REPATHA® (evolocumab) SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE/ PRE-FILLED AUTOINJECTOR 140 mg/mL

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Prevention of Cardiovascular Events

REPATHA® is indicated as an adjunct to diet and standard of care therapy (including moderate- to high-intensity statin therapy alone or in combination with other lipid-lowering therapy), to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adult patients with atherosclerotic cardiovascular disease.

Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia)

REPATHA is indicated for the reduction of elevated low-density lipoprotein cholesterol (LDL-C) in adult patients with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]):

- as an adjunct to diet and statin therapy, with or without other lipid-lowering therapies, in patients who require additional lowering of LDL-C,
- as an adjunct to diet, alone or in combination with non-statin lipid-lowering therapies, in patients for whom a statin is contraindicated.

Pediatric Patients with Heterozygous Familial Hypercholesterolemia

REPATHA is indicated as an adjunct to diet and other LDL-C-lowering therapies (e.g., statins, ezetimibe) in pediatric patients aged 10 years and older with HeFH who require additional lowering of LDL-C.

Homozygous Familial Hypercholesterolemia

REPATHA is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in adult and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended subcutaneous dosage of REPATHA in adults with established cardiovascular disease or in adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) is either 140 mg every 2 weeks OR 420 mg once monthly, based on patient preference for dosing frequency and injection volume. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.

In pediatric patients aged 10 years and older with HeFH:

- The recommended dosage of REPATHA is either 140 mg every 2 weeks OR 420 mg once monthly administered subcutaneously.
- If switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.

The recommended subcutaneous dosage of REPATHA in adult and pediatric patients aged 10 years and older with HoFH is 420 mg once monthly. In patients with HoFH, measure LDL-C levels 4 to 8 weeks after starting REPATHA, since response to therapy will depend on the degree of LDL-receptor function.

When monitoring LDL-C for patients receiving REPATHA 420 mg once monthly, note that LDL-C can vary considerably during the dosing interval in some patients *[see Clinical Studies (11)]*.

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

- If an every-2-week dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.

- If a once-monthly dose is not administered within 7 days, instruct the patient to administer the dose and start a new schedule based on this date.

2.2 Important Administration Instructions

- The 420 mg dose of REPATHA can be administered:
  - by giving 3 injections consecutively within 30 minutes using the single-use pre-filled autoinjector or single-use pre-filled syringe.

- Provide proper training to patients and/or caregivers on how to prepare and administer REPATHA prior to use, according to the Instructions for Use, including aseptic technique. Instruct patients and/or caregivers to read and follow the Instructions for Use each time they use REPATHA.

- Keep REPATHA in the refrigerator. Prior to use, allow REPATHA to warm to room temperature for at least 30 minutes for the single-use pre-filled autoinjector or single-use pre-filled syringe. Do not warm in any other way. Alternatively, for patients and caregivers, REPATHA can be kept at room temperature (up to 25°C) in the original carton. However, under these conditions, REPATHA must be used within 30 days *[see How Supplied/Storage and Handling (12)]*.

- Visually inspect REPATHA for particles and discoloration prior to administration. REPATHA is a clear to opalescent, colorless to pale yellow solution. Do not use if the solution is cloudy or discolored or contains particles.

- Administer REPATHA subcutaneously into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated using a single-use pre-filled syringe or single-use pre-filled autoinjector. Avoid injecting into areas with scars or stretch marks. Rotate injection sites for each administration.

- Do not co-administer REPATHA with other injectable drugs at the same administration site.

- Rotate the site of each subcutaneous administration.

3 DOSAGE FORMS AND STRENGTHS

REPATHA is a sterile, clear to opalescent, colorless to pale yellow solution available as follows:

- Injection: 140 mg/mL solution in a single-use pre-filled syringe
- Injection: 140 mg/mL solution in a single-use pre-filled autoinjector

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema, have been reported in patients treated with REPATHA. If signs or symptoms of serious hypersensitivity reactions occur, discontinue treatment with REPATHA, treat according to the standard of care, and monitor until signs and symptoms resolve. REPATHA is contraindicated in patients with a history of serious hypersensitivity reactions to evolocumab or any excipients in REPATHA *[see Contraindications (4)]*.

The needle cover of the glass single-use pre-filled syringe and the single-use pre-filled autoinjector contain dry natural rubber (a derivative of latex) which may cause an allergic reaction in individuals sensitive to latex.

