, Q3	12.5, 20.0	13.0, 23.3	12.5, 22.0
Min, Max	9, 44	9, 56	9, 56
VLDL-C, calculated (mg/dL)			
n	53	104	157
Mean	17.2	19.0	18.4
SD	6.5	8.4	7.8
Median	15.5	17.5	16.5
Q1, Q3	12.5, 20.0	12.8, 23.3	12.5, 22.0
Min, Max	9, 44	9, 56	9, 56
ApoB (mg/dL)			
n	51	103	154
Mean	119.4	123.3	122.0
SD	27.9	27.1	27.3
Median	114.0	119.0	118.0
Q1, Q3	99.0, 138.0	104.0, 139.0	102.0, 138.0
Min, Max	82, 206	75, 220	75, 220

ApoA1 (mg/dL)			
n	51	103	154
Mean	130.0	131.7	131.1
SD	21.0	23.6	22.7
Median	127.0	128.0	128.0
Q1, Q3	114.0, 140.0	118.0, 143.0	117.0, 143.0
Min, Max	100, 183	75, 188	75, 188
non-HDL-C (mg/dL)			
n	53	104	157
Mean	200.2	203.8	202.6
SD	48.2	47.3	47.5
Median	188.5	193.3	192.0
Q1, Q3	164.0, 229.5	172.3, 224.8	169.0, 225.0
Min, Max	139, 344	132, 406	132, 406
Total cholesterol/HDL-C ratio			
n	53	104	157
Mean	5.517	5.702	5.639
SD	1.492	1.791	1.694
Median	5.200	5.315	5.285
Q1, Q3	4.540, 6.190	4.423, 6.400	4.460, 6.365
Min, Max	3.09, 9.72	2.99, 11.58	2.99, 11.58
ApoB/ApoA1 ratio			
n	51	103	154
Mean	0.938	0.970	0.960
SD	0.255	0.302	0.287
Median	0.850	0.920	0.900
Q1, Q3	0.730, 1.080	0.770, 1.090	0.760, 1.080
Min, Max	0.55, 1.59	0.41, 2.23	0.41, 2.23

	Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)	Total (N = 157)
Lp(a) (nmol/L)			
n	51	104	155
Mean	88.7	88.7	88.7
SD	99.7	97.4	97.8
Median	34.0	50.5	43.0
Q1, Q3	21.0, 147.0	18.0, 126.5	19.0, 130.0
Min, Max	2, 360	5, 443	2, 443
Vitamin A (mg/L)			
n	33	72	105
Mean	0.436	0.428	0.431
SD	0.136	0.137	0.136
Median	0.410	0.410	0.410
Q1, Q3	0.350, 0.480	0.340, 0.490	0.340, 0.490
Min, Max	0.24, 0.83	0.21, 0.93	0.21, 0.93
Vitamin D (ng/mL)			
n	49	104	153
Mean	23.3	22.6	22.8
SD	8.4	9.3	9.0
Median	23.0	22.0	22.0
Q1, Q3	18.0, 28.0	17.0, 27.0	17.0, 27.0
Min, Max	7, 49	5, 52	5, 52
Vitamin E (mg/dL)			
n	52	103	155
Mean	1.332	1.410	1.384
SD	0.286	0.285	0.287
Median	1.325	1.350	1.350
Q1, Q3	1.110, 1.510	1.230, 1.560	1.210, 1.550
Min, Max	0.81, 2.36	0.83, 2.47	0.81, 2.47

	Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)	Total (N = 157)
Vitamin K (pg/mL)			
n	21	43	64
Mean	377.5	295.4	322.4
SD	356.4	266.0	298.4
Median	212.0	196.0	203.5
Q1, Q3	164.0, 457.0	138.0, 355.0	146.0, 389.5
Min, Max	77, 1443	71, 1537	71, 1537
hsCRP (mg/L)			
n	51	102	153
Mean	0.94	0.94	0.94
SD	1.49	1.18	1.29
Median	0.38	0.41	0.40
Q1, Q3	0.22, 0.90	0.23, 1.30	0.23, 0.98
Min, Max	0.1, 8.6	0.1, 6.7	0.1, 8.6
PCSK9 (ng/mL)			
n	52	97	149
Mean	294.2	277.2	283.1
SD	101.3	92.1	95.4
Median	268.5	270.0	270.0
Q1, Q3	227.5, 347.0	214.0, 338.0	214.0, 339.0
Min, Max	127, 665	18, 503	18, 665

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N = number of subjects randomized and dosed in the full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous); LDL-C=Low-density lipoprotein; HDL-C = High-density lipoprotein; VLDL-C = Very low-density lipoprotein; Non-HDL-C = Non-High-density lipoprotein cholesterol; ApoA1 = Apolipoprotein A1; ApoB = Apolipoprotein B; Lp(a) = Lipoprotein (a); PCSK9 = Proprotein convertase subtilisin/kexin type 9; hsCRP = High-sensitivity C-reactive Protein

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

Medical history

No subject had CAD at baseline. One (1.9%) placebo subject had a history of stroke at baseline. The most common CHD risk factors at baseline (evolocumab, placebo) were low HDL-C (38.5%, 34.0 %), family history of premature CHD (29.8%, 39.6%), and hypertension (1.9%, 5.7%). Low HDL-C was also the most common risk factor for metabolic syndrome. No subjects had congestive heart failure.

Per Protocol 20120123 entry criteria, subjects in the FAS had a genetic, or if not available, a known clinical diagnosis of HeFH. Sixty-six percent of subjects had documented genetic evidence of an FH-causing mutation (64% in the LDL receptor); 34% of subjects qualified on clinical criteria alone set by Simon-Broome, Dutch Lipid Clinic Network, or MEDPED.

Data are summarized in the **Table 14**.

Table 14. Summary of baseline coronary heart disease characteristics (full analysis set).

Category Subcategory	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)	Total (N = 157) n (%)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular or peripheral arterial disease	1 (1.9)	0 (0.0)	1 (0.6)
Stroke/Cerebral infarction	1 (1.9)	0 (0.0)	1 (0.6)
Baseline CHD Risk Factors			
Current cigarette smoking	2 (3.8)	1 (1.0)	3 (1.9)
Hypertension	3 (5.7)	2 (1.9)	5 (3.2)
Type II diabetes mellitus	0 (0.0)	1 (1.0)	1 (0.6)
Family history of premature coronary heart disease	21 (39.6)	31 (29.8)	52 (33.1)
Low HDL-C [a]	18 (34.0)	40 (38.5)	58 (36.9)
Subjects with 2 or more baseline CHD risk factors	7 (13.2)	11 (10.6)	18 (11.5)
Baseline factors for metabolic syndrome			
Elevated waist circumference	8 (15.1)	14 (13.5)	22 (14.0)
Triglycerides ≥ 150 mg/dL	2 (3.8)	7 (6.7)	9 (5.7)
Low HDL-C [a]	18 (34.0)	40 (38.5)	58 (36.9)
SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or Hypertension	7 (13.2)	7 (6.7)	14 (8.9)
Fasting glucose ≥ 100 mg/dL	3 (5.7)	4 (3.8)	7 (4.5)
Subjects with baseline metabolic syndrome (3 or more factors) and without Type II diabetes mellitus	3 (5.7)	1 (1.0)	4 (2.5)
Diagnosis of HeFH	53 (100.0)	104 (100.0)	157 (100.0)
Genetic evidence of an FH-causing mutation			
Yes	32 (60.4)	72 (69.2)	104 (66.2)
LDL Receptor	30 (56.6)	70 (67.3)	100 (63.7)
Apo B	1 (1.9)	2 (1.9)	3 (1.9)
PCSK9 Gain of Function	1 (1.9)	0 (0.0)	1 (0.6)
No	21 (39.6)	32 (30.8)	53 (33.8)
Simon-Broome	7 (13.2)	9 (8.7)	16 (10.2)
Dutch Lipid Clinic Network	10 (18.9)	22 (21.2)	32 (20.4)
MEDPED	4 (7.5)	1 (1.0)	5 (3.2)

ApoB = Apolipoprotein B; CHD = Coronary Heart Disease; DBP = Diastolic Blood Pressure; EvoMab = Evolocumab (AMG 145); FH = Familial Hypercholesterolemia; HDL-C = High-density lipoprotein cholesterol; HeFH = Heterozygous Familial Hypercholesterolemia; LDL-C = Low-density lipoprotein cholesterol; PCSK9 = Proprotein Convertase Subtilisin/kexin type 9; QM = monthly (subcutaneous); SBP = Systolic Blood Pressure
N = number of subjects randomized and dosed in the full analysis set.
Family history of premature coronary heart disease (CHD) was CHD in first degree relative male at less than or equal to 55 years or female at less than or equal to 65 years of age.
[a] low HDL-C defined as baseline HDL-C < 40 mg/dL for both males and females with age 10 to < 16 years; < 40 mg/dL in male and < 50 mg/dL in female with age ≥ 16 years.

Lipid lowering background therapy

All 157 (100%) subjects in the FAS were taking lipid-regulating medication at baseline. One hundred and fifty-six (99%) subjects were on a statin at baseline. Consistent with American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the majority (79%) of subjects were on moderate- or high-intensity statins at baseline and 20% were on low-intensity statins. Twenty subjects were on a statin plus ezetimibe; 1 subject took only ezetimibe (**Table 15**).

Table 15. Lipid-regulating concomitant medications of interest use at baseline by medication category and preferred term (full analysis set).

	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)	Total (N = 157) n (%)
Number of subjects reporting use of lipid-regulating medication	53 (100.0)	104 (100.0)	157 (100.0)
STATINS	52 (98.1)	104 (100.0)	156 (99.4)
Atorvastatin	26 (49.1)	42 (40.4)	68 (43.3)
Pravastatin	6 (11.3)	13 (12.5)	19 (12.1)
Rosuvastatin	12 (22.6)	39 (37.5)	51 (32.5)
Simvastatin	8 (15.1)	10 (9.6)	18 (11.5)
BILE ACID SEQUESTRANTS	1 (1.9)	0 (0.0)	1 (0.6)
Colesevelam	1 (1.9)	0 (0.0)	1 (0.6)
OTHER LIPID MODIFYING AGENTS	9 (17.0)	17 (16.3)	26 (16.6)
Ezetimibe	8 (15.1)	13 (12.5)	21 (13.4)
Fish Oil	2 (3.8)	5 (4.8)	7 (4.5)
Phytosterols Nos	0 (0.0)	1 (1.0)	1 (0.6)

Randomization was stratified by age and baseline LDL-C and was generally balanced between groups (**Table 16**).

Table 16. Summary of randomization stratifications - Study 20120123 (full analysis set)

Stratification Factor Category	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)	Total (N = 157) n (%)
Age group - n (%)			
< 14 years	25 (47.2)	48 (46.2)	73 (46.5)
≥ 14 years	28 (52.8)	56 (53.8)	84 (53.5)
Screening LDL-C level			
< 160 mg/dL	16 (30.2)	33 (31.7)	49 (31.2)
≥ 160 mg/dL	37 (69.8)	71 (68.3)	108 (68.8)

N = Number of subjects randomized and dosed in full analysis set; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous); LDL-C = Low-density lipoprotein cholesterol

Tanner staging

The distribution of Tanner staging using gender criteria (genital size for males and breast development for females) and using criteria of pubic hair were similar between treatment groups at baseline (data not shown).

Overall baseline data, including those on co-medications, distribution of Tanner staging and risk factors, and stratification factors, are well distributed across treatment groups, which is reassuring for the interpretation of the data.

The study population can be considered representative of a paediatric HeFH population. HeFH diagnosis was sufficiently established as the diagnosis was for a large part of the population by genetic testing (66%). Thirty-nine (24.7%) subjects were children 10-≤11 years of age, and 119 (75.3%) subjects were adolescents between 12-≤17 years of age. Moreover, the elevated mean LDL-C baseline value of 4.8 mmol/L reasonably corresponds to an LDL-C level generally observed within a HeFH population. All subjects were received statin therapy, except for one subject in the placebo group who took only ezetimibe. The majority (79%) of subjects were on moderate- or high-intensity statins at baseline, and 20% were on low-intensity statins.

Numbers analysed

Unless otherwise specified, efficacy and safety analyses were performed on the full analysis set (FAS) and data were summarized by randomized treatment group. One hundred fifty-seven subjects received at least 1 dose of investigational product and were included in the FAS.

Outcomes and estimation

Primary endpoint

- percent change from baseline to week 24 in LDL-C

Evolocumab was superior to placebo ($p < 0.0001$) in lowering LDL-C in paediatric subjects with HeFH (**Table 17**). The least-squares (LS) mean (SE) reduction in LDL-C from baseline at week 24 was 44.5% (2.2%) in the evolocumab group and 6.2% (3.1%) in the placebo group with a mean treatment difference (95% CI) of 38.3% (31.1, 45.5). Mean (SE) absolute LDL-C values at week 24 were 2.7 (0.15) mmol/L in the evolocumab group and 4.5 (0.21) mmol/L in the placebo group (**Table 17**).

Reductions in LDL-C were observed by the first assessment at the week 12-time point and were maintained throughout the study (24 weeks); the increase observed at week 24 is indicative of the end of the dosing interval (**Figure 2**).

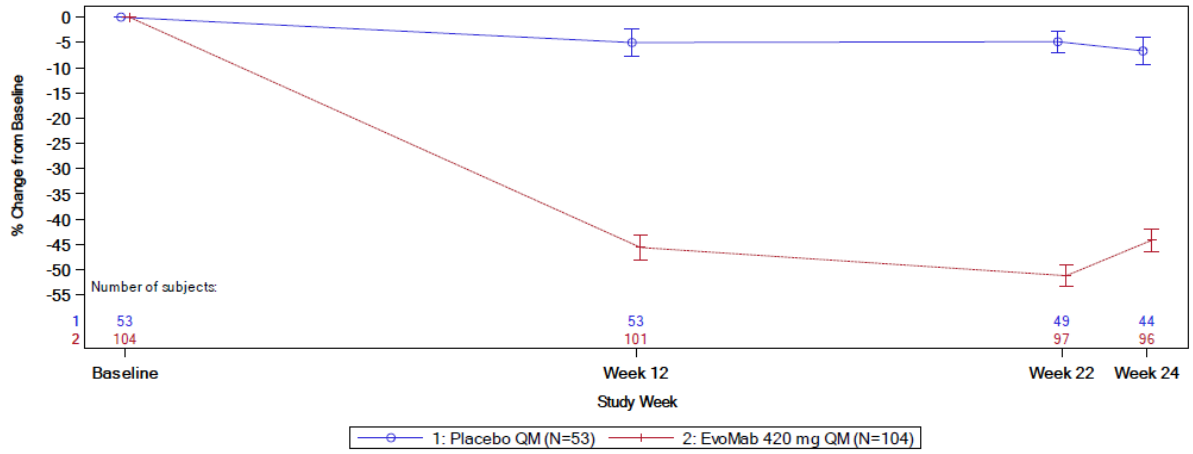
Sensitivity analyses of the primary endpoint of percent change from baseline to week 24 using the CAS and using nonparametric analysis were consistent with the primary analysis of the primary endpoint. Sensitivity analysis of the primary endpoint using multiple imputation could not be conducted due to too few subjects (< 25 subjects) who had missing primary endpoint data.

Table 17. Primary analysis of primary endpoint for percent change in LDL-C (in mmol/L) from baseline to week 24 (full analysis set).

		Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)
Baseline			
n		53	104
Mean		4.738	4.791
SD		1.222	1.165
SE		0.168	0.114
Median		4.480	4.475
Q1, Q3		3.835, 5.400	4.013, 5.373
Min, Max		3.15, 8.44	3.04, 9.52
Week 24			
n		44	96
Mean		4.453	2.690
SD		1.361	1.421
SE		0.205	0.145
Median		4.105	2.345
Q1, Q3		3.430, 5.195	1.790, 3.495
Min, Max		1.84, 7.82	0.80, 8.88
Change from baseline to week 24			
n		44	96
Mean		-0.365	-2.040
SD		0.964	1.143
SE		0.145	0.117
Median		-0.245	-2.165
Q1, Q3		-0.843, 0.265	-2.608, -1.505
Min, Max		-4.12, 1.29	-5.04, 2.70
Percent change from baseline to week 24			
n		44	96
Mean		-6.68	-44.23
SD		18.25	22.43
SE		2.75	2.29
Median		-6.13	-46.89
Q1, Q3		-18.27, 5.71	-58.98, -35.09
Min, Max		-69.1, 30.8	-84.0, 43.7
LS Mean[a]			
Estimate (SE)		-6.23 (3.08)	-44.53 (2.17)
95% CI		(-12.31, -0.15)	(-48.81, -40.25)
Treatment difference[b]			
Estimate (SE)		- (-)	-38.30 (3.66)
95% CI		(-, -)	(-45.54, -31.06)
p-value		-	<0.0001
Adjusted p-value[c]		-	<0.0001

CI = Confidence Interval; EvoMab = Evolocumab (AMG 145); LDL-C = low density lipoprotein cholesterol; QM = monthly (subcutaneous).
N = number of subjects randomized and dosed in the full analysis set. n = number of subjects with observed data.
When the calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, calculated LDL-C was replaced with ultracentrifugation LDL-C from the same blood sample, if available.
[a] Least squares mean was from the repeated measures model which included treatment group, stratification factor of age and screening LDL-C (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates. The model used an unstructured covariance.
[b] Treatment differences used placebo as the reference.
[c] Adjusted p-value was based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value was compared to 0.05 to determine statistical significance.

Figure 2. Mean percent change from baseline in reflexive LDL-C by scheduled visit and treatment group



EvoMab = Evolocumab (AMG 145); LDL-C = low density lipoprotein cholesterol; QM = monthly (subcutaneous)
N = number of subjects randomized and dosed in the full analysis set.
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.
When calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, the UC LDL-C value from the same blood sample was used instead, if available.

Evolocumab demonstrated a substantial reduction in the primary endpoint of percent change from baseline to week 24 in LDL-C of 44% with an actual LDL-C level of 4.8 mmol/L at baseline and 2.7 mmol/L at week 24 (reduction by 2.1 mmol/L). The mean treatment difference between evolocumab and placebo was 38.3 % (p<0.0001). In addition, this effect was maintained up to 104 weeks of treatment as demonstrated in the open-label extension Study 20120124.

The effect size in LDL-C lowering of 38.3% observed in this study in pediatric subjects with HeFH was lower than the LDL-C lowering effect of 60% observed in adults with HeFH in the RUTHERFORD study (Study 20110117) and other previous clinical studies (range: 60-70%) submitted during the initial MAA. During the procedure, the Applicant stated that they are not aware of any clear biological or pharmacokinetic basis for a discrepant effect across the pediatric and adult HeFH population. According to the Applicant, one possible reason for the lower treatment effect size in the pediatric population could be that the baseline LDL-C values were higher in the pediatric population in Study 20120123 compared with the adult population in previous evolocumab studies. Nevertheless, it is acknowledged that the LDL-C lowering effect in the paediatric HeFH population is substantial and clinically relevant.

Secondary endpoints

- mean percent change from baseline to weeks 22 and 24 in LDL-C

The secondary endpoint of mean percent change from baseline to weeks 22 and 24 in LDL-C, where week 22 reflects the peak and week 24 the trough of the QM dosing interval, provides important information about the time-averaged effect of evolocumab therapy over the entire dosing interval. Results from this analysis showed a reduction from baseline (treatment difference [95% CI]) at the mean of weeks 22 and 24 of 42.1% (35.9, 48.4). The LS mean (SE) reduction in calculated LDL-C from baseline at the mean of weeks 22 and 24 was 48.0% (1.9%) in the evolocumab group and 5.9% (2.7%) in the placebo group (**Table 17**, **Figure 2**, and **Table 18**).

Table 18. Analysis of mean percent change in calculated LDL-C from baseline to weeks 22 and 24 - Study 20120123 (full analysis set)

	Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)
Mean of Weeks 22 and 24 Summary Statistics		
n	52	103
Mean	-5.57	-48.25
SE	2.10	1.98
Median	-2.95	-51.87
Q1, Q3	-17.76, 4.51	-61.73, -38.30
Min, Max	-46.7, 20.6	-80.5, 39.0
LS Mean[a]		
Estimate (SE)	-5.85 (2.67)	-47.97 (1.92)
95% CI	(-11.13, -0.57)	(-51.77, -44.17)
Treatment difference[b]		
Estimate (SE)	- (-)	-42.12 (3.18)
95% CI	(-, -)	(-48.40, -35.85)
p-value	-	<0.0001

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N = number of subjects randomized and dosed in the full analysis set; n=number of subjects with observed data

EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous); CI = Confidence Interval; LDL-C = low-density lipoprotein cholesterol

[a] Least squares mean is from the repeated measures model which includes treatment group, stratification factor of screening LDL-C level and age (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates. The model uses an unstructured covariance.

[b] Treatment differences uses placebo as the reference.

Treatment with evolocumab demonstrated a substantial reduction in LDL-C from baseline to the mean of weeks 22 and 24. The mean reduction in LDL-C from baseline at the mean of weeks 22 and 24 was 48.0% in the evolocumab group compared with 5.9% in the placebo group with a treatment difference of 42.1% (p<0.0001).

- percent change from baseline to week 24 in the following: non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/apoA1 ratio

Evolocumab was superior to placebo (all p < 0.0001) in improving all secondary lipid endpoints, including change in reflexive and calculated LDL-C from baseline to week 24, and the percent changes from baseline to week 24 in non HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/apolipoprotein A1 (ApoA1) ratio (**Table 19**).

Table 19. Summary of Treatment Differences for Secondary Efficacy Endpoints Study 20120123 (Full Analysis Set)

	Treatment Difference EvoMab 420 mg QM vs Placebo QM
Calculated LDL-C	
Change from baseline to wk 24 (95% CI) - mg/dL	-68.3 (-82.9, -53.8)
Change from baseline to wk 24 (95% CI) - mmol/L	-1.771 (-2.147, -1.395)

	Treatment Difference EvoMab 420 mg QM vs Placebo QM
Adjusted p-value	<0.0001
Reflexive LDL-C[a]	
Change from baseline to wk 24 (95% CI) - mg/dL	-68.6 (-83.1, -54.0)
Change from baseline to wk 24 (95% CI) - mmol/L	-1.777 (-2.153, -1.401)
Adjusted p-value	<0.0001
Non-HDL-C	
% change from baseline to wk 24 (95% CI)	-35.04 (-41.79, -28.30)
Adjusted p-value	<0.0001
ApoB	
% change from baseline to wk 24 (95% CI)	-32.47 (-38.82, -26.13)
Adjusted p-value	<0.0001
Total cholesterol/HDL-C ratio	
% change from baseline to wk 24 (95% CI)	-30.30 (-36.40, -24.21)
Adjusted p-value	<0.0001
ApoB/ApoA1 ratio	
% change from baseline to wk 24 (95% CI)	-36.38 (-42.97, -29.80)
Adjusted p-value	<0.0001

Exploratory Efficacy Endpoints

- change and percent change from baseline at each scheduled assessment in the following: LDL-C, Non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, total cholesterol, VLDL-C, HDL-C, ApoA1, Triglycerides, Lp(a), and PCSK9 change from baseline at each scheduled assessment (week 12, week 22, and week 24).

The treatment effect of evolocumab on each lipid parameter and PCSK9 was generally consistent across all timepoints. Overall, the treatment effect on each lipid parameter and PCSK9 was slightly larger at week 22 (middle of the dosing interval) than at week 12 or week 24 (end of the dosing interval) which is consistent with other studies of evolocumab.

Primary endpoint analyses were supported by the secondary cholesterol profile evaluation showing significant reductions in, e.g. non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/apoA1 ratio.

Furthermore, the exploratory efficacy endpoints showed that the treatment effect of evolocumab was generally consistent across the timepoints week 12, week 22 and week 24. The smaller reductions at week 12 and 24 compared with week 22 are indicative of the end of the dosing interval.

- Carotid Intima-media Thickness Test (cIMT)

Carotid intima-media thickness (cIMT) uses ultrasound to measure the thickness of the inner 2 layers of the carotid artery, the intima and media, and can detect thickening. Lateral, anterior, and posterior measurements of the right common carotid artery (RCCA) and left common carotid artery were assessed at baseline and at week 24. Mean baseline values in each treatment group at each site were < 0.6 mm. The mean change from baseline to week 24 at every site assessed was negative in the

evolocumab group (indicating a reduction in thickness) with the exception of posterior LCCA which was marginally positive. The mean change from baseline to week 24 at all 6 sites assessed was positive in the placebo group (indicating thickening).

Table 20. Summary of Carotid intima-media Thickness (cIMT) - Average of largest RCCA and LCCA by scheduled visit- Study 20120123 (Full analysis set – actual treatment)

	Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)
Baseline		
n	46	82
Mean	0.568	0.586
SD	0.063	0.064
SE	0.009	0.007
Median	0.555	0.580
Q1, Q3	0.520, 0.620	0.540, 0.620
Min, Max	0.45, 0.71	0.46, 0.76
Week 24		
n	39	87
Mean	0.579	0.580
SD	0.060	0.055
SE	0.010	0.006
Median	0.560	0.580
Q1, Q3	0.530, 0.620	0.540, 0.610
Min, Max	0.50, 0.70	0.46, 0.69
Change from baseline to week 24		
n	37	76
Mean	0.006	-0.003
SD	0.054	0.052
SE	0.009	0.006
Median	0.010	-0.010
Q1, Q3	-0.040, 0.040	-0.030, 0.020
Min, Max	-0.11, 0.14	-0.19, 0.13

EvoMab = Evolocumab (AMG 145); LCCA = Left Common Carotid Artery; QM = monthly (subcutaneous); RCCA = Right Common Carotid Artery;
N = number of subjects randomized and dosed in the full analysis set; n = number of subjects with observed data.
Program: /userdata/stat/amg145/lipid/20120123/analysis/final/tables/program/t-cimt-average-sumvisit-fas.sas
Output: t14-08-005-007-cimt-average-sumvisit-fas.rtf (Date Generated: 27FEB20:00:11:57)
Source: adam.adsl, adam.admo

Carotid intima-media thickness (cIMT) at baseline and week 24, showed small reductions in cIMT observed with evolocumab compared with small increases in cIMT in the placebo group, suggestive of a beneficial effect of evolocumab concerning atherogenesis. Nevertheless, the results in cIMT are considered too limited (short study period and small reduction) to draw firm conclusions. Moreover, statistical significance analyses have not been provided.

Subgroup analyses

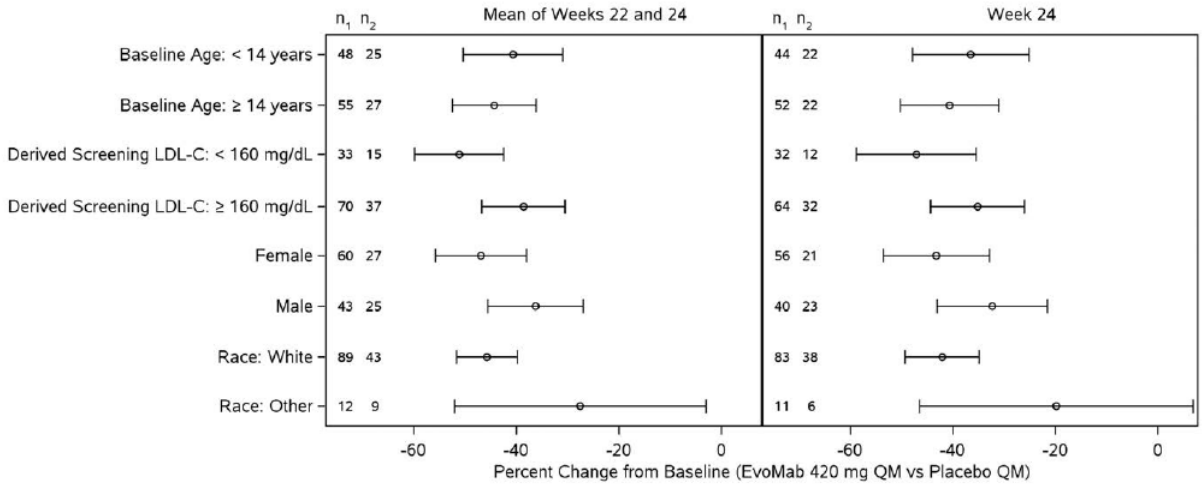
Prespecified subgroup analyses of the primary endpoint are depicted in **Figure 3** below.

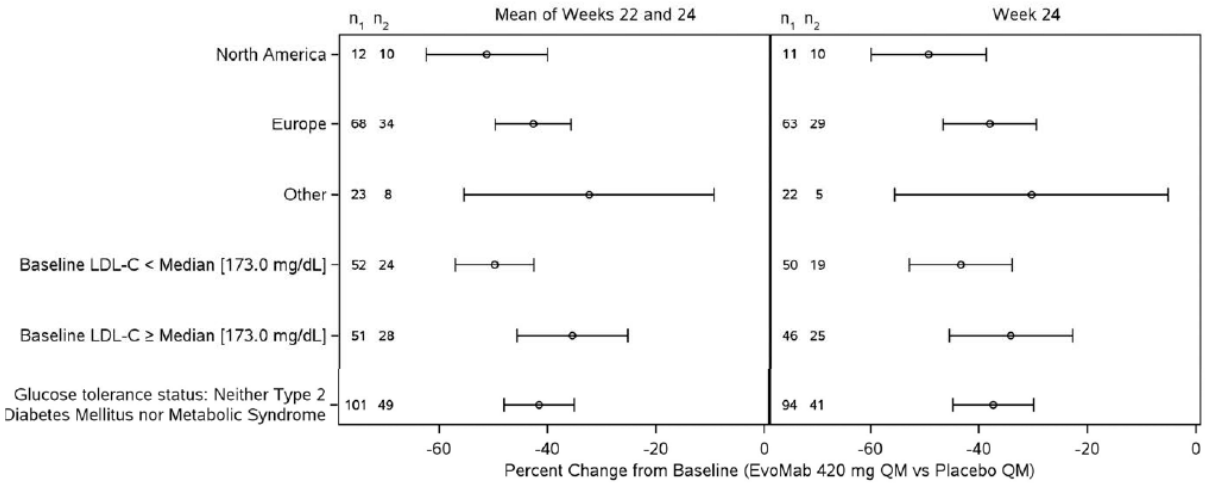
These included subgroups by age (< 14, ≥ 14; screening LDL-C value (< 160 mg/dL, ≥160 mg/dL), gender, race (white, black, or other), region, baseline LDL-C < or ≥ median (173.0 mg/dL), glucose tolerance status (type 2 diabetes [T2D], metabolic syndrome, or neither, baseline PCSK9 < or ≥ median (270.0 ng/mL), and statin intensity (high, moderate, low).

