This medicine is not currently marketed in New Zealand

1. REPATHA® (140 mg solution for injection)

Repatha 140 mg solution for injection pre-filled syringe

Repatha 140 mg solution for injection pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL single-use pre-filled syringe and pen contain 140 mg of evolocumab in 1 mL (140 mg/mL).

Evolocumab is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Repatha is a sterile, preservative-free solution, clear to opalescent; colourless to yellowish solution for injection, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Repatha is indicated as an adjunct to diet and exercise in:

Prevention of Cardiovascular Events

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

Hypercholesterolaemia

Repatha is indicated in adults with primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia and non-familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C):

- in combination with a statin or statin with other lipid lowering therapies, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant.

Homozygous Familial Hypercholesterolaemia

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

4.2 Dose and method of administration

Dose

Hypercholesterolaemia and Prevention of Cardiovascular Events

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

Homozygous Familial Hypercholesterolaemia in adults and adolescents aged 12 years and over

The recommended dose for Repatha is 420 mg, either once monthly or every 2 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule.

Elderly patients

No dose adjustment is necessary in elderly patients (see Section 4.8, Elderly Population).

Patients with renal impairment

No dose adjustment is necessary in patients with renal impairment (see Section 4.4, Renal Impairment and 5.2, Renal Impairment).

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment (see Section 4.4, Hepatic Impairment and 5.2, Hepatic Impairment).

Paediatric population

The safety and effectiveness of Repatha have not been established in paediatric patients with hypercholesterolaemia (see Section 4.8, Paediatric Population). No data are available.

The safety and efficacy of Repatha in children aged less than 12 years has not been established in the indication for Homozygous Familial Hypercholesterolaemia. No data are available.

Method of administration

Repatha is administered subcutaneously and intended for patient self-administration. Administration should be performed by an individual who has been trained to administer the product.

Indication	Recommended Dosage and Frequency	Method of Administration
Hypercholesterolaemia and Prevention of Cardiovascular Events	140 mg every 2 weeks	One single-use prefilled syringe (PFS) or single-use prefilled pen (SureClick®)
	420 mg once monthly	3 single-use PFSs or 3 single-use prefilled pens (SureClick) administered consecutively within 30 minutes
Homozygous Familial Hypercholesterolaemia	420 mg once monthly or every 2 weeks	3 single-use PFSs or 3 single-use prefilled pens (SureClick) administered consecutively within 30 minutes

Precautions to be taken before handling or administering the medicine

Prior to subcutaneous administration, allow Repatha to sit at room temperature for at least 30 minutes. Do not warm in any other way. Avoid vigorous shaking the product. Visually inspect the solution for particles and discolouration. Do not use if the solution is discoloured, cloudy, or if flakes or particles are present. Doses may be administered in the upper arm, thigh, or abdomen. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard.

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

Concomitant Lipid-Lowering Therapies

When using Repatha in combination with statins or other lipid-lowering therapies (e.g., ezetimibe), the prescriber should refer to the Contraindications and the Warnings and Precautions sections of the prescribing information for those medications.

Hepatic Impairment

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see Section 5.2, 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 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), may cause allergic reactions.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

No formal medicine interaction studies have been conducted for Repatha.

The pharmacokinetic interaction between statins and Repatha was evaluated in the Repatha clinical studies. 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 PCSK9 which did not adversely impact the pharmacodynamic effect of Repatha on lipids. No statin dose adjustments are necessary when used in combination with Repatha.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category: B1

There are no adequate and well-controlled studies of Repatha in pregnant women. In cynomolgus monkeys, no effects on embryo-foetal or postnatal development (up to 6 months of age) were observed when evolocumab was dosed throughout pregnancy at exposure levels 12-fold higher than those achieved in patients receiving Repatha at the 420 mg once monthly clinical dosing regimen based on the area under the concentration curve (AUC).

Animal studies are not always predictive of human response. Therefore, it is not known whether Repatha can cause foetal harm when administered to a pregnant woman and Repatha should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

When Repatha is administered with a statin or other lipid-lowering therapies (e.g., ezetimibe) in women of childbearing potential, refer to the pregnancy section of the prescribing information for those medications (see Section 4.4).

Breastfeeding

It is not known whether Repatha is present in human milk. Many medicines are present in human milk and because of the potential for adverse effects in nursing infants from Repatha, a decision should be made whether to discontinue nursing or discontinue Repatha, taking into account the potential benefit of Repatha to the mother and the potential benefit of breast feeding to the infant.

Fertility

No data are available on the effect of Repatha on human fertility. Animal studies did not show any effects on fertility endpoints at AUC exposure levels up to 300-fold higher than in patients receiving Repatha at 420 mg once monthly (see Section 5.3).

4.7 Effects on ability to drive and use machines

The effects of Repatha on the ability to drive or use machinery is not known.

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions during hypercholesterolaemia pivotal trials, at the recommended doses, were 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%).

Adverse reactions are displayed by system organ class and frequency 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).

Tabulated list of adverse reactions

System Organ Class	Very common ≥ 10%	Common ≥ 1% and < 10%	Uncommon ≥ 0.1% and < 1%	Rare ≥ 0.01% and < 0.1%
Gastrointestinal Disorders		Nausea		
General Disorders and Administration Site Conditions		Injection Site Reactions*		
Infections and Infestations		Influenza Nasopharyngitis Upper Respiratory Tract Infection		
Musculoskeletal and Connective Tissue Disorders		Arthralgia Back pain		
Skin and Subcutaneous Tissue Disorders		Rash	Urticaria	

* Injection Site Reactions includes injection site pain, injection site erythema, injection site bruising, injection site swelling, and injection site haemorrhage

The safety profile in the HoFH population was consistent with that demonstrated in the hypercholesterolaemia population.

