1. NAME OF THE MEDICINAL PRODUCT

Repatha® solution for injection in pre-filled syringe 140 mg
Repatha® solution for injection in pre-filled autoinjector 140 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Repatha solution for injection in pre-filled syringe 140 mg
Each pre-filled syringe contains 140 mg of evolocumab in 1 mL of solution.

Repatha solution for injection in pre-filled autoinjector 140 mg
Each pre-filled autoinjector contains 140 mg of evolocumab in 1 mL of solution.

Repatha is a human IgG2 monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is sterile and preservative-free, clear to opalescent, colourless to yellowish, and practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Cardiovascular Events

In adults with established cardiovascular disease, Repatha in combination with an optimally dosed statin and/or other lipid-lowering therapies is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularisation (see section 5.1 Pharmacodynamic properties).

Primary Hypercholesterolaemia and Mixed Dyslipidaemia

Repatha is indicated as an adjunct to diet, for the treatment of adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, and paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia to reduce low density lipoprotein cholesterol (LDL-C):

- In combination with a statin or statin with other lipid-lowering therapies in patients who are unable to reach LDL-C goals with 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 paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

4.2 Posology and method of administration

Prior to initiating evolocumab, secondary causes of hyperlipidaemia or mixed dyslipidaemia (e.g., nephrotic syndrome, hypothyroidism) should be excluded.

<u>Posology</u>

Prevention of Cardiovascular Events in Adults
The recommended dose of evolocumab is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent.

Primary Hypercholesterolaemia (Heterozygous Familial and Non-Familial) and Mixed Dyslipidaemia

Adults and paediatric patients (aged 10 years and over)
The recommended dose of evolocumab is either 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent.

When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.

Homozygous Familial Hypercholesterolaemia in adults and paediatric patients aged 10 years and over
The initial recommended dose is 420 mg once monthly. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

Missed dose
If a dose is missed, instruct the patient to administer Repatha within 7 days from the missed dose and resume the patient's original schedule.

- If an every-2-week dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.
- If a once-monthly dose is not administered within 7 days, instruct the patient to administer the dose and start a new schedule based on this date.

<u>Special populations</u>

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

Patients with renal impairment
No dose adjustment is necessary in patients with renal impairment (see section 5.2).

Patients with hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment, see section 4.4 for patients with moderate and severe hepatic impairment.

Paediatric population
The safety and effectiveness of Repatha have not been established in paediatric patients with heterozygous familial hypercholesterolaemia (HeFH) or homozygous familial hypercholesterolaemia (HoFH) who are younger than 10 years old or in paediatric patients with other types of hyperlipidaemia.

<u>Method of administration</u>

Subcutaneous use.

Evolocumab is for subcutaneous injection into the abdomen, thigh, or upper arm region. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard.

Evolocumab must not be administered intravenously or intramuscularly.

Repatha solution for injection in pre-filled syringe 140 mg
The 140 mg dose should be delivered using a single pre-filled syringe.
The 420 mg dose should be delivered using three pre-filled syringes administered consecutively within 30 minutes.

Repatha solution for injection in pre-filled autoinjector 140 mg
The 140 mg dose should be delivered using a single pre-filled autoinjector.
The 420 mg dose should be delivered using three pre-filled autoinjectors administered consecutively within 30 minutes.

Repatha is intended for patient self-administration after proper training. Administration of evolocumab can also be performed by an individual who has been trained to administer the product.

For single use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

<u>Hepatic impairment</u>

In patients with moderate hepatic impairment, a reduction in total evolocumab exposure was observed that may lead to a reduced effect on LDL-C reduction. Therefore, close monitoring may be warranted in these patients.

Patients with severe hepatic impairment (Child-Pugh class C) have not been studied (see section 5.2). Evolocumab should be used with caution in patients with severe hepatic impairment.

<u>Dry natural rubber</u>

Repatha solution for injection in pre-filled syringe 140 mg
The needle cover of the glass pre-filled syringe is made from dry natural rubber (a derivative of latex), which may cause severe allergic reactions.

Repatha solution for injection in pre-filled autoinjector 140 mg
The needle cover of the glass pre-filled autoinjector is made from dry natural rubber (a derivative of latex), which may cause severe allergic reactions.

<u>Sodium content</u>

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The pharmacokinetic interaction between statins and evolocumab was evaluated in the clinical trials. An approximately 20% increase in the clearance of evolocumab was observed in patients coadministered statins. This increased clearance is in part mediated by statins increasing the concentration of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) which did not adversely impact the pharmacodynamic effect of evolocumab on lipids. No statin dose adjustments are necessary when used in combination with evolocumab.

No studies on pharmacokinetic and pharmacodynamics interaction between evolocumab and lipid-lowering medicinal products other than statins and ezetimibe have been conducted.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Repatha in pregnant women.

Animal studies do not indicate direct or indirect effects with respect to reproductive toxicity (see section 5.3).

Repatha should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab.

Breast-feeding

It is unknown whether evolocumab is excreted in human milk.

A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or discontinue/abstain from Repatha therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data on the effect of evolocumab on human fertility are available. Animal studies did not show any effects on fertility endpoints at area under the concentration time curve (AUC) exposure levels much higher than in patients receiving evolocumab at 420 mg once monthly (see section 5.3).

4.7 Effects on ability to drive and use machines

Repatha has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions at the recommended doses are nasopharyngitis (7.4%), upper respiratory tract infection (4.6%), back pain (4.4%), arthralgia (3.9%), influenza (3.2%), and injection site reactions (2.2%). The safety profile in the homozygous familial hypercholesterolaemia population was consistent with that demonstrated in the primary hypercholesterolaemia and mixed dyslipidaemia population.

Tabulated list of adverse reactions

Adverse reactions reported in pivotal, controlled clinical studies, and spontaneous reporting, are displayed by system organ class and frequency in table 1 below using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

Table 1. Adverse reactions

MedDRA system organ class (SOC)	Adverse reactions	Frequency category
Infections and infestations	Influenza	Common
	Nasopharyngitis	Common
	Upper respiratory tract infection	Common
Immune system disorders	Hypersensitivity	Common
	Rash	Common
	Urticaria	Uncommon
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Nausea	Common
Skin and subcutaneous tissue disorders	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Back pain	Common
	Arthralgia	Common
	Myalgia	Common
General disorders and administration site conditions	Injection site reactions[1]	Common
	Influenza-like illness	Uncommon

[1]See section Description of selected adverse reactions.

<u>Description of selected adverse reactions</u>

Injection site reactions
The most frequent injection site reactions were injection site bruising, erythema, haemorrhage, injection site pain, and swelling.