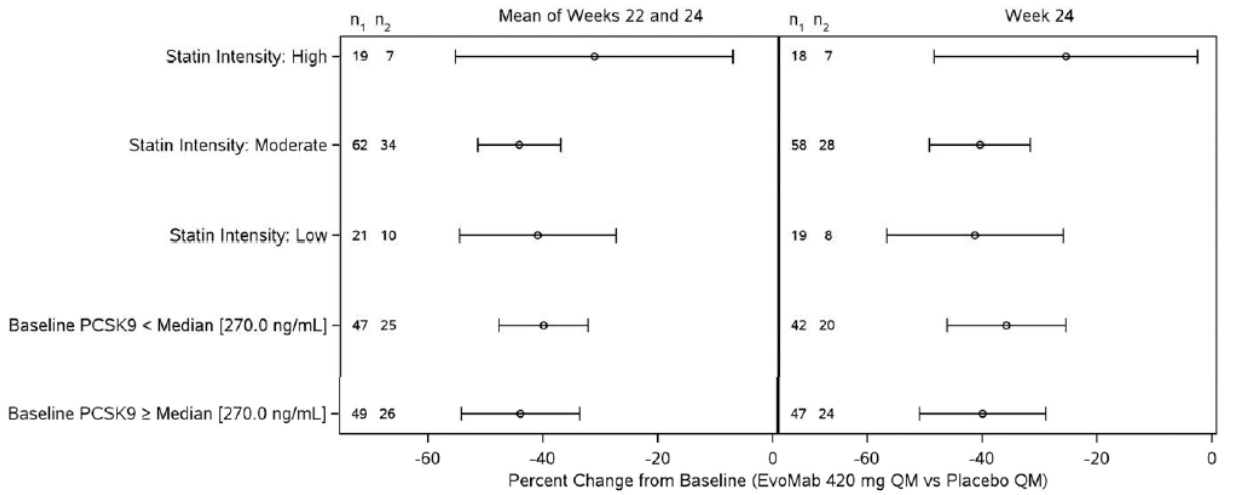
Subgroup analyses of the primary and secondary endpoints for LDL-C (both at week 24 and the mean of weeks 22 and 24) showed a greater reduction in LDL-C with evolocumab, compared with placebo, within all subgroups (all $p < 0.05$) except for categories of black race, "other" race, glucose tolerance status of metabolic syndrome, and glucose tolerance status of T2D, where in each case there were too few subjects per subgroup for the analysis.

Interaction by subgroup analyses showed evidence of a greater treatment effect of evolocumab for subjects with screening LDL-C values < 160 mg/dL and baseline LDL-C values < median (173 mg/dL) at the mean of week 22 and week 24, but not at week 24, compared with screening LDL-C values ≥ 160 mg/dL and baseline LDL-C values ≥ median (173 mg/dL). There was no evidence of a different treatment effect across other subgroups.

Figure 3. Forest plot of treatment differences in percent change from baseline in LDL-C at the mean of weeks 22 and 24 and week 24 by subgroups







n1 = number of subjects in the subgroup of interest included in the repeated measures model receiving EvoMab; n2 = number of subjects in the subgroup of interest included in the repeated measures model receiving placebo; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous)
When calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, the UC LDL-C value from the same blood sample was used instead, if available.
Least squares mean differences and 95% CI were from the repeated measures model. No imputation was used for missing values.

Additionally, subgroup analysis of the primary efficacy endpoint by age category 10 to ≤ 11 years vs 12 to ≤ 17 years has been conducted. The least squares (LS) mean (SE) reduction in LDL-C from baseline at week 24 was 44.54% (4.67%) and 44.80% (2.31%) in the evolocumab group and 15.97% (6.28%) and 2.80% (3.41%) in the placebo group for the 10 to ≤ 11 years and 12 to ≤ 17 years groups, respectively. The least squares mean treatment difference (95% CI) was 28.57% (12.71, 44.43) for 10 to ≤ 11 years and 42.00% (33.85, 50.16) for 12 to ≤ 17 years. The interaction p-value was 0.13, indicating there is no evidence of a different treatment effect for the 2 age subgroups.

Prespecified subgroup analyses of the primary endpoint showed no large relevant differences for the subgroups of gender, race, age, region and baseline PCSK9; no large relevant differences were observed.

However, a slightly larger LDL-C reduction was observed in the subgroup of screening LDL-C values < 160 mg/dL and baseline LDL-C values < median (173 mg/dL) at the mean of week 22 and 24, but not at week 24 compared with compared with screening LDL-C values ≥ 160 mg/dL and baseline LDL-C values ≥ median (173 mg/dL) (interaction p-value of 0.037 and 0.024, respectively). Nevertheless, the LDL-C lowering effect in all these subgroups are considered clinically relevant.

Study 20120124 (HAUSER-OLE) (ongoing):

Methods

Study participants

Inclusion criteria

Subjects who completed Study 20120123 (and did not experience a treatment-related serious adverse event), and males and females 10 -≤ 17 years of age with a diagnosis of HoFH and receiving optimized standard of care lipid-lowering therapy per locally applicable guidelines, were eligible for this study.

The diagnosis of HoFH had to be by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 500 mg/dL (13 mmol/L) together with either xanthoma before 10

years of age in the subject, or evidence of HeFH in both parents. At screening, HoFH subjects had to be on a low-fat diet and had to be receiving background lipid-lowering therapy (such as statins, cholesterol absorption inhibitors, bile acid sequestrants, nicotinic acid or combinations thereof). Lipid-lowering therapy must have been stable for ≥ 4 weeks prior to screening. Fasting LDL-C for HoFH subjects had to be ≥ 130 mg/dL (3.4 mmol/L) and fasting triglycerides had to be ≤ 400 mg/dL (4.5 mmol/L) as determined by the central laboratory at screening.

Exclusion criteria

The following were exclusion criteria for subjects with HoFH (those not rolling over from a prior evolocumab study): estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m2; CK > 3 x upper limit of normal (ULN); AST or ALT > 2 x ULN; (all screening by central laboratory); known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction; subject has taken a cholesterylester transfer protein (CETP) inhibitor in the last 12 months, or mipomersen or lomitapide in the last 5 months prior to LDL-C screening, or has received any therapy to inhibit PCSK9 within 12 weeks prior to screening.

General inclusion criteria seem appropriate to reflect the patients for which an indication is being sought, i.e. pediatric patients with HeFH and HoFH. Since Study 20120124 is the open-label extension study of Study 20120123, pediatric patients with HeFH who completed the parent study and did not experience treatment-related adverse events were eligible to enrol in this OLE study. Additionally, de-novo pediatric patients aged 10 to 17 years with a diagnosis of HoFH and receiving optimized SOC lipid-lowering therapy were also eligible to enrol in this OLE study. HoFH was diagnosed by genetic confirmation or by clinical diagnosis based on a history of an untreated LDL cholesterol concentration greater than 500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age or evidence of HeFH in both parents. These criteria are in line with previous studies with HoFH and considered appropriate.

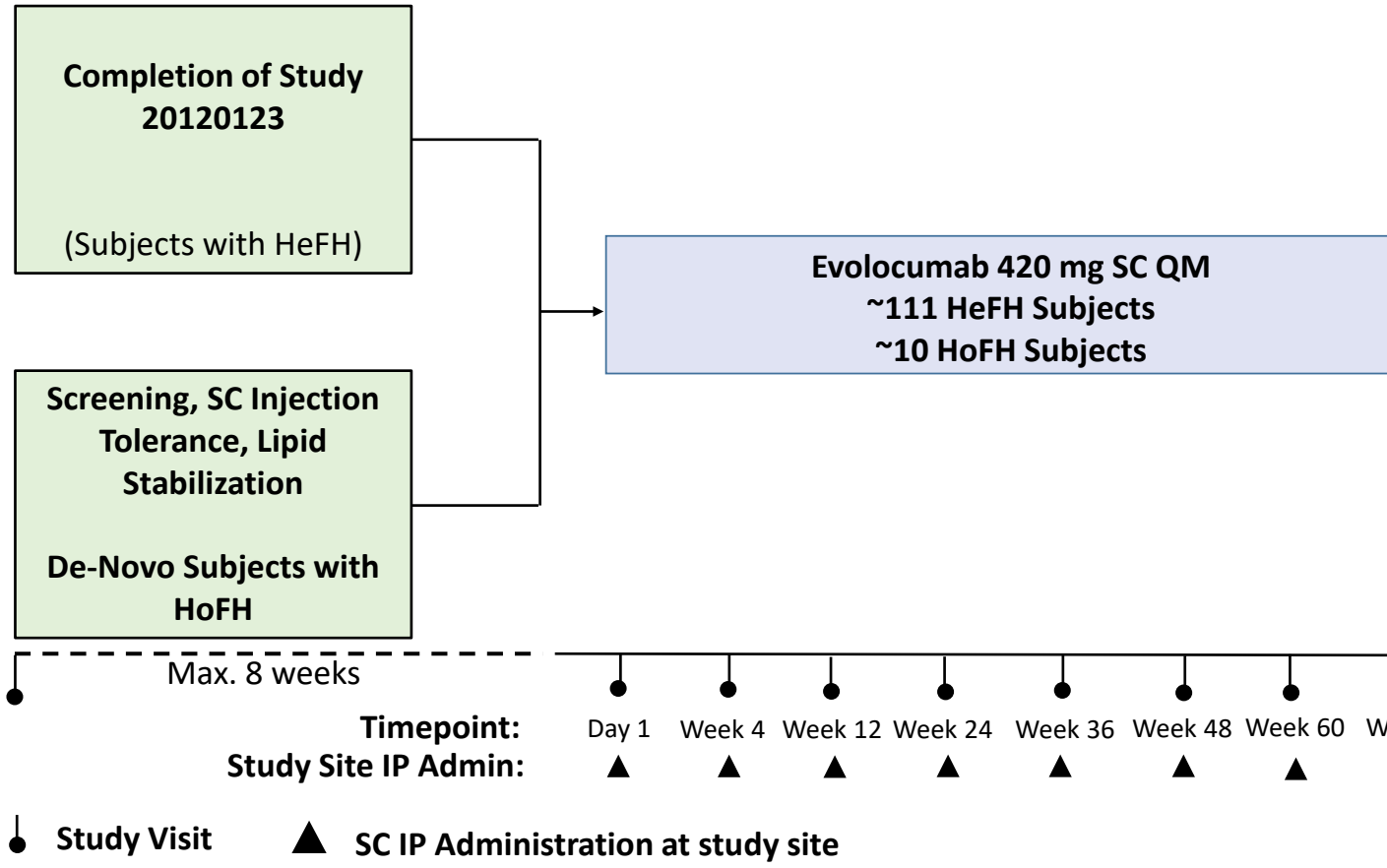
Exclusion criteria can also generally be accepted.

Treatments

Study 20120124 is an open-label-single-arm, multicenter study (**Figure 4**) All subjects received evolocumab 420 mg SC QM using either AI/Pen or automated mini-doser (AMD) administration. Each QM administration of evolocumab with the AI/Pen consisted of 3 injections of 140 mg evolocumab in 1.0 mL for a total of 420 mg/3.0 mL of evolocumab administered. Each QM administration of evolocumab AMD consisted of 1 injection of 420 mg/3.5 mL of evolocumab. Subjects had the opportunity to switch between the AI/Pen and AMD at any scheduled time point where evolocumab was supplied to the subject, provided the appropriate supply was available. The planned study duration is approximately 80 weeks; interim data from a minimum of 28 weeks of investigational product exposure for all subjects who did not discontinue the study is included in the submission.

In this study, subjects had the option of self-administration, defined as SC administration of evolocumab by the subject, designee or a qualified health care professional in a non-investigator site setting (eg, at home). The subject (or designee, if not a qualified healthcare professional) must have demonstrated competency at administration of SC injections at the study site before self-administration was permitted

Figure 4. Study design and treatment schema for study 20120124



EOS = End of Study; HeFH = Heterozygous Familial Hypercholesterolemia; HoFH = Homozygous Familial Hypercholesterolemia; IP = Investigational Product; QM = every 4 weeks

The open-label, single-arm design and the treatment duration of 80 weeks of this study is appropriate to achieve the primary objective of the study. All subjects received evolocumab 420 mg SC QM using either 3 AI/Pen injections or 1 automated mini-doser (AMD) administration.

Objectives/endpoints

The objectives/endpoint of Study 20120124 are presented in **Table 21**.

Table 21. Objectives and endpoints of Study 20120124

Objectives	**Endpoints**
Primary	
• to describe the safety and tolerability of 80 weeks of subcutaneous (SC) evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• treatment-emergent adverse events at week 80
Secondary	
• to describe percent change and change from baseline in LDL-C, and on percent change from baseline in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio, in pediatric subjects 10 to 17 years of	• percent change from baseline at week 80 in: - LDL-C - non-HDL-C - ApoB - total cholesterol/HDL-C ratio

age with HeFH or HoFH after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	- ApoB/ApoA1 ratio • change from baseline in LDL-C at week 80
• to describe change from baseline in steroid hormones and the subject incidence of abnormal muscle and liver enzyme levels after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• change from baseline in steroid hormones (estradiol in females, testosterone in males; follicle-stimulating hormone [FSH], luteinizing hormone [LH], adenocorticotropic hormone [ACTH], dehydroepiandrosterone sulfate [DHEA-S], cortisol in all subjects) at week 80 • abnormal muscle and liver enzyme levels (creatine kinase [CK], aspartate aminotransferase [AST], or alanine aminotransferase [ALT]) at week 80
• to describe changes from baseline in carotid intima-media thickness (cIMT) after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• change in cIMT from baseline at week 80
• to describe change from baseline in growth and pubertal development parameters at measured timepoints with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• change from baseline in growth (height and weight) and pubertal development (Tanner staging) at weeks 24, 48, and 80
Exploratory	
• to describe change and percent change at measured timepoints in LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, very low-density lipoprotein cholesterol (VLDL-C), HDL-C, ApoA1, Lp(a), with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• change from baseline and percent change from baseline at each scheduled assessment in the following: - LDL-C - total cholesterol - non-HDL-C - ApoB - total cholesterol/HDL-C ratio - ApoB/ApoA1 ratio - triglycerides - VLDL-C - HDL-C - ApoA1 - Lp(a)
• to describe change at measured timepoints in proprotein convertase subtilisin/kexin type 9 (PCSK9) and high sensitivity C-reactive protein (hsCRP) with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• change from baseline at each scheduled assessment in the following: - PCSK9 - hsCRP
• to evaluate the incidence of abnormal neurological examination findings after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• abnormal neurological examination findings
• to assess cognitive function, assessed using the change from baseline in the components of the Cogstate battery at each scheduled administration, after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH	• change from baseline score in the components of the Cogstate battery at each scheduled administration
• to investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of	• select safety laboratory values and vital signs at each scheduled assessment • anti-evolocumab antibody (binding and neutralizing) formation

evolocumab in pediatric subjects 10 to 17 years of age with HeFH	• electrocardiogram (ECG) parameters (such as RR, PR, QRS, QT, and corrected QT interval [QTc] intervals) at each scheduled assessment
• in subjects consenting to the optional pharmacogenetics analysis, to investigate potential correlations of study data including the subject response to evolocumab with genetic variation in markers of PCSK9 signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability	• serum concentration of evolocumab at each scheduled assessment

The primary and secondary objectives/endpoints are considered appropriate. The primary objective of this study was to characterize the safety and tolerability of long-term administration of evolocumab among pediatric patients with HeFH or HoFH. The key secondary objective was to characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C and other lipid parameters.

Sample size

This study planned to enroll approximately 124 subjects, including an estimated 70% rollover rate for subjects with HeFH from parent Study 20120123 and approximately 10 de novo subjects with HoFH.

Randomisation

N/A

Blinding (masking)

N/A

Statistical methods

The interim analysis was conducted when all the enrolled subjects in the study had the opportunity to experience 28 weeks of investigation product exposure or had early terminated from the study. At that time, the database related to the interim analyses of the study was cleaned, locked and a snapshot was taken. Statistical analysis in this interim analysis was descriptive in nature for all safety and efficacy endpoints if applicable. No statistical hypotheses testing or missing value imputation was planned.

There was no study stopping rule for either futility or efficacy and the current design and execution of the study will continue without any changes regardless of the result of the interim analysis.

Results

Participant flow

<u>HeFH subjects</u>

A total of 150 pediatric HeFH subjects who participated in Study 20120123 entered open-label extension Study 20120124; 101 subjects received evolocumab in the parent study and 49 subjects received placebo in the parent study (**Table 22**). As of the data cut-off, 40 (26.7%) HeFH subjects

were still on evolocumab and 104 (69.3%) subjects completed evolocumab in the study. Six (4.0%) subjects discontinued evolocumab; all discontinued evolocumab at the subject's request. As of data cut-off, 105 (70.0%) subjects have completed the study, 42 (28.0%) subjects are still on study, and 3 (2.0%) have discontinued the study by withdrawing consent.

HoFH subjects

Thirteen de-novo pediatric HoFH subjects were enrolled in the open-label extension study. One HoFH subject did not receive any evolocumab and was not included in the FAS (**Table 22**). As of the data cut-off, all the remaining subjects have either completed evolocumab (11 [84.6%]) or discontinued evolocumab (1 [7.7%]; at subject's request). As of data cut-off, all subjects have either completed the study (11 [84.6%]) or discontinued the study (2 [15.4%], 11 years old and 12 years old patients).

Table 22. Subject disposition with discontinuation reason - Study 20120124 (all enrolled subjects)

	HeFH			HoFH	Total
	Placebo QM in Parent Study (N = 49) n (%)	EvoMab 420 mg QM in Parent Study (N = 101) n (%)	Overall (N = 150) n (%)	EvoMab 420 mg QM (N = 13) n (%)	EvoMab 420 mg QM (N = 163) n (%)
Investigational product accounting					
Subjects who never received investigational product	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (0.6)
Subjects who received investigational product	49 (100.0)	101 (100.0)	150 (100.0)	12 (92.3)	162 (99.4)
Subjects who are still on investigational product	15 (30.6)	25 (24.8)	40 (26.7)	0 (0.0)	40 (24.5)
Subjects who completed investigational product	32 (65.3)	72 (71.3)	104 (69.3)	11 (84.6)	115 (70.6)
Subjects who discontinued investigational product	2 (4.1)	4 (4.0)	6 (4.0)	1 (7.7)	7 (4.3)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject request	2 (4.1)	4 (4.0)	6 (4.0)	1 (7.7)	7 (4.3)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol-specified criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study completion accounting					
Subjects who are still on study	15 (30.6)	27 (26.7)	42 (28.0)	0 (0.0)	42 (25.8)
Subjects who completed study	33 (67.3)	72 (71.3)	105 (70.0)	11 (84.6)	116 (71.2)
Subjects who discontinued study	1 (2.0)	2 (2.0)	3 (2.0)	2 (15.4)	5 (3.1)
Withdrawal of consent from study	1 (2.0)	2 (2.0)	3 (2.0)	1 (7.7)	4 (2.5)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (0.6)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = number of subjects with HeFH enrolled from parent study 20120123 and number of subjects with HoFH enrolled in this study; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous); HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; COVID-19 = coronavirus disease 2019

Interim analysis data cutoff date: 08JUN2020

Number of subjects screened: 163; First subject enrolled: 10SEP2016; Last subject completed study: 28MAY2020.

HeFH

Almost all patients from Study 20120123, i.e. 150 out of 157 patients, rolled over to the OLE study, of which 101 subjects received evolocumab in the parent study and 49 subjects received placebo. At the data cut-off, already a high proportion of HeFH patients (70.0%) completed the study and 28.0 % HeFH were still participating the study. At the data cut-off, the percentage of HeFH patients who discontinued the study was relatively low (2.0%, n=3); all discontinued due to withdrawal of consent from the study.

HoFH

Thirteen de-novo pediatric HoFH patients enrolled in the OLE study, of which one HoFH subject did not receive any evolocumab and was not included in the FAS. At the data cut-off, HoFH patients have either completed the study (84.6%, n=11) or discontinued the study (15.4%, n=2). The reasons for the discontinuation of the study was withdrawal of consent and lost to follow-up. Six HoFH subjects aged 10-≤11 years (for whom an indication is being sought) were enrolled in this study of which one discontinued the study. As such, the number of HoFH subjects aged 10-≤11 years who completed the study (n=5) is limited, however, acceptable considering the rarity of the disease.

To date, none of the HeFH or HoFH patients discontinued evolocumab treatment due to an adverse event, which is reassuring.

Protocol deviations

HeFH Subjects

Overall, 9 (6.0%) HeFH subjects had at least 1 IPD in the categories described in the **Table 23**. Four (2.7%) subjects had IPDs reported as 'other'; these consisted of 1 subject enrolling into the Study 2 days prior to completing all procedures for the parent Study 20120123 and 3 instances of incomplete consent/assent forms in which either the subject, investigator, or both had not signed the appropriate sections of the consent form. All 3 instances of incomplete consent/assent were resolved. One (0.7%) HeFH subject had an eligibility deviation for not having a legally acceptable representative consent.

Thirty-seven (24.7%) HeFH subjects had a non-important protocol deviation due to COVID-19. All COVID-19 protocol deviations occurred in HeFH subjects. The most frequent protocol deviation due to COVID-19 was alternative site visits (25 [15.3%]), partial missed visit (25 [15.3%]), and alternative evolocumab administration (21 [12.9%]).

HoFH subjects

No HoFH had an IPD or protocol deviation due to COVID-19.

Table 23. Summary of important protocol deviations - Study 20120124 (all enrolled subjects)

	HeFH		HoFH	Total
	Placebo QM in Parent Study (N = 49) n (%)	EvoMab 420 mg QM in Parent Study (N = 101) n (%)	EvoMab 420 mg QM (N = 13) n (%)	EvoMab 420 mg QM (N = 163) n (%)
Number of subjects with at least 1 important protocol deviation	1 (2.0)	8 (7.9)	0 (0.0)	9 (5.5)
Important protocol deviations	1 (2.0)	8 (7.9)	0 (0.0)	9 (5.5)
No legally acceptable representative consent	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.6)
Other	0 (0.0)	4 (4.0)	0 (0.0)	4 (2.5)
Received prohibited lipid-regulating medications	1 (2.0)	1 (1.0)	0 (0.0)	2 (1.2)
Received wrong IP box	0 (0.0)	2 (2.0)	0 (0.0)	2 (1.2)

EvoMab = Evolocumab (AMG 145); HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; IP = Investigational Product; N = number of subjects with HeFH enrolled from parent Study 20120123 and number of subjects with HoFH enrolled in this study; QM = monthly (subcutaneous)
Interim analysis data cutoff date: 08JUN2020
Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.

The percentage of clinically important protocol deviations were relatively low (5.5%) and not considered to impact data interpretation.

Recruitment

This study was conducted at 46 centers in 23 countries in the regions of Asia Pacific (7.4%), Europe (64.4%), Latin America (16.0%), and North America (12.3%)The first subject was enrolled on 10 September 2016. The last subject last visit on or prior to data cut off date (08 June 2020) was 28 May 2020.

The interim analyses presented in this report are based on a database snapshot date of 29 July 2020.

This study was a multicentre study (n=46). Considering that more than half of the subjects (64.4%) were from Europe, the population is sufficiently representative of Europe.

Conduct of the study

The original protocol was finalized on 27 May 2015 (0 subjects enrolled between this date and the date of the first amendment). Subsequently, contingency measures were implemented to manage study conduct during the COVID-19 pandemic. These measures included remote source data review and source data verification, direct to patient delivery of evolocumab supply (home delivery), and alternative subject visit procedures (virtual or remote visits) (**Table 24**).

Table 24. Protocol Amendment Summary

Amendment	**Major changes**
Original Protocol 27 May 2015	

(0 subjects enrolled between this date and the date of the first amendment)	
Amendment 1 *10 September 2015* *(0 subjects enrolled between this date and the date of the next amendment)*	• added safety endpoint of incidence of abnormal neurological examination at week 80 • changed endpoint of change from baseline in cognitive function at week 80 as assessed by Cogstate battery from an exploratory endpoint to a safety endpoint • added that adverse device effects and disease related events would be collected at every study visit • added collection of sample for assessment of fasting vitamins A, D, E, and K levels • deleted papilla elevation from tanner stages (sexual maturity • ratings) for stage 1 male genital size
Amendment 2 *22 June 2016* *(42 subjects enrolled under this amendment)*	• clarified primary endpoint timepoint at week 80 • added language that defines baseline lab values for rollover and de novo subjects • clarified eligibility criteria; rollover subjects should not have experienced treatment-related serious adverse events in Study 20120123 • updated schedule of assessments and study procedures: - allowed for a 4-week screening window for rollover subjects and for those subjects who exceed the 4-week window noted which procedures must be redone - updated collection points for creatinine kinase - added additional analytes for urinalysis - removed thyroid stimulating hormone (TSH) as an analyte
Amendment 3 *26 April 2017* *(121 subjects enrolled under this amendment)*	• updated the number of sites expected • added AMD product information and option for device use • clarified enrollment should be on day 1 or as close as possible to day 1 and no earlier than 5 days prior to day 1 • aligned safety definitions and reporting procedures with current protocol template
Amendment 4 *27 May 2020* *(0 subjects enrolled under this amendment)*	• added interim analysis for all enrolled subjects • updated number of subjects expected to roll over from Study 20120123 into Study 20120124 • aligned with current protocol template: - removed language regarding the collection of disease related events - removed details from study monitoring and data collection to restrict Amgen (or designee) correcting obvious data errors in the clinical trial database

No amendments were made that would compromise the endpoints or outcomes of the study.

Baseline data

Demographics

HeFH subjects

Study 20120124 was primarily designed as an open-label extension for pediatric HeFH subjects participating in Study 20120123. Demographic and baseline characteristics for HeFH subjects in this study were consistent with those provided above for Study 20120123.

In short, 55.3% of HeFH subjects were female, the majority (84.0%) were white, and 8.7% were of Hispanic/Latino ethnicity. Subjects were from Europe (65.3%), Latin America (17.3%), North America (13.3%), and Asia Pacific (4.0%). The mean (SD) age at the time of enrollment in Study 20120124 was 14.1 (2.5) years with the range of 10 to 18 years of age and 113 (75.3%) subjects were adolescents between 12 and 17 years of age. Eight HeFH subjects were 18 years old at the time of rollover into Study 20120124, however all subjects were ≤ 17 years old at the time of enrollment into the parent Study 20120123.

Mean (SD) LDL-C at baseline was 184.3 (46.1) mg/dL, total cholesterol was 249.5 (48.1) mg/dL, non-HDL-C was 202.6 (48.0) mg/dL, and PCSK9 was 282.9 (96.4) ng/mL. Mean (SD) hsCRP at baseline was 0.956 (1.311) mg/L and mean concentrations of vitamin A, D, E, and K were within normal reference ranges.

HoFH subjects

Study 20120124 also enrolled 13 de novo pediatric subjects with HoFH; 12 of these subjects received investigational product. The majority of HoFH subjects were male (83.3%) and white (75.0%). No HoFH subjects were of Hispanic/Lantino ethnicity. Subjects were from Europe (50.0%) and Asia Pacific (50.0%). The median (Q1, Q3) age at the time of enrollment was 11.5 (11.0, 13.0) years; 6 (46.2%) subjects were < 12 years old and 7 (53.8%) subjects were between 12- ≤17 years of age. All 12 HoFH subjects who received evolocumab in the study had documented genetic evidence of HoFH.

In general, de novo HoFH subjects had higher median (Q1, Q3) lipid parameter values at baseline compared to HeFH subjects rolling over from the parent study including LDL-C, non-HDL-C, total cholesterol, ApoB, Lp(A), and PCSK9. Median (Q1, Q3) HDL-C and vitamin D was lower in HoFH subjects at baseline compared to HeFH subjects. In HoFH subjects, median (Q1, Q3) LDL-C at baseline was 397.5 (342.5, 475.0) mg/dL, total cholesterol was 447.5 (411.8, 529.3) mg/dL, non-HDL-C was 410.8 (360.8, 491.0) mg/dL, and PCSK9 was 472.0 (339.0, 669.0) ng/mL. Median (Q1, Q3) hsCRP at baseline was 0.275 (0.185, 1.530) mg/L and median concentrations of vitamin A, D, E, and K were within normal reference ranges.

Medical history and background therapy

HeFH Subjects

Coronary heart disease (CHD) characteristics at baseline, including HeFH diagnosis, are summarized in **Table 25**. One (0.7%) subject had a history of stroke. The most common CHD risk factors were low HDL-C (38.0%) and family history of premature CHD (34.0%). All subjects in the FAS had diagnosis of HeFH at baseline. For HeFH subjects, 99 (66.0%) had genetic evidence of an FH-causing mutation, of which 96 showed evidence in the LDL receptor. No subjects had congestive heart failure.

All 150 (100.0%) HeFH subjects in the FAS were taking lipid-regulating medication at baseline including statins (149 [99.3%]) and ezetimibe (21 [14.0%]).

HoFH Subjects

Coronary heart disease characteristics at baseline, including HoFH diagnosis, are summarized in **Table 25**. One (8.3%) HoFH subject had a history of a coronary artery bypass graft. The most common CHD risk factors were low HDL-C (75.0%) and family history of premature CHD (41.7%). For HoFH

subjects, all 12 (100.0%) subjects showed genetic evidence supporting the diagnosis of HoFH via the LDL receptor at baseline of which 3 subjects with receptor negative mutation (<2% residual activity), 4 subjects with receptor defective (2 to 25% residual activity), and 5 subjects with receptor unknown (unclassified). No subjects had congestive heart failure.

All 12 (100.0%) subjects in the FAS were talking lipid-regulating medication at baseline including statins (100.0%) and ezetimibe (100.0%). No HoFH subjects in Study 20120124 were receiving lipoprotein apheresis therapy.

