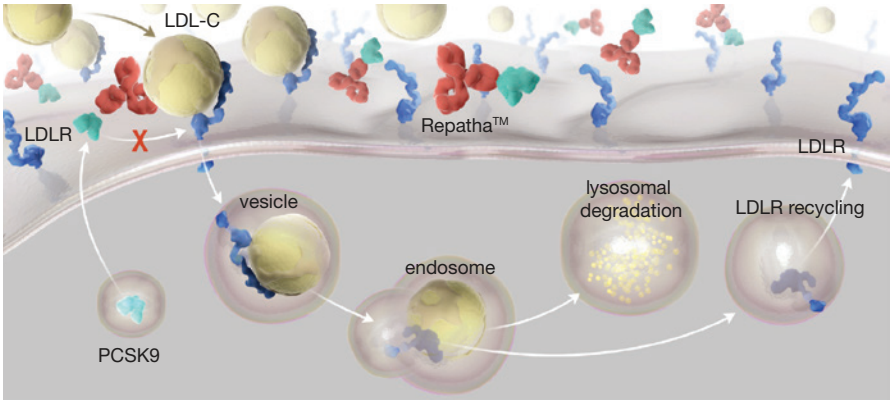
Repatha® (evolocumab) Clinical Fact Sheet

Indication[1]

Repatha® is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated:

- To reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization in adults with established cardiovascular (CV) disease.
- As an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C).
- As an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

The safety and effectiveness of Repatha® have not been established in pediatric patients with HoFH who are younger than 13 years old or in pediatric patients with primary hyperlipidemia or HeFH.



Repatha® Mechanism of Action. Repatha®, a human monoclonal Ab (mAb) directed against PCSK9, binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDL receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. The increased number of LDLRs available to clear LDL from the blood results in lower LDL-C levels.[1-5]

Repatha® Clinical Trial Summaries:[1]

Prevention of CV events in patients with established CV disease

FOURIER was a double-blind, randomized, placebo-controlled, event-driven trial in 27,564 adult patients with established CV disease and with LDL-C ≥ 70 mg/dL and/or non-HDL-C ≥ 100 mg/dL despite high- (69%) or moderate-intensity (30%) statin therapy. Patients received either subcutaneous injections of Repatha® (140 mg every 2 weeks or 420 mg once monthly) or placebo.

Table 1: Key Baseline Characteristics in FOURIER

Mean Age	63 years (45% ≥ 65); 25% women
History of CV Disease	81% with prior MI, 19% prior non-hemorrhagic stroke, and 13% had symptomatic PAD
Additional CV Risk Factors	80% HTN; 36% DM-2; 28% smokers; 23% HF; and 6% eGFR < 60 mL/min per 1.73 m^2
Background CV Therapies	93% anti-platelet agents; 76% beta blockers; 56% ACEi, or 23% ARB
LDL-C Level	Median: 92 mg/dL; Mean 98 mg/dL

The difference between Repatha® and placebo in mean % change in LDL-C from baseline was -63% at week 12 and -57% at week 72. At week 48, the median LDL-C was 26 mg/dL in the Repatha® group.

Repatha® significantly reduced the risk for the primary composite endpoint (time to first occurrence of CV death, MI, stroke, hospitalization for unstable angina (UA), or coronary revascularization; $p < 0.0001$) and the key secondary composite endpoint (time to first occurrence of CV death, MI, or stroke; $p < 0.0001$). The Kaplan-Meier estimates of the cumulative incidence of the primary and key secondary composite endpoints over time are shown in Figure 1 and 2 below.

Considering all assessments, among the patients treated with Repatha®, 10,401 (76%) had at least one LDL-C value < 25 mg/dL. Although not a randomized comparison, the safety profile was similar between Repatha®-treated patients with post-baseline LDL-C < 25 mg/dL compared with Repatha®-treated patients with higher post-baseline LDL-C (LDL-C ≥ 40 mg/dL).