<u>Paediatric population</u>

The safety and effectiveness of Repatha have been established in paediatric patients with heterozygous and homozygous familial hypercholesterolaemia. A clinical study to evaluate the effects of Repatha was conducted in 158 paediatric patients aged ≥ 10 to < 18 years old with heterozygous familial hypercholesterolaemia. No new safety concerns were identified and the safety data in this paediatric population was consistent with the known safety profile of the product in adults with heterozygous familial hypercholesterolaemia. Twenty-six paediatric patients with homozygous familial hypercholesterolaemia have been treated with Repatha in clinical studies conducted in patients aged ≥ 10 to < 18 years. No difference in safety was observed between paediatric and adult patients with homozygous familial hypercholesterolaemia.

<u>Elderly population</u>

Of the 18,546 patients treated with evolocumab in double-blind clinical studies 7,656 (41.3%) were ≥ 65 years old, while 1,500 (8.1%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

<u>Immunogenicity</u>

In clinical studies, 0.3% of patients (48 out of 17,992 patients) treated with at least one dose of evolocumab tested positive for binding antibody development. The patients whose sera tested positive for binding antibodies were further evaluated for neutralising antibodies and none of the patients tested positive for neutralising antibodies. The presence of anti-evolocumab binding antibodies did not impact the pharmacokinetic profile, clinical response, or safety of evolocumab.

The development of anti-evolocumab antibodies was not detected in clinical trials of pediatric patients treated with Repatha.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions as per local regulations.

4.9 Overdose

No adverse effects were observed in animal studies at exposures up to 300-fold higher than those in patients treated with 420 mg evolocumab once monthly.

There is no specific treatment for evolocumab overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents, other lipid modifying agents. ATC code: C10AX13

Mechanism of action

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

Pharmacodynamic effects

In clinical trials, evolocumab reduced unbound PCSK9, LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG, and Lp(a), and increased HDL-C and ApoA1 in patients with primary hypercholesterolaemia and mixed dyslipidaemia.

A single subcutaneous administration of 140 mg or 420 mg evolocumab resulted in maximum suppression of circulating unbound PCSK9 by 4 hours followed by a reduction in LDL-C reaching a mean nadir in response by 14 and 21 days, respectively. Changes in unbound PCSK9 and serum lipoproteins were reversible upon discontinuation of evolocumab. No increase in unbound PCSK9 or LDL-C above baseline was observed during the washout of evolocumab suggesting that compensatory mechanisms to increase production of PCSK9 and LDL-C do not occur during treatment.

Subcutaneous regimens of 140 mg every 2 weeks and 420 mg once monthly were equivalent in average LDL-C lowering (mean of weeks 10 and 12) resulting in -72% to -57% from baseline compared with placebo. Treatment with evolocumab resulted in a similar reduction of LDL-C when used alone or in combination with other lipid-lowering therapies.

Clinical efficacy in primary hypercholesterolaemia and mixed dyslipidaemia

LDL-C reduction of approximately 55% to 75% was achieved with evolocumab as early as week 1 and maintained during long-term therapy. Maximal response was generally achieved within 1 to 2 weeks after dosing with 140 mg every 2 weeks and 420 mg once monthly. Evolocumab was effective in all subgroups relative to placebo and ezetimibe, with no notable differences observed between subgroups, such as age, race, gender, region, body-mass index, National Cholesterol Education Program risk, current smoking status, baseline coronary heart disease (CHD) risk factors, family history of premature CHD, glucose tolerance status, (i.e. diabetes mellitus type 2, metabolic syndrome, or neither), hypertension, statin dose and intensity, unbound baseline PCSK9, baseline LDL-C and baseline TG.

In 80-85% of all primary hyperlipidaemia patients treated with either dose, evolocumab demonstrated a ≥ 50% reduction in LDL-C at the mean of weeks 10 and 12. Up to 99% of patients treated with either dose of evolocumab achieved an LDL-C of < 2.6 mmol/L and up to 95% achieved an LDL-C < 1.8 mmol/L at the mean of weeks 10 and 12.

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

LAPLACE-2 was an international, multicentre, double-blind, randomised, 12-week study in 1,896 patients with primary hypercholesterolaemia or mixed dyslipidaemia who were randomised to receive evolocumab in combination with statins (rosuvastatin, simvastatin, or atorvastatin). Evolocumab was compared to placebo for the rosuvastatin and simvastatin groups and compared with placebo and ezetimibe for the atorvastatin group.

Repatha significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with placebo for the rosuvastatin and simvastatin groups and compared with placebo and ezetimibe for the atorvastatin group ($p < 0.001$). Repatha significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a) and increased HDL-C from baseline to mean of weeks 10 and 12 as compared to placebo for the rosuvastatin and simvastatin groups ($p < 0.05$) and significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1 and Lp(a), compared with placebo and ezetimibe for the atorvastatin group ($p < 0.001$) (see tables 2 and 3).

RUTHERFORD-2 was an international, multicentre, double-blind, randomised, placebo-controlled, 12-week study in 329 patients with heterozygous familial hypercholesterolaemia on lipid-lowering therapies. Repatha significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with placebo ($p < 0.001$). Repatha significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a) and increased HDL-C and ApoA1 from baseline to mean of weeks 10 and 12 compared to placebo ($p < 0.05$) (see table 2).

Table 2. Treatment effects of evolocumab compared with placebo in patients with primary hypercholesterolaemia and mixed dyslipidaemia - mean percent change from baseline to average of weeks 10 and 12 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC (%)	Lp(a) (%)	VLDL-C (%)	HDL-C (%)	TG (%)	ApoA1 (%)	TC/HDL-C ratio %	ApoB/ApoA1 ratio %
LAPLACE-2 (HMD) (combined rosuvastatin, simvastatin, & atorvastatin groups)	140 mg Q2W (N = 555)	-72[b] (-75,-69)	-60[b] (-63,-58)	-56[b] (-58,-53)	-41[b] (-43,-39)	-30[b] (-35,-25)	-18[b] (-23,-14)	6[b] (4,8)	-17[b] (-22,-13)	3[b] (1,5)	-45[b] (-47,-42)	-56[b] (-59,-53)
	420 mg QM (N = 562)	-69[b] (-73,-65)	-60[b] (-63,-57)	-56[b] (-58,-53)	-40[b] (-42,-37)	-27[b] (-31,-24)	-22[b] (-28,-17)	8[b] (6,10)	-23[b] (-28,-17)	5[b] (3,7)	-46[b] (-48,-43)	-58[b] (-60,-55)
RUTHERFORD-2 (HeFH)	140 mg Q2W (N = 110)	-61[b] (-67,-55)	-56[b] (-61,-51)	-49[b] (-54,-44)	-42[b] (-46,-38)	-31[b] (-38,-24)	-22[b] (-29,-16)	8[b] (4,12)	-22[b] (-29,-15)	7[a] (3,12)	-47[b] (-51,-42)	-53 (-58,-48)
	420 mg QM (N = 110)	-66[b] (-72,-61)	-60[b] (-65,-55)	-55[b] (-60,-50)	-44[b] (-48,-40)	-31[b] (-38,-24)	-16[b] (-23,-8)	9[b] (5,14)	-17[b] (-24,-9)	5[a] (1,9)	-49[b] (-54,-44)	-56[b] (-61,-50)
MENDEL-2 (Monotherapy)	140 mg Q2W (N=153)	-57[b] (-61, -54)	-49[b] (-52, -46)	-47[b] (-51, -44)	-35[b] (-37, -32)	-25[b] (-31, -18)	0 (-7, 7)	6[b] (3, 9)	0 (-8, 7)	3[a] (1, 6)	-39[b] (-42, -36)	-49[b] (-53, -45)
	420 mg QM (N=153)	-60[b] (-63, -56)	-53[b] (-56, -50)	-51[b] (-54, -48)	-37[b] (-40, -35)	-26[b] (-33, -19)	-22[b] (-31, -13)	9[b] (6, 12)	-22[b] (-31, -13)	5[b] (2, 8)	-46[b] (-49, -42)	-55[b] (-59, -51)