Table 25. Summary of baseline coronary heart disease characteristics - Study 20120124 (full analysis set)

	HeFH			HoFH	Total
Category Subcategory	Placebo QM in Parent Study (N = 49) n (%)	EvoMab 420 mg QM in Parent Study (N = 101) n (%)	Overall (N = 150) n (%)	EvoMab 420 mg QM (N = 12) n (%)	EvoMab 420 mg QM (N = 162) n (%)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (0.6)
Angina	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery bypass graft	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (0.6)
Percutaneous coronary intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular or peripheral arterial disease	1 (2.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)
Transient ischemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke/Cerebral infarction	1 (2.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)
Carotid or vertebral artery disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral arterial disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline CHD Risk Factors					
Current cigarette smoking	2 (4.1)	1 (1.0)	3 (2.0)	0 (0.0)	3 (1.9)
Hypertension	3 (6.1)	2 (2.0)	5 (3.3)	0 (0.0)	5 (3.1)
Type II diabetes mellitus	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Family history of premature coronary heart disease	20 (40.8)	31 (30.7)	51 (34.0)	5 (41.7)	56 (34.6)
Low HDL-C[a]	17 (34.7)	40 (39.6)	57 (38.0)	9 (75.0)	66 (40.7)
Subjects with 2 or more baseline CHD risk factors	6 (12.2)	11 (10.9)	17 (11.3)	5 (41.7)	22 (13.6)
Baseline factors for metabolic syndrome					
Elevated waist circumference[c]	7 (14.3)	14 (13.9)	21 (14.0)	0 (0.0)	21 (13.0)
Triglycerides ≥ 150 mg/dL	2 (4.1)	7 (6.9)	9 (6.0)	0 (0.0)	9 (5.6)
Low HDL-C [a]	17 (34.7)	40 (39.6)	57 (38.0)	9 (75.0)	66 (40.7)
SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or Hypertension	7 (14.3)	7 (6.9)	14 (9.3)	1 (8.3)	15 (9.3)
Fasting glucose ≥ 100 mg/dL	3 (6.1)	4 (4.0)	7 (4.7)	1 (8.3)	8 (4.9)
Subjects with baseline metabolic syndrome (3 or more factors) and without Type II diabetes mellitus	3 (6.1)	1 (1.0)	4 (2.7)	1 (8.3)	5 (3.1)

	HeFH			HoFH	Total
	Placebo QM in Parent Study (N = 49) n (%)	EvoMab 420 mg QM in Parent Study (N = 101) n (%)	Overall (N = 150) n (%)	EvoMab 420 mg QM (N = 12) n (%)	EvoMab 420 mg QM (N = 162) n (%)
Diagnosis of HeFH	49 (100.0)	101 (100.0)	150 (100.0)	0 (0.0)	150 (92.6)
Genetic evidence of an FH-causing mutation					
Yes	30 (61.2)	69 (68.3)	99 (66.0)	0 (0.0)	99 (61.1)
LDL Receptor	29 (59.2)	67 (66.3)	96 (64.0)	0 (0.0)	96 (59.3)
Apo B	1 (2.0)	2 (2.0)	3 (2.0)	0 (0.0)	3 (1.9)
PCSK9 Gain of Function	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	19 (38.8)	32 (31.7)	51 (34.0)	0 (0.0)	51 (31.5)
Simon-Broome	7 (14.3)	9 (8.9)	16 (10.7)	0 (0.0)	16 (9.9)
Dutch Lipid Clinic Network	10 (20.4)	22 (21.8)	32 (21.3)	0 (0.0)	32 (19.8)
MEDPED	2 (4.1)	1 (1.0)	3 (2.0)	0 (0.0)	3 (1.9)
Diagnosis of HoFH	0 (0.0)	0 (0.0)	0 (0.0)	12 (100.0)	12 (7.4)
Genetic evidence supporting the diagnosis of HoFH					
Yes	0 (0.0)	0 (0.0)	0 (0.0)	12 (100.0)	12 (7.4)
LDL Receptor	0 (0.0)	0 (0.0)	0 (0.0)	12 (100.0)	12 (7.4)
Apo B	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PCSK9 Gain of Function	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ARH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
LDLR activity in homozygosis[b]					
< 5% (null mutation)	0 (0.0)	0 (0.0)	0 (0.0)	3 (25.0)	3 (1.9)
5%-99% (defective mutation)	0 (0.0)	0 (0.0)	0 (0.0)	6 (50.0)	6 (3.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	6 (50.0)	6 (3.7)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Zygosity of mutation					
Homozygous	0 (0.0)	0 (0.0)	0 (0.0)	9 (75.0)	9 (5.6)
Heterozygous	0 (0.0)	0 (0.0)	0 (0.0)	3 (25.0)	3 (1.9)

ApoB = apolipoprotein B; ARH = autosomal recessive hypercholesterolemia; CHD = coronary heart disease; DBP = diastolic blood pressure; EvoMab = Evolocumab (AMG 145); FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL Receptor = low-density lipoprotein Receptor; LDLR = low-density lipoprotein Receptor; MEDPED = make early diagnosis to prevent early deaths; PCSK9 = proprotein convertase subtilisin/kexin type 9; QM = monthly (subcutaneous); SBP = systolic blood pressure

Interim analysis data cutoff date: 08JUN2020

N = number of subjects with HeFH enrolled and dosed from parent Study 20120123 and number of subjects with HoFH enrolled and dosed in this study.

Family history of premature coronary heart disease (CHD) is CHD in first degree relative male at less than or equal to 55 years or female at less than or equal to 65 years of age.

[a] low HDL-C defined as baseline HDL-C < 40 mg/dL for both males and females with age 10 to < 16 years; < 40 mg/dL in male and < 50 mg/dL in female with age ≥ 16 years.

[b] Subjects may have multiple mutations. The subcategories are not mutually exclusive.

HeFH

Since almost all patients (96%) from Study 20120123 rolled over to Study 20120124, the baseline data is generally consistent with those described for Study 20120123.

HoFH

In Study 20120124, 12 HoFH patients received IP. Most of the pediatric HoFH patients were male (83.3%, n=10) and white (75.0%, n=9). Six (46.2%) patients were 10 to < 12 years of age and 7 (53.8%) were between 12 and 17 years of age. The mean LDL-C at baseline was 10.3 mmol/L and all the HoFH patients in this study had HoFH diagnosis by genetic testing. Furthermore, all HoFH patients were on statin (100%) and ezetimibe (100%) therapy at baseline. No HoFH subjects in Study 20120124 were receiving lipoprotein apheresis therapy.

Numbers analysed

Overall, 162 subjects received at least 1 dose of evolocumab and were included in the FAS. One (0.6%) subject was excluded from the FAS as this subject did not receive any dose of evolocumab.

Outcomes and estimation

Secondary efficacy endpoints

- percent change from baseline to week 80 in LDL-C, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio as well as change from baseline in LDL-C at week 80

HeFH Subjects

Mean (SE) absolute reflexive LDL-C was 4.77 (1.24) mmol/L at baseline and 3.11 (0.15) mmol/L at week 80. The mean (SE) reduction from baseline (of parent Study 20120123) in reflexive LDL-C was 36.3% (2.5%) at week 80.

Reductions in reflexive LDL-C were observed by the first assessment at the week 12 timepoint and were maintained throughout the study both for subjects randomized to the evolocumab in the parent and subjects randomized to placebo in the parent study; mean (SE) reductions of 44.4% (1.7) at week 12, 40.6% (2.2) at week 48, and 36.3% (2.5) at week 80 (**Table 17**, **Table 26** and

Figure 5). Similar reductions from baseline in calculated LDL-C were observed; mean (SE) reductions of 44.4% (1.7) at week 12, 40.5% (2.2) at week 48, and 36.2% (2.5) at week 80.

Evolocumab also improved other secondary lipid endpoints, including reduction from baseline to week 80 of non-HDL-C (mean [SE] 33.0% [2.4]), ApoB (26.0% [2.3]), total cholesterol/HDL-C ratio (28.9% [2.3]), and ApoB/ApoA1 (30.6% [2.5]).

HoFH Subjects

To note: Due to the small sample size and non-normal distribution, efficacy results for HoFH are presented using the median rather than mean.

Median (Q1, Q3) absolute reflexive LDL-C was 10.30 mmol/L (8.87, 12.31) at baseline and 8.00 mmol/L (5.67, 12.12) at week 80 (**Table 27** and

Figure 5).

Reductions in reflexive LDL-C were observed by the first assessment at the week 12 timepoint and was maintained throughout the study; median (Q1, Q3) reductions of 12.2 % (-2.6, 32.5) at week 12, 14.5 % (-3.7, 38.6) at week 48, and 14.3 % (-3.5, 40.6) at week 80. Near identical reductions from baseline in calculated LDL-C were observed at week 12, 24, and 80.

An analysis of efficacy in the subset of 6 HoFH subjects < 12 years of age in Study 20120124 was carried out to evaluate consistency of effect in these younger subjects relative to subjects 12 to 17 years of age enrolled in Study 20110271. For the 6 HoFH subjects < 12 years of age in Study 20120124, the median (Q1, Q3) reduction from baseline in calculated LDL-C was 12.2% (0.6%, 26.2%) at week 12, 4.6% (-3.7%, 41.3%) at week 48, and 19.2 % (1.2%, 37.2%) at week 80.

Evolocumab also improved other secondary lipid endpoints, including reductions from baseline to week 80 in non-HDL-C (median [Q1, Q3] 13.0 % [-2.7%, 40.7%]), ApoB (19.2% [-11.6%, 33.3%]), and ApoB/ApoA1 ratio (3.0% [-9.3, 35.7]). For total cholesterol/HDL-C ratio, inter-subject variability was large; reductions were observed at week 12 (median [Q1, Q3]; 6.2% [-12.8, 29.1]) and week 48 (5.5% [-6.6, 28.2]), but not at week 80 (3.7% [-7.6, 41.2].

Table 26. Summary of secondary efficacy results for HeFH subjects at week 80 - Study 20120124 (full analysis set; interim analysis)

		HeFH		
-		Placebo QM in Parent Study (N = 49)	EvoMab 420 mg QM in Parent Study (N = 101)	Overall (N = 150)
Calculated LDL-C - % change from baseline to week 80	Mean	-38.90	-35.01	-36.23
	SE	4.58	3.04	2.53
Reflexive LDL-C - % change from baseline to week 80	Mean	-38.90	-35.08	-36.27
	SE	4.58	3.03	2.52
Calculated LDL-C - change from baseline (mg/dL) to week 80	Mean	-74.0	-63.7	-66.9
	SE	9.2	5.4	4.7
Reflexive LDL-C - change from baseline (mg/dL) to week 80	Mean	-74.0	-63.8	-66.9
	SE	9.2	5.4	4.7
Non-HDL-C - % change from baseline to week 80	Mean	-35.05	-32.06	-33.00
	SE	4.22	2.87	2.36
ApoB - % change from baseline to week 80	Mean	-29.40	-24.35	-25.98
	SE	3.30	2.94	2.26
TC/HDL-C ratio - % change from baseline to week 80	Mean	-31.03	-27.91	-28.88
	SE	4.13	2.71	2.26
ApoB/ApoA1 ratio - % change from baseline to week 80	Mean	-32.94	-29.40	-30.55
	SE	4.15	3.13	2.50

ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; EvoMab = Evolocumab (AMG145); HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; N = number of subjects with HeFH enrolled and dosed from parent Study 20120123; QM = monthly (subcutaneous); TC = total cholesterol

Interim analysis data cutoff date: 08JUN2020

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

Table 27. Summary of Secondary Efficacy Results in HoFH subjects at week 80 - Study 20120124 (full analysis set; interim analysis)

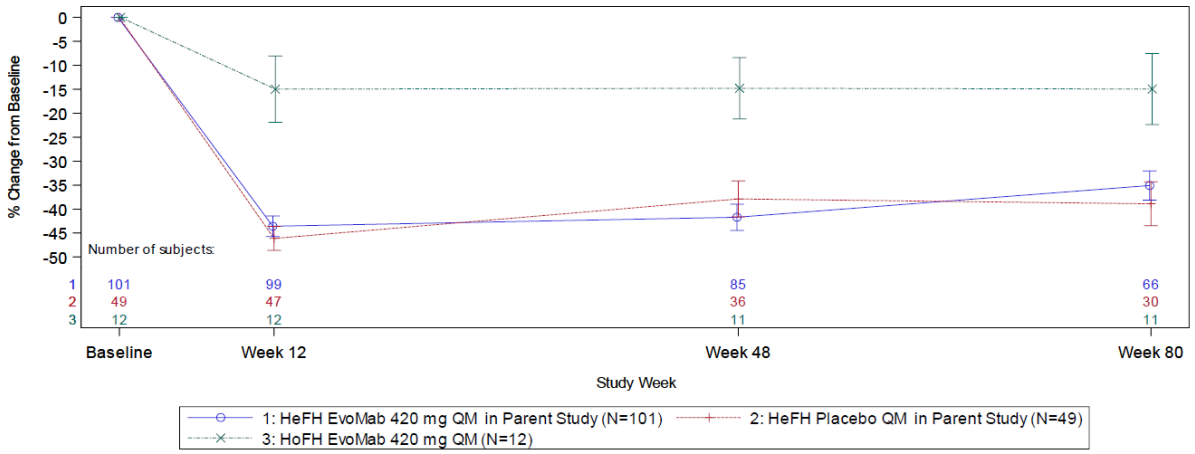
		HoFH
		EvoMab 420 mg QM (N = 12)
Calculated LDL-C - % change from baseline to week 80	Median	-14.29
	Q1, Q3	-40.61, 3.54
Reflexive LDL-C - % change from baseline to week 80	Median	-14.29
	Q1, Q3	-40.61, 3.54
Calculated LDL-C - change from baseline (mg/dL) to week 80	Median	-36.5
	Q1, Q3	-180.5, 16.0
Reflexive LDL-C - change from baseline (mg/dL) to week 80	Median	-36.5
	Q1, Q3	-180.5, 16.0
Non-HDL-C - % change from baseline to week 80	Median	-13.03
	Q1, Q3	-40.68, 2.69
ApoB - % change from baseline to week 80	Median	-19.17
	Q1, Q3	-33.33, 11.59
Total cholesterol/HDL-C ratio - % change from baseline to week 80	Median	3.71
	Q1, Q3	-41.17, 7.57
ApoB/ApoA1 ratio - % change from baseline to week 80	Median	-2.96
	Q1, Q3	-35.71, 9.30

ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; EvoMab = Evolocumab (AMG145); HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; N = number of subjects with HoFH enrolled and dosed in this study; QM = monthly (subcutaneous); TC = total cholesterol

Interim analysis data cutoff date: 08JUN2020

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

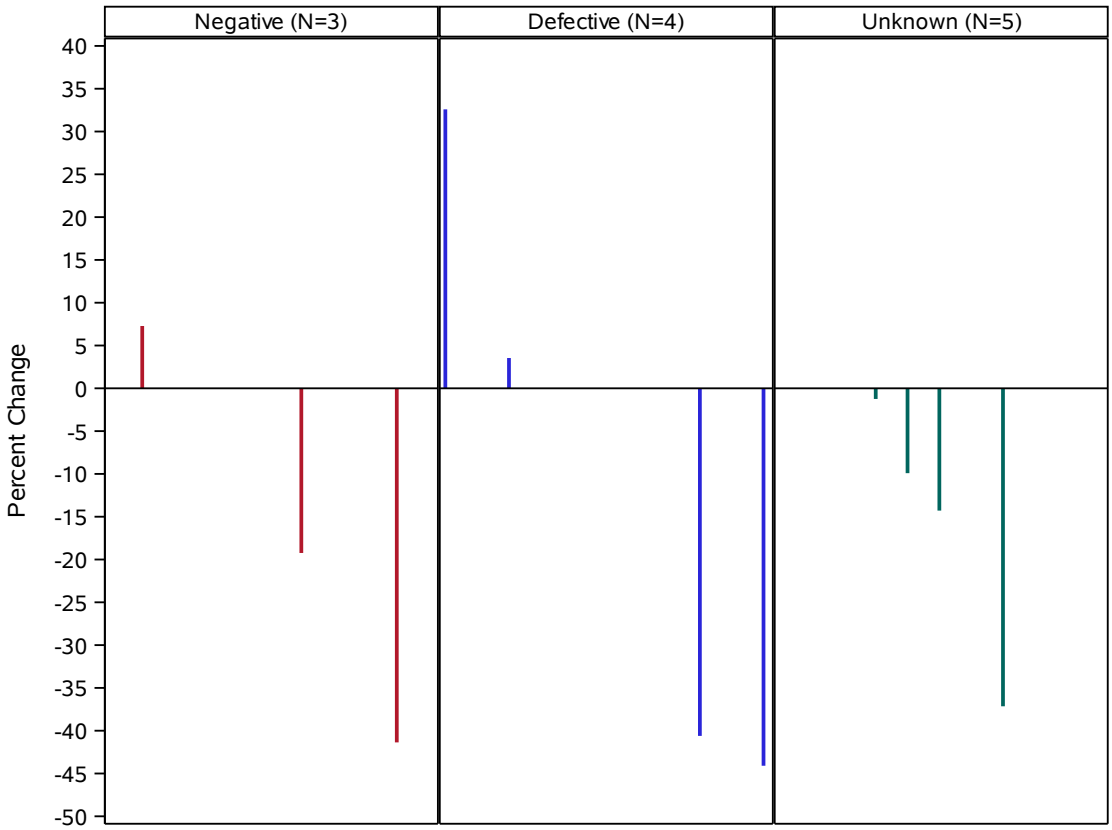
Figure 5. Plot of Mean Percent Change From Baseline in LDL-C by Scheduled Visit – Study 20120124 (full analysis set)



N = number of subjects with HeFH enrolled and dosed from parent Study 20120123 and number of subjects with HoFH enrolled and dosed in this study.
EvoMab = Evolocumab(AMG 145); QM = monthly (subcutaneous); LDL-C = low-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.
When calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, the ultracentrifugation LDL-C value from the same blood sample will be used instead, if available.

A waterfall plot of the LDL-C lowering effect at week 80 by LDLR mutation status at baseline for pediatric subjects with HoFH in Study 20120124 is provided in **Figure 6**. There were 3 subjects with receptor negative, 4 subjects with receptor defective, and 5 subjects with receptor unknown.

Figure 6. Water Waterfall Plot of Percent Change from Baseline in LDL-C at Week 80 for HoFH Subjects by LDLR Mutation Status - Study 20120124 (Full Analysis Set)



Evolocumab therapy resulted in a consistent LDL-C lowering effect from the start of the OLE study up to week 80 in both subsets of pediatric HeFH and HoFH subjects. For the HeFH subjects randomized to evolocumab treatment in the parent study, the reductions in LDL-C were maintained through week 80, thereby demonstrating maintenance of effect over a period of 2 years (104 weeks across both studies). The HeFH subjects randomized to placebo in the parent study demonstrated LDL-C reductions by the first time points of 12 weeks. Overall, the mean LDL-C reductions in the HeFH subset were 44.4%, 40.6% and 36.3% at week 12, 48 and 80, respectively. As expected, LDL-C reductions were lower in HoFH subjects compared with HeFH subjects. For HoFH subjects, the median LDL-C reductions were 12.2%, 14.5%, and 14.3% at week 12, 48 and 80, respectively. The effect size in median LDL-C reduction of 12-14.5% with the 420 mg QM regimen observed in the pediatric HoFH population in Study 20120124 appears somewhat lower than those observed with the 420 mg QM regimen in the studies previously submitted, i.e. Study 20110233 (TESLA) and Study 20110271 (TAUSSIG) in the overall HoFH population consisting adult and pediatric subjects 12 years of age and over (32% and 16.3%, respectively). However, the effect size was consistent with the median LDL-C reduction in the subset of 14 adolescents HoFH from Study 20110271 who received the 420 mg QM regimen or the (higher dose) 420 mg Q2W regimen (13.3%, 8.1%, 8.7%, 9.5%, and 20.0% at weeks 48, 96, 144, 192, and 216, respectively; see also section "supportive study"). Although the pediatric HoFH subjects showed a slightly less LDL-C lowering effect compared with the overall HoFH population, the LDL-C lowering effect in the pediatric patients is still considered substantial. The efficacy results according to LRLR mutation demonstrated that treatment with evolocumab leads to a reduction in LDL-C levels regardless of the type of LDLR mutation. However, within each subgroup of LDLR mutation there was a large degree of intersubject variability including non-responders which, however, were in the minority.

For the HoFH subjects 10 - ≤11 years of age, the median LDL-C reduction was comparable with the overall pediatric HoFH population (12.2%, 4.6% and 19.2% at week 12, week 48 and week 80, respectively).

Furthermore, for both the pediatric HeFH and HoFH subsets, the findings of LDL-C lowering effect were supported by beneficial effects observed for other lipid parameters in e.g. non-HDL-C, ApoB, Total cholesterol/HDL-C ratio and ApoB/apoA1 ratio.

Overall, the data of this OLE study confirmed the earlier finding of the long-term lowering LDL-C effect with evolocumab.

- change in cIMT from baseline at week 80

HeFH Subjects

In HeFH subjects, mean baseline values in each treatment group at each site were < 0.6 mm (**Table 28**). The mean change from baseline to week 24, 48, and 80 at every site assessed was negative (indicating a reduction in thickness) for subjects who received evolocumab in the parent study with the exception of anterior and posterior left common carotid artery (LCCA) at week 48 which were marginally positive. Similarly, the mean change from baseline to week 24, 48, and 80 at all 6 sites assessed were negative for subjects who received placebo in the parent study with the exception of lateral right common carotid artery (RCCA) week 24 and posterior LCCA week 24 and 48.

HoFH Subjects

Eight of 12 HoFH subjects had cIMT data. In HoFH subjects, median baseline value in the lateral and posterior LCCA was < 0.6 mm. The median changes from baseline to week 24, 48, and 80 were largely negative in the HoFH group with a few exceptions; week 24 (lateral LCCA), week 48 (lateral RCCA, lateral LCCA), and week 80 (anterior RCCA, posterior RCCA).

Table 28. Summary of Carotid intima-media thickness (cIMT) - Average of largest RCCA and LCCA by scheduled visit – Study 2010124 (full analysis set – actual treatment)

	HeFH			HoFH	Total
	Placebo QM in Parent Study (N = 49)	EvoMab 420 mg QM in Parent Study (N = 101)	Overall (N = 150)	EvoMab 420 mg QM (N = 12)	EvoMab 420 mg QM (N = 162)
Baseline					
n	43	79	122	8	130
Mean	0.571	0.587	0.581	0.620	0.584
SD	0.063	0.065	0.064	0.067	0.065
SE	0.010	0.007	0.006	0.024	0.006
Median	0.560	0.580	0.580	0.615	0.580
Q1, Q3	0.530, 0.630	0.540, 0.630	0.540, 0.630	0.570, 0.650	0.540, 0.630
Min, Max	0.45, 0.71	0.46, 0.76	0.45, 0.76	0.54, 0.75	0.45, 0.76
Week 24					
n	21	46	67	8	75
Mean	0.587	0.572	0.576	0.626	0.582
SD	0.067	0.057	0.060	0.101	0.067
SE	0.015	0.008	0.007	0.036	0.008
Median	0.580	0.570	0.570	0.625	0.580
Q1, Q3	0.540, 0.630	0.540, 0.600	0.540, 0.620	0.585, 0.635	0.540, 0.620
Min, Max	0.43, 0.71	0.47, 0.77	0.43, 0.77	0.48, 0.84	0.43, 0.84
Change from baseline to week 24					
n	19	36	55	7	62
Mean	-0.005	-0.019	-0.014	-0.027	-0.016
SD	0.047	0.047	0.047	0.076	0.050
SE	0.011	0.008	0.006	0.029	0.006
Median	0.010	-0.010	-0.010	0.000	-0.005
Q1, Q3	-0.010, 0.030	-0.045, 0.010	-0.040, 0.010	-0.080, 0.040	-0.040, 0.010
Min, Max	-0.13, 0.04	-0.12, 0.09	-0.13, 0.09	-0.16, 0.06	-0.16, 0.09
Week 48					
n	24	47	71	8	79
Mean	0.560	0.571	0.567	0.644	0.575
SD	0.057	0.057	0.057	0.111	0.068
SE	0.012	0.008	0.007	0.039	0.008
Median	0.555	0.570	0.570	0.630	0.570
Q1, Q3	0.515, 0.610	0.540, 0.610	0.530, 0.610	0.600, 0.650	0.530, 0.620
Min, Max	0.45, 0.68	0.41, 0.72	0.41, 0.72	0.50, 0.89	0.41, 0.89

	HeFH			HoFH	Total
	Placebo QM in Parent Study (N = 49)	EvoMab 420 mg QM in Parent Study (N = 101)	Overall (N = 150)	EvoMab 420 mg QM (N = 12)	EvoMab 420 mg QM (N = 162)
Change from baseline to week 48					
n	22	38	60	7	67
Mean	-0.019	-0.016	-0.017	-0.023	-0.018
SD	0.034	0.044	0.040	0.060	0.042
SE	0.007	0.007	0.005	0.023	0.005
Median	-0.025	-0.020	-0.020	-0.010	-0.020
Q1, Q3	-0.050, 0.010	-0.030, 0.010	-0.040, 0.010	-0.060, 0.020	-0.040, 0.010
Min, Max	-0.08, 0.04	-0.14, 0.11	-0.14, 0.11	-0.14, 0.03	-0.14, 0.11
Week 80					
n	23	43	66	7	73
Mean	0.555	0.571	0.566	0.657	0.574
SD	0.056	0.052	0.053	0.090	0.063
SE	0.012	0.008	0.007	0.034	0.007
Median	0.570	0.580	0.570	0.630	0.580
Q1, Q3	0.500, 0.590	0.530, 0.600	0.530, 0.600	0.590, 0.670	0.530, 0.600
Min, Max	0.47, 0.68	0.46, 0.69	0.46, 0.69	0.59, 0.85	0.46, 0.85
Change from baseline to week 80					
n	21	33	54	6	60
Mean	-0.021	-0.015	-0.017	-0.015	-0.017
SD	0.032	0.045	0.040	0.072	0.044
SE	0.007	0.008	0.005	0.030	0.006
Median	-0.030	-0.010	-0.020	0.005	-0.015
Q1, Q3	-0.040, 0.000	-0.040, 0.020	-0.040, 0.020	0.000, 0.030	-0.040, 0.020
Min, Max	-0.07, 0.04	-0.12, 0.06	-0.12, 0.06	-0.16, 0.03	-0.16, 0.06

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EvoMab = Evolocumab (AMG 145); HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LCCA = left common carotid artery; Max = maximum; Min = minimum; N = number of subjects with HeFH enrolled and dosed from parent Study 20120123 and number of subjects with HoFH enrolled and dosed in this study; n = number of subjects with observed data; QM = monthly (subcutaneous); RCCA = right common carotid artery
Interim analysis data cutoff date: 08JUN2020

Similarly, as observed in Study 20120123, treatment with evolocumab resulted in small mean reductions in cIMT from baseline to week 24, 48 and 80 in both subsets of subjects with HeFH and HoFH, suggestive of a beneficial effect of evolocumab with respect to atherogenesis. Nevertheless, the results in cIMT are considered too limited (short study period and small reduction) to draw firm conclusions. Moreover, statistical significance analyses have not been provided.

Exploratory efficacy endpoints

- percent change at measured timepoints (week 12, 48 and 80) in LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, very low-density lipoprotein cholesterol (VLDL-C), HDL-C, ApoA1, Lp(a)

HeFH Subjects

Overall, evolocumab improved lipid parameters at each study assessment with the following exceptions, no reduction in percent change from baseline was observed in triglycerides at week 12, reflective VLDL-C at week 12, and Lp(a) at week 80.

HoFH Subjects

Overall, evolocumab generally improved lipid parameters at each study assessment with the following exceptions, no reduction in percent change from baseline was observed in TC/HDL-C ratio at week 80, triglycerides at week 12 or 48, and calculated and reflective VLDL-C at week 12 or 48; and no increase in percent change from baseline was observed in ApoA1 at week 12 or HDL-C at any timepoint.

The exploratory efficacy endpoints showed that the treatment effect of evolocumab was generally consistent across the timepoints week 12, week 48 and week 80, with respect to total cholesterol, non-HDL-C, ApoB, TC/HDL-C ratio, ApoB/ApoA1 of the HeFH subset and total cholesterol, non-HDL-C, ApoB, TC/HDL-C ratio, ApoB/ApoA1 with some exceptions at several timepoints. Similar as observed in previous studies submitted during the initial MAA, evolocumab resulted in a small increase in HDL-C (range: 6-8.5% change from baseline) in the HeFH subset, whereas no increase in percent change from baseline was observed in the HoFH subset.

Summary of main studies

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

Table 29. Summary of Efficacy for trial Study 20120123

Title: Double-blind, Randomized, Multicenter, Placebo-controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-cholesterol (LDL-C) Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HAUSER-RCT)		
Study identifier	20120123	
Design	Double-blind, randomized, multicentre, placebo-controlled, parallel	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks Maximal 8 weeks After completion of the study, subjects were offered to participate in the 80 weeks OLE Study 20120124
Hypothesis	Superiority of evolocumab over placebo in reducing respective lipid values	
Treatments groups	Evolocumab	Evolocumab 420 mg QM, 24 weeks, n= 104.
	Placebo	Placebo, 24 weeks, n=53

Endpoints and definitions	Primary endpoint	% change in LDL-C from baseline to week 24	percent change from baseline to week 24 in LDL-C
	Secondary efficacy endpoint	Mean % change from baseline to weeks 22 and 24 in LDL-C	mean percent change from baseline to weeks 22 and 24 in LDL-C
		Change from baseline to week 24 in LDL-C	change from baseline to week 24 in LDL-C
		% change in non-HDL-C from baseline to week 24	percent change from baseline to week 24 in non-HDL-C
		% change in ApoB from baseline to week 24	percent change from baseline to week 24 in ApoB
		% change in TC/HDL-C ratio from baseline to week 24	percent change from baseline to week 24 in total cholesterol/HDL-C ratio
		% change in ApoB/ApoA1 from baseline to week 24	percent change from baseline to week 24 in ApoB/ApoA1 ratio

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS): subjects who received at least 1 dose of IP		
Descriptive statistics and estimate variability	Treatment group	Placebo	Evolocumab 420 mg QM
	Number of subject	53	104
	% change in LDL-C from baseline to week 24 (LS mean (SE))	-6.23 (3.08)	-44.53 (2.17)
Effect estimate per comparison	**Primary endpoint** % change in LDL-C from baseline to week 24 (LS mean (SE))	Comparison groups	Evinacumab versus placebo
		Treatment difference	-38.30
		95% CI	(-45.54, -31.06)
		p-value	<0.0001
Analysis description	**Secondary analysis**		
Effect estimate per comparison		-5.85 (2.67)	-47.97 (1.92)

	Mean % change from baseline to weeks 22 and 24 in LDL-C (LS mean (SE))	Treatment difference	-42.12
		95% CI	(-48.40, -35.85)
		p-value	<0.0001
	Change from baseline to week 24 in reflexive LDL-C (mg/dL) (LS mean (SE))	-9.0 (6.2)	-77.5 (4.4)
		Treatment difference	-68.6
		95% CI	(-83.1, -54.0)
		p-value	<0.0001
	% change in non-HDL-C from baseline to week 24 (LS mean (SE))	-6.14 (2.87)	-41.19 (2.01)
		Treatment difference	-35.04
		95% CI	(-41.79,-28.30)
		p-value	<0.0001
	% change in ApoB from baseline to week 24 (LS mean (SE))	-2.37 (2.70)	-34.85 (1.88)
		Treatment difference	-32.47
		95% CI	(-38.82, -26.13)
		p-value	< 0.0001
	% change in TC/HDL-C ratio from baseline to week 24 (LS mean (SE))	-4.66 (2.60)	-34.96 (1.82)
		Treatment difference	-30.30
		95% CI	(-36.40, -24.21)
		p-value	<0.0001
	% change in ApoB/ApoA1 from baseline to week 24 (LS mean (SE))	-0.63 (2.80)	-37.02 (1.95)
		Treatment difference	-36.38
		95% CI	(-42.97, -29.80)
		p-value	<0.0001

Table 30. Summary of Efficacy for trial Study 20120124 (Interim Analysis)

Open-label, Single-Arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for low-density lipoprotein (LDL-C) Reduction, as Add-On to Diet and Lipid-Lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH) HAUSER-OLE			
Study identifier	20120124		
Design	Open-label, single-arm, multicenter		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		80 weeks Maximal 8 weeks N/A
Hypothesis	No hypothesis. Objective was to describe the safety and tolerability of 80 weeks SC evolocumab		
Treatments groups	Evolocumab		Evolocumab 420 mg QM, 24 weeks, n= 104.
Endpoints and definitions	Secondary efficacy endpoint	% change in LDL-C from baseline to week 80	percent change from baseline to week 80 in LDL-C

	Secondary efficacy endpoint	% change in non-HDL-C from baseline to week 80	percent change from baseline to week 80 in non-HDL-C
		% change in ApoB from baseline to week 80	percent change from baseline to week 80 in ApoB
		% change in TC/HDL-C ratio from baseline to week 80	percent change from baseline to week 80 in total cholesterol/HDL-C ratio
		% change in ApoB/ApoA1 from baseline to week 80	percent change from baseline to week 80 in ApoB/ApoA1 ratio
		Change from baseline to week 80 in LDL-C	change from baseline to week 80 in LDL-C
Database lock	Interim analysis based on database snapshot date of 29 July 2020		

Results and Analysis

Analysis description	**Secondary analysis**	
	HeFH subset	
Effect estimate per comparison	% change in reflexive LDL-C from baseline to week 80 (mean (SE))	-36.27 (2.52)
	% change in non-HDL-C from baseline to week 80 (mean (SE))	-33.00 (2.36)
	% change in ApoB from baseline to week 80 (mean (SE))	-25.98 (2.26)
	% change in TC/HDL-C ratio from baseline to week 80 (mean (SE))	-28.88 (2.26)
	% change in ApoB/ApoA1 from baseline to week 80 (mean (SE))	-30.55 (2.50)
	Change from baseline to week 80 in LDL-C in mg/dL (mean(SE))	-66.9 (4.7)
	HoFH subset	
Effect estimate per comparison	% change in reflexive LDL-C from baseline to week 80 (median (Q1, Q3))	-14.29 (-40.61, 3.54)

	% change in non-HDL-C from baseline to week 80 (median (Q1, Q3))	-13.03 (-40.68, 2.69)
	% change in ApoB from baseline to week 80 (median (Q1, Q3))	-19.17 (-33.33, 11.59)
	% change in TC/HDL-C ratio from baseline to week 80 (median (Q1, Q3))	3.71 (-41.17, 7.57)
	% change in ApoB/ApoA1 from baseline to week 80 (median (Q1, Q3))	-2.96 (-35.71, 9.30)
	Change from baseline to week 80 in LDL-C in mg/dL (median (Q1, Q3))	-36.5 (-180.5, 16.0)

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

N/A

Clinical studies in special populations

No separate studies were performed in special patient populations.