6 ADVERSE REACTIONS

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

- Hypersensitivity 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 (DESCARTES, NCT01516879), 599 patients received 420 mg of REPATHA subcutaneously once monthly *[see Clinical Studies (11)]*. 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 ≥ 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; 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 ≥ 1% of REPATHA-treated Patients and More Frequently than with Placebo in Pooled 12-Week Trials

	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.

Hypersensitivity Reactions
Hypersensitivity 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 (REPATHA Cardiovascular Outcomes Trial, FOURIER, NCT01764633), 27,525 patients received at least one dose of REPATHA or placebo *[see Clinical Studies (11)]*. 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. 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 treated with REPATHA compared with 7.7% in patients that received placebo.

Adverse Reactions in Pediatric Patients with HeFH
In a 24-week, randomized, placebo-controlled, double-blind trial of 157 pediatric patients with HeFH, 104 patients received 420 mg REPATHA subcutaneously once monthly *[see Clinical Studies (11)]*. The mean age was 13.7 years (range: 10 to 17 years), 56% were female, 85% White, 1% Black, 1% Asian, and 13% other; 8% identified as Hispanic ethnicity. Common adverse reactions (> 5% of patients treated with REPATHA and occurring more frequently than placebo) included:

- Nasopharyngitis (12% versus 11%)
- Headache (11% versus 2%)
- Oropharyngeal pain (7% versus 0%)
- Influenza (6% versus 4%)
- Upper respiratory tract infection (6% versus 2%)

Adverse Reactions in Adult and Pediatric Patients with HoFH
In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH (TESLA, NCT01588496), 33 patients received 420 mg of REPATHA subcutaneously once monthly *[see Clinical Studies (11)]*. 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%)

In a multicenter, open-label 5-year extension study, 106 patients with HoFH, including 14 pediatric patients, received 420 mg of REPATHA subcutaneously once monthly or every 2 weeks *[see Clinical Studies (11)]*. The mean age was 34 years (range: 13 to 68 years), 51% were women, 80% White, 12% Asian, 1% Native American, and 7% other; 5% identified as Hispanic ethnicity. No new adverse reactions were observed during the open-label extension study.

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 adult 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.

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

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.

- Hypersensitivity reactions: Angioedema
- Influenza-like illness

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

Available data from clinical trials and postmarketing reports on REPATHA use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. 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. Monoclonal antibodies are transported across the placenta in increasing amounts especially near term; therefore, evolocumab has the potential to be transmitted from the mother to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. 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.

7.2 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. 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. 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.

7.3 Pediatric Use

The safety and effectiveness of REPATHA in combination with diet and other LDL-C-lowering therapies for the treatment of HoFH have been established in pediatric patients aged 10 years and older. Use of REPATHA for this indication is supported by evidence from an adequate and well-controlled trial in adults and pediatric patients aged 13 years and older with HoFH (including 7 pediatric patients treated with REPATHA) and from open-label studies which included an additional 19 pediatric patients aged 11 years and older with HoFH not previously treated with REPATHA *[see Adverse Reactions (6.1) and Clinical Studies (11)]*.

The safety and effectiveness of REPATHA as an adjunct to diet and other LDL-C-lowering therapies for the treatment of HeFH have been established in pediatric patients aged 10 years and older. Use of REPATHA for this indication is based on data from a 24-week, randomized, placebo-controlled, double-blind trial in pediatric patients with HeFH. In the trial, 104 patients received REPATHA 420 mg subcutaneously once monthly and 53 patients received placebo; 39 patients (25%) were 10 to 11 years of age *[see Adverse Reactions (6.1) and Clinical Studies (11)]*.

The safety and effectiveness of REPATHA have not been established in pediatric patients with HeFH or HoFH who are younger than 10 years old or in pediatric patients with other types of hyperlipidemia.

7.4 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.

7.5 Renal Impairment

No dose adjustment is needed in patients with renal impairment *[see Clinical Pharmacology (9.3)]*.

7.6 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 (9.3)]*.

8 DESCRIPTION

Evolocumab is a human monoclonal immunoglobulin G2 (IgG2) directed against human proprotein convertase subtilisin kexin 9 (PCSK9). Evolocumab has an approximate molecular weight (MW) of 144 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

REPATHA is a sterile, preservative-free, clear to opalescent, colorless to pale yellow solution for subcutaneous use. Each 1 mL single-use pre-filled syringe and single-use pre-filled autoinjector contains 140 mg evolocumab, acetate (1.2 mg), polysorbate 80 (0.1 mg), proline (25 mg) in Water for Injection, USP. Sodium hydroxide may be used to adjust to a pH of 5.0.