Key: Q2W = once every 2 weeks, QM = once monthly, HMD = Primary hypercholesterolaemia and mixed dyslipidaemia, HeFH = Heterozygous familial hypercholesterolaemia, [a] p value < 0.05 when compared with placebo, [b] p value < 0.001 when compared with placebo.

Statin-intolerant patients

GAUSS-2 was an international, multicentre, double-blind, randomised, ezetimibe-controlled, 12-week study in 307 patients who were statin-intolerant or unable to tolerate an effective dose of a statin. Repatha significantly reduced LDL-C compared with ezetimibe ($p < 0.001$). Repatha significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1 and Lp(a), from baseline to mean of weeks 10 and 12 compared to ezetimibe ($p < 0.001$) (see table 3).

Monotherapy

MENDEL-2 was an international, multicentre, double-blind, randomised, placebo and ezetimibe-controlled, 12-week study of Repatha in 614 patients with primary hypercholesterolaemia and mixed dyslipidaemia. Repatha significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with both placebo and ezetimibe ($p < 0.001$). Repatha significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1 and Lp(a), from baseline to mean of weeks 10 and 12 compared with both placebo and ezetimibe ($p < 0.001$) (see tables 2 and 3).

Table 3. Treatment effects of evolocumab compared with ezetimibe in patients with primary hypercholesterolaemia and mixed dyslipidaemia - mean percent change from baseline to average of weeks 10 and 12 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC (%)	Lp(a) (%)	VLDL-C (%)	HDL-C (%)	TG (%)	ApoA1 (%)	TC/ HDL-C ratio %	ApoB/ ApoA1 ratio %
LAPLACE-2 (HMD) (combined atorvastatin groups)	140 mg Q2W (N = 219)	-43[c] (-50, -37)	-34[c] (-39, -30)	-34[c] (-38, -30)	-23[c] (-26, -19)	-30[c] (-35, -25)	-1 (-7, 5)	7[c] (4, 10)	-2 (-9, 5)	7[c] (4, 9)	-27[c] (-30, -23)	-38[c] (-42, -34)
	420 mg QM (N = 220)	-46[c] (-51, -40)	-39[c] (-43, -34)	-40[c] (-44, -36)	-25[c] (-29, -22)	-33[c] (-41, -26)	-7 (-20, 6)	8[c] (5, 12)	-8 (-21, 5)	7[c] (2, 11)	-30[c] (-34, -26)	-42[c] (-47, -38)
GAUSS-2 (statin-intolerant)	140 mg Q2W (N = 103)	-38[b] (-44, -33)	-32[b] (-36, -27)	-32[b] (-37, -27)	-24[b] (-28, -20)	-24[b] (-31, -17)	-2 (-10, 7)	5 (1, 10)	-3 (-11, 6)	5[a] (2, 9)	-27[b] (-32, -23)	-35[b] (-40, -30)
	420 mg QM (N = 102)	-39[b] (-44, -35)	-35[b] (-39, -31)	-35[b] (-40, -30)	-26[b] (-30, -23)	-25[b] (-34, -17)	-4 (-13, 6)	6 (1, 10)	-6 (-17, 4)	3 (-1, 7)	-30[b] (-35, -25)	-36[b] (-42, -31)
MENDEL-2 (Monotherapy)	140 mg Q2W (N = 153)	-40[b] (-44, -37)	-36[b] (-39, -32)	-34[b] (-37, -30)	-25[b] (-28, -22)	-22[b] (-29, -16)	-7 (-14, 1)	6[a] (3, 9)	-9 (-16, -1)	3 (0, 6)	-29[b] (-32, -26)	-35[b] (-39, -31)
	420 mg QM (N = 153)	-41[b] (-44, -37)	-35[b] (-38, -33)	-35[b] (-38, -31)	-25[b] (-28, -23)	-20[b] (-27, -13)	-10 (-19, -1)	4 (1, 7)	-9 (-18, 0)	4[a] (1, 7)	-28[b] (-31, -24)	-37[b] (-41, -32)

Key: Q2W = once every 2 weeks, QM = once monthly, HMD = Primary hypercholesterolaemia and mixed dyslipidaemia, [a] p value < 0.05 when compared with ezetimibe, [b] p value < 0.001 when compared with ezetimibe, [c] nominal p value < 0.001 when compared with ezetimibe.

Long-term efficacy in primary hypercholesterolaemia and mixed dyslipidaemia

DESCARTES was an international, multicentre, double-blind, randomised, placebo-controlled, 52-week study in 901 patients with hyperlipidaemia who received diet alone, atorvastatin, or a combination of atorvastatin and ezetimibe. Repatha 420 mg once monthly significantly reduced LDL-C from baseline at 52 weeks compared with placebo (p < 0.001). Treatment effects were sustained over 1 year as demonstrated by reduction in LDL-C from week 12 to week 52. Reduction in LDL-C from baseline at week 52 compared with placebo was consistent across background lipid-lowering therapies optimised for LDL-C and cardiovascular risk.

Repatha significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG, and Lp(a), and increased HDL-C and ApoA1 at week 52 compared with placebo (p < 0.001) (see table 4).

Table 4. Treatment effects of evolocumab compared with placebo in patients with primary hypercholesterolaemia and mixed dyslipidaemia - mean percent change from baseline to week 52 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC (%)	Lp(a) (%)	VLDL-C (%)	HDL-C (%)	TG (%)	ApoA1 (%)	TC/ HDL-C ratio %	ApoB/ ApoA1 ratio %
DESCARTES	420 mg QM (N = 599)	-59[b] (-64, -55)	-50[b] (-54, -46)	-44[b] (-48, -41)	-33[b] (-36, -31)	-22[b] (-26, -19)	-29[b] (-40, -18)	5[b] (3, 8)	-12[b] (-17, -6)	3[a] (1, 5)	-37[b] (-40, -34)	-46[b] (-50, -43)

Key: QM = once monthly, [a] nominal p value < 0.001 when compared with placebo, [b] p value < 0.001 when compared with placebo.