2.3.3. Supportive study

Study 20110271: 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 (final clinical study report) - TAUSSIG

Interim data from Study 20110271, along with data from the parent Study 20110233, was presented in the initial MAA for evolocumab supporting the approval of the indication in adults and pediatric (12 years and over) subjects with HoFH. Subsequently, the final results from Study 20110271 has been submitted and assessed during a Type II variation application procedure in 2019 (EMEA/H/C/003766/II/0031). In the current extension procedure, the focus primarily lies on the data from pediatric subjects with HoFH from the final analysis of Study 20110271.

Methods

The study design has already been discussed during the initial MAA and the Type II variation application, but for understanding briefly described below.

This phase 2/3 open-label extension study was designed to characterize the safety, tolerability, and efficacy of long-term administration of evolocumab in subjects 12 to ≤ 80 years of age with HoFH or severe FH (ie, all those not meeting the protocol criteria for HoFH). Non-apheresis subjects were

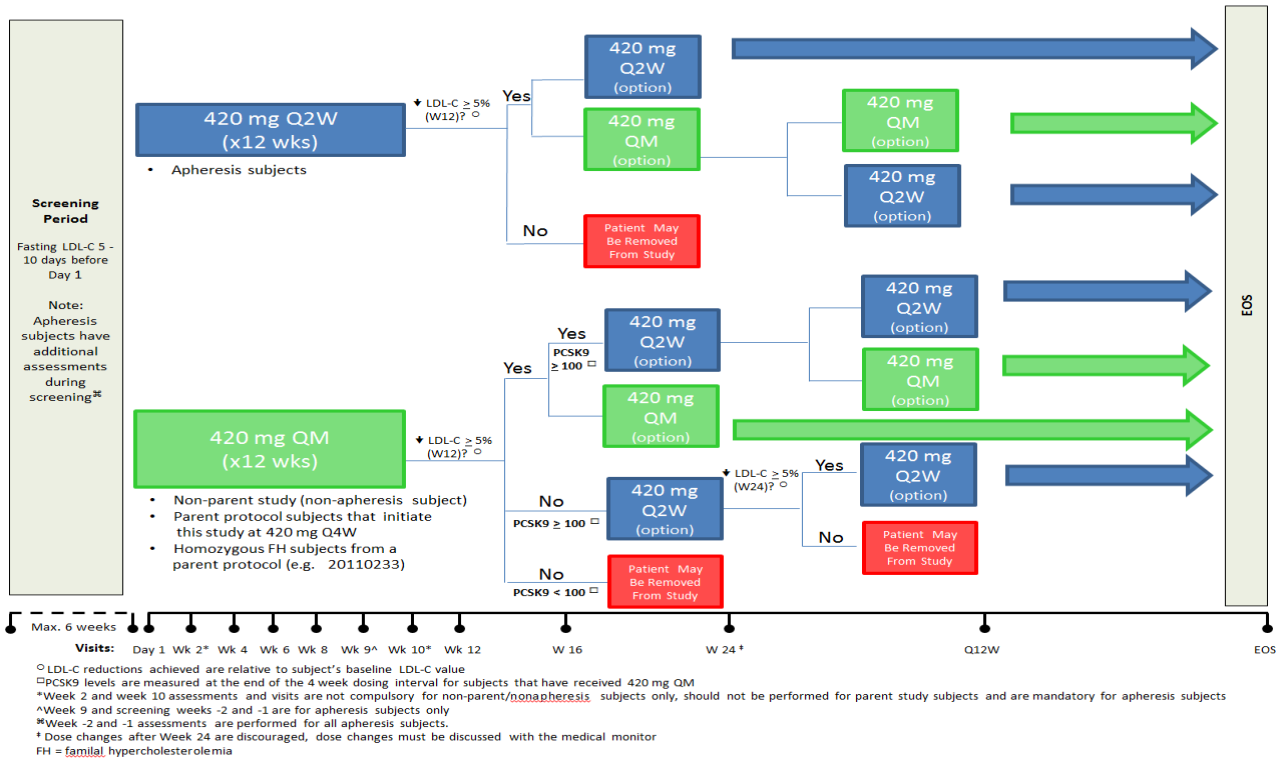
required to have elevated LDL C (≥ 100 mg/dL [2.6 mmol/L] for subjects with diagnosed CHD or risk equivalent and ≥130 mg/dL [3.4 mmol/L] for subjects without diagnosed CHD or risk equivalent). Apheresis subjects did not have a minimum LDL C requirement.

Subjects not on lipid apheresis at enrollment or within the prior 8 weeks (referred to throughout as non-apheresis subjects) initiated treatment with evolocumab 420 mg QM. Subjects on lipid apheresis at enrollment (referred to throughout as apheresis subjects) initiated treatment with evolocumab 420 mg once every 2 weeks (Q2W). Dose frequency changes (420 mg QM vs 420 mg Q2W) were permitted at open-label extension week 12, 24, or other visits with Amgen approval if subjects met specific protocol criteria. Subjects with < 5% LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL could discontinue evolocumab. If serum unbound PCSK9 was ≥ 100 ng/mL with QM dosing, the subject could switch to evolocumab 420 mg Q2W treatment, if clinically indicated (e.g., LDL-C goals not met). Subjects on apheresis with ≥ 5% LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL with Q2W treatment could switch to QM dosing.

Subjects visited the study centre Q2W or QM for evolocumab administration. After open-label extension week 24, subjects either continued to visit the study centre for administration of evolocumab or could decide to self-administer evolocumab in a non-clinic setting (eg, in the home) once they demonstrated competency with self-administration. The study design and treatment schema is provided in **Figure 7**.

The primary endpoint was the subject incidence of treatment-emergent adverse events. The secondary efficacy endpoints were percent change in LDL-C, non-HDL-C, Lp(a), ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio from baseline at each scheduled visit and response rate of subjects with 15% or greater reduction in LDL-C by scheduled visit.

Figure 7. Study Design and Treatment Schema for Study 20110271



○LDL-C reductions achieved are relative to subject's baseline LDL-C value
□PCSK9 levels are measured at the end of the 4 week dosing interval for subjects that have received 420 mg QM
*Week 2 and week 10 assessments and visits are not compulsory for non-parent/nonapheresis subjects only, should not be performed for parent study subjects and are mandatory for apheresis subjects
^Week 9 and screening weeks -2 and -1 are for apheresis subjects only
⌘Week -2 and -1 assessments are performed for all apheresis subjects.
ǂ Dose changes after Week 24 are discouraged, dose changes must be discussed with the medical monitor
FH = familal hypercholesterolemia

Results

Disposition of subjects

A total of 300 subjects were enrolled (a total of 246 subjects enrolled directly in Study 20110271 and 54 subjects rolled over from Study 20110233); 106 HoFH subjects including 14 (4.7%) pediatric subjects and 194 severe FH subjects. Of the 14 adolescent subjects, 3 subjects discontinued the study (withdrew consent). After the completion of the large, double-blind, placebo-controlled cardiovascular outcomes Study 20110118 (FOURIER), the study was closed as further collection of data from this open-label study would not contribute meaningfully to the long-term understanding of evolocumab safety.

Demography and Other Baseline Characteristics

The 14 pediatric subjects in Study 20110271 included 9 (64.3%) men/boys and 5 (35.7%) women/girls; median (Q1, Q3) age at baseline was 14.0 (14.0, 16.0) years. Most subjects were white (78.6%), followed by other (14.3%), and American Indian or Alaskan native (7.1%). Ethnicity was Hispanic or Latino for 14.3% of subjects. All 14 pediatric subjects had a diagnosis of HoFH, of which 10 were not on lipid apheresis at baseline and 4 were receiving lipid apheresis. Median (Q1, Q3) serum concentration of calculated LDL-C at baseline for pediatric subjects was 9.10 (7.97, 11.62) mmol/L. At baseline, all pediatric subjects were on moderate- (14.3%) or high-intensity statins (85.7%). Four subjects were receiving apheresis and 10 were not.

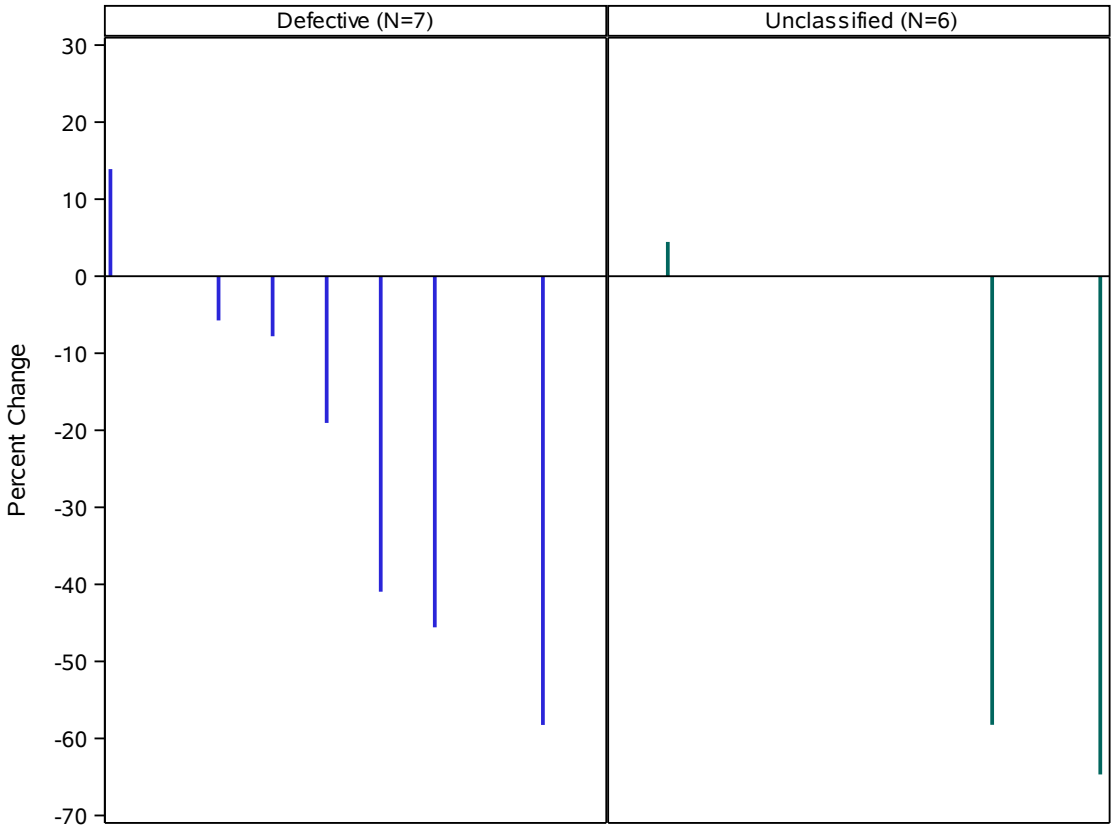
Efficacy results

In the 14 adolescent HoFH subjects in Study 20110271, median (Q1, Q3) reductions from baseline in calculated LDL-C at open-label extension weeks 48, 96, 144, 192, and 216 were 13.3% (3.7%, 56.2%), 8.1% (5.1%, 28.1%), 8.7% (- 16.6%, 26.2%), 9.5% (-7.4%, 21.2%), and 20.0% (-22.4%, 42.6%), respectively. To note, efficacy data at week 216 was available for 9 adolescent subjects with HoFH (n=2 apheresis and n=7 non-apheresis).

Furthermore, at most visits of open-label Study 20110271, pediatric subjects with HoFH had improvements in secondary lipid parameters. Reductions from baseline at week 216 of Study 20110271 included non-HDL-C (median [Q1, Q3] of 12.0% [-23.0%, 38.6%]), ApoB (8.9% [-15.5%, 28.1%]), and ApoB/ApoA1 ratio (17.2% [-1.2%, 37.8%]). For total cholesterol/ HDL-C ratio, inter-subject variability was large; reductions were observed at most, but not all, timepoints.

A waterfall plot of the LDL-C lowering effect at week 84 by LDLR mutation status at baseline for pediatric subjects with HoFH in Study 20110271 is provided in **Figure 8**. There were no subjects with a measurement at week 84 for receptor negative, 7 subjects with receptor defective, and 3 subjects with receptor unclassified.

Figure 8. Waterfall Plot of Percent Change from Baseline in LDL-C at Week 84 by LDLR Mutation Status Subgroup = Age < 18 - Study 20110271 (HoFH Analysis Set)



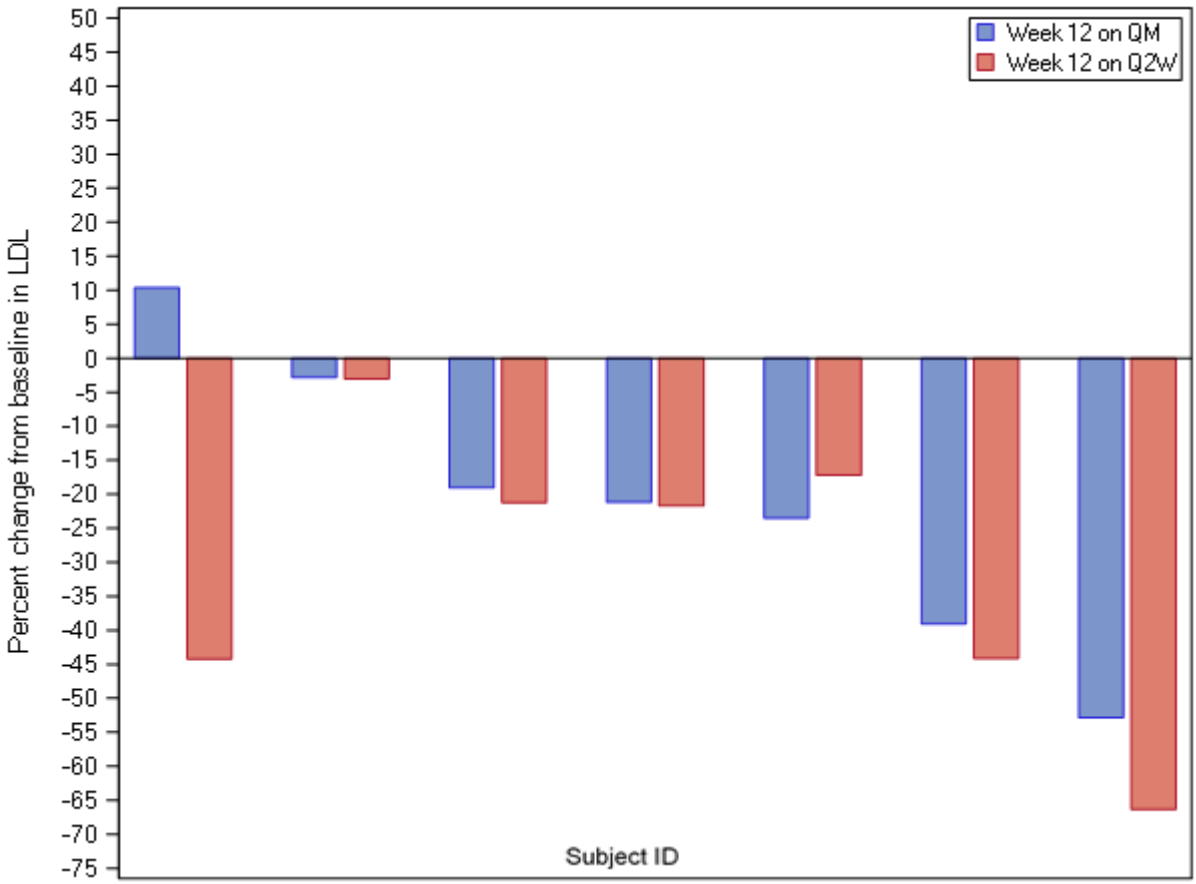
N = number of HoFH subjects enrolled and dosed in study 20110271.
HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor
Plot is based on observed data and no imputation is used for missing values.
Baseline LDL-C for parent study rollover subjects are defined at parent study baseline.
When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.
Program:/userdata/stat/amg145/meta/sbla_2020peds/analysis/reg_quest/figures/f-lb-wfplot-pchg-ldlrfc-ldlr-ads-s271.sas
Output:ffeu210521-04-001-501-lb-wfplot-pchg-ldlrfc-ldlr-ads-s271.rtf (Date Generated:29JUL21:00:47:41) Source Data:a0271ad.adlbeff2, a0271f.adsl, a0271f.adslbl

In comparing the dosing regimens in Study 20110271, the titration analysis set (TAS) was analyzed. The TAS was the subset of subjects who were exposed to evolocumab 420 mg QM for at least 12 weeks and then to evolocumab 420 mg Q2W for at least 12 weeks. There were 7 pediatric subjects with HoFH in the TAS. The median (Q1, Q3) percent reductions in calculated LDL-C from baseline for pediatric subjects with HoFH in the TAS were similar for the 2 dosing regimens with 21.18 % (2.78, 39.05) after 12 weeks of 420 mg QM dosing and 21.72 % (17.21, 44.21) after 12 weeks of 420 mg Q2W dosing. However, the mean (SE) percent reductions in calculated LDL-C from baseline were 21.15% (7.97) after 12 weeks of 420 mg QM dosing and 31.12 % (8.09) after 12 weeks of 420 mg Q2W dosing. Median absolute reduction in calculated LDL C from baseline was 78.5 mg/dL and 81.0 mg/dL, (mean: 54.1 mg/dL and 82.4 mg/dL) after 12 weeks of QM and Q2W dosing, respectively.

A waterfall plot of percent change from baseline in calculated LDL-C at open-label extension week 12 of 420 mg QM dosing and week 12 of 420 mg Q2W dosing for the 7 pediatric patients in the TAS is provided in **Figure 9**. For all but 1 subject, the LDL C reduction following Q2W dosing was equal to or greater than the LDL-C reduction following QM dosing. The results support the additional reduction in

LDL-C observed with evolocumab 420 mg Q2W dosing compared with 420 mg QM dosing in this at-risk population of pediatric subjects with HoFH.

Figure 9. Waterfall Plot of Percent Change From Baseline at OLE Week 12 on QM and OLE Week 12 on Q2W in Calculated LDL-C Subgroup = Age < 18 Years



N = number of subjects in the analysis set aged < 18 years at baseline; OLE = Open-Label Extension; QM = Monthly; Q2W=Every 2 weeks

Note: Plot is based on observed data and no imputation is used for missing values.

Study 20110271 was a phase 2/3 open-label extension study designed to evaluate the safety, tolerability, and efficacy of long-term administration of evolocumab in subjects 12 -≤ 80 years of age with HoFH or severe FH (i.e., all those not meeting the protocol criteria for HoFH). Non-apheresis subjects were required to have elevated LDL C (≥ 100 mg/dL [2.6 mmol/L] for subjects with diagnosed CHD or risk equivalent and ≥130 mg/dL [3.4 mmol/L] for subjects without diagnosed CHD or risk equivalent). Two dose regimens were evaluated, i.e. evolocumab 420 mg QM and 420 mg Q2W. Subjects not on lipid apheresis at enrollment or within the prior 8 weeks initiated treatment with evolocumab 420 mg QM, whereas subjects on lipid apheresis at enrollment initiated treatment with evolocumab 420 mg Q2W. Dose frequency changes (420 mg QM vs 420 mg Q2W) were permitted during the study if subjects met specific protocol criteria. Subjects with < 5% LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL could discontinue evolocumab. If serum unbound PCSK9 was ≥ 100 ng/mL with QM dosing, the subject could switch to evolocumab 420 mg Q2W treatment if clinically indicated (e.g., LDL-C goals not met). Subjects on apheresis with ≥ 5% LDL-C

reduction from baseline and serum unbound PCSK9 < 100 ng/mL with Q2W treatment could switch to QM dosing.

In Study 20110271, 14 adolescent subjects with HoFH were enrolled, of which 9 (64.3%) men/boys and 5 (35.7%) women/girls with a median (Q1, Q3) age at baseline of 14.0 years. The median LCL-C levels at baseline were 9.10 mmol/L, and all subjects were on moderate- (14.3%) of high-intensity (85.7%) statin therapy. Ten subjects were not on lipid apheresis at baseline, and 4 subjects received lipid apheresis at baseline. Three subjects discontinued the study due to withdrawal consent. Evolocumab therapy resulted in a consistent LDL-C lowering effect from the start of the OLE study up to week 216 in pediatric subjects with HoFH. The median (Q1, Q3) reductions from baseline in LDL-C at weeks 48, 96, 144, 192, and 216 were 13.3%, 8.1%, 8.7%, 9.5%, and 20.0%, respectively. To note, efficacy data at week 216 was available for 9 adolescent subjects with HoFH (n=2 apheresis and n=7 non-apheresis). These findings with respect to LDL-C lowering were consistent with the median LDL-C reductions of 12.2%, 14.5%, and 14.3% at week 12, 48 and 80, respectively, observed in HoFH subjects age 10-18 years in Study 20120124.

In Study 20110271, there were no subjects with a measurement at week 84 for receptor negative, 7 subjects with receptor defective, and 3 subjects with receptor unclassified. The efficacy results according to LRLR mutation demonstrated that treatment with evolocumab leads to a reduction in LDL-C levels in patients with LDLR defective and unclassified mutation. However, within each subgroup of LDLR mutation there was a large degree of intersubject variability including non-responders which, however, were in the minority.

As already described above, two different dose regimens were allowed in this study. Pediatric subjects who started this study receiving evolocumab 420 mg QM could change their dose to 420 mg Q2W if insufficient suppression of PCSK9 (> 100 ng/mL) was observed at week 12 or 24. In this study, the titration analysis set (TAS), defined as the subset of subjects who were exposed to evolocumab 420 mg QM for at least 12 weeks and then to evolocumab 420 mg Q2W for at least 12 weeks, showed that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W resulted in an additional mean LDL-C reduction of 10.0% corresponding to a mean absolute reduction of 28.3 mg/dL. Considering that in Study 20120124, the median LDL-C reduction was comparable between the HoFH subjects 10 - ≤11 years of age and the overall pediatric HoFH population, it can be anticipated that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W in HoFH subjects 10 - ≤11 years of age results in a comparable additional mean LDL-C reduction of 10%. Previously, secondary prevention LDL-C lowering trials have shown that reduction of 38.7 mg/dL (1 mmol/L) in LDL-C is associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes (Cholesterol Treatment Trialists' Collaboration [CTTC], 2010). Based on above, this additional mean absolute reduction of 28.3 mg/dL upon increasing the frequency of the 420 mg dose to Q2W can be considered clinically relevant, particularly in pediatric HoFH subjects which are at high cardiovascular risk.

Similarly, as in Study 20120123 and 20120124, the findings of LDL-C lowering effect were supported by beneficial effects observed for other lipid parameters in, e.g. non-HDL-C, ApoB, Total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio.

Since the current application concerns extension of the indication to include pediatric patients with HoFH 10-≤11 years of age and Study 20110271 only enrolled pediatric HoFH patients of 12 years and over (in line with the inclusion criteria), this study is only considered supportive.

2.3.4. Discussion on clinical efficacy

Based on the initial MAA in 2015, evolocumab is indicated in adult patients with primary hypercholesterolemia or mixed dyslipidemia, including those with HeFH. Additionally, based on the same MAA, evolocumab is also approved for adults and adolescent patients aged 12 years and over with HoFH. The current extension of indication application concerns the inclusion of pediatric HeFH patients aged 10 years and older and expanding the age range for the approved pediatric HoFH indication to include pediatric patients 10-≤11 years of age. This extension of indication application is based on efficacy and safety data from the phase 3 Study 20120123 (HAUSER-RCT) and its *ongoing* phase 3 open-label extension Study 20120124 (HAUSER-OLE) supplemented with data of the open-label long-term Study 20110271.

Design and conduct of clinical studies

Dose selection

The approved dosing regimen for adults patients with HeFH is 140 mg every 2 weeks (Q2W) or 420 mg once monthly (QM); both doses are clinically equivalent. For adult patients and adolescents aged 12 years and over with HoFH, the 420 mg QM and 420 mg Q2W are approved. The initial recommended dose in the HoFH population is 420 mg QM, which can be up-titrated to 410 mg Q2W if a clinically meaningful response is not achieved. HoFH patients on apheresis may initiate treatment with 420 mg Q2M to correspond with their apheresis schedule. Based on PK data in the initial MAA, the approved 420 SC QM regimen has been selected for the studies 20120123 and 20120124, which evaluated the efficacy and safety of evolocumab in pediatric patients from 10-≤17 years of age with HeFH or HoFH.

Pharmacokinetic data from Study 20120123 and Study 20120124 confirmed that mean serum evolocumab values of the 420 mg QM regimen in pediatric HeFH and HoFH subjects aged 10-≤17 years were within the range of values observed in adults with HeFH and non-apheresis pediatric subjects with HoFH presented in the initial marketing application. Additionally, efficacy and safety results of the 420 mg QM regimen observed in these studies were consistent with those found in previous clinical studies in the evolocumab clinical program (see efficacy and safety section). Therefore, no changes to the approved evolocumab dosing regimens were proposed for the populations of pediatric HeFH subjects aged 10-≤17 years and the HoFH subjects aged 10-≤11 years, which are currently under review. However, in Study 20120123 and 20120124, only the 420 mg QM regimen has been evaluated, whereas in addition to this regimen also the 140 mg Q2W regimen in pediatric HeFH subjects aged 10-≤17 years and the 420 mg Q2W regimen in pediatric HoFH subjects 10-≤11 years are currently proposed (same regimens as those currently stated in the labelling for the approved HeFH and HoFH populations). As such, the efficacy and safety of the 140 mg Q2W dose regimen for pediatric HeFH patients aged 10-≤17 years and the 420 mg Q2W dose regimen for pediatric HoFH patients aged 10-≤11 years have not been evaluated. PK data have adequately shown that the PK is dose-linear and that relative to primary hyperlipidaemia and mixed dyslipidemia, HeFH, HoFH and age do not have a clinically meaningful effect on the PK profile of evolocumab. As such, the 140 mg Q2W regimen, which is considered clinically equivalent to the 420 mg QM regimen proposed for pediatric HeFH patients aged 10-≤17 years, is considered acceptable. However, the 420 mg Q2W dose regimen proposed for HoFH subjects 10-≤11 years of age concerns a 2-fold higher dose than the 420 mg QM regimen for which the efficacy and safety in the proposed population of pediatric HoFH patients aged 10-≤11 years are currently unknown. Despite similar PK across different types of FH and age categories, the safety profile of the 420 mg Q2W regimen in the pediatric patients with HoFH aged 10-≤11 years can differ compared with the adult population and the older pediatric HoFH population of 12-≤17 years for which this dose regimen is currently already approved. The efficacy and safety of the

420 mg Q2W dose (together with the 420 mg QM) have only been evaluated in the adult subjects with HoFH or severe FH and in the older pediatric HoFH population of 12-≤17 years in Study 20110271. In this study, dose frequency changes (420 mg QM vs 420 mg Q2W) were permitted if a clinically meaningful response is not achieved. The titration analysis set (TAS), defined as the subset of subjects who were exposed to evolocumab 420 mg QM for at least 12 weeks and then to evolocumab 420 mg Q2W for at least 12 weeks, showed that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W resulted in an additional mean LDL-C reduction of 10.0% corresponding to a mean absolute reduction of 28.3 mg/dL. Considering that in Study 20120124, the median LDL-C reduction was comparable between the HoFH subjects 10 - ≤11 years of age and the overall pediatric HoFH population, it can be anticipated that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W in HoFH subjects 10 - ≤11 years of age results in a comparable additional mean LDL-C reduction of 10%. Previously, secondary prevention LDL-C lowering trials have shown that reduction of 38.7 mg/dL (1 mmol/L) in LDL-C is associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes (Cholesterol Treatment Trialists' Collaboration [CTTC], 2010). Based on above this additional mean absolute reduction of 28.3 mg/dL upon increasing the frequency of the 420 mg dose to Q2W can be considered clinically relevant, particularly in pediatric HoFH subjects which are at high cardiovascular risk.

However, the safety profile of the 420 mg Q2W dose in pediatric HoFH subjects 10-≤11 years of age is still unknown. The Applicant argued that in Study 20120124 and Study 20110271 no unexpected safety concerns has been found. Additionally, none of the adverse events were related to growth, pubertal development, or hormonal status. However, firm conclusion on growth and pubertal development and hormonal status can still not be made due to limited sample size and treatment duration. Moreover, in Study 20120124, only the 420 mg QM regimen has been evaluated, while in Study 20110271 both QM and Q2W regimens has been evaluated but only in HoFH subjects 12-≤17 years of age. In this context, an justification in order to extrapolate these safety results to HoFH subjects aged 10-≤11 years of age receiving the Q2W regimen has not been provided. Nevertheless, it is acknowledged that the benefits of the additional clinically relevant reduction in LDL-C in HoFH subjects aged 10-≤11 years who are at very high cardiovascular risk outweigh the adverse events observed in this HoFH population to date.

Pediatric HeFH population

The evaluate the effect of evolocumab in pediatric HeFH subjects aged 10 years and older, the phase 3 Study 20120123 (HAUSER-RCT) and its *ongoing* phase 3 open-label extension Study 20120124 (HAUSER-OLE) have been conducted.