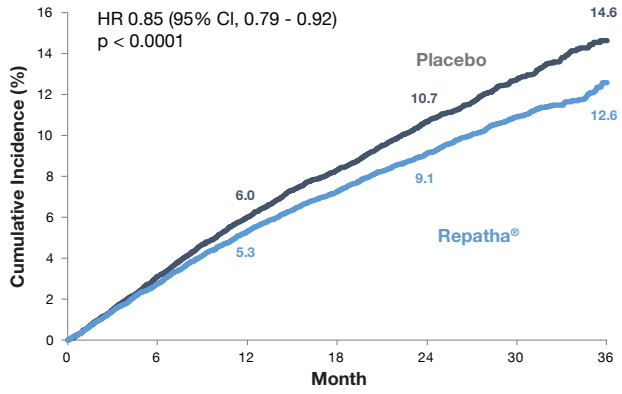


Figure 1: Key Primary Endpoint Kaplan-Meier Curve

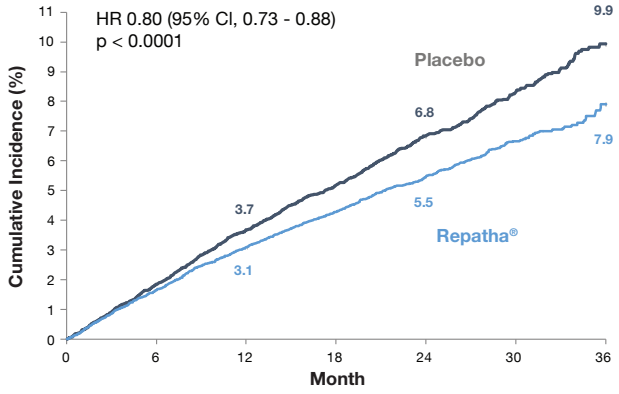


Figure 2: Key Secondary Endpoint Kaplan-Meier Curve

IMPORTANT SAFETY INFORMATION[1]

- Repatha® is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha®. Hypersensitivity reactions (e.g., rash, urticaria) have been reported in patients treated with Repatha®, including some that led to discontinuation of therapy.

HTN = hypertension; DM-2 = diabetes mellitus type 2; HF = heart failure; eGFR = estimated glomerular filtration rate; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blockers.

Please see additional Important Safety Information on the reverse.

Repatha® (evolocumab) Clinical Fact Sheet

Repatha Clinical Trial Summaries (continued)

Primary Hyperlipidemia (Including HeFH)[1]

LAPLACE-2 (N = 1,896)

- 12-week RCT in which patients with primary hyperlipidemia received Repatha®, placebo, or ezetimibe as add-on therapy to daily doses of statins (atorvastatin, rosuvastatin, or simvastatin)
- Mean baseline LDL-C ranged from 77-127 mg/dL
- Compared to placebo, mean % change in LDL-C from baseline to week 12 was -71% (140 mg every 2 weeks) and -63% (420 mg once monthly)
- Compared to ezetimibe, mean % change in LDL-C from baseline to Week 12 was -45% (140 mg every 2 weeks) and -41% (420 mg once monthly)

DESCARTES (N = 901)

- 52-week RCT in which patients with primary hyperlipidemia received Repatha® 420 mg once monthly or placebo in addition to cholesterol-lowering regimens of diet alone, atoravastin (10 or 80 mg), or atorvastatin 80 mg with ezetimibe
- Mean baseline LDL-C ranged from 90-117 mg/dL across treatment groups
- Compared to placebo, mean % change from baseline to week 52 was -55% for LDL-C, and -46% for non–HDL-C

MENDEL-2 (N = 614)

- 12-week RCT comparing Repatha, ezetimibe, or placebo in patients who were not receiving lipid-lowering therapy at baseline
- Patients with primary hyperlipidemia not taking lipid-lowering therapy at baseline were randomized to Repatha® 140 mg every 2 weeks, 420 mg once monthly or placebo for 12 weeks
- Mean baseline LDL-C was 143 mg/dL
- Compared to placebo, the mean % change in LDL-C from baseline to week 12 was -55% (140 mg every 2 weeks) and -57% (420 mg once monthly)
- Compared to ezetimibe, mean % change in LDL-C from baseline to Week 12 was -37% (140 mg every 2 weeks) and -38% (420 mg once monthly)

RUTHERFORD-2 (N = 329)

- 12-week RCT comparing Repatha® and placebo in patients with HeFH who were receiving statins +/- other lipid-lowering therapies
- Mean baseline LDL-C was 156 mg/dL with 76% of the patients on high-intensity statin therapy
- Compared to placebo, mean % change from baseline to week 12 in: LDL-C was -61% (140 mg every 2 weeks) and -60% (420 mg once monthly); non–HDL-C was -54% (140 mg every 2 weeks) and -53% (420 mg once monthly)

Homozygous Familial Hypercholesterolemia (HoFH)[1]

TESLA (N = 49)