Paediatric population

The safety and effectiveness of Repatha have not been established in paediatric patients with hypercholesterolaemia. Fourteen adolescent patients aged 12 years and over have been included in HoFH clinical studies. No overall differences in safety or efficacy were observed between adolescent and adult patients with HoFH.

Elderly population

Of the 18,546 hypercholesterolaemia patients treated with Repatha in double blind clinical studies, 7656 (41.3%) were ≥ 65 years old, while 1500 (8.1%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

Post marketing Experience

Hypersensitivity reactions including angioedema

Influenza-like illness

Myalgia

Headache

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents – Other lipid modifying agents, ATC code: C10AX13

Pharmacodynamic effects

Mechanism of Action

Repatha is a fully human monoclonal IgG2 directed against human PCSK9. Repatha binds selectively and with high affinity to PCSK9 and inhibits 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-C.

Pharmacodynamic Effects

Clinical studies have demonstrated that elevated levels of TC, non-HDL-C, LDL-C and ApoB, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of TC, non-HDL-C, LDL-C, ApoB and Lp(a), and inversely with the

level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering TG or Lp(a) on the risk of cardiovascular morbidity and mortality has not been determined.

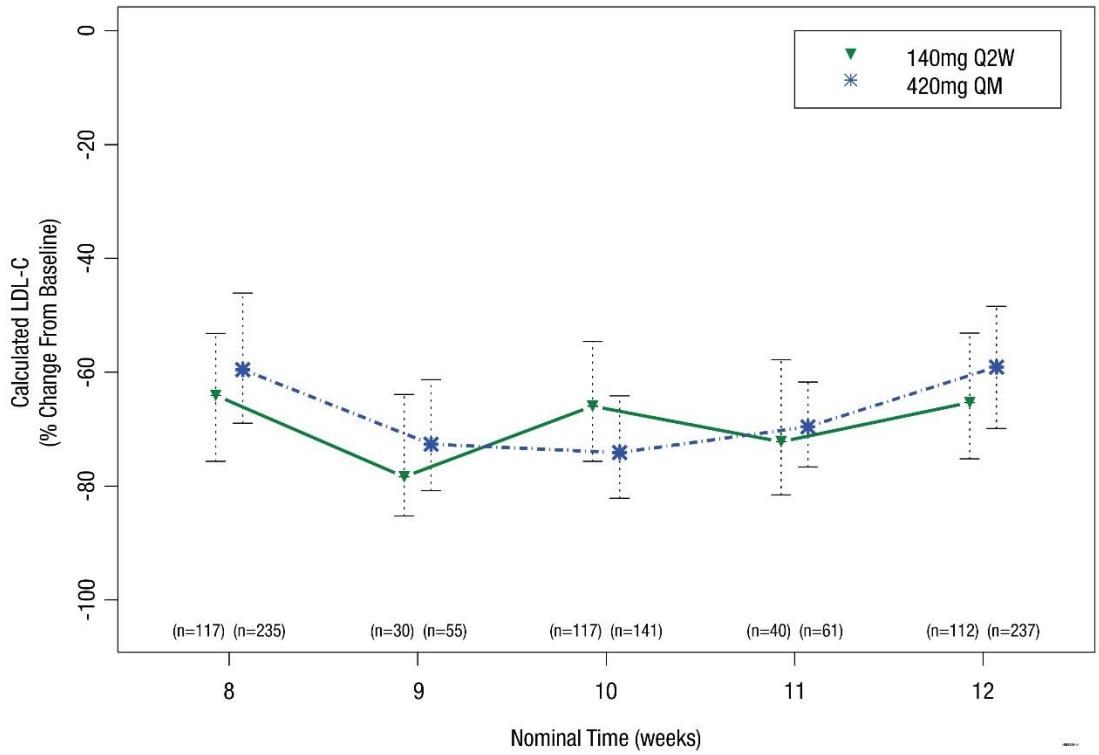
In clinical studies, Repatha reduced unbound PCSK9, LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG, and Lp(a), and increased HDL-C and ApoA1 in patients with hypercholesterolaemia.

A single subcutaneous administration of Repatha 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 Repatha. 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.

Based on dose-range finding studies, subcutaneous regimens of 140 mg every 2 weeks and 420 mg once monthly were identified as the optimal regimens to achieve maximal LDL-C lowering (Figure 1) and were equivalent in average LDL-C lowering (mean of weeks 10 and 12), resulting in -72% to -57% from baseline compared with placebo (Figure 2). Treatment with Repatha resulted in a similar reduction of LDL-C when used alone or in combination with other lipid-lowering therapies (Figure 2). The effect of LDL-C lowering is sustained.