Study 20120123 is a 24-week double-blind, randomized, placebo-controlled study in patients from 10-≤ 17 years of age with HeFH. General inclusion criteria seem appropriate to reflect the patients for whom an indication is being sought. Eligible subjects to be enrolled were male or female ≥10-≤17 years of age at the time of randomization diagnosed with HeFH based on genetic testing or following the clinical Broome criteria, the Dutch Lipid Clinic Network and MEDPED with LDL-C levels of ≥ 3.4 mmol/L at screening and receiving optimized background lipid-lowering therapy for ≥ 4 weeks prior to screening. The design of the RCT Study 20120123 is appropriated to achieve the primary objective of the study. The duration of the screening period of a maximum of 8 weeks should be sufficient to establish a stable run-in cholesterol level. The 24-week double-blind treatment period (evolocumab 420mg SC QM or matching placebo SC QM, randomized 2:1) is considered appropriate to provide reasonable results on the LDL-C (and other cholesterol parameters) lowering effect of evolocumab. Each QM administration of investigational product (IP) consisted of 3 injections of 140 mg evolocumab

or placebo in 1.0 mL (administration by 3 AI/Pens). The primary endpoint of percent change from baseline to week 24 in LDL-C is considered appropriate to establish the LDL-C lowering effect of evolocumab. Key secondary endpoints evaluation of other lipid parameters (i.e., non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio) are considered appropriate to provide further insight on the overall lipid profile and confirmation of the primary objective. The sample size calculation, randomization and blinding procedures are acceptable. With respect to statistical analysis, the definition of the analysis population is considered standard and acceptable. The primary and secondary analyses will be performed with a linear effects model, and missing values are not imputed. This is in line with the PIP (EMEA-001268-PIP01-12) and thus acceptable.

Study 20120124 is an open-label, single-arm extension study in patients from 10-≤17 years of age with HeFH or HoFH. Pediatric patients with HeFH who completed the parent study 20120123 and did not experience treatment-related adverse events were eligible to enrol in this OLE study. Additionally, de-novo pediatric patients aged 10-≤17 years with a diagnosis of HoFH were eligible to enrol in this OLE study. HoFH was diagnosed by genetic confirmation or by clinical diagnosis based on a history of an untreated LDL-C concentration greater than 500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age or evidence of HeFH in both parents. All subjects received evolocumab 420 mg SC QM using either 3 AI/Pen injections or 1 automated mini-doser (AMD) administration. The design and the treatment duration of 80 weeks of this OLE study is appropriate to achieve the primary objective of the study to characterize the safety and tolerability of long-term administration of evolocumab among pediatric patients with HeFH or HoFH. The key secondary objective was to characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C and other lipid parameters.

Pediatric HoFH population

Expanding the HoFH age range to include pediatric patients 10-≤11 years of age is based on the interim results of the *ongoing* OLE Study 20120124 supplemented with Study 20110271.

The design of OLE Study 20120124 has already been described above.

Interim data from Study 20110271, along with data from the parent Study 20110233, was presented in the initial MAA for evolocumab supporting the approval of the indication in adults and pediatric (12 years and over) subjects with HoFH. Subsequently, the final results from Study 20110271 have been submitted and assessed during a Type II variation application procedure in 2019 (EMEA/H/C/003766/II/0031). In the current extension procedure, the focus primarily lies on the data of pediatric subjects with HoFH from the final analysis of Study 20110271.

Study 20110271 was a phase 2/3 open-label extension study to characterize the safety, tolerability, and efficacy of long-term administration of evolocumab in subjects 12 -≤ 80 years of age with HoFH or severe FH (i.e., all those not meeting the protocol criteria for HoFH). Non-apheresis subjects were required to have elevated LDL C (≥ 100 mg/dL [2.6 mmol/L] for subjects with diagnosed CHD or risk equivalent and ≥130 mg/dL [3.4 mmol/L] for subjects without diagnosed CHD or risk equivalent). Two dose regimens were evaluated, i.e. evolocumab 420 mg QM and 420 mg Q2W. Subjects not on lipid apheresis at enrollment or within the prior 8 weeks initiated treatment with evolocumab 420 mg QM, whereas subjects on lipid apheresis at enrollment initiated treatment with evolocumab 420 mg Q2W. Dose frequency changes (420 mg QM vs 420 mg Q2W) were permitted during the study if subjects met specific protocol criteria. Subjects with < 5% LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL could discontinue evolocumab. If serum unbound PCSK9 was ≥ 100 ng/mL with QM dosing, the subject could switch to evolocumab 420 mg Q2W treatment, if clinically indicated (e.g.,

LDL-C goals not met). Subjects on apheresis with ≥ 5% LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL with Q2W treatment could switch to QM dosing. The primary objective of this study was to characterize the safety and tolerability of long-term administration of evolocumab among pediatric patients with HoFH. The key secondary objective was to characterize the efficacy of long-term administration of evolocumab as assessed by LDL-C and other lipid parameters.

Since the application under review concerns extension of the indication to include pediatric patients with HoFH 10-≤11 years of age and Study 20110271 only enrolled pediatric HoFH patients of 12 years and over (in line with the inclusion criteria), this study is only considered supportive.

Efficacy data and additional analyses

Assessment of paediatric data on clinical efficacy

Pediatric HeFH population

In the RCT Study 20120123, 157 subjects were enrolled and received at least one dose of IP (104 and 53 subjects in the evolocumab and placebo group, respectively). The percentage of subjects who completed the study was high and similar between the evolocumab and placebo group (99.0% and 100.0%, respectively). Discontinuations due to an adverse event occurred in only one subject treated with evolocumab, which is reassuring. With respect to protocol deviations, the percentage of important protocol deviations were relatively low (7.0%) and were not considered to impact data interpretation. The study was multicentre and recruited patients across the globe, with more than half of the subjects (65.8%) from Europe, which is sufficiently representative for Europe.

Overall baseline data, including those on co-medications, distribution of Tanner staging and risk factors, and stratification factors, are well distributed across the two treatment groups. The study population can be considered representative of a pediatric HeFH population. HeFH diagnosis was sufficiently established as the diagnosis was for a large part of the population by genetic testing (66%). Thirty-nine (24.7%) subjects were children 10-≤11 years of age, and 119 (75.3%) were adolescents between 12-≤17 years of age. Moreover, the elevated mean LDL-C baseline value of 4.8 mmol/L reasonably corresponds to an LDL-C level generally observed within an adult HeFH population. All subjects received statin therapy, except for one subject in the placebo group who took only ezetimibe. The majority (79%) of subjects were on moderate- or high-intensity statins at baseline, and 20% were on low-intensity statins.

In the primary efficacy analysis, treatment with evolocumab resulted in a substantial decrease in LDL-C at week 24 of 44% with an absolute mean change in LDL-C of 2.1 mmol/L (4.8 mmol/L at baseline and 2.7 mmol/L at week 24). The treatment difference between evolocumab and placebo was 38.3% ($p<0.001$). The effect size in LDL-C lowering of 38.3% observed in this RCT study in pediatric subjects with HeFH was lower than the LDL-C lowering effect of 60% observed in adults with HeFH in the RUTHERFORD study (Study 20110117) and other previous clinical studies (range: 60-70%) submitted during the initial MAA. There is no clear biological or pharmacokinetic explanation for this discrepant effect across the paediatric and adult HeFH population, although higher baseline LDL-C values in the pediatric population could be one possible reason for the lower treatment effect size in the paediatric population. Nevertheless, the LDL-C lowering effect in the pediatric HeFH population is still considered substantial and clinically relevant. Primary endpoint analyses were supported by the secondary endpoint analysis showing significant reductions in e.g. non-HDL-C (-35.04%), ApoB (-32.47%), total cholesterol/HDL-C ratio (-30.30%) and ApoB/ApoA1 ratio (-36.38%).

Further, the LDL-C lowering effect already started at week 12 and was maintained up to 104 weeks of treatment as demonstrated in the OLE Study 20120124 (discussed hereafter). Moreover, the effect appears generally consistent among several subgroups, including gender, race, age, region, baseline LDL-C values, statin intensity, and baseline PCSK9.

Almost all patients from Study 20120123, i.e. 150 out of 157 patients, rolled over to the OLE Study 20120124, of which 101 subjects received evolocumab in the parent study and 49 subjects received placebo. At the data cut-off, already a high proportion of HeFH patients (70.0%) completed the study and 28.0 % HeFH were still participating the study. At the data cut-off, the percentage of HeFH patients who discontinued the study was relatively low (2.0%, n=3); all discontinued due to withdrawal of consent from the study, which is reassuring. Evolocumab therapy resulted in a consistent LDL-C lowering effect from the start of the OLE study up to week 80 in pediatric HeFH subjects aged 10-≤17 years of age. For the HeFH subjects randomized to evolocumab treatment in the parent study, the reductions in LDL-C were maintained through week 80, thereby demonstrating maintenance of effect over a period of 2 years (104 weeks across both studies). The HeFH subjects randomized to placebo in the parent study demonstrated LDL-C reductions by the first time points of 12 weeks. Overall, the mean LDL-C reductions in the pediatric HeFH subset were 44.4%, 40.6% and 36.3% at week 12, 48 and 80, respectively.

Carotid intima-media thickness (cIMT) analysis showed small reductions in cIMT with evolocumab therapy from baseline to week 24, 48, and 80 in Study 20120123 and 20120124, suggestive of a beneficial effect of evolocumab with respect to atherogenesis. However, these results are too limited (short study period and small reduction) to draw firm conclusions.

Pediatric HoFH population

Thirteen de-novo pediatric HoFH patients aged 10-≤17 years were enrolled in the OLE Study 20120124. At the data cut-off, these HoFH patients either completed the study (84.6%, n=11) or discontinued the study (15.4%, n=2; withdrawal of consent and lost follow-up). Concerning baseline data, most of these pediatric HoFH patients were male (83.3%, n=10) and white (75.0%, n=9). Six (46.2%) patients were 10-≤11 years of age, and 7 (53.8%) were between 12-≤ 17 years of age. The number of HoFH subjects aged 10-≤11 years who completed the study (n=5) is limited, however, acceptable considering the rarity of the disease. The mean LDL-C at baseline was 10.3 mmol/L, and all the HoFH patients in this study had HoFH diagnosis by genetic testing. Furthermore, all HoFH patients were on a statin (100%) and ezetimibe (100%) therapy at baseline and none of the HoFH subjects were receiving lipoprotein apheresis therapy.

In Study 20120124, treatment with evolocumab resulted in a consistent LDL-C lowering effect from the start of the OLE study up to week 80 in HoFH subjects. The median LDL-C reductions were 12.2%, 14.5%, and 14.3% at week 12, 48 and 80, respectively. For the HoFH subjects 10 - ≤11 years of age, the median LDL-C reduction was generally comparable with the overall pediatric HoFH population (12.2%, 4.6% and 19.2% at week 12, week 48 and week 80, respectively).

The effect size in median LDL-C reduction of 12-14.5% with the 420 mg QM regimen observed in the overall pediatric HoFH population in Study 20120124 appears somewhat lower than those observed with the 420 mg QM regimen in the studies previously submitted, i.e. Study 20110233 (TESLA) and Study 20110271 (TAUSSIG) in the overall HoFH population consisting adult and pediatric subjects 12 years of age and over (32% and 16.3%, respectively). However, the effect size was consistent with the median LDL-C reduction in the subset of the 14 adolescents HoFH aged 12-≤17 from Study 20110271 who received the 420 mg QM regimen or the (higher dose) 420 mg Q2W regimen (13.3%, 8.1%, 8.7%, 9.5%, and 20.0% at weeks 48, 96, 144, 192, and 216, respectively). Although the

pediatric HoFH subjects showed a slightly less LDL-C lowering effect compared with the overall HoFH population, the LDL-C lowering effect in the pediatric patients is still considered clinically relevant. The efficacy results according to LRLR mutation (negative, defective, or unknown) demonstrated that treatment with evolocumab results in a reduction in LDL-C levels regardless of the type of LDLR mutation. However, within each subgroup of LDLR mutation there was a large degree of intersubject variability including non-responders which, however, were in the minority. In Study 20110271, two different dose regiments were allowed in pediatric HoFH subjects 12-≤ 17 years of age. Pediatric subjects who started this study receiving evolocumab 420 mg QM could change their dose to 420 mg Q2W if insufficient suppression of PCSK9 (> 100 ng/mL) was observed at week 12 or 24. In this study, the titration analysis set (TAS), defined as the subset of subjects who were exposed to evolocumab 420 mg QM for at least 12 weeks and then to evolocumab 420 mg Q2W for at least 12 weeks, showed that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W resulted in an additional mean LDL-C reduction of 10.0% corresponding to a mean absolute reduction of 28.3 mg/dL.

Similarly, as previously found, the findings of the LDL-C lowering effect were supported by beneficial effects observed for the other lipid parameters, non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio in study 20120124 and 20110271.

Additional expert consultation

N/A

2.3.5. Conclusions on the clinical efficacy

In conclusion, evolocumab demonstrated a substantial reduction in LDL-C and other lipid parameters on top of standard of care for both HoFH and HeFH patients aged 10-≤17 years. The open-label extension studies provide data of maintenance of effect in the long term. As expected, LDL-C reductions were lower in HoFH subjects compared with HeFH subjects since the mechanism of action depends on the activity of the LDL receptor.

However, one uncertainty remain, which concerns the lack of confirmation of additional LDL-C reduction with the higher evolocumab 420 mg Q2W regimen in HoFH subjects aged 10 -≤11 years of age. However, considering that the median LDL-C reduction with the 420 mg QM dose regimen was comparable between the HoFH subjects 10 - ≤11 years of age and the overall pediatric HoFH population in Study 20120124, it can be anticipated that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W in HoFH subjects 10 - ≤11 years of age results in a comparable additional mean LDL-C reduction of 10%, which can be considered clinically relevant.

2.4. Clinical safety

Introduction

The focus of this safety section is pediatric safety data from the double-blind, randomized Study 20120123 and its ongoing open-label extension Study 20120124 (**Table 1**). Additional long-term safety data from 14 homozygous familial hypercholesterolemia (HoFH) pediatric subjects who

participated in Study 20110271 is also included. Because of considerable differences in study design, patient populations enrolled, and study durations, safety data across studies were not integrated.

The safety analysis sets consisted of all subjects in the full analysis set (FAS) who received at least 1 dose of investigational product (evolocumab or placebo).

The safety evaluation is primarily based on the on the double-blind, randomized Study 20120123 and its ongoing OLE study 2012014 and supplemented by safety data from the phase 2/3 open-label extension Study 20110271, which is appropriate. The safety data of the different studies were presented separately due to differences in study design and patient populations, which is acceptable.

Patient exposure

HeFH subjects

For pediatric HeFH subjects in Studies 20120123 and 20120124, 153 pediatric HeFH subjects were administered evolocumab ((in combination with standard of care), representing 249 patient years of exposure (**Table 31**). Across these 2 studies, 149 (97.4%) HeFH subjects had evolocumab exposure ≥ 28 weeks (6.4 months), 135 (88.2%) subjects had evolocumab exposure ≥ 52 weeks (12 months), and 76 (49.7%) subjects had evolocumab exposure ≥ 96 weeks (22.1 months).

In Study 20120123, mean investigational product exposure was similar between the evolocumab (5.5 months) and placebo (5.5 months) groups. Overall, 98 (94%) subjects in the evolocumab group and 51 (96%) subjects in the placebo group received all 6 doses of investigational product. Study exposure was also similar between the 2 treatment groups at 5.6 months in the evolocumab group and 5.7 months in the placebo group.

Table 31. Overall Summary of Exposure to Investigational Product

	Evolocumab - HeFH	Evolocumab - HoFH	Evolocumab - Total
Number of subjects[a]	153	12	165
Total pt-year exposure	249	17	267
Number of subjects on IP exposure categorization - n (%)[b]			
≥ 24 weeks (5.5 months)	149 (97.4)	12 (100.0)	161 (97.6)
≥ 28 weeks (6.5 months)	149 (97.4)	12 (100.0)	161 (97.6)
≥ 36 weeks (8.3 months)	143 (93.5)	11 (91.7)	154 (93.3)
≥ 48 weeks (11.1 months)	141 (92.2)	11 (91.7)	152 (92.1)
≥ 52 weeks (12.0 months)	135 (88.2)	11 (91.7)	146 (88.5)
≥ 60 weeks (13.8 months)	128 (83.7)	11 (91.7)	139 (84.2)
≥ 72 weeks (16.6 months)	122 (79.7)	11 (91.7)	133 (80.6)
≥ 84 weeks (19.4 months)	80 (52.3)	0 (0.0)	80 (48.5)
≥ 96 weeks (22.2 months)	76 (49.7)	0 (0.0)	76 (46.1)

HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; IP = investigational product; pt-year = patient years, where years are calculated as the sum of period durations (in days) for evolocumab exposure across subjects divided by 365.25.

Based on the final database snapshot date (25 February 2020) data for 20120123 and the interim analysis data cutoff date (08 June 2020) data for 20120124.

[a] Subjects who ever received evolocumab in Study 20120123 or 20120124.

[b] % calculation based on total number of subjects who ever received evolocumab in Study 20120123 or 20120124 within each of HeFH and HoFH as well as total.

HoFH subjects

In Study 20120124, 12 HoFH subjects received at least 1 dose of 420 mg evolocumab QM. One subject dropped out after 28 weeks, all other subjects have completed evolocumab dosing and have completed the study at week 80. Median evolocumab exposure was 18.4 months and median study exposure was 18.6 months; representing 17 total patient-years of exposure. The corresponding durations in the 10-≤11 years of age subgroup were 16.608 (4.466) and 16.756 (4.507) months, respectively and for the 12-≤17 years of age subgroup these were 18.382 (0.085) and 18.535 (0.145) months, respectively. As of the interim analysis data cutoff (08 June 2020), all subjects (100.0%) had evolocumab exposure ≥ 28 weeks and 11 (91.7%) had evolocumab exposure ≥ 72 weeks (**Table 31**).

In Study 20110271, 14 pediatric subjects 12 to 17 years of age with HoFH received open-label evolocumab 420 mg for up to 5 years. Ten subjects were not on lipid apheresis at enrollment or within the prior 8 weeks, initiated treatment, and were dosed with 420 mg QM; 4 subjects were on lipid apheresis at enrollment and initiated treatment with evolocumab 420 mg once every 2 weeks (Q2W). Exposure to evolocumab in pediatric subjects was 45.2 patient-years and the median (Q1, Q3) duration of exposure was 54.0 (9.2, 58.7) months.

Combined exposure for pediatric subjects with HoFH across Studies 20120124 and 20110271 was 62.2 patient-years.

In the initial MA dossier**,** 5710 patients (the majority were adult subjects) were exposed to evolocumab in > 25 clinical trials across broad patient populations, representing 5246 patient-years of exposure. With the submission of the cardiovascular outcome trial FOURIER, with a total of 27525 adult subjects and the GLAGOV study with 968 adult subjects included, the overall exposure data from clinical studies has substantially increased although exposure in the FOURIER study was limited to a median of 2.6 years. Furthermore, it has been estimated that 748 312 patients (551 687 patient-years) have been exposed worldwide to evolocumab in the post-marketing setting (See section "Post-marketing experience). So, there was a large safety experience with evolocumab, although the experience in pediatric patients was limited, however, increased based on the safety data of Study 20120123 and 20120124 currently under review.

HeFH

Across the RCT Study 20120123 and OLE Study 20120124, a total of 153 pediatric HeFH patients received at least 1 dose of evolocumab, with a total patient-year exposure of 249. Of these patients, 149 (97.4%), 135 (88.2%), and 76 (49.7%) HeFH subjects were exposed to evolocumab for at least 24, 48 and 96 weeks, respectively, which is considered sufficient. More specifically, placebo-controlled safety data of pediatric HeFH subjects who received all 6 doses of IP, i.e. 24 weeks of exposure, in the RCT Study 20120123 is available for 98 subjects (out of 104, 94%) in the evolocumab group and 51 (out of 53, 96%) subjects in the placebo group.

HoFH

In the OLE Study 20120124, 12 de-novo pediatric HoFH subjects 10-≤17 years of age received at least one dose of evolocumab, with a total patient-year exposure of 17. Of these patients, all do-novo HoFH subjects (100.0%) had evolocumab exposure ≥ 28 weeks, and 11 (91.7%) completed the study and, as such, were exposed to evolocumab for 80 weeks.

Demographic data showed that 6 HoFH subjects aged 10-≤11 years and 7 HoFH subjects 12-≤17 years were enrolled in the OLE Study 20120124, of which one subject never received IP, and one subject discontinued the study. However, the age of these two subjects has not been provided. Based on the above, it can be concluded that 4-≤6 HoFH subjects aged 10-≤11 years (for whom an

indication is being sought) received evolocumab for up to 80 weeks, which is considered limited but expected and acceptable considering the rarity of the HoFH disease.

In the OLE Study 20110271, 14 pediatric subjects 12 to 17 years of age with HoFH received evolocumab for up to 5 years.

Combined exposure for pediatric subjects with HoFH across Studies 20120124 and 20110271 was 62.2 patient-years.

Adverse events

General frequency of adverse events

HeFH subjects

The HeFH subject incidence of treatment-emergent adverse events (TEAEs) of Studies 20120123 and 20120124 are summarized in **Table 32** and **Table 33**, respectively.

During Study 20120123, 64 (62%) subjects in the evolocumab group and 34 (64%) subjects in the placebo group experienced at least 1 TEAE. The majority of TEAEs were mild or moderate in severity (grade 1 and 2, respectively). The percentage of subjects with serious adverse events (SAEs) and TEAEs leading to discontinuation was both 1% in the evolocumab group and 0% in the placebo group, respectively.

During Study 20120124, 100 (66.7%) HeFH subjects experienced at least 1 TEAE. Subject incidence of TEAEs was similar between HeFH subjects receiving evolocumab (66.3%) or placebo (67.35) in the parent study. The majority of TEAEs were mild or moderate in severity. One (0.7%) HeFH subject experienced a SAE.

Table 32. Summary of Subject Incidence of Treatment-emergent Adverse Events – Study 20120123 (full analysis set – actual treatment)

	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)
All treatment-emergent adverse events	34 (64.2)	64 (61.5)
Grade ≥ 2	22 (41.5)	46 (44.2)
Grade ≥ 3	0 (0.0)	4 (3.8)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	1 (1.0)
Leading to discontinuation of investigational product	0 (0.0)	1 (1.0)
Serious	0 (0.0)	0 (0.0)
Nonserious	0 (0.0)	1 (1.0)
Fatal adverse events	0 (0.0)	0 (0.0)
Device-related treatment-emergent adverse events	2 (3.8)	3 (2.9)
Grade ≥ 2	0 (0.0)	0 (0.0)
Grade ≥ 3	0 (0.0)	0 (0.0)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)

EvoMab = Evolocumab (AMG 145); MedDRA = Medical Dictionary for Regulatory Activities; QM = monthly (subcutaneous)

N = number of subjects randomized and dosed in the full analysis set;

Table 33. Summary of Subject Incidence of Treatment-emergent Adverse Events – Study 20120124 – HeFH subjects (full analysis set – actual treatment)

	HeFH		
	Placebo QM in Parent Study (N = 49) n (%)	EvoMab 420 mg QM in Parent Study (N = 101) n (%)	Overall (N = 150) n (%)
All treatment-emergent adverse events	33 (67.3)	67 (66.3)	100 (66.7)
Grade ≥ 2	23 (46.9)	56 (55.4)	79 (52.7)
Grade ≥ 3	4 (8.2)	2 (2.0)	6 (4.0)
Grade ≥ 4	0 (0.0)	1 (1.0)	1 (0.7)
Serious adverse events	2 (4.1)	2 (2.0)	4 (2.7)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)
Serious	0 (0.0)	0 (0.0)	0 (0.0)
Nonserious	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Device-related treatment-emergent adverse events	6 (12.2)	5 (5.0)	11 (7.3)
Grade ≥ 2	2 (4.1)	1 (1.0)	3 (2.0)
Grade ≥ 3	0 (0.0)	0 (0.0)	0 (0.0)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)

EvoMab = Evolocumab (AMG 145); HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; MedDRA = Medical Dictionary of Regulatory Activity; N = number of subjects with HeFH enrolled and dosed from parent Study 20120123 and number of subjects with HoFH enrolled and dosed in this study; QM = once monthly.
Interim analysis data cut-off date: 08JUN2020

HoFH subjects

The HoFH subject incidence of TEAEs of Studies 20120124 and 20110271 are summarized in **Table 34** and **Table 35.**

In Study 20120124, 7 (58.3%) HoFH subjects experienced at least 1 TEAEs of which the majority were mild or moderate in severity. SAEs were reported for 2 (16.7%) HoFH subjects and none of the subjects experienced AEs leading to discontinuation of study drug.

In Study 20110271, 12 (84.7%) of the pediatric HoFH subjects experienced at least 1 TEAE of which the majority were mild or moderate in severity. SAEs were reported for 4 (28.6%) HoFH subjects and 1 (7.1%) subject experienced AEs leading to discontinuation of study drug.

Table 34. Summary of Subject Incidence of Treatment-emergent Adverse Events – Study 20120124 – HoFH subjects (full analysis set – actual treatment)

	HoFH
	EvoMab 420 mg QM (N = 12) n (%)
All treatment-emergent adverse events	7 (58.3)
Grade ≥ 2	5 (41.7)
Grade ≥ 3	2 (16.7)
Grade ≥ 4	0 (0.0)
Serious adverse events	2 (16.7)
Leading to discontinuation of investigational product	0 (0.0)
Serious	0 (0.0)
Nonserious	0 (0.0)
Fatal adverse events	0 (0.0)
Device-related treatment-emergent adverse events	1 (8.3)
Grade ≥ 2	0 (0.0)
Grade ≥ 3	0 (0.0)
Grade ≥ 4	0 (0.0)
Serious adverse events	0 (0.0)

Table 35. Summary of Subject Incidence of Treatment-emergent Adverse Events: Subgroup = Age < 18 – Study 20110271 (HoFH analysis set)

	Apheresis at Enrollment in s271 (N = 4) n (%)	Non-apheresis at Enrollment in s271 (N = 10) n (%)	Total (N = 14) n (%)
All treatment-emergent adverse events	2 (50.0)	10 (100.0)	12 (85.7)
Grade ≥ 2	2 (50.0)	7 (70.0)	9 (64.3)
Grade ≥ 3	0 (0.0)	5 (50.0)	5 (35.7)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	4 (40.0)	4 (28.6)
Leading to discontinuation of investigational product	0 (0.0)	1 (10.0)	1 (7.1)
Serious	0 (0.0)	0 (0.0)	0 (0.0)
Nonserious	0 (0.0)	1 (10.0)	1 (7.1)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Device-related treatment-emergent adverse events	0 (0.0)	0 (0.0)	0 (0.0)

Common TEAEs

HeFH subjects

In Study 20120123, the most commonly reported adverse event was nasopharyngitis (11.5% in the evolocumab group versus 11.3% in the placebo group), followed by headache (10.6% vs 1.9%), gastroenteritis (4.8% vs 7.5%), influenza (5.8% vs 3.8%), oropharyngeal pain (6.7%] vs 0.0%), upper respiratory tract infection (5.8% vs 1.9%), pyrexia (2.9% vs 5.7%), and cough (1.9% vs 5.7%) (**Table 36**). These adverse events were nonserious and mostly grade 1 or 2 (one event of headache was grade 3), and none led to discontinuation of investigational product.

For HeFH subjects in Study 20120124, the most commonly reported AEs (reported in > 5% of subjects) nasopharyngitis (14.7%), followed by headache (8.7%), influenza-like illness (8.7%), gastroenteritis (6.0%), upper respiratory tract infection (5.3%), and oropharyngeal pain (5.3%) (**Table 37**). These events were nonserious and grade 1 or 2 in severity, with the exception of a grade 3 serious adverse event of a headache.