OSLER and OSLER-2 were two randomised, controlled, open-label extension studies to assess the long-term safety and efficacy of Repatha in patients who completed treatment in a ‘parent’ study. In each extension study, patients were randomised 2:1 to receive either Repatha plus standard of care (evolocumab group) or standard of care alone (control group) for the first year of the study. At the end of the first year (week 52 in OSLER and week 48 in OSLER-2), patients entered the all Repatha period in which all patients received open-label Repatha for either another 4 years (OSLER) or 2 years (OSLER-2).

A total of 1,324 patients enrolled in OSLER. Repatha 420 mg once monthly significantly reduced LDL-C from baseline at week 12 and week 52 compared with control (nominal $p < 0.001$). Treatment effects were maintained over 272 weeks as demonstrated by reduction in LDL-C from week 12 in the parent study to week 260 in the open-label extension. A total of 3,681 patients enrolled in OSLER-2. Repatha significantly reduced LDL-C from baseline at week 12 and week 48 compared with control (nominal $p < 0.001$). Treatment effects were maintained as demonstrated by reduction in LDL-C from week 12 to week 104 in the open-label extension. Repatha significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and increased HDL-C and ApoA1 from baseline to week 52 in OSLER and to week 48 in OSLER-2 compared with control (nominal $p < 0.001$). LDL-C and other lipid parameters returned to baseline within 12 weeks after discontinuation of Repatha at the beginning of OSLER or OSLER-2 without evidence of rebound.

TAUSSIG was a multicentre, open-label, 5-year extension study to assess the long-term safety and efficacy of Repatha, as an adjunct to other lipid-lowering therapies, in patients with severe familial hypercholesterolaemia (FH), including homozygous familial hypercholesterolaemia. A total of 194 severe familial hypercholesterolaemia (non-HoFH) patients and 106 homozygous familial hypercholesterolaemia patients enrolled in TAUSSIG. All patients in the study were initially treated with Repatha 420 mg once monthly, except for those receiving lipid apheresis at enrolment who began with Repatha 420 mg once every 2 weeks. Dose frequency in non-apheresis patients could be titrated up to 420 mg once every 2 weeks based on LDL-C response and PCSK9 levels. Long-term use of Repatha demonstrated a sustained treatment effect as evidenced by reduction of LDL-C in patients with severe familial hypercholesterolaemia (non-HoFH) (see table 5).

Changes in other lipid parameters (TC, ApoB, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a sustained effect of long-term Repatha administration in patients with severe familial hypercholesterolaemia (non-HoFH).

Table 5. Effect of evolocumab on LDL-C in patients with severe familial hypercholesterolaemia (non-HoFH) – mean percent change from baseline to OLE week 216 (and associated 95% CI)

Patient Population (N)	OLE Week 12 (n = 191)	OLE Week 24 (n = 191)	OLE Week 36 (n = 187)	OLE Week 48 (n = 187)	OLE Week 96 (n = 180)	OLE Week 144 (n = 180)	OLE Week 192 (n = 147)	OLE Week 216 (n = 96)
Severe FH (non-HoFH) (N = 194)	-54.9 (-57.4, -52.4)	-54.1 (-57.0, -51.3)	-54.7 (-57.4, -52.0)	-56.9 (-59.7, -54.1)	-53.3 (-56.9, -49.7)	-53.5 (-56.7, -50.2)	-48.3 (-52.9, -43.7)	-47.2 (-52.8, -41.5)

Key: OLE = open-label extension, N (n) = Number of evaluable patients (N) and patients with observed LDL-C values at specific scheduled visit (n) in the severe familial hypercholesterolaemia (non-HoFH) final analysis set.

The long-term safety of sustained very low levels of LDL-C (i.e. < 0.65 mmol/L [< 25 mg/dL]) has not yet been established. Available data demonstrate that there are no clinically meaningful differences between the safety profiles of patients with LDL-C levels < 0.65 mmol/L and those with higher LDL-C, see section 4.8.

<u>Treatment of heterozygous familial hypercholesterolaemia in paediatric patients</u>

HAUSER-RCT was a randomised, multicenter, placebo-controlled, double-blind, parallel-group, 24-week trial in 158 paediatric patients aged 10 to < 18 years with heterozygous familial hypercholesterolaemia. Patients were required to be on a low-fat diet and must have been receiving optimised background lipid-lowering therapy (statin at optimal dose, not requiring up titration). Enrolled patients were randomised in a 2:1 ratio to receive 24 weeks of subcutaneous once monthly 420 mg Repatha or placebo.

The primary efficacy endpoint in this trial was percent change from baseline to week 24 in LDL-C. The difference between Repatha and placebo in mean percent change in LDL-C from baseline to week 24 was 38% (95% CI: 45%, 31%; p < 0.0001). The least squares mean Standard Error (SE) reduction (p < 0.0001) in LDL-C from baseline at week 24 was 44% (2%) in the Repatha group and 6% (3%) in the placebo group. Mean absolute LDL-C values at week 24 were 104 mg/dL in the Repatha group and 172 mg/dL in the placebo group. Reductions in LDL-C were observed by the first post-baseline assessment at the week 12 time point and were maintained throughout the trial.

The secondary endpoint of this trial was 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 subcutaneous once monthly dosing interval, and provides information about the time-averaged effect of Repatha therapy over the entire dosing interval. The least squares mean treatment difference between Repatha and placebo in mean percent change in LDL-C from baseline to the mean of week 22 and week 24 was 42% (95% CI: 48%, 36%; p < 0.0001). For additional results, see table 6.

Table 6. Treatment effects of Repatha compared with placebo in paediatric patients with heterozygous familial hypercholesterolaemia – mean percent change from baseline to week 24 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC/ HDL-C Ratio (%)	ApoB/ ApoA1 Ratio (%)
HAUSER-RCT (HeFH Paediatric Patients)	420 mg QM (N = 104)	-38.3 (-45.5, -31.1)	-35.0 (-41.8, -28.3)	-32.5 (-38.8, -26.1)	-30.3 (-36.4, -24.2)	-36.4 (-43.0, -29.8)

QM = monthly (subcutaneous); CI =Confidence Interval; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; ApoB = apolipoprotein B; ApoA1 = apolipoprotein A1, TC = total cholesterol
All adjusted p-values <0.0001
N = number of patients randomized and dosed in the full analysis set.

HAUSER-OLE was an open-label, single-arm, multicentre, 80 week study of Repatha in 150 paediatric patients aged 10 to 17 years with HeFH that rolled-over from HAUSER-RCT and enrolled 13 *de novo* paediatric HoFH patients. Patients had to be on a low-fat diet and receiving background lipid-lowering therapy. All HeFH patients in this study received 420 mg Repatha subcutaneously once monthly (median exposure duration: 18.4 months). The mean (SE) percent changes in calculated LDL-C from baseline were: -44.4% (1.7%) at week 12, -41.0% (2.1%) at week 48, and -35.2% (2.5%) at week 80.
The mean (SE) percent change from baseline to week 80 in other lipid endpoints were: -32.1% (2.3%) non-HDL-C, -25.1% (2.3%) ApoB, -28.5% (2.0%) TC/HDL-C ratio, -30.3% (2.2%) ApoB/ApoA1 ratio, and -24.9% (1.9%) TC.

