This article was sponsored by Amgen Inc.

Clinical Review of a PCSK9 Inhibitor in Cardiovascular Disease

Atherosclerotic cardiovascular disease (ASCVD) is associated with increased risk of secondary cardiovascular (CV) events, such as myocardial infarction (MI), stroke, and CV-related death.[1] More than 25 years of evidence supports the linear relationship between the reduction of low-density lipoprotein cholesterol (LDL-C) and reduction in CV risk.[2]

The American College of Cardiology and the American Heart Association have jointly issued guidelines on the management of blood cholesterol. High-intensity statin therapy or maximally tolerated statin therapy is recommended for patients with clinical ASCVD.[3] Nonstatin medications, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, are considered for very high-risk ASCVD patients with elevated LDL-C (≥70 mg/dL) despite maximally tolerated statin therapy.[3] Very high-risk ASCVD patients includes those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.[3] Additionally, patients who are unable to tolerate statin therapy because of adverse effects, such as statin-associated muscle symptoms, may benefit from a nonstatin medication.[3]

PCSK9 INHIBITION WITH REPATHA® (EVOLOCUMAB)

Repatha® is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia, to reduce LDL-C.[4] In adults with established CV disease, Repatha® is indicated to reduce the risk of MI, stroke, and coronary revascularization.[4]

Mechanism of Action

Repatha® is a human monoclonal immunoglobulin G2 directed against human PCSK9. Repatha® binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDL-C receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. Repatha® increases the number of LDLRs available to clear LDL-C from the blood, thereby lowering LDL-C levels.[4]

CLINICAL EFFICACY AND SAFETY OF REPATHA®

The Repatha® CV outcomes study (FOURIER) was a multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate CV risk reduction by dramatically lowering LDL-C in high-risk patients with established CVD, including patients with prior MI, prior stroke, or symptomatic peripheral arterial disease, with LDL-C ≥70 mg/dL and/or non-HDL-C ≥100 mg/dL.[4,5] In addition to having background moderate- to high-intensity statin therapy, patients were randomized 1:1 to receive Repatha® 140 mg every 2 weeks or 420 mg once a month (n = 13,784) or placebo (n = 13,780); the median follow-up duration was 2.2 years.[4,5]

Reduction in the Risk of CV Events

In the Repatha® CV Outcomes Study, high-risk patients with established CVD treated with Repatha® achieved significant reduction in the risk of the primary composite end point of time to CV

IMPORTANT SAFETY INFORMATION

- **Contraindication:** Repatha® is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha®. Serious hypersensitivity reactions including angioedema have occurred in patients treated with Repatha®.
- **Allergic Reactions:** Hypersensitivity reactions (e.g. angioedema, 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 patients treated with Repatha® and occurring more frequently than placebo) were: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

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.

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 most common adverse reactions (>5% of patients treated with Repatha® and occurring more frequently than placebo) were: diabetes mellitus (8.8% Repatha®, 8.2% placebo), nasopharyngitis (7.8% Repatha®, 7.4% placebo), and upper

Please see additional Important Safety Information throughout.

death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (HR, 0.85; 95% CI, 0.79-0.92; *P* <0.0001).[4,5] Repatha® demonstrated significant reduction in the risk of the key secondary composite end point of time to CV death, MI, or stroke by 20% compared with placebo (HR, 0.80; 95% Cl, 0.73-0.88; *P* <0.0001), and the benefit improved over time in the study.[4,5] The observed HR for CV death was 1.05 (95% CI, 0.88-1.25) and for hospitalizations due to unstable angina was 0.99 (95% CI, 0.82-1.18).[4]

LDL-C Reduction

In the Repatha® CV Outcomes Study, at Week 12, Repatha® added to a statin demonstrated a 63% reduction in LDL-C (95% CI, 62-63) and 59% at Week 48 (95% CI, 58-60; *P* <0.001).[4,5] Nearly 90% of patients treated with Repatha® added to a statin achieved LDL-C levels of 70 mg/dL or lower compared with 18% of patients in the placebo group (*P* <0.001) at Week 48.[5]