Table 36. Treatment-emergent Adverse Events Reported by ≥ 2 Subjects: Overall by preferred term in descending order of frequency in the evolocumab group – Study 20120123 (full analysis set – actual treatment)

Preferred Term	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)
Number of subjects reporting treatment-emergent adverse events	34 (64.2)	64 (61.5)
Nasopharyngitis	6 (11.3)	12 (11.5)
Headache	1 (1.9)	11 (10.6)
Oropharyngeal pain	0 (0.0)	7 (6.7)
Influenza	2 (3.8)	6 (5.8)
Upper respiratory tract infection	1 (1.9)	6 (5.8)
Gastroenteritis	4 (7.5)	5 (4.8)
Pyrexia	3 (5.7)	3 (2.9)
Constipation	0 (0.0)	3 (2.9)
Influenza like illness	0 (0.0)	3 (2.9)
Cough	3 (5.7)	2 (1.9)
Abdominal pain	1 (1.9)	2 (1.9)
Abdominal pain upper	1 (1.9)	2 (1.9)
Contusion	1 (1.9)	2 (1.9)
Injection site pain	1 (1.9)	2 (1.9)
Vomiting	1 (1.9)	2 (1.9)
Arthralgia	0 (0.0)	2 (1.9)
Dermatitis allergic	0 (0.0)	2 (1.9)
Pain	0 (0.0)	2 (1.9)
Pharyngitis	0 (0.0)	2 (1.9)
Viral upper respiratory tract infection	0 (0.0)	2 (1.9)
Blood creatine phosphokinase increased	2 (3.8)	1 (1.0)
Diarrhoea	1 (1.9)	1 (1.0)
Gastroenteritis viral	1 (1.9)	1 (1.0)
Injection site erythema	1 (1.9)	1 (1.0)
Injection site haematoma	1 (1.9)	1 (1.0)
Ligament sprain	1 (1.9)	1 (1.0)
Toothache	1 (1.9)	1 (1.0)
Wound	1 (1.9)	1 (1.0)
Depression	2 (3.8)	0 (0.0)
Rhinitis	2 (3.8)	0 (0.0)

Table 37. Treatment-emergent adverse events reported by ≥ 2 subjects overall by preferred term in descending order of frequency – Study 20120124 (full analysis set – actual treatment)

	HeFH			HoFH	Total
Preferred Term	Placebo QM in Parent Study (N = 49) n (%)	EvoMab 420 mg QM in Parent Study (N = 101) n (%)	Overall (N = 150) n (%)	EvoMab 420 mg QM (N = 12) n (%)	EvoMab 420 mg QM (N = 162) n (%)

	HeFH			HoFH	Total
Preferred Term	Placebo QM in Parent Study (N = 49) n (%)	EvoMab 420 mg QM in Parent Study (N = 101) n (%)	Overall (N = 150) n (%)	EvoMab 420 mg QM (N = 12) n (%)	EvoMab 420 mg QM (N = 162) n (%)
Number of subjects reporting treatment-emergent adverse events	33 (67.3)	67 (66.3)	100 (66.7)	7 (58.3)	107 (66.0)
Nasopharyngitis	8 (16.3)	14 (13.9)	22 (14.7)	0 (0.0)	22 (13.6)
Headache	4 (8.2)	9 (8.9)	13 (8.7)	1 (8.3)	14 (8.6)
Influenza like illness	5 (10.2)	8 (7.9)	13 (8.7)	0 (0.0)	13 (8.0)
Gastroenteritis	3 (6.1)	6 (5.9)	9 (6.0)	0 (0.0)	9 (5.6)
Upper respiratory tract infection	3 (6.1)	5 (5.0)	8 (5.3)	1 (8.3)	9 (5.6)
Oropharyngeal pain	3 (6.1)	5 (5.0)	8 (5.3)	0 (0.0)	8 (4.9)
Abdominal pain upper	1 (2.0)	5 (5.0)	6 (4.0)	1 (8.3)	7 (4.3)
Fatigue	3 (6.1)	3 (3.0)	6 (4.0)	0 (0.0)	6 (3.7)
Pharyngitis	2 (4.1)	4 (4.0)	6 (4.0)	0 (0.0)	6 (3.7)
Attention deficit hyperactivity disorder	2 (4.1)	2 (2.0)	4 (2.7)	1 (8.3)	5 (3.1)
Back pain	2 (4.1)	3 (3.0)	5 (3.3)	0 (0.0)	5 (3.1)
Diarrhoea	2 (4.1)	3 (3.0)	5 (3.3)	0 (0.0)	5 (3.1)
Gastroenteritis viral	2 (4.1)	3 (3.0)	5 (3.3)	0 (0.0)	5 (3.1)
Injection site erythema	4 (8.2)	1 (1.0)	5 (3.3)	0 (0.0)	5 (3.1)
Myalgia	2 (4.1)	3 (3.0)	5 (3.3)	0 (0.0)	5 (3.1)
Tonsillitis	0 (0.0)	4 (4.0)	4 (2.7)	1 (8.3)	5 (3.1)
Influenza	0 (0.0)	3 (3.0)	3 (2.0)	1 (8.3)	4 (2.5)
Injection site reaction	2 (4.1)	2 (2.0)	4 (2.7)	0 (0.0)	4 (2.5)
Viral infection	1 (2.0)	3 (3.0)	4 (2.7)	0 (0.0)	4 (2.5)
Vitamin D deficiency	0 (0.0)	3 (3.0)	3 (2.0)	1 (8.3)	4 (2.5)
Acne	0 (0.0)	2 (2.0)	2 (1.3)	1 (8.3)	3 (1.9)
Depression	2 (4.1)	1 (1.0)	3 (2.0)	0 (0.0)	3 (1.9)
Epistaxis	0 (0.0)	1 (1.0)	1 (0.7)	2 (16.7)	3 (1.9)
Fungal skin infection	1 (2.0)	2 (2.0)	3 (2.0)	0 (0.0)	3 (1.9)
Injection site pain	2 (4.1)	1 (1.0)	3 (2.0)	0 (0.0)	3 (1.9)
Iron deficiency anaemia	1 (2.0)	2 (2.0)	3 (2.0)	0 (0.0)	3 (1.9)
Ligament sprain	0 (0.0)	3 (3.0)	3 (2.0)	0 (0.0)	3 (1.9)
Seasonal allergy	0 (0.0)	3 (3.0)	3 (2.0)	0 (0.0)	3 (1.9)
Sinusitis	1 (2.0)	2 (2.0)	3 (2.0)	0 (0.0)	3 (1.9)
Alopecia	0 (0.0)	2 (2.0)	2 (1.3)	0 (0.0)	2 (1.2)
Arthralgia	0 (0.0)	2 (2.0)	2 (1.3)	0 (0.0)	2 (1.2)
Blood creatine phosphokinase increased	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Cough	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Cystitis	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Dyspepsia	0 (0.0)	2 (2.0)	2 (1.3)	0 (0.0)	2 (1.2)
Ear infection	0 (0.0)	2 (2.0)	2 (1.3)	0 (0.0)	2 (1.2)
Food poisoning	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Head injury	2 (4.1)	0 (0.0)	2 (1.3)	0 (0.0)	2 (1.2)
Injection site bruising	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Injection site haemorrhage	0 (0.0)	1 (1.0)	1 (0.7)	1 (8.3)	2 (1.2)
Injection site swelling	2 (4.1)	0 (0.0)	2 (1.3)	0 (0.0)	2 (1.2)
Joint injury	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Myopathy	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)

	HeFH			HoFH	Total
Preferred Term	Placebo QM in Parent Study (N = 49) n (%)	EvoMab 420 mg QM in Parent Study (N = 101) n (%)	Overall (N = 150) n (%)	EvoMab 420 mg QM (N = 12) n (%)	EvoMab 420 mg QM (N = 162) n (%)
Nausea	0 (0.0)	1 (1.0)	1 (0.7)	1 (8.3)	2 (1.2)
Otitis media	0 (0.0)	1 (1.0)	1 (0.7)	1 (8.3)	2 (1.2)
Restless legs syndrome	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Toothache	0 (0.0)	2 (2.0)	2 (1.3)	0 (0.0)	2 (1.2)

HoFH subjects

In Study 20120124, 7 (58.3%) HoFH subjects experienced at least 1 TEAE. All adverse events occurred in only 1 subject except for epistaxis, which occurred in 2 (16.7%) subjects (***Table 37***).

In the pediatric subjects of Study 20110271, the most frequently reported adverse events (≥ 10%) were anxiety, migraine, and upper respiratory tract infection (21.4% (n=3) each), and acne, increase in blood creatine phosphokinase, influenza, non-cardiac chest pain, rash, and urinary tract infection (14.3% (n=2) each). All other TEAE occurred in only 1 pediatric HoFH subject each.

HeFH

In the RCT Study 20120123, treatment-emergent adverse events (TEAEs) were frequently reported; however, the percentage of subjects with TEAEs was slightly lower in the evolocumab group (61.5%) compared with the placebo group (64.2%). In the OLE Study 20120124, the percentage of TEAEs was comparable between subjects who received evolocumab and placebo in the parent study (67.3% vs 66.3%).

In the RCT Study 20120123, the most frequent AEs (> 5% of subjects) with a higher incidence with evolocumab compared with placebo were nasopharyngitis (11.5% vs 11.3%), headache (10.6% vs 1.9%), oropharyngeal pain (6.7% vs 0.0%), influenza (5.8% vs 3.8%), upper respiratory tract infection (5.8% vs 1.9%). In the OLE Study 20120124, the most frequent AEs (reported in > 5% of subjects) were nasopharyngitis (14.7%), headache (8.7%), influenza-like illness (8.7%), gastroenteritis (6.0%), upper respiratory tract infection (5.3%), and oropharyngeal pain (5.3%).

The safety findings are consistent with the safety data observed in adults in the initial MAA dossier and the FOURIER dossier, except for the disbalance in oropharyngeal pain. The TEAEs of oropharyngeal pain observed in HeFH subjects in Study 20120123 (and 20120124) were nonserious, mild to moderate in severity and all considered not related to treatment with evolocumab.

HoFH

In the OLE Study 20120124, 7 of the 12 (58.3%) HoFH subjects experienced TEAEs. The reported TEAES occurred in no more than 1 subject, with the exception of epistaxis which occurred in 2 (16.7%) subjects.

In the pediatric subset of the OLE study 20110271, 12 of the 14 subjects (85.7%) experienced TEAEs. The higher frequency of TEAEs compared with those observed for HeFH subjects in Study 20120123 and for the HeFH and HoFH subjects in Study 20120123 can be explained by the longer (5-years) study duration of Study 20110271. The most frequently reported adverse events (⩾ 10%) in the pediatric subset of the OLE study 20110271 were anxiety, migraine, and upper respiratory tract infection (21.4% (n=3) each), and acne, increase in blood creatine phosphokinase, influenza, non-

cardiac chest pain, rash, and urinary tract infection (14.3% (n=2) each). All other TEAE occurred in only 1 pediatric HoFH subject each.

Device related TEAEs

HeFH subjects

In Study 20120123, 3 (2.9%) subjects in the evolocumab group and 2 (3.8%) subjects in the placebo group experienced an adverse event assessed as related to the device; all of the events were consistent with injection site reactions and all were mild in severity (***Table 38***).

Table 38. Subject incidence of device-related adverse events by preferred term - Study 20120123 (full analysis set - actual treatment)

Preferred Term	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)
Number of subjects reporting treatment-emergent adverse events	2 (3.8)	3 (2.9)
Injection site pain	1 (1.9)	2 (1.9)
Application site pain	0 (0.0)	1 (1.0)
Erythema	0 (0.0)	1 (1.0)
Injection site haematoma	1 (1.9)	0 (0.0)

EvoMab = Evolocumab (AMG 145); MedDRA = Medical Dictionary for Regulatory Activities; QM = monthly (subcutaneous)
N = number of subjects randomized and dosed in the full analysis set.

In Study 20120124, a total of 11 (7.3%) HeFH subjects reported at least 1 device related AE. Most device related adverse events were mild in severity; 3 subjects experienced events of injection site pain, injection site reaction, and pyrexia which were moderate in severity (**Table 39**).

Table 39. Subject incidence of device-related treatment-emergent adverse events by preferred term – Study 20120124 (full analysis set – actual treatment)

	HeFH			HoFH	Total
Preferred Term	Placebo QM in Parent Study (N = 49) n (%)	EvoMab 420 mg QM in Parent Study (N = 101) n (%)	Overall (N = 150) n (%)	EvoMab 420 mg QM (N = 12) n (%)	EvoMab 420 mg QM (N = 162) n (%)
Number of subjects reporting treatment-emergent adverse events	6 (12.2)	5 (5.0)	11 (7.3)	1 (8.3)	12 (7.4)
Injection site pain	2 (4.1)	1 (1.0)	3 (2.0)	0 (0.0)	3 (1.9)
Injection site bruising	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Injection site erythema	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Injection site reaction	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Application site haematoma	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Injection site haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (0.6)
Injection site induration	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (0.6)
Post procedural haemorrhage	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Pyrexia	1 (2.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)

Interim analysis data cutoff date: 08JUN2020
N = number of subjects with HeFH enrolled and dosed from parent study 20120123 and number of subjects with HoFH enrolled and dosed in this study; EvoMab = Evolocumab (AMG 145); QM = monthly (subcutaneous); HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia

HoFH subjects

In Study 20120124, one (8.3%) HoFH subject reported 1 device-related adverse event of nausea and injection site hemmorrhage which were mild in severity (***Table 39***). In Study 20110271, no subjects reported a device-related adverse event.

Overall, these findings in pediatric subjects with HeFH and HoFH are consistent with those observed in the initial MA dossier and the FOURIER dossier.

Treatment related TEAEs

Overall, most treatment-related events were reported in 1 subject in either group, and most treatment-related adverse events in these 3 studies were known adverse drug reactions with evolocumab.

In Study 20120123 (HeFH subjects only) (**Table 40**), treatment-related adverse events were reported for 11 (10.6%) subjects in the evolocumab group and 4 (7.5%) subjects in the placebo group. Most related adverse events were reported for 1 subject in either group, except for injection site pain (2 [1.9%] subjects in the evolocumab group, 1 [1.9%] subject in the placebo group).

In open-label extension Study 20120124 (**Table 41**), among subjects with HeFH, treatment-related adverse events were reported for 10 (6.7%) subjects overall. Most related events were reported for 1 subject each, except for injection site erythema (4 [2.7%] subjects), injection site pain (2 [1.3%]),

and injection site swelling (2 [1.3%]). Among subjects with HoFH, treatment-related adverse events were reported for 2 (16.7%) subjects, and these events were nausea (1 [8.3%]) and epistaxis (1 [8.3%]).

In open-label extension Study 20110271 (HoFH subjects) (**Table 42**), treatment-related adverse events were reported for 1 pediatric subject, and these events were rash and urticaria.

Table 40. Treatment-emergent Treatment-related Adverse Events by System Organ Class, High Level Group Term, and Preferred Term - Study 20120123 (Full Analysis Set – Actual Treatment)

System Organ Class High Level Group Term Preferred Term	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)
Number of subjects reporting treatment-emergent treatment-related adverse events	4 (7.5)	11 (10.6)
GASTROINTESTINAL DISORDERS	1 (1.9)	0 (0.0)
Gastrointestinal signs and symptoms	1 (1.9)	0 (0.0)
Abdominal pain	1 (1.9)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (5.7)	6 (5.8)
Administration site reactions	2 (3.8)	5 (4.8)
Injection site erythema	1 (1.9)	1 (1.0)
Injection site haematoma	0 (0.0)	1 (1.0)
Injection site pain	1 (1.9)	2 (1.9)
Injection site reaction	0 (0.0)	1 (1.0)
Injection site urticaria	0 (0.0)	1 (1.0)
Injection site vesicles	1 (1.9)	0 (0.0)
General system disorders NEC	1 (1.9)	1 (1.0)
Fatigue	1 (1.9)	0 (0.0)
Influenza like illness	0 (0.0)	1 (1.0)
HEPATOBILIARY DISORDERS	1 (1.9)	0 (0.0)
Hepatic and hepatobiliary disorders	1 (1.9)	0 (0.0)
Jaundice	1 (1.9)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0.0)	1 (1.0)
Joint disorders	0 (0.0)	1 (1.0)
Arthropathy	0 (0.0)	1 (1.0)
NERVOUS SYSTEM DISORDERS	0 (0.0)	1 (1.0)
Mental impairment disorders	0 (0.0)	1 (1.0)
Disturbance in attention	0 (0.0)	1 (1.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	4 (3.8)
Epidermal and dermal conditions	0 (0.0)	4 (3.8)
Dermatitis allergic	0 (0.0)	1 (1.0)
Erythema	0 (0.0)	1 (1.0)
Papule	0 (0.0)	1 (1.0)
Psoriasis	0 (0.0)	1 (1.0)

EvoMab = Evolocumab (AMG 145); MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects randomized and dosed in the full analysis set; QM = monthly (subcutaneous)
Notes: Adverse events were coded using MedDRA version 22.1.

Source: Table 14-6.001.400

Table 41. Subject Incidence of Treatment-emergent Treatment-related Adverse Events by System Organ Class and Preferred Term - Study 20120124 (Full Analysis set - Actual Treatment)

System Organ Class Preferred Term	HeFH Placebo QM in Parent Study (N = 49) n (%)	HeFH EvoMab 420 mg QM in Parent Study (N = 101) n (%)	HeFH Overall (N = 150) n (%)	HoFH EvoMab 420 mg QM (N = 12) n (%)	Total EvoMab 420 mg QM (N = 162) n (%)
Number of subjects reporting treatment-emergent treatment-related adverse events	4 (8.2)	6 (5.9)	10 (6.7)	2 (16.7)	12 (7.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (8.2)	2 (2.0)	6 (4.0)	0 (0.0)	6 (3.7)
Injection site erythema	3 (6.1)	1 (1.0)	4 (2.7)	0 (0.0)	4 (2.5)
Injection site pain	1 (2.0)	1 (1.0)	2 (1.3)	0 (0.0)	2 (1.2)
Injection site oedema	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Injection site pruritus	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Injection site rash	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Injection site swelling	2 (4.1)	0 (0.0)	2 (1.3)	0 (0.0)	2 (1.2)
Injection site warmth	1 (2.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)
Pyrexia	1 (2.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	2 (2.0)	2 (1.3)	0 (0.0)	2 (1.2)
Acne	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Skin reaction	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Post procedural haemorrhage	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
INVESTIGATIONS	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Blood creatine phosphokinase increased	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
Myalgia	0 (0.0)	1 (1.0)	1 (0.7)	0 (0.0)	1 (0.6)
GASTROINTESTINAL DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (0.6)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (0.6)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (0.6)

EvoMab = Evolocumab (AMG 145); HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects with HeFH from parent Study 20120123 who are enrolled and dosed and number of subjects with HoFH who are enrolled and dosed in this study; QM = monthly (subcutaneous)
Notes: Data cutoff date: 08JUN2020. Adverse events were coded using MedDRA version 23.0.

Source: Table teu210521-6.3.1

Table 42. Subject Incidence of Treatment-emergent Treatment-related Adverse Events by System Organ Class and Preferred Term
Subgroup = Age < 18 Years - Study 20110271 (HoFH Analysis Set)

System Organ Class Preferred Term	Apheresis at Enrollment in s271 (N = 4) n (%)	Non-apheresis at Enrollment in s271 (N = 10) n (%)	Total (N = 14) n (%)
Number of subjects reporting treatment-emergent treatment-related adverse events	0 (0.0)	1 (10.0)	1 (7.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	1 (10.0)	1 (7.1)
Rash	0 (0.0)	1 (10.0)	1 (7.1)
Urticaria	0 (0.0)	1 (10.0)	1 (7.1)

HoFH = Homozygous Familial Hypercholesterolemia; MedDRA = Medical Dictionary for Regulatory Activities; N = number of HoFH subjects enrolled and dosed in Study 20110271
Note: Adverse events were coded using MedDRA version 21.0.

Source: Table teu210521-6.3.2

Treatment related TEAEs in pediatric subjects with HeFH and HoFH are consistent with those observed in the initial MA dossier and the FOURIER dossier. No new treatment related TEAEs have been identified, which is reassuring. Most of the TEAEs considered related to IP were injections site reactions, which is a known ADR of evolocumab.

Adverse events of special interest

Adverse events associated with other injectable protein therapies (i.e., potential hypersensitivity events and potential injection site reactions) were evaluated using narrow and broad Standard MedDRA Queries (SMQs). An assessment of potential neurocognitive adverse events using high level group terms was also carried out in Study 20120123 and Study 20120124. These search strategies are used to contribute to signal detection in retrieving any type of adverse event cases (MedDRA preferred terms) potentially related to the condition under review when heterogeneous medical presentations may be expected.

Potential hypersensitivity and potential injection site reactions

HeFH subjects

In Study 20120123, potential hypersensitivity events, which are ADRs with evolocumab, occurred in a higher percentage of evolocumab subjects (4 [3.8%] narrow SMQ; 7 [6.7%] broad SMQ) than placebo subjects (0% for both narrow and broad SMQ); the reported events were all nonserious and mild or moderate in severity. Using the narrow search strategy for potential hypersensitivity events, 4 subjects in the evolocumab group experienced events of hypersensitivity (1), allergic dermatitis (2), and injection site urticaria (1); the reported events were all nonserious and grade 1 or 2. No placebo subject experienced a potential hypersensitivity event.

The overall subject incidence of potential injection site reactions was similar between the evolocumab (5 subjects [4.8%] using both narrow and broad SMQ) and placebo (3 subjects [5.7%] using both narrow and broad SMQ) treatment groups.

In Study 20120124, potential hypersensitivity events occurred in 6 (4.0%) subjects using the narrow SMQ and 11 (7.3%) subjects using the broad SMQ. Potential injection site reaction events occurred in 13 (8.7%) subjects using both the narrow and broad AMQ. All potential hypersensitivity and injection site reaction events were nonserious and mild or moderate in severity.

HoFH subjects

In Study 20120124, no potential hypersensitivity events were noted and only 1 (8.3%) subject had a potential injection site reaction (nonserious, grade 1 injection site haemorrhage).

In Study 20110271, 2 (14.3%) pediatric HoFH subjects reported a potential hypersensitivity event using the narrow SMQ. One of these subjects had a grade 3 nonserious adverse event of rash leading to discontinuation of evolocumab. No pediatric subject in this study had a potential injection site reaction event.

There were no events of potential injection site reaction in Study 20110271 and no events of hypersensitivity in Study 20120124 reported.

HeFH subjects

In the RCT Study 20120123, a higher incidence of hypersensitivity was observed in the evolocumab group (3.8% and 6.7% using narrow and broad SMQ, respectively) compared with the placebo group (0% using both narrow and broad SMQ). In contrast, a lower incidence in potential injection site reactions was observed in the evolocumab group (4.8% using both broad and narrow SMQ) compared with the placebo group (5.7% using both broad and narrow SMQ). The incidence of hypersensitivity (4.0% and 7.3% using narrow and broad SMQ) observed in the OLE Study 20120124 was comparable with that observed in the RCT study. The incidence in injection site reaction events of 8.7% (using both the narrow and broad SMQ) in the OLE Study 20120124 was slightly higher than the RCT Study, which can be explained by the longer study duration the OLE study.

Anti-evolocumab antibodies

Across all included studies (20120123, 20120124, and 20110271), no subject receiving evolocumab had baseline or postbaseline anti-evolocumab binding antibodies detected at any time point during the study.

Neurocognitive adverse events

HeFH subjects

In Study 20120123, the subject incidence of potential neurocognitive events was also similar between the evolocumab (1 subject [1.0%]) and placebo (0 subjects [0.0%]) groups.

In Study 20120124, five HeFH subjects in this study had potential neurocognitive events of attention deficit hyperactivity disorder (4), amnesia (1), and disturbance in attention (1). All events were nonserious, mild or moderate in severity, and considered unrelated to evolocumab by the investigator.

HoFH subjects

In Study 20120124, one (8.3%) subject had a potential neurocognitive event (nonserious, grade 2 attention deficit hyperactivity disorder); the subject had pre-existing ADHD.

Cogstate Cognitive Battery of neurological tests

Results of the Cogstate Cognitive Battery of neurological tests assessed in Study 20120123 in Study 20120124 did not reveal any trends indicative of a treatment effect of evolocumab on cognition in these subjects. This was also true when the results were summarized by age (<14 years and ≥ 14

years). Findings from neurological physical examinations in each study also did not reveal any clinically relevant abnormalities.

Specific attention has been given to neurocognitive abnormalities, as very low LDL-C levels have been associated with increased risk of neurocognitive abnormalities, although this was not observed in the initially submitted dossier and in a subset of the FOURIER study (EBBINGHAUS subset).

Six pediatric HeFH subjects (1 subject in the evolocumab group of the RCT Study 20120123 and 4 subjects in the OLE Study 20120124), and one HoFH subject (OLE Study 2012024) experienced potential neurocognitive events. Overall, the data are considered limited, which precludes appropriate assessment.

Additionally, the Cogstate Cognitive Battery of neurological tests assessed in Study 20120123 in Study 20120124 also did not reveal any clinically relevant abnormalities.

Muscle adverse events

Muscle adverse events were evaluated using narrow and broad Standardized MedDRA Queries (SMQs) for rhabdomyolysis/myopathy events. Overall, no noteworthy findings were observed in the few muscle adverse events that were reported.

HeFH subjects

In Study 20120123, no muscle adverse events were found using the narrow search terms. Muscle adverse events using broad search terms were reported for 2 (1.9%) subjects in the evolocumab 420 mg QM group (1 [1.0%] subject had musculoskeletal pain, 1 [1.0%] subject had blood creatine phosphokinase increased), and 2 (3.8%) subjects in the placebo group (1 [1.9%] subject had myalgia, 2 [3.8%] subjects had blood creatine phosphokinase increased). No subject had a postbaseline creatine kinase (CK) elevation > 5 x upper limit normal (ULN).

In Study 20120124, myopathy (2 [1.3%] subjects) was the only muscle adverse event found using narrow search terms; both events were nonserious and considered unrelated to evolocumab by the investigator, and neither led to discontinuation of evolocumab. Muscle adverse events using broad search terms were reported for 10 (6.7%) subjects overall. Most of these events were reported for 1 subject each, except for myalgia (5 [3.3%]), myopathy (2 [1.3%]), and blood creatine phosphokinase increased (2 [1.3%]). Two (1.6%) HeFH subjects with normal CK at baseline had a postbaseline CK value that was > 5 x ULN, including 1 (0.8%) subject with a postbaseline CK value that was > 10 x ULN. Of these 2 subjects, 1 subject with CK > 5 x ULN at week 12 had no reported etiology for the elevation, and when queried, the investigator reported that the CK increase was not clinically significant and did not meet the definition of an adverse event. The second subject had CK > 10 x ULN at week 12, and per the investigator the CK increase was sports-related and did not meet the definition of an adverse event. Both subjects had normal CK values at their next scheduled assessment

HoFH subjects

In Study 20120124, no muscle events were found using narrow search terms, and myositis was reported for 1 (8.3%) subject using the broad search terms. Two (18.2%) HoFH subjects with normal baseline CK had at least 1 postbaseline CK value that was > 5 x ULN; of these, 1 subject reported a muscle adverse event of myositis, which was attributed by the investigator to a concomitant upper respiratory tract infection and considered unrelated to evolocumab. No HoFH subjects had a postbaseline CK value > 10 x ULN.

In Study 20110271, among pediatric subjects with HoFH, no muscle adverse events were found using the narrow search terms. Muscle adverse events using broad search terms were reported for 2 (14.3%) subjects, both of whom had blood creatine phosphokinase increased. Of these 2 subjects, one had CK > 10 x ULN at week 36 and week 108; in both instances, the subject had engaged in vigorous exercise before the study visit/blood draw. A nonserious Common Terminology Criteria for Adverse Events (CTCAE) grade 1 adverse event of increased blood creatine phosphokinase was reported at the week 36 visit; the event resolved after 11 days and was considered unrelated to evolocumab by the investigator. The second subject had CK elevations at week 36 (> 10 x ULN), week 48 (> 5 x ULN), and week 132 (> 10 x ULN). Nonserious, CTCAE grade 1 treatment-emergent adverse events of increased blood creatine phosphokinase were reported at the week 36 and week 48 visits; the events resolved after 11 and 10 days, respectively. The subject had engaged in vigorous exercise prior to the week 36 and week 48 study visit/blood draw and both events were considered unrelated to evolocumab by the investigator. At week 132, the subject reported feeling well with no muscle symptoms, and the CK elevation was considered not clinically significant by the investigator; no adverse event was reported. No other HoFH subjects with normal CK values at baseline had CK > 5 x ULN at any postbaseline visit.

Hepatic adverse events

Hepatic adverse events were evaluated using narrow and broad SMQs for drug-related hepatic disorders events. Overall, no noteworthy findings were observed in the few hepatic adverse events that were reported, which is consistent with the full dataset available for evolocumab..

HeFH subjects

In Study 20120123, there were no reported drug-related hepatic disorders events among subjects in the evolocumab treatment group, while 2 (3.8%) subjects in the placebo group had such events (1 [1.9%] subject had jaundice, 1 [1.9%] subject had alanine aminotransferase increased), using both narrow and broad search terms. One (1.0%) evolocumab subject with normal total bilirubin at baseline had postbaseline total bilirubin > 2 x ULN. No subject had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x ULN at any time during the study.

In Study 20120124, a drug-related hepatic disorders adverse event using narrow and broad search terms was reported for 1 (0.7%) subject with HeFH who had blood bilirubin increased; this subject was subsequently diagnosed with Gilbert's syndrome. In HeFH subjects with normal total bilirubin at baseline, 2 (1.4%) subjects had postbaseline total bilirubin > 2 x ULN, including the subject who reported an adverse event of blood bilirubin increased. No HeFH subject with normal ALT and AST at baseline had a postbaseline ALT or AST > 3 x ULN.

HoFH subjects

In Study 20120124, there were no events of drug-related hepatic disorders using either narrow or broad search strategies. No HoFH subjects with normal total bilirubin at baseline had total bilirubin > 2 x ULN at any time during the study, and no HoFH subject had ALT or AST > 3 x ULN at any time during the study.

In Study 20110271, a drug-related hepatic disorders adverse event using narrow and broad search terms was reported for 1 (7.1%) pediatric subject with HoFH who had an abnormal liver function test. One (7.1%) subject had a postbaseline ALT or AST > 5 x ULN and 1 (7.1%) subject had total bilirubin > 2 x ULN.

Adverse events in subject who achieved LDL-C< 40 mg/dL) (<1.0 mmol/L).

Few subjects in Studies 20120123, 20120124, and 20110271 achieved LDL-C values < 40 mg/dL, given their high LDL-C values at baseline. No new safety concerns were identified based on the review of safety data for the 4 subjects with low LDL-C values who had an adverse event. The most frequently reported adverse events, presented below for each study, were generally consistent with the known adverse drug reactions for evolocumab, as described in the product labeling, and related symptoms (ie, nasopharyngitis, upper respiratory tract infection).

HeFH subjects

In Study 20120123, no treatment-emergent adverse events were reported among subjects in the evolocumab group who achieved LDL-C < 40 mg/dL. Among subjects who achieved LDL-C ≥ 40 mg/dL, 59 (61.5%) in the evolocumab group and 34 (64.2%) in the placebo group had at least 1 adverse event.

In Study 20120124, 4 subjects with HeFH who achieved LDL-C < 40 mg/dL had a treatment-emergent adverse event, including contusion, nasopharyngitis, depression, anxiety, dermatitis allergic, which were reported for 1 subject each; the 1 subject with the contusion adverse event achieved LDL-C < 25 mg/dL. Among those who achieved LDL-C ≥ 40 mg/dL, 94 (65.7%) subjects had an adverse event.

HoFH subjects

In Study 20120124, no subjects with HoFH achieved LDL-C < 40 mg/dL, and among those who achieved ≥ 40 mg/dL, 7 (58.3%) subjects had at least 1 adverse event.

In Study 20110271, no subjects with HoFH achieved LDL-C < 40 mg/dL. Among those who achieved LDL-C > 40 mg/dL, treatment-emergent adverse events were reported for 2 (50.0%) subjects with apheresis and 10 (100.0%) subjects without apheresis at enrollment.

There is no evidence of an unexpected safety concern regarding muscle adverse events, hepatic events and adverse events in subjects who achieved low LDL-C levels. These findings are consistent with the full dataset available for evolocumab. Serious adverse event/deaths/other significant events

Serious adverse event

HeFH

In Study 20120123, 1 (1.0%) subject in the evolocumab group experienced a serious adverse event of cholelithiasis, which was not considered related to investigational product by the investigator. No subject in the placebo group experienced either a serious adverse event.

In Study 20120124, SAEs were reported for 4 (2.7%) HeFH subjects (wrist fracture, headache, perforated appendicitis and peritonitis, and anorexia nervosa) of which none were considered related to study drug.

Moreover, none of the SAEs, which included an event of cholelithiasis, wrist fracture, headache, perforated appendicitis and peritonitis, and anorexia nervosa, occurred in more than one subject, and none was considered related to IP.

HoFH

In Study 20120124, SAEs were reported for 2 (16.7%) HoFH subjects (appendicitis and arteriovenous fistula aneurysm) which were considered not related to study drug.

In Study 20110271, SAEs were reported for 4 (28.6%) HoFH subjects including 3 subjects with 1 event each of pleuritic pain, coronary artery occlusion, and ovarian germ cell teratoma, and 1 subject with 4 serious adverse events (non-cardiac chest pain, appendicitis, aortic stenosis, and nephrolithiasis). None of these SAEs were considered related to study drug.

Deaths

There were no fatal adverse events among pediatric subjects in Studies 20120123, 20120124, and 20110271.

Other significant events

Events of death by any cause, cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure were adjudicated by an independent CEC in Study 20120123 and Study 20110271. These events were not adjudicated in open-label Study 20120124. Across the 2 studies where these events were adjudicated, no pediatric subject had a positively adjudicated cardiovascular endpoint adverse event.

Laboratory findings

Clinical Laboratory abnormalities

HeFH subjects

In Study 20120123, laboratory values that shifted from baseline grades 0, 1, or 2 to postbaseline grades 3 or 4 were single occurrences with the exception of uric acid which occurred more frequently in the evolocumab group. No subject experienced a grade 4 laboratory toxicity. For uric acid, 7 (6.7%) subjects in the evolocumab group and 2 (3.8%) subjects in the placebo group experienced shifts from baseline grade 0 to postbaseline grade 3. One placebo subject had an associated adverse event of increased uric acid reported; no other adverse events associated with increases uric acid were reported.

Hemoglobin A1c (HbA1c) and fasting blood glucose values were similar between treatment groups at baseline and remained overall unchanged throughout the study. Shifts in hsCRP from baseline to maximum postbaseline were generally similar between the evolocumab and placebo groups. In each treatment group, there was little change in the percentage of subjects within each grade category at baseline and postbaseline; a reduction in the proportion of subjects with postbaseline hsCRP > 3 mg/L, compared with baseline, was observed in both treatment groups.

No evidence of an impact of evolocumab on steroid hormone biosynthesis was observed; changes from baseline to week 24 were minimal in both groups and not clinically meaningful.

