PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

REPATHA® 140 mg solution for injection in pre-filled syringe

REPATHA® 140 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REPATHA® 140 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 140 mg of evolocumab in 1 ml of solution.

REPATHA® 140 mg solution for injection in pre-filled pen

Each pre-filled pen 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 full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Solution for injection (injection) in pre-filled pen (SureClick).

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

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Hypercholesterolaemia and mixed dyslipidaemia

REPATHA® is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) 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 paediatric patients aged 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.

4.2. Posology and Method of Administration

Date of Registration:	***25 February 2020***	***Date of SAHPRA Approval:***	***23 June 2025***
Date of Amendment:	***23 June 2025***	**Initialled by: A. Jayaram (BPharm)**	23/06/2025

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

Posology

Primary hypercholesterolaemia and mixed dyslipidaemia (including heterozygous familial hypercholesterolaemia)

Adults and paediatric patients (aged 10 years and over)

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

Homozygous familial hypercholesterolaemia in adults and paediatric patients aged 10 years and over

The initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up-titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule.

Established atherosclerotic cardiovascular disease in adults

The recommended dose of evolocumab is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Special Populations

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.

Method of Administration

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® 140 mg solution for injection in pre-filled syringe

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® 140 mg solution for injection in pre-filled pen

The 140 mg dose should be delivered using a single pre-filled pen.

The 420 mg dose should be delivered using three pre-filled pens 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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hepatic impairment

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.

Dry natural rubber

REPATHA® 140 mg solution for injection in pre-filled syringe

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® 140 mg solution for injection in pre-filled pen

The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex), which may cause severe allergic reactions.

Sodium content

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 Medicines 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 co-administered with 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.

Breastfeeding

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 breastfeeding or discontinue/abstain from REPATHA® therapy, taking into account the benefit of breastfeeding 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 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.

The safety profile was consistent between subjects with post-baseline LDL-C < 25 mg/dl (0,65 mmol/l) or < 40 mg/dl (1,03 mmol/l) compared to subjects with higher post-baseline LDL-C (≥ 40 mg/dl[1,03 mmol/l]), with median (Q1, Q3) REPATHA® exposure of 84,2 (78,1; 89,8) months in subjects who continued on REPATHA® and 59,8 (52,8; 60,3) months in subjects on placebo who switched to REPATHA® in an open-label extension study.

Description of selected adverse reactions

Injection site reactions

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

Paediatric population

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.

Elderly population

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.

Immunogenicity

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 paediatric patients treated with REPATHA®

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8

Alternatively, suspected adverse events can be reported to:

Amgen South Africa (Pty) Ltd.

Tel: +27 (0)11 100 5300

Email: safety-south-africa@amgen.com

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 REPATHA® 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

A 30.1 Antibodies

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 evolocumab 140 mg or 420 mg 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 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 with 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 to 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.

<u>Combination with statin or statin with other lipid-lowering therapies</u>

LAPLACE-2 was an international, multicentre, double-blind, double-dummy 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 with 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 compared with 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 hypercholesterolemia 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 with 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)

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 with ezetimibe (p < 0,001) (Table 3).

Treatment in the absence of a statin

MENDEL-2 was an international, multicentre, double-blind, double-dummy 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 table 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 (treatment in the absence of a statin)	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.

<u>Long-term efficacy in primary hypercholesterolaemia and mixed dyslipidaemia</u>

DESCARTES was an international, multicentre, double-blind, randomised, placebo- controlled, 52-week study in 901 patients with hyperlipidaemia who were receiving 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) (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-1 and OSLER-2 were two multicentre, 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 hypercholesterolemia (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 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-HDLC, 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.

Treatment of heterozygous familial hypercholesterolaemia in paediatric patients

HAUSER-RCT was a randomised, multicentre, 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 randomised 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.

Treatment of homozygous familial hypercholesterolemia

TESLA was an international, multicentre, double-blind, randomised, placebo-controlled 12-week study in 49 homozygous familial hypercholesterolaemia patients between 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.

Long-term efficacy in homozygous familial hypercholesterolaemia

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)	-19,1 (-33,3, 11,6)	-3,7 (-41,6, 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 randomised 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).