Safety

In the Repatha® CV Outcomes Study, adverse reactions that occurred in more than 5% of patients treated with Repatha® and more frequently than with placebo included diabetes mellitus, nasopharyngitis, and upper respiratory tract infection.[4] In EBBINGHAUS, a substudy of 1974 patients enrolled in the FOURIER trial, Repatha® was noninferior to placebo on selected cognitive function domains as assessed with the use of neuropsychological function tests over a median follow-up of 19 months.[4]

ROLE OF THE PHARMACIST

As an integral part of the health care team, pharmacists are well suited to make interventions when it comes to gaps in care. For patients with established CVD with LDL-C levels ≥70 mg/dL despite maximally tolerated statin therapy, the risk of another cardiovascular event remains.[3] Pharmacists are able to recognize these types of patients and work with physicians to provide appropriate care.

Pharmacists play a key role in educating patients about the importance of medication adherence. They are able to explain to patients the importance of achieving low LDL-C levels in order to reduce the risk of a recurrent CV event.[3] In addition, pharmacists are able to guide patients to maintain a healthy lifestyle (eg, diet, physical activity, avoiding tobacco use) in conjunction with medication use.

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REPATHA® (evolocumab) injection, for subcutaneous use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information

1. INDICATIONS AND USAGE

1.1 Prevention of Cardiovascular Events

In adults with established cardiovascular disease, REPATHA® is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization.

1.2 Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia)

REPATHA is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).

1.3 Homozygous Familial Hypercholesterolemia

REPATHA is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

4. CONTRAINDICATIONS

REPATHA is contraindicated in patients with a history of a serious hypersensitivity reaction to REPATHA. Serious hypersensitivity reactions including angioedema have occurrred in patients treated with REPATHA *[see Warnings and Precautions (5.1)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

Hypersensitivity reactions (e.g., angioedema, 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 *[see Contraindications (4)]*.

6. ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the label:

• Allergic Reactions *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Adults with Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

The data described below reflect exposure to REPATHA in 8 placebo-controlled trials that included 2651 patients treated with REPATHA, including 557 exposed for 6 months and 515 exposed for 1 year (median treatment duration of 12 weeks). The mean age of the population was 57 years, 49% of the population were women, 85% White, 6% Black, 8% Asians, and 2% other races.

Adverse Reactions in a 52-Week Controlled Trial

In a 52-week, double-blind, randomized, placebo-controlled trial (Study 3 [DESCARTES, NCT01516879]), 599 patients received 420 mg of REPATHA subcutaneously once monthly *[see Clinical Studies (14.2)]*. The mean age was 56 years (range: 22 to 75 years), 23% were older than 65 years, 52% women, 80% White, 8% Black, 6% Asian; 6% identified as Hispanic ethnicity. Adverse reactions reported in at least 3% of REPATHA-treated patients, and more frequently than in placebo-treated patients in DESCARTES, are shown in Table 1. 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).

Table 1. Adverse Reactions Occurring in Greater than or Equal to 3% of REPATHA-treated Patients and More Frequently than with Placebo in DESCARTES

	Placebo (N=302) %	REPATHA (N=599) %
Nasopharyngitis	9.6	10.5
Upper respiratory tract infection	6.3	9.3
Influenza	6.3	7.5
Back pain	5.6	6.2
Injection site reactions*	5.0	5.7
Cough	3.6	4.5
Urinary tract infection	3.6	4.5
Sinusitis	3.0	4.2
Headache	3.6	4.0
Myalgia	3.0	4.0
Dizziness	2.6	3.7
Musculoskeletal pain	3.0	3.3
Hypertension	2.3	3.2
Diarrhea	2.6	3.0
Gastroenteritis	2.0	3.0

* includes erythema, pain, bruising

Adverse Reactions in Seven Pooled 12-Week Controlled Trials

In seven pooled 12-week, double-blind, randomized, placebo-controlled trials, 993 patients received 140 mg of REPATHA subcutaneously every 2 weeks and 1059 patients received 420 mg of REPATHA subcutaneously monthly. The mean age was 57 years (range: 18 to 80 years), 29% were older than 65 years, 49% women, 85% White, 5% Black, 9% Asian, and 5% identified as Hispanic ethnicity. Adverse reactions reported in at least 1% of REPATHA-treated patients, and more frequently than in placebo-treated patients, are shown in Table 2.