9 CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Evolocumab is a human monoclonal IgG2 directed against human proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein (LDL) receptor (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. By inhibiting the binding of PCSK9 to LDLR, evolocumab increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels.

9.2 Pharmacodynamics

Following single subcutaneous administration of 140 mg or 420 mg of evolocumab, maximum suppression of circulating unbound PCSK9 occurred by 4 hours. Unbound PCSK9 concentrations returned toward baseline when evolocumab concentrations decreased below the limit of quantitation.

9.3 Pharmacokinetics

Evolocumab exhibits non-linear kinetics as a result of binding to PCSK9. Administration of the 140 mg dose in healthy volunteers resulted in a C_{max} mean of 18.6 µg/mL and AUC_{last} mean of 188 day•µg/mL. Administration of the 420 mg dose in healthy volunteers resulted in a C_{max} mean of 59.0 µg/mL and AUC_{last} mean of 924 day•µg/mL. Following a single 420 mg intravenous dose, the mean systemic clearance was estimated to be 12 mL/hr. An approximate 2- to 3-fold accumulation was observed in trough serum concentrations (C_{min} 7.21) following 140 mg doses administered subcutaneously every 2 weeks or following 420 mg doses administered subcutaneously monthly (C_{min} 11.2), and serum trough concentrations approached steady-state by 12 weeks of dosing.

Absorption
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, and estimated absolute bioavailability was 72%.

Distribution
Following a single 420 mg intravenous dose, the mean steady-state volume of distribution was estimated to be 3.3 L.

Elimination
Two elimination phases were observed for REPATHA. At low concentrations, the elimination is predominately through saturable binding to target (PCSK9), while at higher concentrations the elimination of REPATHA is largely through a non-saturable proteolytic pathway. REPATHA was estimated to have an effective half-life of 11 to 17 days.

Specific Populations
The pharmacokinetics of evolocumab were not affected by age, gender, race, or creatinine clearance across all approved populations *[see Use in Specific Populations (7.5)]*.

The exposure of evolocumab decreased with increasing body weight. These differences are not clinically meaningful.

Pediatric Patients
The pharmacokinetics of REPATHA were evaluated in 103 pediatric patients aged 10 to 17 years with HeFH *[see Use in Specific Populations (7.3), Clinical Studies (11)]*. Following subcutaneous administration of 420 mg REPATHA once monthly, mean trough serum concentrations were 22.4 mcg/mL and 25.8 mcg/mL over the Week 12 and Week 24 time points, respectively. The pharmacokinetics of REPATHA were evaluated in 12 pediatric patients aged 11 to 17 years with HoFH *[see Use in Specific Populations (7.3), Clinical Studies (11)]*. Following subcutaneous administration of 420 mg REPATHA once monthly, mean serum trough concentrations were 20.3 mcg/mL and 17.6 mcg/mL at Week 12 and Week 80, respectively.

Renal Impairment
Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of evolocumab.

In a clinical trial of 18 patients with either normal renal function (estimated glomerular filtration rate [eGFR] $\geq$ 90 mL/min/1.73 m^2, n = 6), severe renal impairment (eGFR < 30 mL/min/1.73 m^2, n = 6), or end-stage renal disease (ESRD) receiving hemodialysis (n = 6), exposure to evolocumab after a single 140 mg subcutaneous dose was decreased in patients with severe renal impairment or ESRD receiving hemodialysis. Reductions in PCSK9 levels in patients with severe renal impairment or ESRD receiving hemodialysis was similar to those with normal renal function *[see Use in Specific Populations (7.6)]*.

Hepatic Impairment
Following a single 140 mg subcutaneous dose of evolocumab in patients with mild or moderate hepatic impairment, a 20-30% lower mean C_{max} and 40-50% lower mean AUC were observed as compared to healthy patients *[see Use in Specific Populations (7.6)]*.

Drug Interaction Studies
An approximately 20% decrease in the C_{max} and AUC of evolocumab was observed in adult patients co-administered with a high-intensity statin regimen. This difference is not clinically meaningful.

10 NONCLINICAL TOXICOLOGY

10.1 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.

10.2 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.