<u>Treatment of homozygous familial hypercholesterolaemia</u>

TESLA was an international, multicentre, double-blind, randomised, placebo-controlled 12-week study in 49 homozygous familial hypercholesterolaemia patients aged 12 to 65 years. Repatha 420 mg once monthly, as an adjunct to other lipid-lowering therapies (e.g., statins, bile-acid sequestrants), significantly reduced LDL-C and ApoB at week 12 compared with placebo (p < 0.001) (see table 7). Changes in other lipid parameters (TC, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a treatment effect of Repatha administration in patients with homozygous familial hypercholesterolaemia.

Table 7. Treatment effects of evolocumab compared with placebo in patients with homozygous familial hypercholesterolaemia - mean percent change from baseline to week 12 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC (%)	Lp(a) (%)	VLDL-C (%)	HDL-C (%)	TG (%)	TC/ HDL-C ratio %	ApoB/ ApoA1 ratio %
TESLA (HoFH)	420 mg QM (N = 33)	-32[b] (-45, -19)	-30[a] (-42, -18)	-23[b] (-35, -11)	-27[a] (-38, -16)	-12 (-25, 2)	-44 (-128, 40)	-0.1 (-9, 9)	0.3 (-15, 16)	-26[a] (-38, -14)	-28[a] (-39, -17)

Key: HoFH = homozygous familial hypercholesterolaemia, QM = once monthly, [a] nominal p value < 0.001 when compared with placebo, [b] p value < 0.001 when compared with placebo.

<u>Long-term efficacy in homozygous familial hypercholesterolaemia</u>

In TAUSSIG, long-term use of Repatha demonstrated a sustained treatment effect as evidenced by reduction of LDL-C of approximately 20% to 30% in patients with homozygous familial hypercholesterolaemia not on apheresis and approximately 10% to 30% in patients with homozygous familial hypercholesterolaemia on apheresis (see table 8). Changes in other lipid parameters (TC, ApoB, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a sustained effect of long-term Repatha administration in patients with homozygous familial hypercholesterolaemia. Reductions in LDL-C and changes in other lipid parameters in 14 adolescent patients (aged ≥ 12 to < 18 years) with homozygous familial hypercholesterolaemia are comparable to those in the overall population of patients with homozygous familial hypercholesterolaemia.

Table 8. Effect of evolocumab on LDL-C in patients with homozygous familial hypercholesterolaemia - mean percent change from baseline to OLE week 216 (and associated 95% CI)

Patient Population (N)	OLE Week 12	OLE Week 24	OLE Week 36	OLE Week 48	OLE Week 96	OLE Week 144	OLE Week 192	OLE Week 216
HoFH (N = 106)	-21.2 (-26.0, -16.3) (n = 104)	-21.4 (-27.8, -15.0) (n = 99)	-27.0 (-32.1, -21.9) (n = 94)	-24.8 (-31.4, -18.3) (n = 93)	-25.0 (-31.2, -18.8) (n = 82)	-27.7 (-34.9, -20.5) (n = 79)	-27.4 (-36.9, -17.8) (n = 74)	-24.0 (-34.0, -14.0) (n = 68)
Non-apheresis (N = 72)	-22.7 (-28.1, -17.2) (n = 70)	-25.8 (-33.1, -18.5) (n = 69)	-30.5 (-36.4, -24.7) (n = 65)	-27.6 (-35.8, -19.4) (n = 64)	-23.5 (-31.0, -16.0) (n = 62)	-27.1 (-35.9, -18.3) (n = 60)	-30.1 (-37.9, -22.2) (n = 55)	-23.4 (-32.5, -14.2) (n = 50)
Apheresis (N = 34)	-18.1 (-28.1, -8.1) (n = 34)	-11.2 (-24.0, 1.7) (n = 30)	-19.1 (-28.9, -9.3) (n = 29)	-18.7 (-29.5, -7.9) (n = 29)	-29.7 (-40.6, -18.8) (n = 20)	-29.6 (-42.1, -17.1) (n = 19)	-19.6 (-51.2, 12.1) (n = 19)	-25.9 (-56.4, 4.6) (n = 18)

Key: OLE = open-label extension. N (n) = Number of evaluable patients (N) and patients with observed LDL values at specific schedule visit (n) in the HoFH final analysis set.

HAUSER-OLE was an open-label, single-arm, multicentre, 80-week trial in 12 HofH subjects to evaluate the safety, tolerability and efficacy of Repatha for LDL-C reduction in paediatric patients from aged ≥ 10 to < 18 years of age with homozygous familial hypercholesterolaemia. Patients had to be on a low-fat diet and receiving background lipid-lowering therapy. All patients in the study received 420 mg Repatha subcutaneously once monthly. Median (Q1, Q3) LDL-C at baseline was 398 (343, 475) mg/dL. The median (Q1, Q3) percent change in LDL-C from baseline to week 80 was -14% (-41, 4). Reductions in LDL-C were observed by the first assessment at week 12 and was maintained throughout the trial, median (Q1, Q3) reductions ranging between 12% (-3, 32) and 15% (-4, 39). For additional results, please see table 9.

Table 9. Treatment effects of evolocumab compared with placebo in patients with homozygous familial hypercholesterolaemia – median (Q1, Q3) percent change from baseline to week 80

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC/ HDL-C Ratio (%)	ApoB/ ApoA1 Ratio (%)
HAUSER-OLE (HoFH Paediatric Patients)	420 mg QM (N = 12)	-14.3 (-40.6, 3.5)	-13 (-40.7, 2.7)	-19.2 (-33.3, 11.6)	-3.7 (-41.2, 7.6)	-3 (-35.7, 9.3)

QM = monthly (subcutaneous); LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; ApoB = apolipoprotein B; ApoA1 = apolipoprotein A1, TC = total cholesterol
N = number of patients randomized and dosed in the interim analysis set.

Effect on atherosclerotic disease burden

The effects of Repatha 420 mg once monthly on atherosclerotic disease burden, as measured by intravascular ultrasound (IVUS), were evaluated in a 78-week double-blind, randomised, placebo-controlled study in 968 patients with coronary artery disease on a stable background of optimal statin therapy. Repatha reduced both percent atheroma volume (PAV; 1.01% [95% CI 0.64, 1.38], $p < 0.0001$) and total atheroma volume (TAV; 4.89 mm^3 [95% CI 2.53, 7.25], $p < 0.0001$) compared with placebo. Atherosclerotic regression was observed in 64.3% (95% CI 59.6, 68.7) and 47.3% (95% CI 42.6, 52.0) of patients who received Repatha or placebo respectively, when measured by PAV. When measured by TAV, atherosclerotic regression was observed in 61.5% (95% CI 56.7, 66.0) and 48.9% (95% CI 44.2, 53.7) of patients who received Repatha or placebo respectively. The study did not investigate the correlation between atherosclerotic disease regression and cardiovascular events.