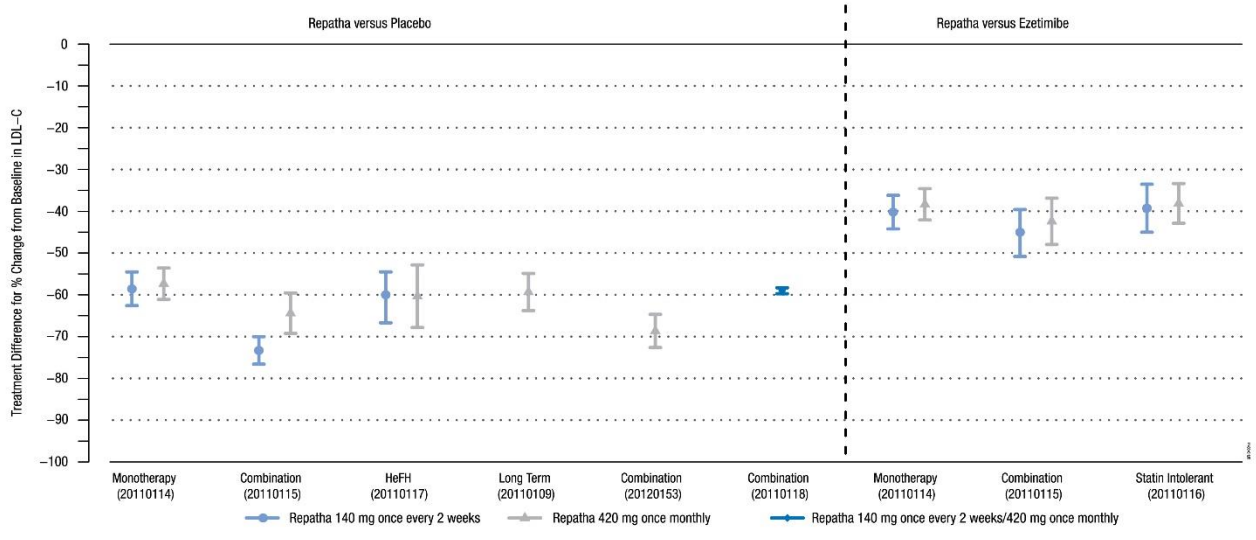
Doses of 140 mg subcutaneously every 2 weeks and 420 mg subcutaneously once monthly achieve approximately 80% of the theoretical maximal reduction in calculated LDL-C at the mean of weeks 10 and 12 based on exposure response models. Intrinsic and extrinsic covariates, such as demographics, co-medications, laboratory variables, and disease states, are not expected to modify the LDL-C response (see Section 4.2).

Figure 1. Effect of Repatha 140 mg Subcutaneously Every 2 Weeks or 420 mg Subcutaneously Once Monthly on LDL-C



Vertical lines represent median values of calculated LDL-C with 25th and 75th percentiles.

Figure 2. Effect of Repatha on LDL-C in the Repatha Phase 3 Studies – Mean LDL-C Percent Change from Baseline



Vertical lines represent the 95% confidence interval around the mean differences of Repatha compared with control.
Least squares means from repeated measures model and associated 95% confidence intervals. Week 12 for all studies except 20110109 at week 52, 20120153 at week 78 and 20110118 at week 48. Results for Study 20110115 are from the random effects meta-analysis.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of Repatha has been evaluated using an electrochemiluminescent bridging screening immunoassay for the detection of binding anti-evolocumab antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralising antibodies.

In clinical studies, 48 patients (0.3%) out of 17,992 patients treated with at least one dose of Repatha tested positive for the development of anti-evolocumab binding antibodies. 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 Repatha.

The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to evolocumab with the incidence of antibodies to other products may be misleading.

Clinical efficacy

Prevention of Cardiovascular Events

FOURIER was a phase 3, double-blind, randomized, 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 ≥ 1.8 mmol/L or non-HDL-C values ≥ 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, ACE inhibitors, or angiotensin receptor blockers.

A total of 27,564 patients were randomized 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 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, hospitalization for unstable angina, or coronary revascularization, 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 1, Figure 3 and Figure 4 below:

Table 1 Treatment Effects of Repatha Compared with Placebo in Patients with Established Cardiovascular Disease

	Placebo (N = 13780) n (%)	Repatha (N = 13784) n (%)	Hazard Ratio (95% CI)	p-value
Primary endpoint	1563 (11.34)	1344 (9.75)	0.85 (0.79, 0.92)	<0.0001[a]
Key secondary endpoint	1013 (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	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 prespecified endpoint; an ad-hoc analysis was performed to ensure results are provided for each individual component of the primary endpoint.