Cardiovascular risk reduction in adults with established atherosclerotic cardiovascular disease

The REPATHA® Outcomes Study (FOURIER) was a randomised, event-driven, double-blind study of 27 564 subjects, aged between 40 and 86 years (mean age 62,5 years), with established atherosclerotic CV disease; 81 % had a prior MI event, 19 % had a prior stroke event and 13 % had peripheral arterial disease. Over 99 % of patients were on moderate to high intensity statin and at least one other cardiovascular medicine such as anti-platelet agents, beta blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, or angiotensin receptor blockers; median (Q1, Q3) baseline LDL-C was 2,4 mmol/l (2,1; 2,8). Absolute CV risk was balanced between treatment groups, in addition to the index event all patients had at least 1 major or 2 minor CV risk factors; 80 % had hypertension, 36 % had diabetes mellitus, and 28 % were daily smokers. Patients were randomised 1:1 to either REPATHA® (140 mg every two weeks or 420 mg once every month) or matching placebo; the mean duration of patient follow-up was 26 months.

A substantial reduction of LDL-C was observed throughout the study, with achieved median LDL-C ranges of 0,8 to 0,9 mmol/l at each assessment; 25 % of patients achieved a LDL-C concentration less than 0,5 mmol/l. Despite the very low levels of LDL-C achieved, no new safety issues were observed (see section 4.8); the frequencies of new onset diabetes and cognitive events were comparable in patients who achieved LDL-C levels < 0,65 mmol/l and those with higher LDL-C.

REPATHA® significantly reduced the risk of cardiovascular events defined as the composite of time to first CV death, MI, stroke, coronary revascularisation, or hospitalisation for unstable angina (see table 10); the Kaplan-Meier curves for the primary and key secondary composite endpoints separated at approximately 5 months (see figure 1 for the MACE three year Kaplan-Meier curve). The relative risk of the MACE composite (CV death, MI, or stroke) was significantly reduced by 20 %. The treatment effect was consistent across all subgroups (including age, type of disease, baseline LDL-C, baseline statin intensity, ezetimibe use, and diabetes) and was driven by a reduction in the risk of myocardial infarction, stroke and coronary revascularisation; no significant difference was seen on cardiovascular or all-cause mortality however the study was not designed to detect such a difference.

Table 10. Effect of evolocumab on major cardiovascular events

	Placebo (N = 13 780) n (%)	Evolocumab (N = 13 784) n (%)	Hazard ratio[a] (95 % CI)	p value[b]
MACE+ (composite of MACE, coronary revascularisation, or hospitalisation for unstable angina)	1 563 (11,34)	1 344 (9,75)	0,85 (0,79, 0,92)	< 0,0001
MACE (composite of CV death, MI, or stroke)	1,013 (7,35)	816 (5,92)	0,80 (0,73, 0,88)	< 0,0001
Cardiovascular death	240 (1,74)	251 (1,82)	1,05 (0,88, 1,25)	0,62
All-cause mortality	426 (3,09)	444 (3,22)	1,04 (0,91, 1,19)	0,54
Myocardial infarction (fatal/non-fatal)	639 (4,64)	468 (3,40)	0,73 (0,65, 0,82)	< 0,0001[c]
Stroke (fatal/non-fatal)[d]	262 (1,90)	207 (1,50)	0,79 (0,66, 0,95)	0,0101[c]
Coronary revascularisation	965 (7,00)	759 (5,51)	0,78 (0,71, 0,86)	< 0,0001[c]
Hospitalisation for unstable angina[e]	239 (1,7)	236 (1,7)	0,99 (0,82, 1,18)	0,89

[a] Based on a Cox model stratified by the randomisation stratification factors collected via Interactive Voice Response System (IVRS).