- 12-week RCT comparing Repatha® 420 mg once monthly and placebo in patients with HoFH (not receiving lipid apheresis) who were on additional lipid-lowering therapies
- The mean LDL-C at baseline was 349 mg/dL with all patients on statins (atorvastatin or rosuvastatin) and 92% on ezetimibe
- Compared to placebo, mean % change from baseline to week 12 in LDL-C was -31%, and in non–HDL-C was -28%
- Patients known to have two LDL receptor negative alleles (little to no residual function) did not respond to Repatha®

2017 American College of Cardiology Expert Consensus Decision Pathway: Select Patient Populations Considered for PCSK9 Inhibitors[6]

Adults ≥ 21 years of age	with clinical atherosclerotic cardiovascular disease (ASCVD), on statin
	with baseline LDL-C ≥ 190 mg/dL (not due to secondary modifiable causes), on statin

Factors to consider for treatment: adherence to lifestyle, statin intolerance, control of other risk factors, clinician-patient discussion regarding potential benefits/potential harms, and patient preferences regarding addition of non-statin medications, percentage LDL-C reduction (may consider absolute LDL-C or non-HDL-C level achieved), monitoring of response to therapy, adherence, and lifestyle

IMPORTANT SAFETY INFORMATION[1]

Contraindication: Repatha® is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha®.

Allergic reactions: Hypersensitivity reactions (e.g. rash, urticaria) have been reported in patients treated with Repatha®, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with Repatha®, treat according to the standard of care, and monitor until signs and symptoms resolve.

Adverse Reactions in Primary Hyperlipidemia, including HeFH: The most common adverse reactions (> 5% of Repatha®-treated patients and occurring more frequently than placebo) in clinical trials in primary hyperlipidemia (including HeFH) were: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

In a 52-week trial, adverse reactions led to discontinuation of treatment in 2.2% of Repatha®-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to Repatha® treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% versus 0% for Repatha® and placebo, respectively).

From a pool of the 52-week trial and seven 12-week trials: Local injection site reactions occurred in 3.2% and 3.0% of Repatha®-treated and placebo-treated patients, respectively. The most common injection site reactions were erythema, pain, and bruising. The proportions of patients who discontinued treatment due to local injection site reactions in Repatha®-treated patients and placebo-treated patients were 0.1% and 0%, respectively.

Allergic reactions occurred in 5.1% and 4.7% of Repatha®-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% versus 0.5% for Repatha® and placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%).

Adverse reactions in the Cardiovascular Outcomes trial: The safety profile of Repatha® in this trial was generally consistent with the safety profile described above in the 12- and 52-week controlled trials involving patients with primary hyperlipidemia (including HeFH). Serious adverse events occurred in 24.8% and 24.7% of Repatha®-treated and placebo-treated patients, respectively. Adverse events led to discontinuation of study treatment in 4.4% of patients assigned to Repatha® and 4.2% assigned to placebo. Common adverse reactions (>5% of patients treated with Repatha® and occurring more frequently than placebo) included diabetes mellitus (8.8% Repatha®, 8.2% placebo), nasopharyngitis (7.8% Repatha®, 7.4% placebo), and upper respiratory tract infection (5.1% Repatha®, 4.8% placebo).

Among the 16,676 patients without diabetes mellitus at baseline, the incidence of new-onset diabetes mellitus during the trial was 8.1% in patients assigned to Repatha® compared with 7.7% in those assigned to placebo.

Adverse Reactions in Homozygous familial hypercholesterolemia (HoFH): In 49 patients with HoFH studied in a 12-week, double-blind, randomized, placebo-controlled trial, 33 patients received 420 mg of Repatha® subcutaneously once monthly. The adverse reactions that occurred in at least two (6.1%) Repatha®-treated patients, and more frequently than in placebo-treated patients, included upper respiratory tract infection (9.1% versus 6.3%), influenza (9.1% versus 0%), gastroenteritis (6.1% versus 0%), and nasopharyngitis (6.1% versus 0%).

Immunogenicity: Repatha® is a human monoclonal antibody. As with all therapeutic proteins, there is a potential for immunogenicity with Repatha®.

REFERENCES

1. Repatha® (evolocumab) Prescribing Information, Amgen. **2.** Kwon HJ, et al. *Proc Natl Acad Sci U S A*. 2008;105:1820-1825. **3.** Nassoury N, et al. *Traffic*. 2007;8:718-732. **4.** McNutt MC, et al. *J Biol Chem*. 2009;284:10561-10570. **5.** Chan JC, et al. *Proc Natl Acad Sci U S A*. 2009;106:9820-9825. **6.** Lloyd-Jones MS, et al. *J Am Coll Cardiol*. 2017;70:1785-1822.

Please see full Prescribing Information for Repatha®.

USA-145-057009