Figure 3. Cumulative Incidence Estimates for the Primary Composite Endpoint

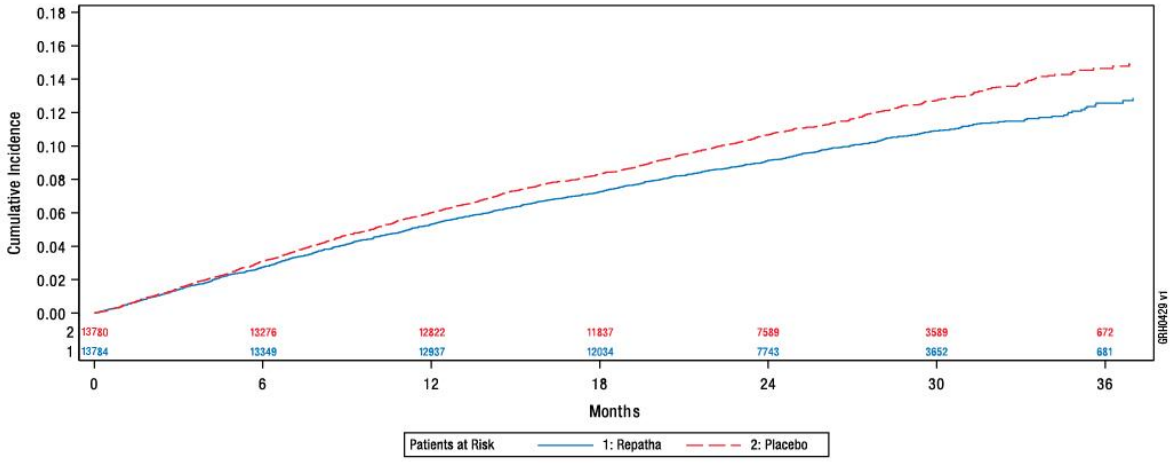
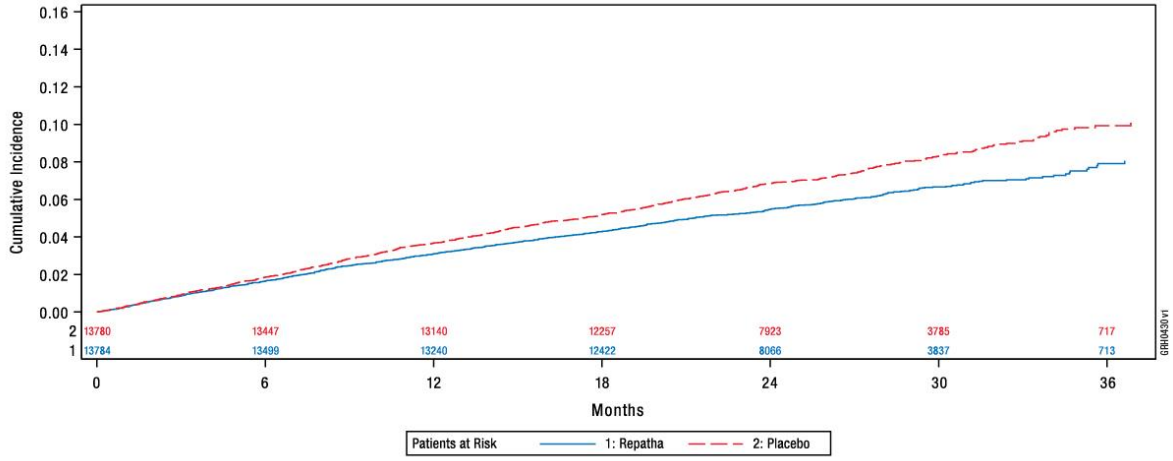


Figure 4. Cumulative Incidence Estimates for the Key Secondary Composite Endpoint



The Kaplan-Meier curves for the primary and key secondary composite endpoints separated at approximately five 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 three years. Corresponding median (Q1, Q3) LDL-C concentrations ranged from 0.7 (0.5, 1.1) mmol/L to 0.9 (0.5, 1.7) mmol/L in the Repatha group and 25% of patients achieved a LDL-C concentration < 0.5 mmol/L.

Of the patients treated with Repatha, 9518 achieved at least one LDL-C value < 0.6 mmol/L. 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 ≥ 1.0 mmol/L. 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 1974 patients with established cardiovascular disease enrolled in the FOURIER study, evolocumab was non-inferior to placebo for effects on the cognitive domain of executive function and other cognitive domains, assessed by the CANTAB Spatial Working Memory strategy index of executive function. There was no evidence that Repatha had a detrimental effect on cognitive domains based on the analysis of data from 1204 patients (586 Repatha, 618 placebo).

Regression of Atherosclerosis

GLAGOV was a phase 3, double-blind, randomised, placebo-controlled study to evaluate the effects of Repatha treatment on coronary atherosclerotic disease as measured by intravascular ultrasound (IVUS).

Enrolled patients were required to be on a stable background lipid-lowering therapy and to have a LDL-C ≥ 2.1 mmol/L or LDL-C ≥ of 1.6 to < 2.1 mmol/L with one major or three minor cardiovascular risk factors. These patients had coronary artery disease and required coronary angiography.

A total of 970 patients were randomised 1:1 into two treatment groups to either receive Repatha 420 mg once monthly or placebo once monthly as subcutaneous injections for 76 weeks. IVUS was performed at baseline and at week 78. A total of 27.8% of patients were female and 93.8% were white. The mean (SD) age was 59.8 (9.2) years. The mean (SD) LDL-C at baseline was 2.4 (0.7) mmol/L.

Repatha reduced the percent atheroma volume (PAV) and total atheroma volume (TAV) from baseline to week 78 compared to placebo. Atherosclerosis regression, defined as any reduction in PAV or TAV at week 78, was observed in more patients treated with Repatha than patients treated with placebo. The results of the study are shown in Table 2 below.

Table 2. Treatment Effects of Repatha Compared with Placebo in Patients with Hypercholesterolaemia– Change in Percent Atheroma Volume and Total Atheroma Volume from Baseline to Week 78

Endpoint	Summary type	Placebo QM (N = 423)	Repatha 420 mg QM (N = 423)	Treatment Difference (Repatha – Placebo)
Change in PAV (%)[a]	Adjusted Mean (95% CI)	0.05 (-0.32, 0.42)	-0.95 (-1.33, -0.58)	-1.01[c] (-1.38, -0.64)
Change in TAV (mm^3)[b]	Adjusted Mean (95% CI)	-0.91 (-3.29, 1.47)	-5.80 (-8.19, -3.41)	-4.89[c] (-7.25, -2.53)
Regression in PAV [b]	n (%) (95% CI)	200 (47.3) (42.6, 52.0)	272 (64.3) (59.6, 68.7)	17.0[c] (10.3, 23.5)
Regression in TAV [b]	n (%) (95% CI)	207 (48.9) (44.2, 53.7)	260 (61.5) (56.7, 66.0)	12.5[d] (5.8, 19.1)

QM = once monthly
[a] Primary Endpoint
[b] Secondary Endpoint
[c] p-value <0.0001
[d] p-value = 0.0002

The treatment difference in LDL-C reduction between Repatha and placebo was 68.7% (95% CI: 64.7%, 72.7%) from baseline to week 78. These reductions were maintained through the end of the study. Corresponding mean (SD) LDL-C concentrations at week 78 were 0.8 (0.7) mmol/L in the Repatha group.