A review of vitamin assessments did not reveal any clinically significant impact of evolocumab on these parameters. Vitamin A and vitamin D concentrations were similar between the treatment groups at baseline and at week 24. Vitamin E concentrations at baseline were similar between the evolocumab and placebo groups. As expected, a reduction in total vitamin E over time was observed in the evolocumab group compared with the placebo group; vitamin E plasma concentrations decreased as the concentrations of lipoproteins transporting vitamin E decreased. While some variation in vitamin K concentrations between the treatment groups was observed, these seemed to be driven by outliers;

median concentrations of vitamin K were similar between the treatment groups at baseline and at week 24.

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

In Study 20120124, laboratory values that shifted from baseline grades 0, 1, or 2 to postbaseline grades 3 or 4 were largely single occurrences with the exception of creatine kinase (CK) and total cholesterol. For CK, 1 subject had a shift from baseline grade 0 to grade 3 and 1 subject had a shift from baseline grade 0 to grade 4; in both subjects the CK shift was transient and there were no relevant adverse events reported. For total cholesterol, 1 subject had a shift from baseline grade 2 to grade 3 and 1 subject had a shift from baseline grade 1 to grade 3. No other grade 4 laboratory toxicities occurred.

In general, HbA1c, fasting blood glucose, and hsCRP values remained unchanged throughout the study. Changes in steroid hormones from baseline to week 80 were minimal and/or not clinically meaningful. This included assessments of estradiol in females, testosterone in male subjects, cortisol, luteinizing hormone, adrenocorticotropic hormone, dehydroepiandrosterone sulfate, and follicle stimulating hormone.

A review of vitamin assessments did not reveal any clinically significant impact of evolocumab on these parameters. Vitamin A, vitamin D, and vitamin E concentrations were similar at baseline and at week 80. Some variation in vitamin K concentrations were noted at week 80 (median [Q1, Q3] change from baseline to week 80 was -60.0 [-330.0, 12.0]); however, these seemed to be driven by outliers and small sample size at week 80 (n = 13/150). Median concentrations of vitamin K were similar at baseline and at week 80.

No trends indicative of clinically important treatment-related laboratory abnormalities were observed with evolocumab in this study.

<u>HoFH subjects</u>

In Study 20120124, laboratory values that shifted from baseline grades 0, 1, or 2 to postbaseline grades 3 or 4 were observed in bilirubin (baseline grade 2 to grade 3 [n = 1]) and CK (baseline grade 0 to grade 3 [n = 2]). For CK, 1 subject had CK elevations at week 12 and week 80 with no relevant co-reported adverse events, and 1 subject had CK elevations at week 48 coincident with an upper respiratory tract infection; a grade 3 nonserious event of myositis was reported for this subject. Five HoFH subjects also had a total cholesterol postbaseline grade 4 toxicity, but all of these subjects had either grade 3 (2 [16.7%]) or grade 4 (3 [25.0%]) toxicities at baseline. No other grade 4 laboratory toxicities occurred.

Overall, no trends indicative of clinically important treatment-related laboratory abnormalities were observed with evolocumab in this study. Interpretation of laboratory trends is minimized by the small sample size, particularly with steroid hormones as there were only 2 female HoFH subjects. In general, HbA1c and fasting blood glucose values remained overall unchanged throughout the study. Shifts in hsCRP from baseline < 3 mg/L to maximum postbaseline > 3 mg/L were observed in 2 (16.7%) subjects. A review of vitamin assessments did not reveal any clinically significant impact of evolocumab on these parameters.

In Study 20110271, no patterns indicative of clinically important treatment-related laboratory abnormalities were observed in this study.

Laboratory values that shifted from baseline grades 0, 1, or 2 to postbaseline grades 3 or 4 were observed in CK; 2 (14.3%) pediatric HoFH subject had a shift from baseline grade 0 to grade 4. For

both subjects, corresponding nonserious grade 1 adverse events of increased blood creatine phosphokinase were reported; the events were considered unrelated to evolocumab by the investigator and evolocumab was continued. No other grade 3 or grade 4 postbaseline laboratory values were noted. No significant change in HbA1c from baseline was noted.

Creatine kinase

HeFH subjects

In Study 20120123, 1 (1.0%) subject in the evolocumab group had CK > 5 x upper limit of normal (ULN) at baseline. No subject had a postbaseline CK value >5 x ULN at week 24.

In Study 20120124, 1(0.7%) HeFH subject had CK > 5 x ULN at baseline only. Two (1.4%) subjects with normal CK at baseline had a postbaseline CK value that was > 5 x ULN at week 12, including 1 (0.7%) subject with a postbaseline CK value that was >10 x ULN. No other instance of postbaseline CK value > 5 x ULN occurred.

HoFH subjects

In Study 20120124, no HoFH subjects had CK> 5 x ULN at baseline. Two (16.7%) subjects with normal baseline CK had at least 1 postbaseline CK value that was > 5 x ULN at week 12 (n = 1), week 48 (n = 1), and week 80 (n = 1). No HoFH subjects had a postbaseline CK value > 10 x ULN.

In Study 20110271, 2 (15.4%) pediatric subjects with normal CK values at baseline had CK > 10 x ULN at any postbaseline visit.

Liver function tests

HeFH subjects

In Study 20120123, 1 (1.9%) placebo subject had total bilirubin > 2 x ULN at baseline, week 12, and week 24. One (1.0%) evolocumab subject with normal total bilirubin at baseline had total bilirubin >2 x ULN at the week 24 visit. No subject had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x ULN at any time during the study.

In Study 20120124, 3 (2.0%) subjects had a postbaseline total bilirubin > 2 x ULN. In subjects with normal total bilirubin at baseline, 2 (1.5%) subjects had total bilirubin > 2 x ULN at the week 12 visit, and of these 1 subject had total bilirubin > 2 x ULN at the week 48 visit, and 1 subject at the week 80 visit.

No HeFH subjects had ALT or AST > 3 x ULN at baseline. One (0.7%) HeFH subject had ALT or AST > 3 x ULN at week 12. No subject had ALT or AST > 5 x ULN at any time during the study.

HoFH subjects

In Study 20120124, 1 (8.3%) subject had total bilirubin > 2 x ULN at each postbaseline time point (week 12, 48, and 80). No subjects with normal total bilirubin at baseline had total bilirubin > 2 x ULN at any time during the study. No HoFH subject had ALT or AST > 3 x ULN at any time during the study.

In the pediatric subset of Study 20110271, 1 (7.1%) subject had ALT or AST > 5 x ULN at any postbaseline visit and 1 (7.1%) subject had total bilirubin > 2 x ULN at any postbaseline visit. No subject had (ALT or AST > 3 x ULN) and (total bilirubin > 2 x ULN or international normalized ratio > 1.5) at any postbaseline visit.

Overall, no trends indicative of clinically important treatment related laboratory abnormalities including haemoglobin A1c, fasting blood glucose, hsCRP, hormone levels, vitamins were observed with evolocumab in Study 20120123, 20120124 and 20110271, as laboratory values were generally within the normal range. Subject incidence of creatine kinase (CK) elevations and liver function tests (LFT) elevations was low, and no imbalance between treatment groups in double-blind, placebo-controlled Study 20120123 was observed. Moreover, safety data on vitamin E levels show to be within the normal range consistent with the initial dossier. In Study 20120123, events of uric acid occurred more frequently in the evolocumab group (6.7%, n-7) compared to the placebo group (3.8%, n=2) from baseline grade 0 to post-baseline grade 3. However, the events in the evolocumab group were all considered non-related to the study drug, which is reassuring.

Vital signs

Across all included studies (20120123, 20120124, and 20110271), there were no trends indicative of important vital sign, including systolic blood pressure, diastolic blood pressure, and heart rate abnormalities observed.

Tanner staging

HEFH subjects

In Study 20120123, a total of 66 male subjects (42 [98%5] evolocumab, 24 [92%] placebo) and 76 female subjects (54 [89%] evolocumab, 22 [825] placebo) had assessment of growth and pubertal development (Tanner stage) reported (**Table 43**). There was no evidence of an effect of evolocumab on Tanner stage. Subjects had normal Tanner staging appropriate for their age at baseline and week 24, with no differences in overall mean (SD) age between the evolocumab and placebo groups at baseline using the criteria of gender (genital size for males and breast development for females) or pubic hair. Furthermore, the number of subjects with changes in Tanner stage while on treatment was generally similar between treatment groups for each criterion. Most subjects in the evolocumab and placebo groups did not have a change in Tanner staging by each criterion during the study.

Table 43. Summary of Tanner staging at baseline and week 24 – Study 20120123 (full analysis set).

Parameter	Placebo	EvoMab
Tanner staging by genital size - Males		
n	26	43
Mean (SD) Age at Baseline	13.3 (2.4)	13.6 (2.4)
Number of subjects with change from baseline[a] – n (%)	5/24 (20.8)	11/42 (26.2)
Tanner staging by breast development - Females		
n	27	61
Mean (SD) Age at Baseline	14.0 (2.5)	13.9 (2.3)
Number of subjects with change from baseline[a] – n (%)	3/22 (13.6)	8/54 (14.8)
Tanner staging by pubic hair - Males		
n	26	43
Mean (SD) Age at Baseline	13.3 (2.4)	13.6 (2.4)
Number of subjects with change from baseline[a] – n (%)	4/24 (16.7)	9/42 (21.4)
Tanner Staging by pubic hair - Females		
n	27	61
Mean (SD) Age at Baseline	14.0 (2.5)	13.9 (2.3)
Number of subjects with change from baseline[a] – n (%)	4/22 (14.8)	9/54 (16.7)

n = number of subjects with Tanner stage data at baseline
[a] Number and percentage with change in Tanner Staging excluded subjects with missing values at week 24.

In Study 20120124, 42 male subjects and 59 female subjects had assessments of growth and pubertal development (Tanner stage) reported at week 80 (**Table 44**).

There was no evidence of an effect of evolocumab on Tanner stage using the criteria of gender (genital size for males and breast development for females) or pubic hair. Subjects had normal Tanner staging appropriate for their age at baseline and week 80.

Table 44. Summary of Tanner staging at baseline and week 80 - Study 20120124 (full analysis set)

Parameter	HeFH			HoFH	Total
	Placebo QM in Parent Study (N = 49)	EvoMab 420 mg QM in Parent Study (N = 101)	Overall (N = 150)	EvoMab 420 mg QM (N = 12)	EvoMab 420 mg QM (N = 162)
Tanner staging by genital size – Males					
n	25	42	67	10	77
Mean (SD) Age at Baseline	13.5 (2.4)	14.1 (2.5)	13.9 (2.5)	12.1 (1.6)	13.6 (2.5)
Number of subjects with change from baseline[a] – n (%)	11/18 (61.1)	12/24 (50.0)	23/42 (54.8)	6/9 (66.7)	29/51 (56.9)
Tanner staging by breast development - Females					
n	24	59	83	2	85
Mean (SD) Age at Baseline	14.0 (2.6)	14.4 (2.4)	14.3 (2.4)	14.0 (4.2)	14.3 (2.4)
Number of subjects with change from baseline[a] – n (%)	5/14 (35.7)	22/43 (51.2)	27/57 (47.4)	1/2 (50.0)	28/59 (47.5)
Tanner staging by pubic hair – Males					
n	25	42	67	10	77
Mean (SD) Age at Baseline	13.5 (2.4)	14.1 (2.5)	13.9 (2.5)	12.1 (1.6)	13.6 (2.5)
Number of subjects with change from baseline[a] – n (%)	12/18 (66.7)	12/24 (50.0)	24/42 (57.1)	6/9 (66.7)	30/51 (58.8)
Tanner staging by pubic hair – Females					
n	24	59	83	2	85
Mean (SD) Age at Baseline	14.0 (2.6)	14.4 (2.4)	14.3 (2.4)	14.0 (4.2)	14.3 (2.4)
Number of subjects with change from baseline[a] – n (%)	6/14 (42.9)	20/43 (46.5)	26/57 (45.6)	1/2 (50.0)	27/59 (45.8)

EvoMab = Evolocumab (AMG 145); HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; QM = monthly (subcutaneous)
Interim analysis data cutoff date: 08JUN2020
n (%) = the number of subjects with observations in both categories (n) and n as a percentage (%) of all subjects in the treatment group (N).
[a] Number and percentage with change in Tanner Staging excluded subjects with missing values at week 80.

HoFH subjects

In Study 20120124, 10 male subjects and 2 female subjects had assessments of growth and pubertal development (Tanner stage) reported at week 80 (**Table 44**). There was no evidence of an effect of evolocumab on Tanner stage using the criteria of gender (genital size for males and breast development for females) or pubic hair. Subjects had normal Tanner staging appropriate for their age at baseline and week 80.

Of the 9 pediatric subjects with Tanner staging growth parameters in Study 20110271, all had normal Tanner staging for their age.

Overall, no meaningful changes in blood pressure or heart rate were observed with evolocumab in Study 20120123, 20120124 and 20110271.

Additionally, assessments of growth and pubertal development (Tanner stage) did not reveal an effect of evolocumab on Tanner stage in Study 20120123, 20120124 and 20110271. However, the placebo-controlled safety data of 24 weeks exposure to evolocumab is considered too limited to draw firm conclusions on the effect of evolocumab on Tanner staging.

Safety in special populations

Age (10-≤11 vs 12 -≤17 years of age)

HeFH

In Study 20120123, among subjects 10 -≤ 11 years old, the overall incidence of treatment-emergent adverse events was similar in the evolocumab (17 [70.8%]) and placebo (10 [71.4%]) treatment groups, and most adverse events were reported for 1 subject in either group. The most comment adverse events (> 5% of subjects in either group) were gastroenteritis (5 [20.8%] evolocumab, 1 [7.1%] placebo), upper respiratory tract infection (4 [16.7%], 0), nasopharyngitis (3 [12.5%], 1 [7.1%]), viral upper respiratory tract infection (2 [8.3%], 0), injection site pain (2 [8.3%], 1 [7.1%]), pyrexia (2 [8.3%], 1 [7.1%]), abdominal pain (2 [8.3%], 0), cough (2 [8.3%], 1 [7.1%]), and headache (2 [8.3%], 0).

Among subjects 12 -≤ 17 years old, the overall incidence of treatment-emergent adverse events was similar in the evolocumab (47 [58.8%]) and placebo (24 [61.5%]) treatment groups, and most adverse events were reported for 1 subject in either group. The most comment adverse events (> 5% of subjects in either group) were nasopharyngitis (9 [11.3%] evolocumab, 5 [12.8%] placebo), headache (9 [11.3%], 1 [2.6%]), oropharyngeal pain (6 [7.5%], 0), influenza (5 [6.3%], 1 [2.6%]), pyrexia (1 [1.3%], 2 [5.1%]), blood creatine phosphokinase increased (1 [1.3%], 2 [5.1%]), gastroenteritis (0, 3 [7.7%]), rhinitis (0, 2 [5.1%]), cough (0, 2 [5.1%]), and depression (0, 2 [5.1%]).

In Study 20120124, among subjects 10 -≤11 years old with HeFH, the overall incidence of treatment-emergent adverse events was 11 (37.9%) subjects. Most adverse events were reported for 1 subject each, except for nasopharyngitis (5 [17.2%]), pyrexia (2 [6.9%]), and headache (2 [6.9%]).

Among subjects 10 -≤11 years old with HoFH, the overall incidence of treatment-emergent adverse events was 3 (50.0%) in the evolocumab treatment group. All reported adverse events occurred in 1 subject each.

Among subjects 12 -≤17 years old with HeFH, the overall incidence of treatment-emergent adverse events was 83 (73.5%) subjects. Most adverse events were reported for 1 or 2 subjects in either group. The most frequently reported adverse events (> 5% of subjects) were nasopharyngitis (16 [14.2%]), headache (11 [9.7%]), influenza like illness (9 [8.0%]), gastroenteritis (7 [6.2%]), oropharyngeal pain (7 [6.2%]), upper respiratory tract infection (7 [6.2%]), and abdominal pain upper (6 [5.3%]).

HoFH

In Study 20120124, among subjects 10 -≤ 11 years old with HoFH, the overall incidence of treatment-emergent adverse events was 3 (50.0%) in the evolocumab treatment group. All reported adverse events occurred in 1 subject each.

Among subjects 12 to ≤ 17 years old with HoFH, the overall incidence of treatment-emergent adverse events was 4 (66.7%). All reported adverse events occurred in 1 subject each, except for epistaxis (2 [33.3%]).

Although higher adverse events rates could be observed in the 12-≤17 years of age subgroup compared with the 10-≤ 11 years of age subgroup in both the HeFH and HoFH subjects, no specific pattern indicative for a safety signal across the subgroups could be observed. Overall, the most frequently reported events were generally consistent with the known adverse drug reactions for evolocumab.

Safety related to drug-drug interactions and other interactions

No new information on drug-drug interaction is available for this submission; Studies 20120123, 20120124, and 20110271 were not designed to evaluate drug-drug or drug food interactions**.**

Discontinuation due to adverse events

HeFH subjects

The incidence in discontinuation due to adverse events was low. In Study 20120123, 1 (1.0%) subject in the evolocumab group experienced a nonserious grade 2 adverse event of arthropathy leading to discontinuation of investigational product that was considered related to investigational product by the investigator. No subject in the placebo group experienced an adverse event leading to discontinuation of investigational product.

In Study 20120124, no subjects experienced a treatment-emergent adverse event that led to discontinuation of evolocumab.

HoFH subjects

In Study 20120124, no subjects experienced TEAEs leading to discontinuation of study drug.

In Study 20110271, one subject had a grade 3 nonserious adverse event of rash leading to discontinuation of evolocumab. In the OLE Study 20110271, 1 out of 14 (7.1%) HoFH subject discontinued the study due to an adverse event of rash.

Post marketing experience

As of 17 July 2020, evolocumab has been approved in 77 countries and an estimated 748 312 patients (551 687 patient-years) have been exposed worldwide to evolocumab in the postmarketing setting (**Table 42**). On 30 January 2020, the Committee for Medicinal Products for Human Use issued a positive opinion for evolocumab renewal covering the last 5 years and an unlimited license for evolocumab in the European Union (EU).

Table 45. Estimated Number of Patients Exposed to Evolocumab by Region in the Postmarketing Setting

Region	Cumulative No. of Patients Exposed[a]
United States	341 713
Europe	244 635
Canada	45 870
Australia	10 285
Other	105 808
Total	748 312

[a] As of 17 July 2020

The evaluation of the safety data from the postmarketing setting has not resulted in the detection of any new important identified or potential risks for inclusion in the EU Risk Management Plan (RMP). Postmarketing evaluation of relevant subgroups (pregnancy and lactation, pediatric, elderly [≥ 75 years], severe renal impairment, severe hepatic impairment, hepatitis C, type 1 diabetes, human immunodeficiency virus, patients with HoFH) has not resulted in any significant safety findings. Cumulatively through 17 July 2020, postmarketing adverse event case reports have been received for 139 pediatric patients ranging in age from 2 to 17 years and exposed to evolocumab. The majority (90%) of reported adverse events were nonserious and overall the most commonly reported event was off-label use (based on age or dosing regimen). Overall, the reported events were consistent with the known safety profile of evolocumab and/or expected events in the patient population independent of drug exposure.

Exposure to evolocumab in the postmarketing setting has identified adverse drug reactions of hypersensitivity including angioedema and influenza like illness; the Summary of Product Characteristics has been updated accordingly. Myalgia has also been identified as an adverse drug reaction based on the postmarketing experience; updates to regional prescribing information is ongoing. Reports of nonserious finger stick events associated with autoinjector use were received which resulted in a revision of the instructions for use in the United States (US), EU, and other regions.

In summary, it has been estimated that 748 312 patients (551 687 patient-years) have been exposed worldwide to evolocumab in the post-marketing setting. Cumulatively through 17 July 2020, post-marketing adverse event case reports have been received for 139 pediatric patients ranging in age from 2 to 17 years and exposed to evolocumab. The majority (90%) of reported adverse events were nonserious, and overall the most commonly reported event was off-label use (based on age or dosing regimen), which is reassuring. Overall, the reported events were consistent with the known safety profile of evolocumab.

2.4.1. Discussion on clinical safety

Assessment of paediatric data on clinical safety

In the current dossier, the safety evaluation is primarily based on the double-blind, randomized Study 20120123 and its *ongoing* OLE study 20120124 and supplemented by safety data from the phase 2/3 open-label extension Study 20110271.

Patient exposure. In the initial MA dossier, 5710 patients, (majority were adult subjects) were exposed to evolocumab in > 25 clinical trials across broad patient populations, representing 5246 patient years of exposure. With the submission of the cardiovascular outcome trial FOURIER, with a

total of 27525 adult subjects and the GLAGOV study with 968 adult subjects included, the overall exposure data from clinical studies has substantially increased although exposure in the FOURIER study was limited to a median of 2.6 years. Furthermore, it has been estimated that 748312 patients (551687 patient years) have been exposed worldwide to evolocumab in the post marketing setting; So, there is large safety experience with evolocumab, although the experience in pediatric patients is limited, however, increased based on the safety data of Study 20120123 and 20120124 currently under review.

For the HeFH population aged 10-≤17 years across the RCT Study 20120123 and OLE Study 20120124, a total of 153 patients received at least 1 dose of evolocumab, with a total patient-year exposure of 249 with 149 (97.4%), 135 (88.2%), and 76 (49.7%) HeFH subjects exposed to evolocumab for at least 24, 48 and 96 weeks, respectively. In terms of numbers this is sufficient according to guideline recommendations and considering that this may be a life-long treatment. Placebo-controlled safety data of pediatric HeFH subjects who received all 6 doses of IP, i.e. 24 weeks of exposure, in the RCT Study 20120123 is available for 98 subjects (out of 104, 94%) in the evolocumab group and 51 (out of 53, 96%) subjects in the placebo group, which is considered sufficient to identify evolocumab related safety effects.

For the HoFH population, 12 de-novo pediatric HoFH subjects 10-≤17 years of age in the OLE Study 20120124 received at least one dose of evolocumab, with a total patient-year exposure of 17. Of these patients, all do-novo HoFH subjects (100.0%) had evolocumab exposure ≥ 28 weeks and 11 (91.7%) completed the study and, as such, were exposed to evolocumab for 80 weeks. The safety exposure data is supplemented with exposure data of 14 HoFH pediatric subjects 12-≤ 17 years of age in the OLE Study 20110271, who received evolocumab for up to 5 years, which resulted in a combined exposure of 62.2 patient-years, which still remains limited especially considering that evolocumab is intended for life-long treatment. The number of HoFH subjects aged 10-≤11 years exposed to evolocumab is limited but expected and acceptable considering the rarity of the HoFH disease.

Adverse events. In pediatric HeFH subjects in the RCT Study 20120123, TEAES were frequently reported, however, with a lower percentage in the evolocumab group compared with the placebo group (61.5% vs 64.2%). The most frequent AEs (> 5% of subjects) with a higher incidence with evolocumab compared with placebo were nasopharyngitis (11.5% vs 11.3%), headache (10.6% vs 1.9%), oropharyngeal pain (6.7% vs 0.0%), influenza (5.8% vs 3.8%), upper respiratory tract infection (5.8% vs 1.9%). When considering longer treatment (OLE Study 20120124), the frequency in TEAEs increased slightly (66.7%), however, an approximately similar safety profile was observed with nasopharyngitis (14.7%), headache (8.7%), influenza-like illness (8.7%), gastroenteritis (6.0%), upper respiratory tract infection (5.3%), and oropharyngeal pain (5.3%) being the most prominent adverse events observed. The safety findings are consistent with the safety data observed in adults in the initial MAA dossier and the FOURIER dossier, with the exception of the disbalance in oropharyngeal pain. The TEAEs of oropharyngeal pain observed in HeFH subjects in Study 20120123 and 20120124 were nonserious, mild to moderate in severity and all considered not related to treatment with evolocumab.

For the pediatric HoFH patients aged 10-≤17 years in the OLE Study 20120124, 7 of the 12 (58.3%) HoFH subjects experienced TEAEs, however, none of the TEAEs occurred in more than 1 subject with the exception of epistaxis (n=2, 16.7%), which is reassuring. In the pediatric subset of HoFH subjects aged 12-≤17 years of the OLE study 20110271, 12 of the 14 subjects (85.7%) experienced TEAEs with anxiety, migraine, and upper respiratory tract infection (21.4% (n=3) each) as being the most common adverse events observed. The higher frequency of TEAEs compared with those observed for HeFH subjects in Study 20120123 and for the HeFH and HoFH subjects in Study 20120124 can be explained by the longer (5 year) study duration of Study 20110271. Overall, no new safety signal as

compared with the initial MAA dossier and the FOURIER dossier is observed, although firm conclusions cannot be made due to the limited exposure data in pediatric HoFH patients.

The incidence in device-related adverse events was low (3 (2.9%) vs 2 (3.8%) HeFH subjects in the evolocumab vs placebo group in Study 20120123 and 7.3% of the HeFH subjects in Study 20120124 and in one HoFH subject in Study 20120124). Moreover, the majority were mild in severity and related to the injection site, which is consistent with those observed in the initial MA dossier and the FOURIER dossier. No new TEAEs considered by the investigator related to IP has been identified, which is reassuring. As also described above, most of treatment related TEAEs were injections site reactions, which is a known ADR of evolocumab.

AEs of special interest. Since evolocumab is a human monoclonal immunoglobulin, specific attention has been given to *potential hypersensitivity*, *potential injection site reactions* and *anti-evolocumab antibodies*. In the HeFH subjects of the RCT Study 20120123, a higher incidence of hypersensitivity was observed in the evolocumab group (3.8% and 6.7% using narrow and broad SMQ, respectively) compared with the placebo group (0% using both narrow and broad SMQ), however, the incidence was relatively low and no specific pattern indicative for a safety signal could be observed. Moreover, the incidence in potential injection site reactions was lower in the evolocumab group (4.8% using both broad and narrow SMQ) compared with the placebo group (5.7% using both broad and narrow SMQ). With respect to long-term treatment, the incidence in hypersensitivity (observed in the OLE Study 20120124) was comparable with that observed in the RCT study. The incidence in injection site reaction events of 8.7% (using both the narrow and broad SMQ) in the OLE Study 20120124 was slightly higher compared with the RCT Study, which can be explained by the longer study duration of the OLE study. For the HoFH population, only one HoFH subject in the OLE Study 20120124 had a potential injection site reaction, which was nonserious and mild in severity and 2 HoFH subjects in the OLE Study 20110271 reported a potential hypersensitivity event. Furthermore, anti-evolocumab antibodies were not reported in any of the studies 20120123, 20120124, and 20110271, which is reassuring. There is no evidence of an unexpected safety concern regarding *muscle adverse events*, *hepatic events* and *adverse events in subjects who achieved low LDL-C levels* in both HeFH and HoFH pediatric subjects.

Specific attention has been given to *neurocognitive abnormalities*, as very low levels of LDL-C have been associated with increased risk of neurocognitive abnormalities, although this was not observed in the initial submitted dossier nor in the FOURIER dossier. No clinically relevant abnormalities were observed with six pediatric HeFH subjects (1 subject in the evolocumab group of the RCT Study 20120123, 4 subjects in the OLE Study 20120124, and one HoFH subject (OLE Study 2012024) experiencing potential neurocognitive events. Additionally, results of the Cogstate Cognitive Battery of *neurological tests* assessed in Study 20120123 and in Study 20120124 also did not reveal any clinically relevant abnormalities. Nevertheless, the data are considered limited, which precludes appropriate assessment.

Serious AEs. The incidence in SAEs was relatively low with 1 (1%) HeFH subject in the evolocumab vs none in placebo group in Study 20120123 and 4 (2.7%) HeFH subjects treated with evolocumab in Study 20120124. For the HoFH population, 2 out of 12 (16.%) subjects in Study 20120124 and in 4 out of 14 (28.6%) subjects in Study 20110271 experienced a SAE. Moreover, none of the SAEs were considered by the investigator related to IP, which is reassuring.

Deaths. No deaths were observed in subjects treated with evolocumab or placebo in the Studies 20120123, 20120124, and 20110271. Furthermore, in the RCT Study 20120123 and OLE Study 20110271, no pediatric subject had a positively adjudicated cardiovascular endpoint adverse event. These events were not adjudicated in the OLE Study 20120124.

Laboratory findings. Overall, no trends indicative of clinically important treatment-related laboratory abnormalities including haemoglobin A1c, fasting blood glucose, hsCRP, hormone levels, vitamins were observed with evolocumab in Study 20120123, 20120124 and 20110271, as laboratory values were generally within the normal range.

Vital Signs. Across the studies 20120123, 20120124, and 20110271, no meaningful changes in blood pressure or heart rate were observed with evolocumab. Additionally, assessments of growth and pubertal development (Tanner stage) did not reveal an effect of evolocumab on Tanner stage in Study 20120123, 20120124 and 20110271. However, the safety data, particularly the placebo-controlled safety data of 24 weeks exposure to evolocumab, is considered too limited to draw firm conclusions on the effect of evolocumab on Tanner staging.

Safety in special populations. Although higher adverse events rates could be observed in the 12-⩽ 17 years of age subgroup compared with the 10-⩽ 11 years of age subgroup of both the HeFH and HoFH subjects, no specific pattern indicative for a safety signal across the subgroups could be observed. Overall, the most frequently reported events were generally consistent with the known adverse drug reactions for evolocumab.

Discontinuations due to AEs. Across all three studies, only two discontinuations due to AEs were observed (1 (1.0%) HeFH subject in the evolocumab group in Study 20120123 due to an AE of arthropathy and 1 out of 14 (7.1%) HoFH subject in the OLE Study 20110271 due to an AE of rash). Both AEs are known adverse drug reactions of evolocumab.

Dose regimens. No safety data are available for the proposed 420 mg Q2W regimen for the pediatric HoFH subjects aged 10-≤11 years.

Post marketing experience. Cumulatively through 17 July 2020, post marketing adverse event case reports have been received for 139 pediatric patients ranging in age from 2 to 17 years and exposed to evolocumab. The majority (90%) of reported adverse events were nonserious and overall the most commonly reported event was off-label use (based on age or dosing regimen), which is reassuring.

Additional expert consultations

N/A

2.4.2. Conclusions on clinical safety

Evolocumab displays an acceptable safety profile in pediatric HeFH and HoFH patients aged 10-≤17 years comparable to those observed in adults with HeFH and adults and adolescents with HoFH in the initial MAA dossier and the FOURIER dossier with very limited patients discontinuing treatment or showing serious adverse events.

However, one uncertainty remain which concerns safety confirmation on the evolocumab 420 mg Q2W regimen in HoFH subjects 10-≤11 years of age.

2.4.3. PSUR cycle

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

2.5. Risk management plan

The MAH submitted an updated RMP version 7.0 and subsequent version 7.1 within this procedure.