11 CLINICAL STUDIES

Adult Patients with Established Cardiovascular Disease

FOURIER (NCT01764633) was a double-blind, randomized, placebo-controlled, event-driven trial in 27,564 (13,784 REPATHA, 13,780 placebo) adult patients with established cardiovascular disease and with LDL-C ≥ 70 mg/dL and/or non-HDL-C ≥ 100 mg/dL despite high- or moderate-intensity statin therapy. Patients were randomly assigned 1:1 to receive either subcutaneous injections of REPATHA (140 mg every 2 weeks or 420 mg once monthly) or placebo; 86% used the every-2-week regimen throughout the trial. The median follow-up duration was 26 months. Overall, 99.2% of patients were followed until the end of the trial or death.

The mean (SD) age at baseline was 63 (9) years, with 45% being at least 65 years old; 25% were women. The trial population was 85% White, 2% Black, and 10% Asian; 8% identified as Hispanic ethnicity. Regarding prior diagnoses of cardiovascular disease, 81% had prior myocardial infarction, 19% prior non-hemorrhagic stroke, and 13% had symptomatic peripheral arterial disease. Selected additional baseline risk factors included hypertension (80%), diabetes mellitus (1% type 1; 36% type 2), current daily cigarette smoking (28%), New York Heart Association class I or II congestive heart failure (23%), and eGFR < 60 mL/min per 1.73 m^2 (6%). Most patients were on a high- (69%) or moderate-intensity (30%) statin therapy at baseline, and 5% were also taking ezetimibe. Most patients were taking at least one other cardiovascular medication including anti-platelet agents (93%), beta blockers (76%), angiotensin converting enzyme (ACE) inhibitors (56%), or angiotensin receptor blockers (23%). On stable background lipid-lowering therapy, the median [Q1, Q3] LDL-C at baseline was 92 [80, 109] mg/dL; the mean (SD) was 98 (28) mg/dL.

REPATHA significantly reduced the risk for the primary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization; $p < 0.0001$) and the key secondary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, 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 Figure 2 below.

The results of primary and secondary efficacy endpoints are shown in Table 3 below.

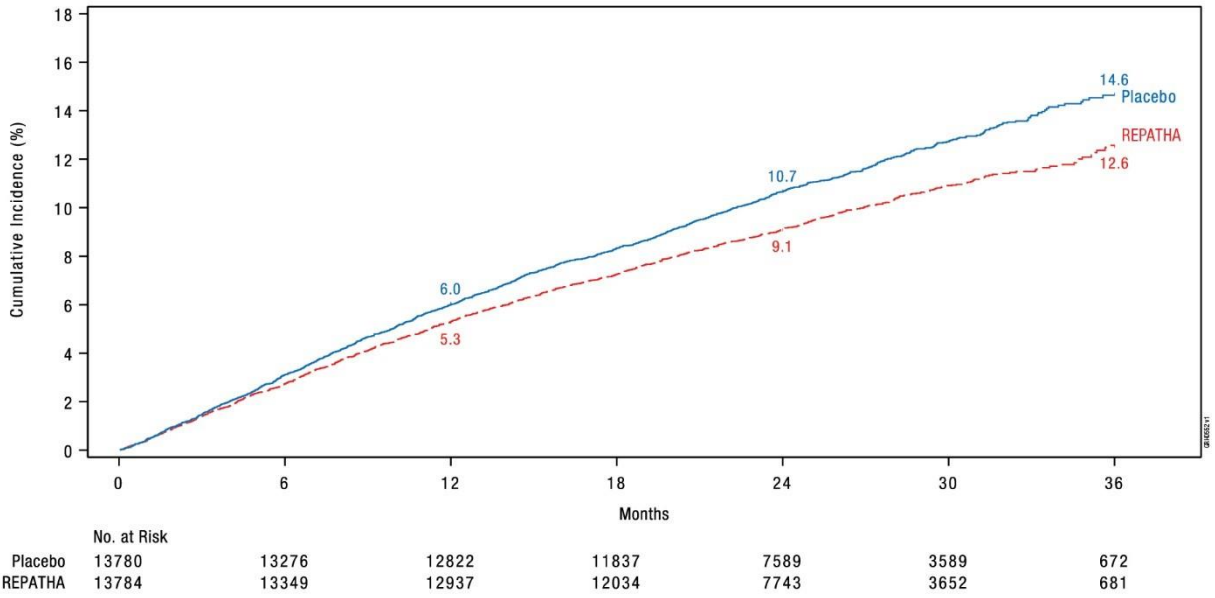
Table 3. Effect of REPATHA on Cardiovascular Events in Patients with Established Cardiovascular Disease in FOURIER