Based on an ad-hoc analysis, lower LDL-C concentrations achieved during the study were associated with greater atherosclerosis regression, as measured by a reduction in PAV.

Hypercholesterolaemia

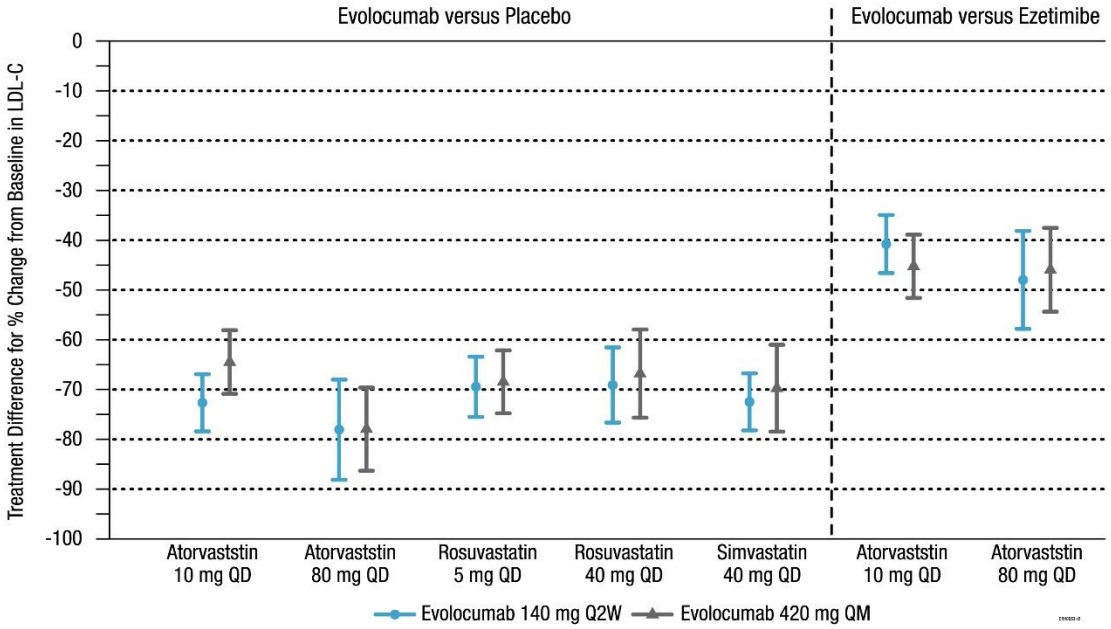
Combination with Statin or Statin with Other Lipid-Lowering Therapies

LAPLACE-2 was an international, multicentre, double-blind, double-dummy randomised, 12-week study of Repatha in 1896 patients with hypercholesterolaemia who were randomised to receive Repatha in combination with statins (rosuvastatin, simvastatin or atorvastatin). Repatha was compared with placebo for the rosuvastatin and simvastatin groups and compared with placebo and ezetimibe for the atorvastatin group.

In LAPLACE-2, Repatha exhibited consistent treatment effects of lowering LDL-C and improving other lipid parameters across all statins and statin doses that were evaluated.

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 ($p < 0.001$) (Figure 5). 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 ($p < 0.001$).

Figure 5. Effect of Repatha on LDL-C When Combined with Statins – Mean LDL-C Percent Change from Baseline of Weeks 10 and 12*



*All differences compared with placebo and ezetimibe are statistically significant ($p < 0.001$)
Vertical lines represent the 95% confidence interval around the mean differences of Repatha compared with control.

In a pre-specified analysis of LAPLACE-2, Repatha significantly reduced LDL-C, 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 for the combined rosuvastatin, simvastatin and atorvastatin groups ($p < 0.001$) (Table 3). Consistent treatment effects were observed in an analysis of Repatha compared with ezetimibe for the combined atorvastatin treatment groups (Table 4).

RUTHERFORD-2 was an international, multicentre, double-blind, randomised, placebo-controlled, 12-week study of Repatha in 329 patients with heterozygous familial hypercholesterolaemia (HeFH) 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 ($p < 0.05$) (Table 3).

Statin-intolerant Therapy

GAUSS-2 was an international, multicentre, double-blind, randomised, ezetimibe-controlled, 12-week study of Repatha 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 4).

Table 3. Treatment Effects of Repatha Compared with Placebo in Patients with Hypercholesterolaemia – 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 (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)	-23[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, HeFH = Heterozygous familial hypercholesterolaemia;
[a] p value < 0.05 when compared with placebo; [b] p value < 0.001 when compared with placebo

Table 4. Treatment Effects of Repatha Compared with Ezetimibe in Patients with Hypercholesterolaemia – 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 (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
[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

Monotherapy

MENDEL-2 was an international, multicentre, double-blind, randomised, placebo and ezetimibe-controlled, 12-week study of Repatha in 614 patients with hypercholesterolaemia. 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 ($p<0.001$) (Table 3 and Table 4).

Long-term Efficacy in Hypercholesterolaemia

DESCARTES was an international, multicentre, double-blind, randomised, placebo-controlled, 52-week study of Repatha in 901 patients with hypercholesterolaemia 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 (Figure 6). 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 420 mg once monthly 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 5).