Effect on coronary atherosclerotic plaque morphology

The effects of Repatha 420 mg once monthly on coronary atherosclerotic plaques as assessed by optical coherence tomography (OCT), were evaluated in a 52-week double-blind, randomised, placebo-controlled study including adult patients initiated within 7 days of a non-ST-segment elevation acute coronary syndrome (NSTEACS) on maximally tolerated statin therapy. For the primary endpoint of absolute change in minimum FCT (fibrous cap thickness) in a matched segment of artery from baseline, least squares (LS) mean (95% CI) increased from baseline by 42.7 μm (32.4, 53.1) in the Repatha group and 21.5 μm (10.9, 32.1) in the placebo group, an additional 21.2 μm (4.7, 37.7) compared to placebo ($p = 0.015$; (38% difference ($p = 0.041$)). The reported secondary findings show treatment differences including change in mean minimum FCT (increase 32.5 μm (12.7, 52.4); $p = 0.016$) and absolute change in maximum lipid arc (-26° (-49.6, -2.4); $p = 0.041$).

Prevention of Cardiovascular Events

FOURIER was a Phase 3, double-blind, randomised, placebo-controlled, event-driven, cardiovascular outcomes study to evaluate the effects of Repatha treatment in adult patients with established cardiovascular disease [prior myocardial infarction (81%), prior non-haemorrhagic stroke (19%), or symptomatic peripheral arterial disease (13%)].

Enrolled patients were on a stable background lipid-lowering therapy and had LDL-C values ≥ 70 mg/dL (1.8 mmol/L) or non-HDL-C values ≥ 100 mg/dL (2.6 mmol/L) with at least one major or two minor risk factors. Most patients (99.7%) were on a high- (69.3%) or moderate-intensity (30.4%) statin therapy at baseline, and most patients (99.6%) were taking at least one other cardiovascular medication such as anti-platelet agents, beta blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, or angiotensin receptor blockers.

A total of 27,564 patients were randomised 1:1 to receive either Repatha (140 mg every 2 weeks or 420 mg once monthly) or placebo (every 2 weeks or once monthly, respectively) subcutaneously with regular assessments every 12 weeks. Patients were followed for a mean (SD) of 26.1 (6.4) months. A total of 24.6% of patients were female, 85.1% were white, 9.9% were Asian, 2.4% were black, and 7.9% were Hispanic/Latino. The mean (SD) age was 62.5 (9.0) years. The median (Q1, Q3) LDL-C at baseline was 91.5 (79.5, 108.5) mg/dL (2.4 [2.0, 2.8] mmol/L).

Repatha significantly reduced the risk for the primary composite endpoint (time to cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation, whichever occurred first) and the key secondary composite endpoint (time to cardiovascular death, myocardial infarction, or stroke, whichever occurred first).

The results of primary and secondary efficacy endpoints are shown in table 10 and Figures 1 and 2 below:

Table 10. Treatment Effects of evolocumab Compared with Placebo in Patients with Established Cardiovascular Disease

	Placebo (N = 13,780) n (%)	Repatha (N = 13,784) n (%)	Hazard Ratio (95% CI)	p-value
Primary endpoint	1,563 (11.34)	1,344 (9.75)	0.85 (0.79, 0.92)	<0.0001[a]
Key secondary endpoint	1,013 (7.35)	816 (5.92)	0.80 (0.73, 0.88)	<0.0001[a]
Other secondary endpoints				
Time to cardiovascular death	240 (1.74)	251 (1.82)	1.05 (0.88, 1.25)	0.6188[b]
Time to death by any cause	426 (3.09)	444 (3.22)	1.04 (0.91, 1.19)	0.5368[b]
Time to first fatal or non-fatal myocardial infarction	639 (4.64)	468 (3.40)	0.73 (0.65, 0.82)	<0.0001[b]
Time to first fatal or non-fatal stroke	262 (1.90)	207 (1.50)	0.79 (0.66, 0.95)	0.0101[b]
Time to first coronary revascularization	965 (7.00)	759 (5.51)	0.78 (0.71, 0.86)	<0.0001[b]
Time to first hospitalization for unstable angina[c]	239 (1.73)	236 (1.71)	0.99 (0.82, 1.18)	0.8889[b]

[a] Repatha was statistically superior in reducing risk for the primary and key secondary composite endpoints compared to placebo ($p < 0.0001$).
[b] Nominal p-values.
[c] Not a pre-specified endpoint; an ad-hoc analysis was performed to ensure results are provided for each individual component of the primary endpoint.

Figure 1. Cumulative Incidence Estimates for the Primary Composite Endpoint

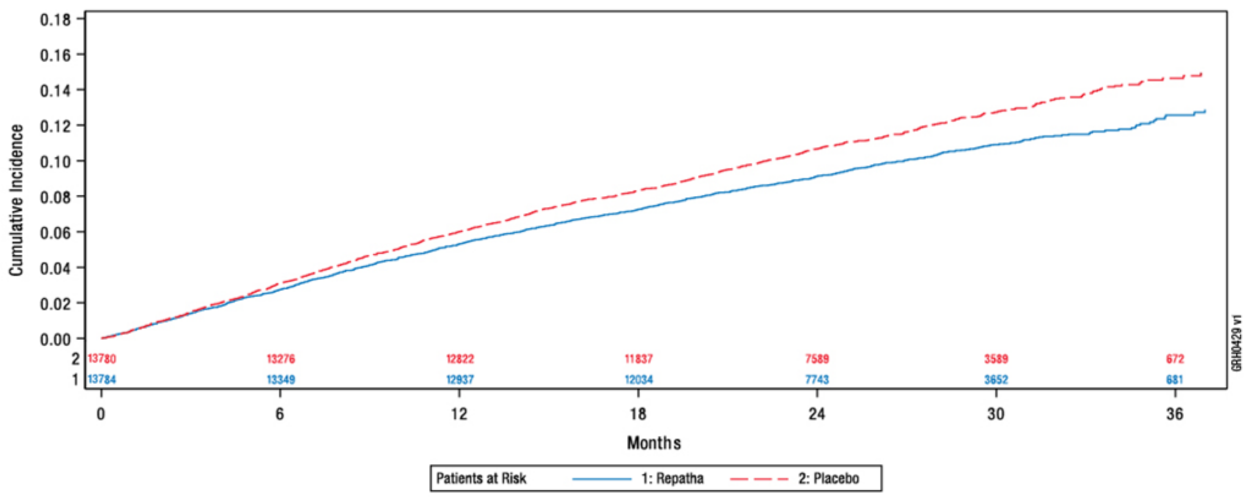
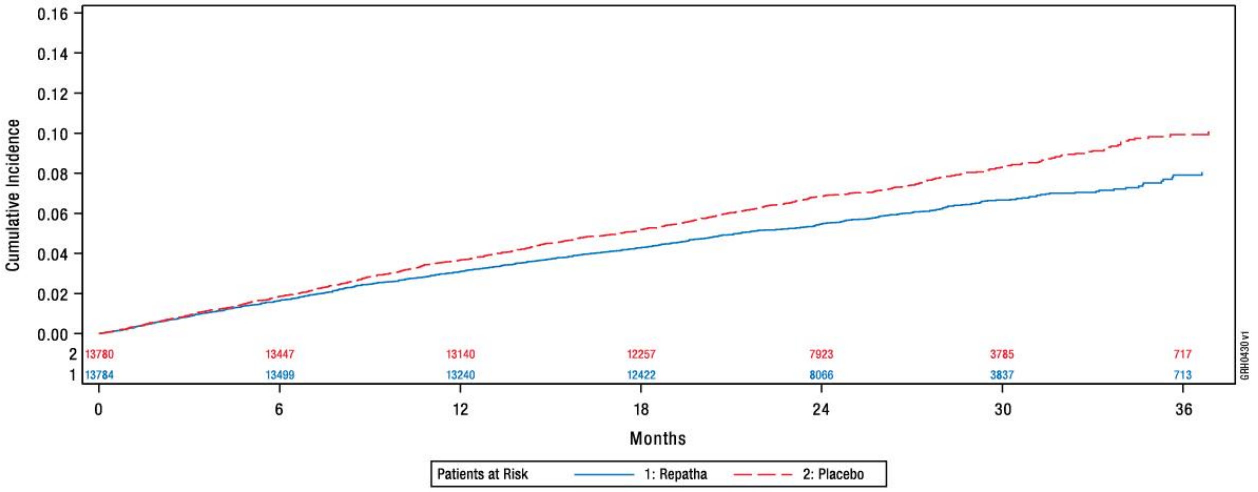