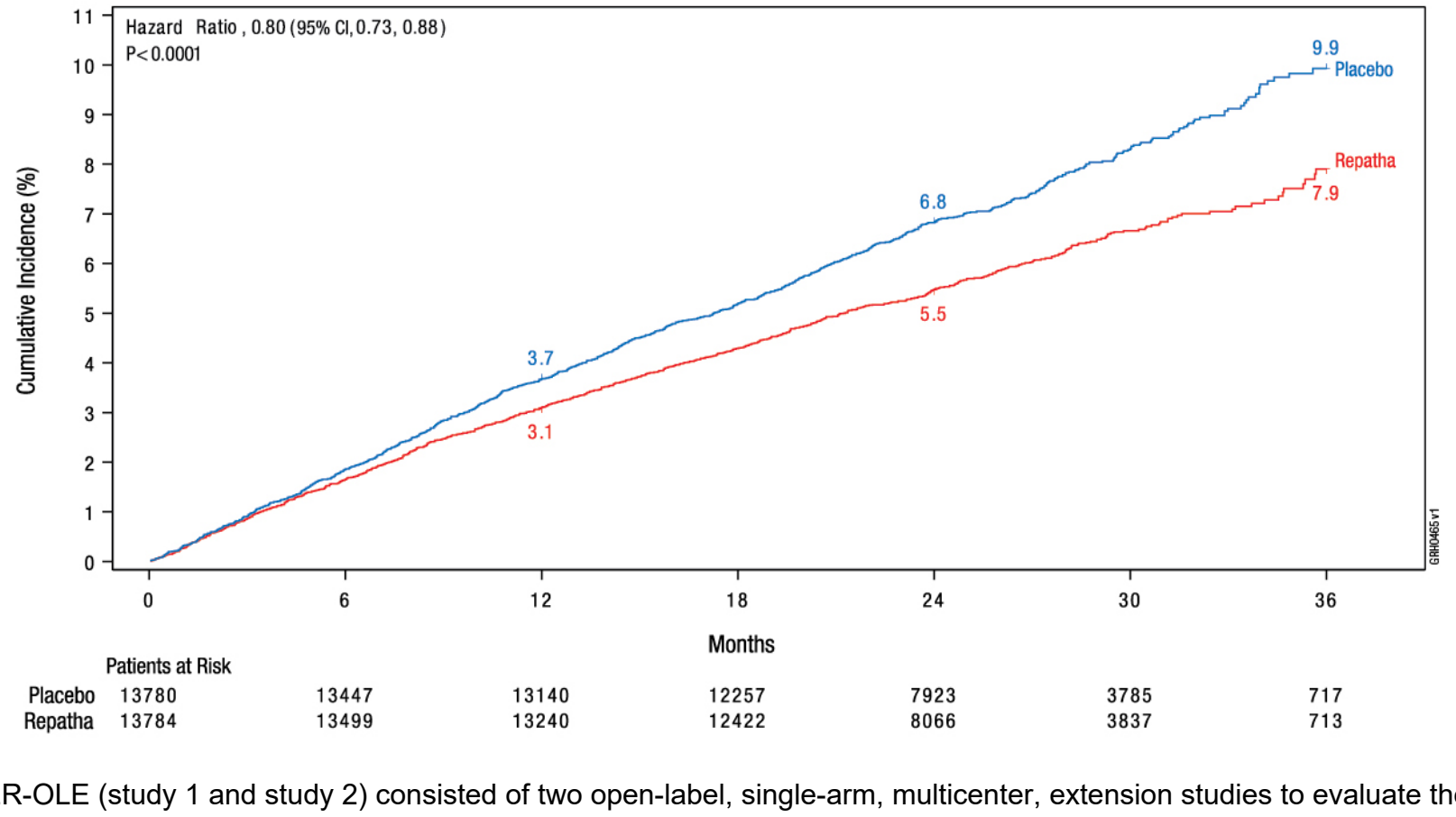
[b] 2-sided log-rank test stratified by randomisation stratification factors collected via IVRS.

[c] Nominal significance.

[d] The treatment effect on stroke was driven by a reduction in risk of ischaemic stroke; there was no effect on haemorrhagic or undetermined stroke.

[e] Assessment of time to hospitalisation for unstable angina was ad-hoc.

Figure 1. Time to a MACE event (composite of CV death, MI, or stroke); 3-year Kaplan-Meier



FOURIER-OLE (study 1 and study 2) consisted of two open-label, single-arm, multicenter, extension studies to evaluate the long-term safety, tolerability, and efficacy of REPATHA® in patients with established cardiovascular disease who completed the FOURIER study. Enrolled patients received REPATHA® 140 mg every 2 weeks or 420 mg once monthly for approximately 5 years and continued moderate- (22,2 %) or high-intensity (74,8 %) background statin therapy. Of the 5 031 patients who received at least one dose of REPATHA® in study 1, 2 499 patients received REPATHA® and 2 532 patients received placebo in the FOURIER study. Of the 1 599 patients who received at least one dose of REPATHA® in study 2 854 patients received REPATHA® and 745 patients received placebo in the FOURIER study. Upon completion of study 1 and study 2, patients randomized to REPATHA® in the FOURIER study had up to 8,4 years (median 85,4 months) and 8,0 years of total REPATHA® exposure (median 80,2 months) and patients randomized to placebo had up to 5,25 years (median 60,0 months) and 4,9 years of total REPATHA® exposure (median 55,1 months), respectively.