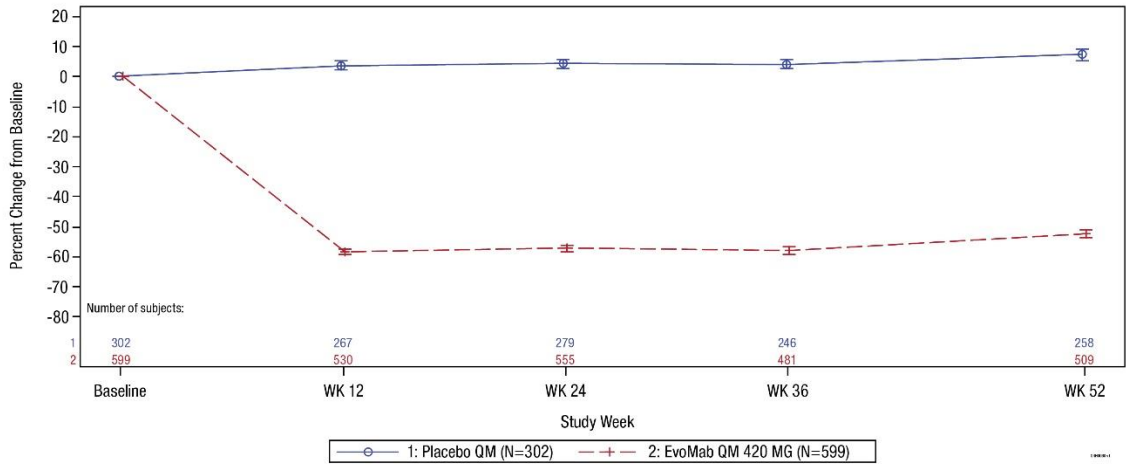
Table 5. Treatment Effects of Repatha Compared with Placebo in Patients with Hypercholesterolaemia – Mean Percent Change from Baseline to Week 52 (%, 95% CI)

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 (hypercholesterolaemia)	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

Figure 6. Effect of Repatha 420 mg Subcutaneously Once Monthly on LDL-C in Patients with Hypercholesterolaemia – Mean Percent Change from Baseline by Scheduled Visit and Treatment Group (DESCARTES)

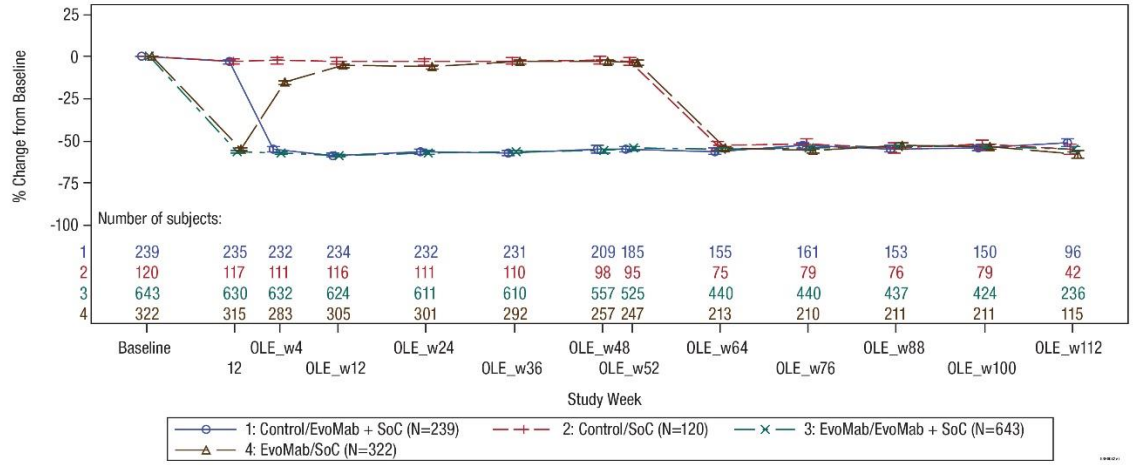


DESCARTES - Full Analysis Set
N = number of patients randomised and dosed in the full analysis set;
EvoMab = Evolocumab; WK = week; QM = once monthly (subcutaneous); MG = milligrams
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.

OSLER-1 is an ongoing multicentre, randomised, controlled, open-label, 5-year extension study to assess the long-term safety and efficacy of Repatha in patients with hypercholesterolaemia. A total of 1324 patients who completed treatment in 1 of 5 parent (Phase 2) studies enrolled in the study. Patients were randomised 2:1 to receive either Repatha 420 mg once monthly plus standard of care (evolocumab group) or standard of care alone (control group) for the first year of the study (year 1). Year 1 of the study was controlled. At the end of the first year, patients entered the all evolocumab period (year 2+) in which all patients received open-label Repatha for up to an additional 4 years approximately. 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 124 weeks as demonstrated by a reduction in LDL-C from week 12 in the parent study to week 112 in the open-label extension (Figure 7). 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 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-1 without evidence of rebound (Figure 7).