Figure 2. Cumulative Incidence Estimates for the Key Secondary Composite Endpoint



The Kaplan-Meier curves for the primary and key secondary composite endpoints separated at approximately 5 months, and the magnitudes of the absolute risk reductions grew steadily over time.

In an exploratory landmark analysis of post-baseline subgroups, Repatha reduced the risk of the primary and key secondary composite endpoints more after the first year than in the first year of the study.

The efficacy of Repatha on the primary and key secondary composite endpoints was consistent across all pre-specified subgroups (e.g., baseline LDL-C, geographic region, age, sex, race, prior non-haemorrhagic stroke, symptomatic PAD, length of prior myocardial infarction, intensity of statin treatment at baseline, history of type 2 diabetes, ezetimibe use at baseline) relative to placebo.

Repatha reduced LDL-C by a median (Q1, Q3) of 63.8% (32.3%, 76.8%) to 69.5% (55.7%, 79.1%). The treatment difference in LDL-C reduction between Repatha and placebo ranged from 52.1% (95% CI: 49.2%, 55.0%) to 60.7% (95% CI: 60.1%, 61.3%). These reductions were maintained for more than 3 years. Corresponding median (Q1, Q3) LDL-C concentrations ranged from 29 (19, 43) mg/dL to 35 (21, 64) mg/dL in the Repatha group, and 25% of patients achieved a LDL-C concentration < 20 mg/dL.

Of the patients treated with Repatha, 9,518 achieved at least one LDL-C value < 25 mg/dL. These patients had similar or lower incidence and similar type of adverse events, including neurocognitive events and new onset diabetes, compared to patients treated with Repatha or placebo who always had LDL-C ≥ 40 mg/dL. Lower LDL-C concentrations achieved during the study were associated with lower rates of cardiovascular events for the primary and secondary composite endpoint.

In a separate study of 1,974 patients with established cardiovascular disease enrolled in the FOURIER study, no clinically meaningful effect of Repatha was observed on cognitive function domains.

Other Supportive Clinical Information

- In an integrated analysis of Phase 2 and 3 randomised placebo- and active-controlled studies of Repatha for a duration of up to 52 weeks, adverse events were reported in 51% (N = 1,609) of patients in the Repatha group who achieved an LDL < 25 mg/dL and 51% (N = 2,565) of patients in the Repatha group who achieved an LDL < 40 mg/dL compared with 52% (N = 1,339) of patients in the Repatha group with an LDL ≥ 40 mg/dL and 50% (N = 2,038) of patients in the control group with LDL ≥ 40 mg/dL.

- An integrated safety analysis of Phase 2 and 3 randomised controlled studies of Repatha with statin therapy for a duration of up to 52 weeks was performed to assess alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and creatine kinase (CK) for patients with normal values at baseline. The incidence of ALT or AST > 5× upper limit of normal was 0.1% in both the Repatha (N = 2,523) and control (N = 1,249) groups. In the same studies, CK > 10 × upper limit of normal was 0.2% (N = 2,486) in the Repatha group and 0.1% (N = 1,217) in the control group.
- The safety of Repatha in the long-term, controlled studies was similar to the findings in the integrated analysis of Phase 2 and 3 placebo- and active-controlled studies.

Effect on LDL-C during acute phase of Acute Coronary Syndromes (ACS)

EVOPACS was a single country, multicenter, double-blind, randomized, placebo-controlled, 8-week study on 308 ACS patients with evolocumab initiated in-hospital within 24 to 72 hours of presentation.

If patients were not on a statin or were on statin treatment other than atorvastatin 40 mg prior to screening, this was stopped and atorvastatin 40 mg once daily was initiated. Randomisation was stratified by study centre and presence of stable statin treatment within ≥ 4 weeks prior to enrolment. Most subjects (241 [78%]) were not on stable statin treatment for ≥ 4 weeks prior to screening and most (235 [76%]) were not taking a statin at baseline. By week 4, 281 (97%) subjects were receiving high-intensity statins. Evolocumab 420 mg once monthly significantly reduced LDL-C from baseline to week 8 compared with placebo ($p < 0.001$). The mean (SD) reduction in calculated LDL-C from baseline at week 8 was 77.1% (15.8%) in the evolocumab group and 35.4% (26.6%) in the placebo group with a least squares (LS) mean difference (95% CI) of 40.7% (36.2%, 45.2%). Baseline LDL-C values were 3.61 mmol/L (139.5 mg/dL) in the evolocumab group and 3.42 mmol/L (132.2 mg/dL) in the placebo group. LDL-C reductions in this study were consistent with previous studies where evolocumab was added to stable lipid-lowering therapy as demonstrated by on-treatment LDL-C levels at week 8 in this study (reflecting steady-state effect of high-intensity statin in both treatment arms) of 0.79 mmol/L (30.5 mg/dL) and 2.06 mmol/L (79.7 mg/dL) in the evolocumab plus atorvastatin and the placebo plus atorvastatin groups, respectively.

The effects of evolocumab in this patient population were consistent with those observed in previous studies in evolocumab clinical development program and no new safety concerns were noted.