Table 2. Adverse Reactions Occurring in Greater than 1% of REPATHA-treated Patients and More Frequently than with Placebo in Pooled 12-Week Studies

	Placebo (N=1224) %	REPATHA† (N=2052) %
Nasopharyngitis	3.9	4.0
Back pain	2.2	2.3
Upper respiratory tract infection	2.0	2.1
Arthralgia	1.6	1.8
Nausea	1.2	1.8
Fatigue	1.0	1.6
Muscle spasms	1.2	1.3
Urinary tract infection	1.2	1.3
Cough	0.7	1.2
Influenza	1.1	1.2
Contusion	0.5	1.0

†140 mg every 2 weeks and 420 mg once monthly combined

Adverse Reactions in Eight Pooled Controlled Trials (Seven 12-Week Trials and One 52-Week Trial)

The adverse reactions described below are from a pool of the 52-week trial (DESCARTES) and seven 12-week trials. The mean and median exposure durations of REPATHA in this pool of eight trials were 20 weeks and 12 weeks, respectively.

Local Injection Site Reactions

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

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

In a double-blind, randomized, placebo-controlled cardiovascular outcomes trial (Study 1 [REPATHA Cardiovascular Outcomes Trial, FOURIER, NCT01764633]), 27,525 patients received at least one dose of REPATHA or placebo *[see Clinical Studies (14.1)]*. The mean age was 62.5 years (range: 40 to 86 years), 45% were 65 years or older, 9% were 75 years or older, 25% women, 85% White, 2% Black, and 10% Asian; 8% identified as Hispanic ethnicity. Patients were exposed to REPATHA or placebo for a median of 24.8 months; 91% of patients were exposed for ≥ 12 months, 54% were exposed for ≥ 24 months, and 5% were exposed for ≥ 36 months.

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 Patients with Homozygous Familial Hypercholesterolemia

In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH (Study 6 [TESLA, NCT01588496]), 33 patients received 420 mg of REPATHA subcutaneously once monthly *[see Clinical Studies (14.3)]*. The mean age was 31 years (range: 13 to 57 years), 49% were women, 90% White, 4% Asian, and 6% other. 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%)

• Nasopharyngitis (6.1% versus 0%)

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing 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 REPATHA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of REPATHA has been evaluated using an electrochemiluminescent bridging screening immunoassay for the detection of binding anti-drug antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies.

In a pool of placebo- and active-controlled clinical trials, 0.3% (48 out of 17,992) of patients treated with at least one dose of REPATHA tested positive for the development of binding antibodies. Patients whose sera tested positive for binding antibodies were further evaluated for neutralizing antibodies; none of the patients tested positive for neutralizing antibodies.

There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of REPATHA, but the long-term consequences of continuing REPATHA treatment in the presence of anti-drug binding antibodies are unknown.

6.3 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use of REPATHA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

• Allergic reactions: Angioedema

• Influenza-like illness

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to REPATHA during pregnancy.

Please contact 1-877-311-8972 or https://mothertobaby.org/ongoing-study/repatha/ to enroll in or to obtain information about the registry.