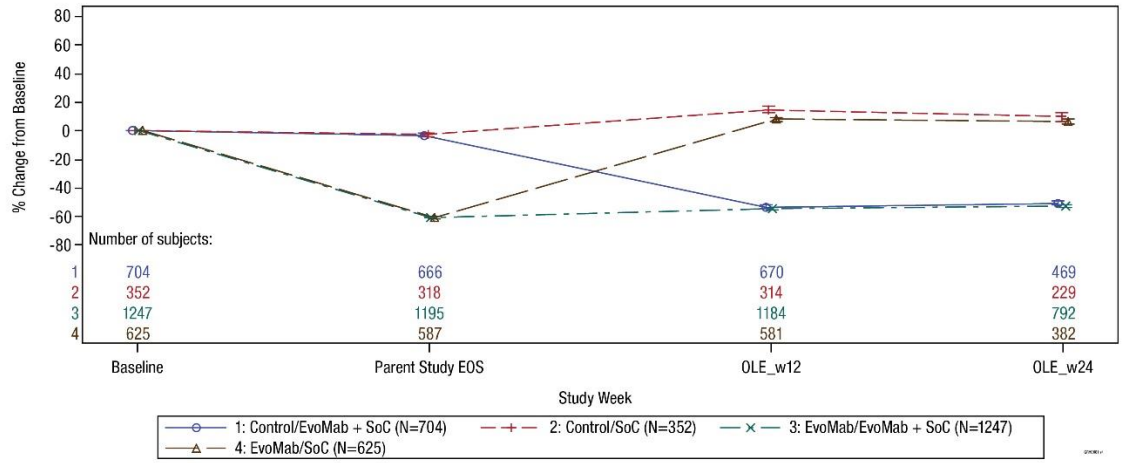
Figure 7. Effect of Repatha on LDL-C in Patients with Hypercholesterolaemia – Mean Percent Change from Baseline by Scheduled Visit and Treatment Group in the SoC-Controlled Period (OSLER-1)



OSLER-1 - Interim SoC-Controlled Period Analysis Set and Interim All-IP Period Analysis Set
N = number of patients that were randomised in Study 7; EvoMab = Evolocumab; SoC = standard of care; OLE = open-label extension.
OLE visits prior to or on OLE_w52 are under SoC-Controlled period and OLE visits after OLE_w52 are under all-IP period. All patients continued or started receiving EvoMab + SOC during all-IP period.
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.
Baseline is defined as the parent study baseline.

OSLER-2 was a multicentre, randomised, controlled, open-label, 2-year extension study designed to assess the long-term safety and efficacy of Repatha in patients with hypercholesterolaemia. A total of 2928 patients who completed treatment in 1 of 7 parent (Phase 3) studies enrolled in the 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 (year 1). Year 1 of the study was controlled. At the end of the first year, patients entered the all evolocumab period (year 2) in which all patients received open-label Repatha for a year. Repatha significantly reduced LDL-C from baseline at week 12 compared with control (nominal $p < 0.001$). Treatment effects were maintained as demonstrated by a reduction in LDL-C from week 12 to week 24 in the open-label extension (Figure 8). 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 24 compared with placebo (nominal $p < 0.001$). LDL-C and other lipid parameters returned to baseline within 12 weeks after discontinuation of Repatha without evidence of rebound (Figure 8).

Figure 8. Effect of Repatha on LDL-C in Patients with Hypercholesterolaemia – Mean Percent Change from Baseline by Scheduled Visit and Treatment Group in the SoC-Controlled Period (OSLER-2)



OSLER-2 - Interim SoC-Controlled Period Analysis Set
N = number of subjects that were randomised in Study 8 and have at least 12 weeks of potential follow-up; EvoMab = Evolocumab; SoC = standard of care; OLE = Open-label extension.
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.
Baseline is defined as the parent study baseline.

TAUSSIG is an ongoing multicentre, open-label 5-year extension study to assess the long-term safety and efficacy of Repatha in patients with severe familial hypercholesterolaemia (FH), including HoFH, who were treated with Repatha as an adjunct to other lipid-lowering therapies. A total of 102 severe FH patients and 96 HoFH patients enrolled in TAUSSIG. All patients in the study were initially treated with Repatha 420 mg once monthly except for those receiving apheresis at enrollment, 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 a reduction of LDL-C in patients with severe FH (Table 6). 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 FH.

Table 6. Effect of Repatha on LDL-C in Patients with Severe FH – Median Percent Change from Baseline to OLE Week 36

Patient Population (N)	OLE Week 12 (n=16)	OLE Week 24 (n=8)	OLE Week 36 (n=5)
Severe FH (N=102)	-47	-45	-48

OLE = open-label extension
N (n) = Number of evaluable patients (N) and patients with observed LDL values at specific schedule visit (n) in the Severe FH Interim Analysis Set

Homozygous Familial Hypercholesterolaemia

TESLA was an international, multicentre, double-blind, randomised, placebo-controlled 12-week study of Repatha in 49 HoFH patients between 12 to 65 years of age (including 10 adolescent patients) evaluated for their response to 420 mg once monthly as an adjunct to other lipid-lowering therapies (e.g., statins, bile-acid sequestrants). Repatha 420 mg once monthly significantly reduced LDL-C and ApoB at week 12 compared with placebo ($p < 0.001$) (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 HoFH.

Table 7. Treatment Effects of Repatha 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)

[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 in patients with HoFH (overall, non-apheresis, apheresis) (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 HoFH. Reductions in LDL-C and changes in other lipid parameters in 13 adolescent patients (12 to < 18 years of age) with HoFH were comparable to those in the overall HoFH study population.

Table 8. Effect of Repatha on LDL-C in Patients with Homozygous Familial Hypercholesterolaemia – Mean Percent Change from Baseline to OLE Week 36

Patient Population (N)	OLE Week 12	OLE Week 24	OLE Week 36
HoFH (N=96)	-20 (n=70)	-23 (n=46)	-24 (n=30)
Non-apheresis (N=65)	-22 (n=46)	-24 (n=33)	-24 (n=27)
Apheresis (N=31)	-17 (n=24)	-20 (n=13)	-21 (n=3)

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 Interim Analysis Set (overall, non-apheresis, and apheresis)

Paediatric population

The safety and effectiveness of Repatha have not been established in paediatric patients with hypercholesterolaemia. Fourteen adolescent patients aged 12 years and over have been included in HoFH clinical studies. No overall differences in safety or efficacy were observed between adolescent and adult patients with HoFH.