5.2 Pharmacokinetic properties

Absorption and distribution

Following a single subcutaneous dose of 140 mg or 420 mg evolocumab administered to healthy adults, median peak serum concentrations were attained in 3 to 4 days. Administration of single subcutaneous dose of 140 mg resulted in a C_{max} mean (SD) of 13.0 (10.4) µg/mL and AUC_{last} mean (SD) of 96.5 (78.7) day•µg/mL. Administration of single subcutaneous dose 420 mg resulted in a C_{max} mean (SD) of 46.0 (17.2) µg/mL and AUC_{last} mean (SD) of 842 (333) day•µg/mL. Three subcutaneous 140 mg doses were bioequivalent to a single subcutaneous 420 mg dose. The absolute bioavailability after SC dosing was determined to be 72% from pharmacokinetic models.

Following a single 420 mg evolocumab intravenous dose, the mean (SD) steady-state volume of distribution was estimated to be 3.3 (0.5) L, suggesting evolocumab has limited tissue distribution.

Biotransformation

Evolocumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination

Evolocumab was estimated to have an effective half-life of 11 to 17 days.

In patients with primary hypercholesterolaemia or mixed dyslipidaemia on high dose statin, the systemic exposure of evolocumab was slightly lower than in subjects on low-to-moderate dose statin (the ratio of AUC_{last} 0.74 [90% CI 0.29; 1.9]). An approximately 20% increase in the clearance is in part mediated by statins increasing the concentration of PCSK9 which did not adversely impact the pharmacodynamic effect of evolocumab on lipids. Population pharmacokinetic analysis indicated no appreciable differences in evolocumab serum concentrations in hypercholesterolaemic patients (non-familial hypercholesterolaemia or familial hypercholesterolaemia) taking concomitant statins.

Linearity/non-linearity

Following a single 420 mg intravenous dose, the mean (SD) systemic clearance was estimated to be 12 (2) mL/hr. In clinical studies with repeated subcutaneous dosing over 12 weeks, dose proportional increases in exposure were observed with dose regimens of 140 mg and greater. An approximate two to three-fold accumulation was observed in trough serum concentrations (C_{min} (SD) 7.21 (6.6)) following 140 mg doses every 2 weeks or following 420 mg doses administered monthly (C_{min} (SD) 11.2 (10.8)), and serum trough concentrations approached steady-state by 12 weeks of dosing.

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

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Data from the evolocumab clinical trials did not reveal a difference in pharmacokinetics of evolocumab in patients with mild or moderate renal impairment relative to non-renally impaired patients.

In a clinical trial of 18 patients with either normal renal function (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m^2, n = 6), severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2, n = 6), or end-stage renal disease (ESRD) receiving haemodialysis (n = 6), exposure to unbound evolocumab as assessed by C_{max} after a single 140 mg subcutaneous dose was decreased by 30% in patients with severe renal impairment and by 45% in patients with ESRD receiving haemodialysis. Exposure as assessed by AUC_{last} was decreased by approximately 24% in patients with severe renal impairment and by approximately 45% in patients with ESRD receiving haemodialysis. The exact mechanism of PK differences is unknown; however, differences in body weight could not explain these differences. Some factors including small sample size and large inter-subject variability should be considered when interpreting the results. The pharmacodynamics and safety of evolocumab in patients with severe renal impairment and ESRD were similar to patients with normal renal function, and there were no clinically meaningful differences in LDL-C lowering. Therefore, no dose adjustments are necessary in patients with severe renal impairment or ESRD receiving haemodialysis.

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). Single 140 mg subcutaneous doses of evolocumab were studied in 8 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment and 8 healthy subjects. The exposure to evolocumab was found to be approximately 40-50% lower compared to healthy subjects. However, baseline PCSK9 levels and the degree and time course of PCSK9 neutralisation were found to be similar between patients with mild or moderate hepatic impairment and healthy volunteers. This resulted in similar time course and extent of absolute LDL-C lowering. Evolocumab has not been studied in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.4).

Body weight

Body weight was a significant covariate in population PK analysis impacting evolocumab trough concentrations, however there was no impact on LDL-C reduction. Following repeat subcutaneous administration of 140 mg every 2 weeks, the 12-week trough concentrations were 147% higher and 70% lower in patients of 69 kg and 93 kg respectively, than that of the typical 81 kg subject. Less impact from body weight was seen with repeated subcutaneous evolocumab 420 mg monthly doses.

Other special populations

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

The pharmacokinetics of Repatha were evaluated in 103 paediatric patients aged ≥ 10 to < 18 years with heterozygous familial hypercholesterolaemia (HAUSER-RCT). Following subcutaneous administration of 420 mg Repatha once monthly, mean (SD) trough serum concentrations were 22.4 (14.7) mcg/mL, 64.9 (34.4) mcg/mL and 25.8 (19.2) mcg/mL over the Week 12, Week 22 and Week 24 time points, respectively. The pharmacokinetics of Repatha were evaluated in 12 paediatric patients aged ≥ 10 to < 18 years with homozygous familial hypercholesterolaemia (HAUSER-OLE). Following subcutaneous administration of 420 mg Repatha once monthly, mean (SD) serum trough concentrations were 20.3 (14.6) mcg/mL and 17.6 (28.6) mcg/mL at Week 12 and Week 80, respectively.

5.3 Preclinical safety data

Evolocumab was not carcinogenic in hamsters at exposures much higher than patients receiving evolocumab at 420 mg once monthly. The mutagenic potential of evolocumab has not been evaluated.

In hamsters and cynomolgus monkeys at exposures much higher than patients receiving 420 mg evolocumab once monthly, no effect on male or female fertility was observed.

In cynomolgus monkeys at exposures much higher than patients receiving 420 mg evolocumab once monthly, no effects on embryo-foetal or postnatal development (up to 6 months of age) were observed.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Proline
Glacial acetic acid
Polysorbate 80
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date is indicated on the packaging.

If removed from the refrigerator, Repatha may be stored at room temperature (up to 25°C) in the original carton and must be used within 1 month.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze or shake.

Repatha solution for injection in pre-filled syringe 140 mg
Store in the original carton in order to protect from light.

Repatha solution for injection in pre-filled autoinjector 140 mg
Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Repatha solution for injection in pre-filled syringe 140 mg

One mL solution in a single use pre-filled syringe made from type I glass with stainless steel 27 gauge needle.

The needle cover of the pre-filled syringe is made from dry natural rubber (a derivative of latex, see section 4.4).

Pack size of one pre-filled syringe.

Repatha solution for injection in pre-filled autoinjector 140 mg

One mL solution in a single use pre-filled autoinjector made from type I glass with stainless steel 27 gauge needle.

The needle cover of the pre-filled autoinjector is made from dry natural rubber (a derivative of latex, see section 4.4).

Pack sizes of one, two, three or multipack of six (3×2) pre-filled autoinjectors.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before administration, the solution should be inspected. The solution should not be injected if it contains particles, or is cloudy or discoloured. To avoid discomfort at the site of injection, the medicinal product should be allowed to reach room temperature (up to 25°C) before injecting. The entire contents should be injected.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Amgen Manufacturing Limited
State Road 31, Km. 24.6, Juncos,
Puerto Rico, 00777-4060, USA

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