	Placebo		REPATHA		REPATHA vs. Placebo
	N = 13780 n (%)	**Incidence Rate (per 100 patient years)**	**N = 13784 n (%)**	**Incidence Rate (per 100 patient years)**	**Hazard Ratio (95% CI)**
Primary composite endpoint					
Time to first occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina	1563 (11.3)	5.2	1344 (9.8)	4.5	0.85 (0.79, 0.92)
Key secondary composite endpoint					
Time to first occurrence of cardiovascular death, myocardial infarction, stroke	1013 (7.4)	3.4	816 (5.9)	2.7	0.80 (0.73, 0.88)
Other secondary endpoints					
Time to cardiovascular death	240 (1.7)	0.8	251 (1.8)	0.8	1.05 (0.88, 1.25)
Time to death by any cause[a]	426 (3.1)	1.4	444 (3.2)	1.5	1.04 (0.91, 1.19)
Time to first fatal or non-fatal myocardial infarction	639 (4.6)	2.1	468 (3.4)	1.6	0.73 (0.65, 0.82)
Time to first fatal or non-fatal stroke	262 (1.9)	0.9	207 (1.5)	0.7	0.79 (0.66, 0.95)
Time to first coronary revascularization	965 (7.0)	3.2	759 (5.5)	2.5	0.78 (0.71, 0.86)
Time to first hospitalization for unstable angina[b]	239 (1.7)	0.8	236 (1.7)	0.8	0.99 (0.82, 1.18)

[a] Time to death by any cause is not a component of either the primary composite endpoint or key secondary composite endpoint.

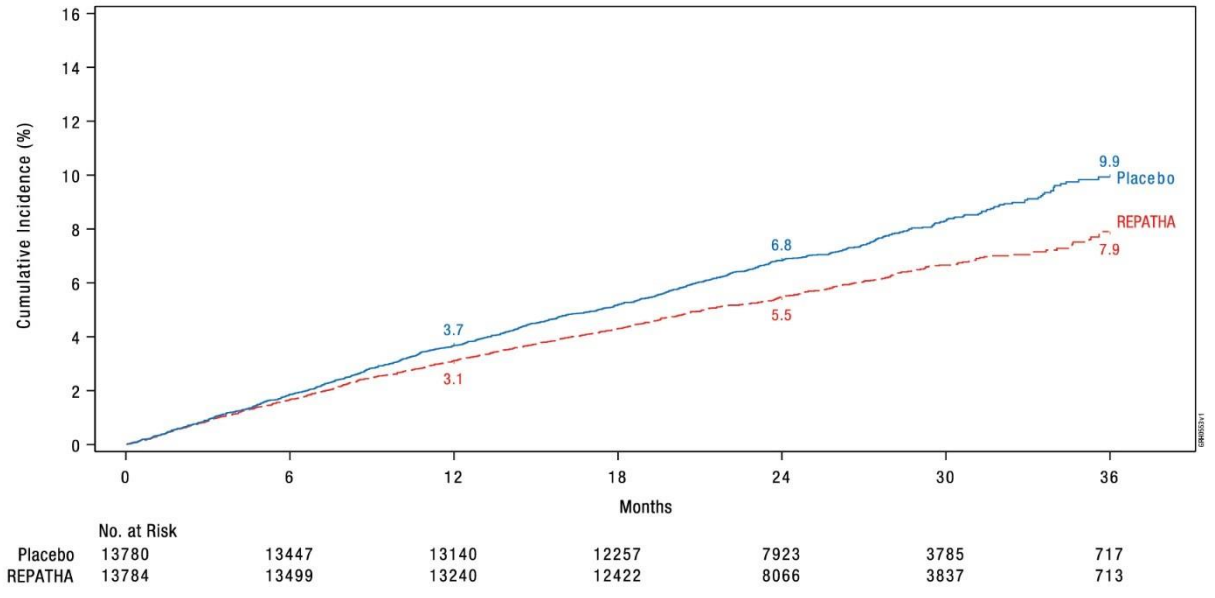
[b] Not a prespecified endpoint; an ad hoc analysis was performed to ensure results are provided for each individual component of the primary endpoint.