5.2 Pharmacokinetic properties

Absorption and Distribution

Following a single subcutaneous dose of 140 mg or 420 mg Repatha administered to healthy adults, median peak serum concentrations were attained in 3 to 4 days and estimated absolute bioavailability was 72%. Administration of the 140 mg dose resulted in a C_{max} mean (SD) of 18.6 (7.3) µg/mL and AUC_{last} mean (SD) of 188 (98.6) day•µg/mL. Administration of the 420 mg dose resulted in a C_{max} mean (SD) of 59.0 (17.2) µg/mL and AUC_{last} mean (SD) of 924 (346) day•µg/mL.

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

Biotransformation and Elimination

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

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

As a fully human IgG2 antibody, the clearance of Repatha is mediated by specific binding and complex formation with its target ligand, PCSK9, as well as by typical IgG clearance processes in the reticuloendothelial system (RES). Repatha is expected to be degraded into small peptides and amino acids via these catabolic pathways.

An approximately 20% increase in the clearance of Repatha was observed in patients co-administered with statins. This increased clearance is in part mediated by statins increasing the concentration of PCSK9 which did not adversely impact the pharmacodynamic effect of Repatha on lipids. Population pharmacokinetic analysis

indicated no appreciable differences in evolocumab serum concentrations in hypercholesterolemic patients (non-FH or FH) taking concomitant statins (see Section 4.5).

Special population

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

Renal Impairment

Population pharmacokinetic analysis of integrated data from the Repatha clinical studies did not reveal a difference in pharmacokinetics in patients with mild or moderate renal impairment relative to non-renally impaired patients.

Single 140 mg subcutaneous doses of Repatha were studied in 6 patients with normal renal function (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m^2), 6 patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), and 6 patients with end stage renal disease (ESRD) receiving haemodialysis. The mean evolocumab exposure, as assessed by C_{max}, was found to be approximately 30% to 45% lower in patients with severe renal impairment and ESRD compared with patients with normal renal function. The median t_{max} was similar across all groups. The pharmacodynamics and safety of Repatha 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 to moderate hepatic impairment (Child-Pugh A or B). Single 140 mg subcutaneous doses of Repatha 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 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 subjects. This resulted in similar time course and extent of absolute LDL-C lowering. Patients with severe hepatic impairment (Child-Pugh C) have not been studied.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of Repatha was evaluated in a lifetime study conducted in the hamster at dose levels up to 100 mg/kg every 2 weeks (AUC exposure 15-fold higher than in patients receiving Repatha at 420 mg once monthly). There were no evolocumab-related tumours. Expected serum LDL-C lowering was observed throughout the study. The mutagenic potential of Repatha has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

In hamsters, there was no effect on male or female fertility (including estrous cycling, sperm analysis, mating performance, and embryonic development) when evolocumab was administered at dose levels up to 100 mg/kg every 2 weeks (AUC exposure estimate 15-fold higher than in patients receiving Repatha at 420 mg once monthly). In sexually mature cynomolgus monkeys, no effects were observed on reproductive organ histopathology, menstrual cycling, or sperm parameters following administration of evolocumab at dose levels up to 300 mg/kg QW for 6 months (AUC exposure up to 300-fold higher than in patients receiving Repatha at 420 mg once monthly).

Animal Toxicology

No adverse effects were observed in hamsters and cynomolgus monkeys administered evolocumab at dose levels up to 300 mg/kg QW for up to 3 and 6 months, respectively (AUC exposure 46- and 300-fold higher than in patients receiving Repatha at 420 mg once monthly). The intended pharmacological effect of decreased serum LDL-C and TC was observed in these studies and was reversible upon cessation of treatment.

No adverse effects were observed when evolocumab (up to 100 mg/kg every 2 weeks; AUC exposure 21-fold higher than in patients receiving Repatha at 420 mg once monthly) was dosed in combination with rosuvastatin (5 mg/kg once daily) to cynomolgus monkeys for 3 months. Reductions in serum LDL-C and TC 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

Water for Injection (USP)

Sodium hydroxide for adjusting pH

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store refrigerated at 2°C to 8°C in the original carton. If removed from the refrigerator, Repatha should be kept at controlled room temperature (up to 25°C) in the original carton and must be used within 30 days. Protect Repatha from direct light and do not expose to temperatures above 25°C. Do not freeze. Do not shake.

6.5 Nature and contents of container

The needle cover of the glass pre-filled syringe and the pre-filled pen is made from dry natural rubber (a derivative of latex).

Repatha is provided as a:

1 mL solution (140 mg/mL evolocumab) in a single use pre-filled syringe made from type I glass with stainless steel needle, supplied as a 1-pack.

1 mL solution (140 mg/mL evolocumab) in a single use pre-filled pen with type 1 glass syringe and stainless steel needle; supplied as a 1-pack, 2-pack, and 3-pack.

6.6 Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Amgen (New Zealand) Limited

Level 22, PwC Tower

15 Customs Street West

Auckland, New Zealand

Telephone: 0800 443 885

Email: medinfo.JAPAC@amgen.com

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 13 June 2019

10. DATE OF REVISION OF THE TEXT

27 June 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 4.8	Addition of Headache under Post Marketing Experience