In study 1 and 2 combined, 72,4 % (n = 4 802) of patients achieved a lowest post-baseline LDL-C < 25 mg/dl (0,65 mmol/l), 87,0 % (n = 5 765) of patients achieved an LDL-C < 40 mg/dl (1,03 mmol/l), and 11,9 % (n = 792) of patients had an all post-baseline LDL-C ≥ 40 mg/dl (1,03 mmol/l). Of the patients who achieved post-baseline low LDL-C (< 25 mg/dl or < 40 mg/dl), the overall subject incidences of treatment emergent adverse events were 80,0 % patients who achieved LDL-C < 25 mg/dl and 82,7 % in patients who achieved LDL-C < 40 mg/dl compared to 85,0 % in patients with LDL-C ≥ 40 mg/dL. The overall subject incidences of serious treatment emergent adverse events were 37,7 % in patients who achieved LDL-C < 25 mg/dl and 40,0 % in patients who achieved LDL-C < 40 mg/dl compared to 41,5 % in patients with LDL-C ≥ 40 mg/dl.

The mean percent reduction from baseline in LDL-C was stable during the OLE study period and ranged from 53,4 % to 59,1 % for study 1 and 62,5 % to 67,2 % for study 2, regardless of the patient's original randomised treatment group in the FOURIER study. This appears to translate into a numerically lower subject incidence rate of adjudicated exploratory CV endpoints of the composite of CV death, MI and stroke for patients who had received REPATHA® in both the FOURIER and FOURIER OLE studies compared with patients who had received placebo in the FOURIER study and REPATHA® in the FOURIER OLE studies.

Overall, no new safety findings were identified in these studies.

<u>Effect on LDL-C during acute phase of Acute Coronary Syndromes (ACS)</u>

EVOPACS was a single country, multicentre, double-blind, randomised, 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 of 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 AUClast 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 (Cmin (SD) 7,21 (6,6)) following 140 mg doses every 2 weeks or following 420 mg doses administered monthly (Cmin (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 Cmax 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 AUClast 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 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 % to 50 % lower compared with healthy volunteers. 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 injection

6.2. Incompatibilities

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

6.3. Shelf life

REPATHA® 140 mg solution for injection in pre-filled syringe

3 years

REPATHA® 140 mg solution for injection in pre-filled pen

3 years

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.

REPATHA® 140 mg solution for injection in pre-filled syringe

Store in the original carton in order to protect from light.

REPATHA® 140 mg solution for injection in pre-filled pen

Store in the original carton in order to protect from light.

6.5. Nature and contents of container

REPATHA® 140 mg solution for injection in pre-filled syringe

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® 140 mg solution for injection in pre-filled pen

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

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

Pack sizes of one, two, three pre-filled pens or multipacks containing 6 (3 packs of 2) pre-filled pens.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Amgen South Africa (Pty) Ltd.

Building D, Ballyoaks Office Park,

35 Ballyclare Drive

Bryanston Ext. 7

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South Africa

8. REGISTRATION NUMBER

49/30.1/1116

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration:	***25 February 2020***	***Date of SAHPRA Approval:***	***23 June 2025***
Date of Amendment:	***23 June 2025***	**Initialled by: A. Jayaram (BPharm)**	23/06/2025

25 February 2020

10. DATE OF REVISION OF THE TEXT

Last updated: 23 June 2025

Date of Registration:	***25 February 2020***	***Date of SAHPRA Approval:***	***23 June 2025***
Date of Amendment:	***23 June 2025***	**Initialled by: A. Jayaram (BPharm)**	23/06/2025

Date of Registration:	***25 February 2020***	***Date of SAHPRA Approval:***	***23 June 2025***
Date of Amendment:	***23 June 2025***	**Initialled by: A. Jayaram (BPharm)**	23/06/2025

REFERENCES:

Reference 2:	Module 1.3.1.1.2 annotated approved professional information: Repatha®