Figure 1. Estimated Cumulative Incidence of Primary Composite Endpoint Over 3 Years in FOURIER



No. at Risk							
Placebo	13780	13276	12822	11837	7589	3589	672
REPATHA	13784	13349	12937	12034	7743	3652	681

Figure 2. Estimated Cumulative Incidence of Key Secondary Composite Endpoint Over 3 Years in FOURIER



No. at Risk							
Placebo	13780	13447	13140	12257	7923	3785	717
REPATHA	13784	13499	13240	12422	8066	3837	713

The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -63% (95% CI: -63%, -62%) and from baseline to Week 72 was -57% (95% CI: -58%, -56%). At Week 48, the median [Q1, Q3] LDL-C was 26 [15, 46] mg/dL in the REPATHA group, with 47% of patients having LDL-C < 25 mg/dL.

In EBBINGHAUS (NCT02207634), a substudy of 1974 patients enrolled in the FOURIER trial, REPATHA was non-inferior to placebo on selected cognitive function domains as assessed with the use of neuropsychological function tests over a median follow-up of 19 months.

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 5031 patients who received at least one dose of REPATHA in study 1, 2499 patients received REPATHA and 2532 patients received placebo in the FOURIER study. Of the 1599 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 = 4802) of patients achieved a lowest post-baseline LDL-C < 25 mg/dL (0.65 mmol/L), 87.0% (n = 5765) 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.

Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia)

LAPLACE-2 (NCT01763866) was a multicenter, double-blind, randomized controlled 12-week trial in which patients were initially randomized to an open-label specific statin regimen for a 4-week lipid stabilization period followed by random assignment to subcutaneous injections of REPATHA 140 mg every 2 weeks, REPATHA 420 mg once monthly, or placebo for 12 weeks. The trial included 1896 patients with hyperlipidemia who received REPATHA, placebo, or ezetimibe as add-on therapy to daily doses of statins (atorvastatin, rosuvastatin, or simvastatin). Ezetimibe was also included as an active control only among those assigned to background atorvastatin. Overall, the mean age at baseline was 60 years (range: 20 to 80 years), 35% were ≥ 65 years old, 46% women, 94% White, 4% were Black, and 1% Asian; 5% identified as Hispanic or Latino ethnicity. After 4 weeks of background statin therapy, the mean baseline LDL-C ranged between 77 and 127 mg/dL across the five background therapy arms.

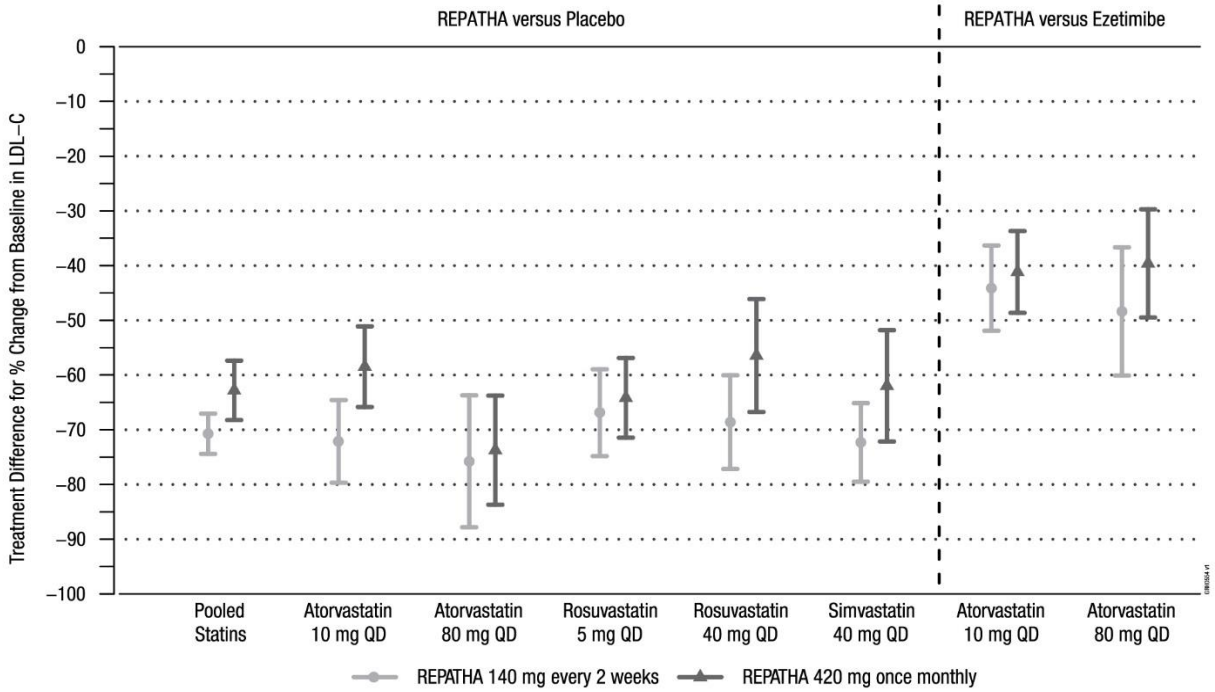
The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -71% (95% CI: -74%, -67%; p < 0.0001) and -63% (95% CI: -68%, -57%; p < 0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. The difference between REPATHA and ezetimibe in mean percent change in LDL-C from baseline to Week 12 was -45% (95% CI: -52%, -39%; p < 0.0001) and -41% (95% CI: -47%, -35%; p < 0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 4 and Figure 3.