Risk Summary

There are no data available on use of REPATHA in pregnant women to inform a drug-associated risk. In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were subcutaneously administered evolocumab from organogenesis through parturition at dose exposures up to 12 times the exposure at the maximum recommended human dose of 420 mg every month. In a similar study with another drug in the PCSK9 inhibitor antibody class, humoral immune suppression was observed in infant monkeys exposed to that drug in utero at all doses. The exposures where immune suppression occurred in infant monkeys were greater than those expected clinically. No assessment for immune suppression was conducted with evolocumab in infant monkeys. Measurable evolocumab serum concentrations were observed in the infant monkeys at birth at comparable levels to maternal serum, indicating that evolocumab, like other IgG antibodies, crosses the placental barrier. FDA's experience with monoclonal antibodies in humans indicates that they are unlikely to cross the placenta in the first trimester; however, they are likely to cross the placenta in increasing amounts in the second and third trimester. Consider the benefits and risks of REPATHA and possible risks to the fetus before prescribing REPATHA to pregnant women.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In cynomolgus monkeys, no effects on embryo-fetal or postnatal development (up to 6 months of age) were observed when evolocumab was dosed during organogenesis to parturition at 50 mg/kg once every 2 weeks by the subcutaneous route at exposures 30- and 12-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. No test of humoral immunity in infant monkeys was conducted with evolocumab.

8.2 Lactation

Risk Summary

There is no information regarding the presence of evolocumab in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REPATHA and any potential adverse effects on the breastfed infant from REPATHA or from the underlying maternal condition. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts.

8.4 Pediatric Use

The safety and effectiveness of REPATHA in combination with diet and other LDL-C-lowering therapies in adolescents with HoFH who require additional lowering of LDL-C were established based on data from a 12-week, placebo-controlled trial that included 10 adolescents (ages 13 to 17 years old) with HoFH *[see Clinical Studies (14.3)]*. In this trial, 7 adolescents received REPATHA 420 mg subcutaneously once monthly and 3 adolescents received placebo. The effect of REPATHA on LDL-C was generally similar to that observed among adult patients with HoFH. Including experience from open-label, uncontrolled studies, a total of 14 adolescents with HoFH have been treated with REPATHA, with a median exposure duration of 9 months. The safety profile of REPATHA in these adolescents was similar to that described for adult patients with HoFH.

The safety and effectiveness of REPATHA have not been established in pediatric patients with HoFH who are younger than 13 years old.

The safety and effectiveness of REPATHA have not been established in pediatric patients with primary hyperlipidemia or HeFH.

8.5 Geriatric Use

In controlled trials, 7656 (41%) patients treated with REPATHA were ≥ 65 years old and 1500 (8%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is needed in patients with renal impairment. *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment (Child-Pugh A or B). No data are available in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of evolocumab was evaluated in a lifetime study conducted in the hamster at dose levels of 10, 30, and 100 mg/kg administered every 2 weeks. There were no evolocumab-related tumors at the highest dose at systemic exposures up to 38- and 15-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. The mutagenic potential of evolocumab has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

There were no adverse effects on fertility (including estrous cycling, sperm analysis, mating performance, and embryonic development) at the highest dose in a fertility and early embryonic developmental toxicology study in hamsters when evolocumab was subcutaneously administered at 10, 30, and 100 mg/kg every 2 weeks. The highest dose tested corresponds to systemic exposures up to 30- and 12-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. In addition, there were no adverse evolocumab-related effects on surrogate markers of fertility (reproductive organ histopathology, menstrual cycling, or sperm parameters) in a 6-month chronic toxicology study in sexually mature monkeys subcutaneously administered evolocumab at 3, 30, and 300 mg/kg once weekly. The highest dose tested corresponds to 744- and 300-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC.

13.2 Animal Toxicology and/or Pharmacology

During a 3-month toxicology study of 10 and 100 mg/kg once every 2 weeks evolocumab in combination with 5 mg/kg once daily rosuvastatin in adult monkeys, there were no effects of evolocumab on the humoral immune response to keyhole limpet hemocyanin (KLH) after 1 to 2 months exposure. The highest dose tested corresponds to exposures 54- and 21-fold higher than the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. Similarly, there were no effects of evolocumab on the humoral immune response to KLH (after 3 to 4 months exposure) in a 6-month study in cynomolgus monkeys at dose levels up to 300 mg/kg once weekly evolocumab corresponding to exposures 744- and 300-fold greater than the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC.

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.repathahcp.com or contact Amgen Medical Information at 1-800-772-6436.

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