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

The PRAC considered that the RMP version 7.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the RMP version 7.1 with the following content:

Safety specification

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	• Use in pregnant/lactating women • Long-term use including effects of low-density lipoprotein cholesterol < 40 mg/dL (< 1.03 mmol/L)

Pharmacovigilance Plan

Ongoing and planned Additional Pharmacovigilance Activities:

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 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) **Ongoing**	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	Protocol Study initiation Last patient last visit Final report	Q4 2015 Q3 2016 Q3 2021 Q3 2022
Study 20160250 A Multicenter, Open-label, Single-arm, Extension Study to Assess Long-term Safety of Evolocumab Therapy in Subjects With Clinically Evident Cardiovascular Disease in Selected European Countries **Ongoing**	To describe the safety and tolerability of long-term administration of evolocumab in a cohort of Western European subjects having received evolocumab or placebo in the completed FOURIER trial	Long-term use including effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Study completion Final report	Q3 2022 Q3 2023

Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures
Use in Pregnant/Lactating Women	Routine risk minimisation measures: • SmPC Section 4.6, where advice is given that Repatha should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab • PL Section 2 Additional risk minimisation measures: • None
Long-term Use Including Effects of LDL-C < 40 mg/dL or < 1.03 mmol/L	Routine risk minimisation measures: • Section 5 Additional risk minimisation measures: • None

2.6. Changes to the Product Information

As a result of this group of variations, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all changes to the Product Information.

2.6.1. User consultation

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

- Only a small number of changes have been made to the package leaflet content.
- The design and layout of the package leaflet remains consistent with the approved package leaflet.
- The overall risks and safety information described in the package leaflet remains unchanged.
- The pharmaceutical form remains unchanged, solution for injection.
- The route of administrations remains unchanged, subcutaneous use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Familial hyperlipidemia is a genetic disorder characterized by elevated serum lipid concentrations. Among the conditions that comprise familial hyperlipidemia, familial hypercholesterolemia (FH) is a more common form of inherited hypercholesterolemia characterized by elevated serum LDL-C and the development of premature cardiovascular disease (CVD).

Heterozygous FH (HeFH) accounts for the large majority of FH overall and is estimated to occur in 1:250 individuals globally (Hu et al., 2020; Wiegman et al., 2015). Untreated LDL-C levels in affected individuals are significantly elevated (7.0 ± 0.2 mmol/L]) compared with controls (2.6 ± 0.1 mmol/L) (Raal et al., 2013). Despite aggressive statin use, there is still a 2-fold excess of coronary heart disease (CHD) related deaths relative to age-matched controls within this population (Neil et al., 2008).

By comparison, the prevalence of **homozygous FH** (HoFH) is approximately 1:1,000,000 individuals and untreated LDL-C levels are 13.4 ± 0.7 mmol/L (Raal et al., 2013). The incidence of major cardiovascular illness among homozygous individuals is even higher than that of HeFH individuals, with events such as myocardial infarction occurring by the second decade of life (Goldstein et al., 2001).

The **goal of therapy** in patients with FH is to reduce LDL-C, which reduces atherogenesis and subsequently reduces CVD events and mortality, as demonstrated by the results of the CVOT FOURIER.

3.1.2. Available therapies and unmet medical need

HeFH and HoFH patients should be treated with intensive LDL-C lowering drug therapy to lower their increased LDL-C levels. Currently, available registered therapies for pediatric HeFH and HoFH patients include statins and ezetimibe. Non-pharmacological therapies include lipid apheresis.

Statin therapy is the cornerstone treatment for LDL-C lowering and causes a LDL-C reduction of 30-40% in pediatric HeFH patients and LDL-C reduction of ~22 % in pediatric patients with HoFH.

Ezetimibe, on top of statins, can reduce LDL-C by 15-30% in pediatric patients with HeFH and HoFH.

Apheresis is a non-pharmacological treatment option; a single treatment reduces LDL-C by 55%-70% relative to pre-treatment levels. However, apheresis may be burdensome and limited available. Also, only temporal reduction in LDL-C is achieved.

Due to the limitations of currently available treatments, some patients, especially those with high LDL-C like HoFH patients, are generally sub-optimally treated, resulting in remaining increased levels of LDL-C (with increased CV risk), as such, there is still an unmet medical need for new treatment options for pediatric patients with HeFH and HoFH.

3.1.3. Main clinical studies

For the pediatric HeFH population, the main evidence was provided by the phase 3 randomized placebo-controlled (RCT) Study 20120123 which compared the reduction of LDL-C by evolocumab 420

mg QM (n= 104) with placebo (n=53) after 24 weeks in HeFH pediatric patients aged 10-≤17 years (with standard of care lipid-lowering background therapy) and its *ongoing* single-arm open-label extension (OLE) Study 20120124 in which all subjects received 420 mg QM for 80 weeks. The primary endpoint of the RCT Study 20120123 was the percent change in LDL-C from baseline to week 24, whereas the percent change in LDL-C from baseline to week 80 was the key secondary endpoint of the OLE Study 20120124. Important (other) secondary endpoints included other lipid parameters, i.e. non-HDL-C, ApoB, total cholesterol, HDL-C ratio and ApoB/ApoA1 ratio.

For the pediatric HoFH population, the main evidence was provided by de-novo HoFH patients aged 10-≤17 years enrolled in the *ongoing* single-arm OLE Study 20120124, supplemented with data of the Phase 2/3 open-label long-term Study 20110271 in subjects 12-≤80 years of age with HoFH or severe FH.

3.2. Favourable effects

Pediatric HeFH population

LDL-C reduction. Evolocumab demonstrated a substantial reduction in LDL-C of 38.3% at week 24 compared with placebo (-44% vs -6.23; p<0.0001) in a population of patients (n=157 with 2:1 ratio) aged 10-≤17 years with genetically or clinically confirmed HeFH on optimized background lipid-lowering therapy with a baseline level of 4.8 mmol/L (absolute mean change -2.1 mmol/L). The LDL-C lowering effect already started at week 12 and was maintained up to 104 weeks of treatment (across both parent and OLE studies).

Other endpoints. The LDL-C lowering effect was supported by other lipid parameters, including non-HDL-C (-35.04%), ApoB (-32.47%), total cholesterol/HDL-C ratio (-30.30%) and ApoB/ApoA1 ratio (-36.38%).

Subgroups. The effect appears generally consistent among several subgroups, including gender, race, age, region, baseline LDL-C values, statin intensity, and baseline PCSK9.

Pediatric HoFH population

LDL-C reduction. In the OLE study 20120124, evolocumab demonstrated a median LDL-C reduction of 12.2%, 14.5%, and 14.3% at week 12, 48 and 80, respectively, in a limited population of patients (n=12) aged 10-≤17 years with genetically or clinically confirmed HoFH on optimized background lipid-lowering therapy with a baseline LDL-C level of 10.3 mmol/L. The effect size was consistent with the median LDL-C reduction in the subset of the 14 adolescents HoFH aged 12-≤17 years from Study 20110271 who received the 420 mg QM regimen or the (higher dose) 420 mg Q2W regimen (13.3%, 8.1%, 8.7%, 9.5%, and 20.0% at weeks 48, 96, 144, 192, and 216, respectively).

The efficacy results according to LRLR mutation (negative, defective, or unknown) demonstrated that treatment with evolocumab leads to a reduction in LDL-C levels regardless of the type of LDLR mutation. However, within each subgroup of LDLR mutation there was a large degree of intersubject variability including non-responders which, however, were in the minority.

In Study 20110271, two different dose regiments were allowed in pediatric HoFH subjects 12-≤ 17 years of age. Pediatric subjects who started this study receiving evolocumab 420 mg QM could change their dose to 420 mg Q2W if insufficient suppression of PCSK9 (> 100 ng/mL) was observed at week 12 or 24. In this study, the titration analysis set (TAS), defined as the subset of subjects who were exposed to evolocumab 420 mg QM for at least 12 weeks and then to evolocumab 420 mg Q2W for at least 12 weeks, showed that increasing the frequency of the evolocumab 420 mg dose from QM to

Q2W resulted in an additional mean LDL-C reduction of 10.0% corresponding to a mean absolute reduction of 28.3 mg/dL.

Subgroups. For the HoFH subjects 10-≤11 years of age, the median LDL-C reduction was comparable with the overall pediatric HoFH population (12.2% and 19.2% at week 12, and week 80, respectively), except for week 48 (4.6%).

Other endpoints. The LDL-C lowering effect was supported by other lipid parameters, including non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio.

3.3. Uncertainties and limitations about favourable effects

Pediatric HeFH population

Proposed dose regimen. In the RCT Study 20120123 and the OLE Study 20120124, only the 420 mg QM regimen has been evaluated, whereas in addition to this regimen also the 140 mg Q2W regimen in pediatric HeFH subjects aged 10-≤17 years is proposed (same posology as currently approved for the adult HeFH population). As such, the efficacy of the 140 mg Q2W dose in pediatric HeFH patients aged 10-≤17 years has not been evaluated. The efficacy of the proposed 140 mg Q2W is extrapolated from the other dosing scheme and from adult studies.

Effect size. The effect size in LDL-C lowering of 38.3% observed in the RCT Study in pediatric subjects with HeFH was lower than the LDL-C lowering effect of 60% observed in adults with HeFH in the RUTHERFORD study (Study 20110117) and other previous clinical studies (range: 60-70%) submitted during the initial MAA, despite comparable LDL-C levels at baseline. Nevertheless, the LDL-C lowering effect is still considered substantial and clinically relevant.

Carotid intima-media thickness. The effect of evolocumab on clinical outcomes in the populations covered by this application of variation are not known. cIMT analysis showed small reductions in cIMT with evolocumab therapy from baseline to week 24, 48, and 80 in the pediatric HeFH populations in Study 20120123 and 20120124, suggesting a beneficial effect of evolocumab concerning atherogenesis. However, these results are too limited (short study period and small reduction) to draw firm conclusions.

Pediatric HoFH population

Proposed dose regimen. In the OLE Study 20120124, only the 420 mg QM regimen has been evaluated, whereas in addition to this regimen also the 420 mg Q2W regimen in pediatric HoFH subjects 10-≤11 years is proposed (same posology as currently approved for the adult and adolescent HoFH population). As such, the efficacy of the 420 mg Q2W dose in pediatric HoFH patients aged 10-≤11 years has not been evaluated.

Effect size. The effect size in median LDL-C reduction of 12-14.5% with the 420 mg QM regimen observed in the pediatric HoFH population in Study 20120124 appears somewhat lower than those observed with the 420 mg QM regimen in the studies previously submitted, i.e. Study 20110233 (TESLA) and Study 20110271 (TAUSSIG) in the overall HoFH population consisting adult and pediatric subjects aged 12-≤17 years (32% and 16.3%, respectively).

Carotid intima-media thickness. cIMT analyses showed small reductions in cIMT with evolocumab therapy from baseline to week 24, 48, and 80 in the pediatric HoFH population in Study 20120124, suggesting a beneficial effect of evolocumab concerning atherogenesis. However, these results are too limited (short study period and small reduction) to draw firm conclusions.

3.4. Unfavourable effects

Pediatric HeFH population

Exposure. A sufficient number of pediatric HeFH patients aged 10-≤17 years have been evaluated for safety according to guideline recommendations, including 149 (97.4%), 135 (88.2%), and 76 (49.7%) pediatric HeFH subjects exposed to evolocumab for at least 24, 48 and 96 weeks, respectively. Placebo-controlled safety data of pediatric HeFH subjects who received all 6 doses of IP, i.e. 24 weeks of exposure, in the RCT Study 20120123 is available for 98 subjects (out of 104, 94%) in the evolocumab group and 51 (out of 53, 96%) subjects in the placebo group, which is considered sufficient to identify evolocumab related safety effects.

Adverse events. TEAEs were frequently reported, however, with a lower percentage in the evolocumab group compared with the placebo group (61.5% vs 64.2%). The most frequent AEs (> 5% of subjects) with a higher incidence with evolocumab compared with placebo were ***nasopharyngitis*** (11.5% vs 11.3%), ***headache*** (10.6% vs 1.9%), ***oropharyngeal pain*** (6.7% vs 0.0%), ***influenza*** (5.8% vs 3.8%), ***upper respiratory tract infection*** (5.8% vs 1.9%). When considering longer treatment, the frequency in TEAEs increased slightly (66.7%); however, an approximately similar safety profile was observed with ***nasopharyngitis*** (14.7%), ***headache*** (8.7%), ***influenza-like illness*** (8.7%), ***gastroenteritis*** (6.0%), ***upper respiratory tract infection*** (5.3%), and ***oropharyngeal pain*** (5.3%) being the most prominent adverse events observed. The safety findings are consistent with the safety data observed in adults in the initial MAA dossier and the FOURIER dossier, with the exception of the disbalance in oropharyngeal pain.

Device-related adverse events were uncommon, mostly not severe, and generally limited to injection site reactions, consistent with those observed in the initial MA dossier and the FOURIER dossier.

Drug-related adverse events. No new TEAEs considered by the investigator related to IP has been identified. Most of treatment related TEAEs were injections site reactions, which is a known ADR of evolocumab.

Adverse events of special interest. A higher incidence of ***potential hypersensitivity*** was observed in the evolocumab group (3.8% and 6.7% using narrow and broad SMQ, respectively) compared with the placebo group (0% using both narrow and broad SMQ); however, the incidence was relatively low, and no specific pattern indicative for a safety signal could be observed. Moreover, the incidence in ***potential injection site reactions*** was lower in the evolocumab group (4.8% using both broad and narrow SMQ) compared with the placebo group (5.7% using both broad and narrow SMQ). With respect to long-term treatment, the incidence in ***potential hypersensitivity*** was consistent comparable with that observed in the RCT study. The incidence ***in injection site reactions*** increased with long-term treatment (8.7%) due to longer study duration. ***Anti-evolocumab antibodies*** were not reported. There is no evidence of an unexpected safety concern regarding ***muscle adverse events***, ***hepatic events*** and ***adverse events in subjects who achieved low LDL-C levels***.

Serious adverse events. The incidence in SAEs was relatively low with 1 (1%) HeFH subject in the evolocumab vs none in the placebo group in the RCT study and 4 (2.7%) HeFH subjects treated with evolocumab in OLE study. Moreover, none of the SAEs were considered by the investigator related to IP.

Deaths. There were no deaths reported.

Laboratory findings. No trends indicative of clinically important treatment-related laboratory abnormalities, including haemoglobin A1c, fasting blood glucose, hsCRP, hormone levels, vitamins,

were observed with evolocumab in Study 20120123 and 20120124, as laboratory values were generally within the normal range.

Tolerability. Evolocumab was well tolerated, with only one HeFH patient discontinuing evolocumab treatment due to an event of arthropathy across the RCT and OLE study.

Pediatric HoFH population

Adverse events. For the pediatric HoFH patients aged 10-≤17 years in the OLE Study 20120124, 7 of the 12 (58.3%) HoFH subjects experienced TEAEs; however, none of the TEAEs occurred in more than 1 subject with the exception of epistaxis (n=2, 16.7%). In the pediatric subset of HoFH subjects aged 12-≤17 years of the OLE study 20110271, 12 of the 14 subjects (85.7%) experienced TEAEs with anxiety, migraine, and upper respiratory tract infection (21.4% (n=3) each) as being the most common adverse events observed. Overall, no new safety signal as compared with the initial MAA dossier and the FOURIER dossier is observed, although firm conclusions cannot be made due to the limited exposure data.

Device-related adverse events were uncommon, mostly not severe, and generally limited to injection site reactions, which is consistent with those observed in the initial MA dossier and the FOURIER dossier.

Drug-related adverse events. No new TEAEs considered by the investigator related to IP has been identified. Most of treatment related TEAEs were injections site reactions, which is a known ADR of evolocumab.

Adverse events of special interest. Across both Studies 20120124 and 20112071, only one HoFH subject in the OLE Study 20120124 had a ***potential injection site reaction***, which was nonserious and mild in severity and only 2 HoFH subjects in the OLE Study 20110271 reported a ***potential hypersensitivity event.*** Across both Studies 20120124 and 20112071, ***anti-evolocumab antibodies*** were not reported. There is no evidence of an unexpected safety concern regarding ***muscle adverse events***, ***hepatic events*** and ***adverse events in subjects who achieved low LDL-C levels***.

Serious adverse events. The incidence in serious AEs was relatively low, with 2 out of 12 (16.%)) HoFH subjects in Study 20120124 and in 4 out of 14 (28.6%) HoFH subjects in Study 20110271 experiencing a SAE. Moreover, none of the SAEs were considered by the investigator related to IP.

Deaths. There were no deaths reported.

Laboratory findings. No trends indicative of clinically important treatment-related laboratory abnormalities including haemoglobin A1c, fasting blood glucose, hsCRP, hormone levels, vitamins were observed with evolocumab in Study 20120124 and 20110271, as laboratory values were generally within the normal range.

Tolerability. Evolocumab was well tolerated, with only one HoFH patient discontinuing evolocumab treatment due to an event of rash in the OLE study.

Post marketing experience

Cumulatively through 17 July 2020, post-marketing adverse event case reports have been received for 139 pediatric patients ranging in age from 2 to 17 years and exposed to evolocumab. The majority (90%) of reported adverse events were nonserious, and overall the most commonly reported event was off-label use (based on age or dosing regimen).

3.5. Uncertainties and limitations about unfavourable effects

Pediatric HeFH population

Proposed dose regimen. In the RCT Study 20120123 and the OLE Study 20120124, only the 420 mg QM regimen has been evaluated, whereas in addition to this regimen also the 140 mg Q2W regimen in pediatric HeFH subjects aged 10-≤17 years is proposed (same posology as currently approved for the adult HeFH population). As such, the safety of the 140 mg Q2W dose in pediatric HeFH patients aged 10-≤17 years has not been evaluated.

Subgroups. Although higher adverse events rates could be observed in the 12-≤17 years of age subgroup compared with the 10-≤ 11 years of age subgroup in HeFH subjects, no specific pattern indicative for a safety signal across the subgroups could be observed. Overall, the most frequently reported events were generally consistent with the known adverse drug reactions for evolocumab**.**

Adverse events of special interest. Increased risk of ***neurocognitive*** and ***neurological abnormalities*** was not observed. However, the data are considered limited, which precludes appropriate assessment. Nevertheless, neurocognitive and neurological abnormalities have comprehensively evaluated in a subset of the FOURIER study (EBBINGHAUS subset) in which no differences between evolocumab and placebo were found.

Tanner stage. Assessments of growth and pubertal development (Tanner stage) did not reveal an effect of evolocumab on Tanner stage in the RCT study and the OLE study. However, the safety data, particularly the placebo-controlled safety data of 24 weeks exposure to evolocumab, is considered too limited to draw firm conclusions on the effect of evolocumab on Tanner staging.

Pediatric HoFH population

Exposure. A limited number of pediatric subjects aged 10-≤17, particularly the subset of 10-≤11 years, were exposed to evolocumab. However, this is expected and acceptable considering the rarity of the HoFH disease. Overall, 12 de-novo pediatric HoFH subjects 10-≤17 years of age in the OLE Study 20120124 received at least one dose of evolocumab, with a total patient-year exposure of 17. Of these patients, all de-novo HoFH subjects (100.0%) had evolocumab exposure ≥ 28 weeks, and 11 (91.7%) completed the study and, as such, were exposed to evolocumab for 80 weeks. The safety exposure data is supplemented with exposure data of 14 HoFH pediatric subjects 12-≤17 years of age in the OLE Study 20110271, who received evolocumab for up to 5 years, which resulted in a combined exposure of 62.2 patient-years.

Proposed dose regimen. In the OLE Study 20120124, only the 420 mg QM regimen has been evaluated, whereas in addition to this regimen, the 420 mg Q2W regimen in pediatric HoFH subjects 10-≤11 years is proposed (same posology as currently approved for the adult and adolescent HoFH population). As such, the safety of the 420 mg Q2W dose in pediatric HoFH patients aged 10-≤11 years has not been evaluated.

Subgroups. Although higher adverse events rates could be observed in the 12-≤17 years of age subgroup compared with the 10-≤ 11 years of age subgroup in HoFH subjects, no specific pattern indicative for a safety signal across the subgroups could be observed. Overall, the most frequently reported events were generally consistent with the known adverse drug reactions for evolocumab.

Adverse events of special interest. Increased risk of ***neurocognitive*** and ***neurological abnormalities*** was not observed. However, the data are considered very limited, which precludes appropriate assessment. Nevertheless, neurocognitive and neurological abnormalities have comprehensively evaluated in a subset of the FOURIER study (EBBINGHAUS subset) in which no differences between evolocumab and placebo were found.

Tanner stage. Assessments of growth and pubertal development (Tanner stage) did not reveal an effect of evolocumab on Tanner stage in the HoFH subset of Study 20120124RCT study. However, the safety data, is considered very limited in order to draw firm conclusions on the effect of evolocumab on Tanner staging.

3.6. Effects Table

Table 46. Effects Table for evolocumab in HeFH patients aged 10-17 years (Study 20120123 completed, Study 20120124 data cut-off: 29 July 2020)

Effect	Short description	Unit	Evolocumab (n=103)	Placebo (n=54)	Uncertainties / Strength of evidence	References
Favourable Effects						
LDL-C	Change from baseline to week 24	%	-44.53	-6.23	**SoE**: Difference -38.30; p<0.0001 Clinical relevant change of -2.1 mmol/L Substantial changes observed in other lipid parameters (non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/apoA1 ratio) Effect maintained up to 80 weeks: -36.3% **Unc:** Lower effect size compared with the adult HeFH population	RCT Study 20120123, OLE Study 20120124
Unfavourable Effects						
Potential hypersensitivity	Using narrow SMQ	n (%)	4 (3.8)	0	**SoE**: comparable incidence observed in the OLE Study 20120124 (n=6, 4.0%)	RCT Study 20120123, OLE Study 20120124
Injection site reactions	-	n (%)	5 (4.8)	3 (5.7)	Higher incidence in the OLE study (n=13, 8.7%) due to longer treatment duration	RCT Study 20120123, OLE Study 20120124
Anti-evolocumab antibodies	-	n (%)	0	0	**SoE**: Also no antibodies reported in the OLE study	RCT Study 20120123, OLE Study 20120124
Neurocognitive adverse events	-	n (%)	1 (1.0)	0	5 subjects in the OLE study	RCT Study 20120123,

Effect	Short description	Unit	Evolocumab (n=103)	Placebo (n=54)	Uncertainties / Strength of evidence	References
						OLE Study 20120124

Abbreviations:

Notes:

Table 47. Effects Table for evolocumab in HoFH patients aged 10-≤17 years (Study 20120124 data cut-off: 29 July 2020)

Effect	Short description	Unit	Evolocumab N=12	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
LDL-C	Change from baseline to week 80	%	- 14.29	n.a	**SoE**: Comparable changes observed in other lipid parameters (non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/apoA1 ratio) Effect is consistent with that observed in pediatric HoFH subset in Study 20110271 Effect maintained up to 216 weeks in Study 20110271	OLE Study 20120124
Unfavourable Effects						
Potential hypersensitivity	Using narrow SMQ	n (%)	0	n.a	2 (14.3%) subjects in Study 20110271	OLE Study 20120124
Injection site reactions	-	n (%)	1 (8.3%)	n.a	0 subjects in Study 20110271	OLE Study 20120124
Anti-evolocumab antibodies	-	n (%)	0	n.a	SoE: Also no antibodies reported Study 20110271	OLE Study 20120124
Neurocognitive adverse events	-	n (%)	1 (8.3%)	n.a	Not evaluated in Study 20110271	OLE Study 20120124

3.7. Benefit-risk assessment and discussion

Evolocumab is a fully human monoclonal immunoglobulin G2 directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9), which inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation.

In the current group of variations, a modified indication was proposed by the Applicant to include one new pediatric indication in pediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia based on results of study 20120123 (HAUSER-RCT) and 20120124 (HAUSER-

OLE) and to modify the existing indication for treatment of adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia based on interim results from study 20120124 (HAUSER-OLE).

The agreed indication reads as follows (new text in bold and underlined; removed text bold and stikethrough):

Hypercholesterolaemia and mixed dyslipidaemia

*Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia**, and in paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia**, as an adjunct to diet:*

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

Homozygous familial hypercholesterolaemia

*Repatha is indicated in adults and **adolescents** **paediatric patients** aged **12** **10** years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.*

Established atherosclerotic cardiovascular disease

Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

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

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

3.7.1. Importance of favourable and unfavourable effects

Evolocumab has demonstrated a substantial and consistent reduction in LDL-C and other lipid parameters on top of optimized lipid-lowering therapies, including statins and ezetimibe, in pediatric HeFH and HoFH subjects aged 10-≤17 years of age. The reductions in LDL-C (and other lipid parameters) were lower in HoFH subjects compared with HeFH subjects, however, expected considering that the mechanism of action depends on the activity of the LDL receptor. The changes in LDL-C are considered to be clinically relevant effects as LDL-C is an important surrogate endpoint with potential benefits in terms of a cardiovascular outcome, as previously confirmed by the results of the CVOT FOURIER. The long-term studies provided data indicating maintenance of effect and safety for the pediatric HeFH and HoFH population. The documented exposure of evolocumab in the pediatric HeFH subjects aged 10-≤17 is according to guideline recommendations and therefore sufficient. Concerning the pediatric HoFH population, the number of pediatric patients exposed to evolocumab, particularly the HoFH patients aged 10-≤11 years, is considered limited but expected and acceptable considering the rarity of the HoFH disease.

Regarding safety, evolocumab displayed an acceptable safety profile consistent with the safety data observed in adults HeFH subjects and adults and adolescents HoFH subjects in the initial MAA dossier and the FOURIER dossier with very limited patients discontinuing treatment or showing serious adverse events. Additionally, evolocumab did not cause any clinically relevant differences in adverse events of

special interest, including hypersensitivity, injection site reactions, anti-evolocumab antibodies, and neurological and neurocognitive abnormalities, muscle AEs, hepatic AEs, AEs in subjects who achieved low LDL-C levels, and AEs according to the age categories 10-≤11 and 12-≤17 years in both pediatric HeFH and HoFH populations.

With respect to the posology, no changes to the approved evolocumab dosing regimens were proposed for the populations of pediatric HeFH subjects aged 10-≤17 years and the HoFH subjects aged 10-≤11 years, which are currently under review. However, in Study 20120123 and 20120124, only the 420 mg QM regimen has been evaluated, whereas in addition to this regimen also the 140 mg Q2W regimen in pediatric HeFH subjects aged 10-≤17 years and the 420 mg Q2W regimen in pediatric HoFH subjects 10-≤11 years are currently proposed (same as those currently stated in the labelling for the approved HoFH and HeFH populations). As such, the efficacy and safety of the 140 mg Q2W dose regimen for pediatric HeFH patients aged 10-≤17 years and the 420 mg Q2W dose regimen for pediatric HoFH patients aged 10-≤11 years have not been evaluated. PK data have adequately shown that the PK is dose-linear and that relative to primary hyperlipidaemia and mixed dyslipidemia, HeFH, HoFH and age do not have a clinically meaningful effect on the pharmacokinetic profile of evolocumab. As such, the 140 mg Q2W regimen, which is considered clinically equivalent to the 420 mg QM regimen proposed for pediatric HeFH patients aged 10-≤17 years, is considered acceptable. However, the 420 mg Q2W regimen proposed for HoFH subjects 10-≤11 years of age concerns a 2-fold higher dose than the 420 mg QM for which the efficacy and safety in the proposed population of pediatric HoFH patients aged 10-≤11 years is currently unknown. Despite similar PK across different types of FH and age categories, the safety profile of the 420 mg Q2W in the pediatric patients with HoFH aged 10-≤11 years can differ compared to the adult population and the older pediatric HoFH population of 12-≤17 years for which this dose regimen is currently already approved. The efficacy and safety of the 420 mg Q2W dose (together with the 420 mg QM) have only been evaluated in the adult subjects with HoFH or severe FH and in the older pediatric HoFH population of 12-≤17 years in Study 20110271. In this study, dose frequency changes (420 mg QM vs 420 mg Q2W) were permitted if a clinically meaningful response is not achieved. The titration analysis set (TAS), defined as the subset of subjects who were exposed to evolocumab 420 mg QM for at least 12 weeks and then to evolocumab 420 mg Q2W for at least 12 weeks, showed that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W resulted in an additional mean LDL-C reduction of 10.0% corresponding to a mean absolute reduction of 28.3 mg/dL. Considering that in Study 20120124, the median LDL-C reduction with the 420 mg QM dose regimen was comparable between the HoFH subjects 10 - ≤11 years of age and the overall pediatric HoFH population, it can be anticipated that increasing the frequency of the evolocumab 420 mg dose from QM to Q2W in HoFH subjects 10 - ≤11 years of age results in a comparable additional mean LDL-C reduction of 10%. Previously, secondary prevention LDL-C lowering trials have shown that reduction of 38.7 mg/dL (1 mmol/L) in LDL-C is associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes (Cholesterol Treatment Trialists' Collaboration [CTTC], 2010). Based on above, this additional mean absolute reduction of 28.3 mg/dL upon increasing the frequency of the 420 mg dose to Q2W can be considered clinically relevant, particularly in pediatric HoFH subjects which are at high cardiovascular risk.

With respect to safety, the safety profile of the 420 mg Q2W regimen in pediatric HoFH subjects 10-≤ 11 years of age is still unknown. The Applicant argued that in Study 20120124 and Study 20110271 no unexpected safety concerns has been found. Additionally, none of the adverse events were related to growth, pubertal development, or hormonal status. However, firm conclusion on growth and pubertal development and hormonal status can still not be made due to limited sample size and treatment duration and the fact that in Study 20120124, only the 420 mg QM regimen in HoFH subjects 10-≤11 years has been evaluated. In this context, an justification in order to extrapolate these safety results to HoFH subjects aged 10-≤11 years of age receiving the Q2W regimen has not been provided.

Nevertheless, it is acknowledged that the benefits of the additional clinically relevant reduction in LDL-C upon increasing the frequency of the 420 mg dose to Q2W in HoFH subjects aged 10-≤11 years who are at very high cardiovascular risk outweigh the adverse events observed in this HoFH population to date.

3.7.2. Balance of benefits and risks

Benefits of evolocumab in terms of a substantial reduction in LDL-C are accompanied by limited risks. Notwithstanding these results, there are some uncertainties including a lack of confirmation of additional LDL-C reduction with an acceptable safety profile with the higher evolocumab 420 mg Q2W regimen in HoFH subjects. Nevertheless, it is acknowledged that the benefits of the additional clinically relevant reduction in LDL-C upon increasing the frequency of the 420 mg dose to Q2W in HoFH subjects aged 10-≤11 years who are at very high cardiovascular risk outweigh the adverse events observed in this HoFH population to date.

3.8. Conclusions

The overall B/R of evolocumab for the pediatric HeFH subjects aged 10-≤17 and HoFH aged 10-≤12 is positive.

4. Recommendations

Outcome

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

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

C.I.6 (EoI)
Extension of indication to include one new pediatric indication in pediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia as an adjunct to diet, alone or in combination with other lipid-lowering therapy, to reduce LDL-C based on results of study 20120123 (HAUSER-RCT) and study 20120124 (HAUSER-OLE). It is a randomized, multicenter, placebo-controlled, double-blind, parallel-group, 24 week trial in 158 pediatric patients aged 10 to > 18 years with heterozygous familial hypercholesterolaemia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.1 of the RMP has also been submitted.

C.I.6 (EoI)
Extension of indications to modify the existing indication for treatment of adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies based on interim results from study 20120124 (HAUSER-OLE). It was an open-label, single-arm, multicenter, 80 week trial to evaluate the safety, tolerability and efficacy of Repatha for LDL-C reduction in pediatric patients from aged ≥ 10 to < 18 years of age with homozygous familial hypercholesterolaemia. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0105/2018 on the agreement of a paediatric investigation plan (PIP).

Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-49G'

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 14 October 2021.