Table 4. Effect of REPATHA on Lipid Parameters in Patients with Hyperlipidemia on Background Statin Regimens (Mean % Change from Baseline to Week 12 in LAPLACE-2)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
REPATHA every 2 weeks vs. Placebo every 2 weeks **(Background statin: atorvastatin 10 mg or 80 mg; rosuvastatin 5 mg or 40 mg; simvastatin 40 mg)**				
Placebo every 2 weeks (n = 281)	8	6	5	4
REPATHA 140 mg every 2 weeks† (n = 555)	-63	-53	-49	-36
Mean difference from placebo (95% CI)	-71 (-74, -67)	-59 (-62, -55)	-55 (-58, -52)	-40 (-43, -38)
REPATHA once monthly vs. Placebo once monthly **(Background statin: atorvastatin 10 mg or 80 mg; rosuvastatin 5 mg or 40 mg; simvastatin 40 mg)**				
Placebo once monthly (n = 277)	4	5	3	2
REPATHA 420 mg once monthly (n = 562)	-59	-50	-46	-34
Mean difference from placebo (95% CI)	-63 (-68, -57)	-54 (-58, -50)	-50 (-53, -47)	-36 (-39, -33)
REPATHA every 2 weeks vs. Ezetimibe 10 mg daily **(Background statin: atorvastatin 10 mg or 80 mg)**				
Ezetimibe 10 mg daily (n = 112)	-17	-16	-14	-12
REPATHA 140 mg every 2 weeks† (n = 219)	-63	-52	-49	-36
Mean difference from Ezetimibe (95% CI)	-45 (-52, -39)	-36 (-41, -31)	-35 (-40, -31)	-24 (-28, -20)
REPATHA once monthly vs. Ezetimibe 10 mg daily **(Background statin: atorvastatin 10 mg or 80 mg)**				
Ezetimibe 10 mg daily (n = 109)	-19	-16	-11	-12
REPATHA 420 mg once monthly (n = 220)	-59	-50	-46	-34
Mean difference from Ezetimibe (95% CI)	-41 (-47, -35)	-35 (-40, -29)	-34 (-39, -30)	-22 (-26, -19)

Estimates based on a multiple imputation model that accounts for treatment adherence
† 140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C

Figure 3. Effect of REPATHA on LDL-C in Patients with Hyperlipidemia when Combined with Statins (Mean % Change from Baseline to Week 12 in LAPLACE-2)



Estimates based on a multiple imputation model that accounts for treatment adherence
Error bars indicate 95% confidence intervals

DESCARTES (NCT01516879) was a multicenter, double-blind, randomized, placebo-controlled, 52-week trial that included 901 patients with hyperlipidemia who received protocol-determined background lipid-lowering therapy of a cholesterol-lowering diet either alone or in addition to atorvastatin (10 mg or 80 mg daily) or the combination of atorvastatin 80 mg daily with ezetimibe. After stabilization on background therapy, patients were randomly assigned to the addition of placebo or REPATHA 420 mg administered subcutaneously once monthly. Overall, the mean age at baseline was 56 years (range: 25 to 75 years), 23% were ≥ 65 years, 52% women, 80% White, 8% Black, and 6% Asian; 6% identified as Hispanic or Latino ethnicity. After stabilization on the assigned background therapy, the mean baseline LDL-C ranged between 90 and 117 mg/dL across the four background therapy groups.

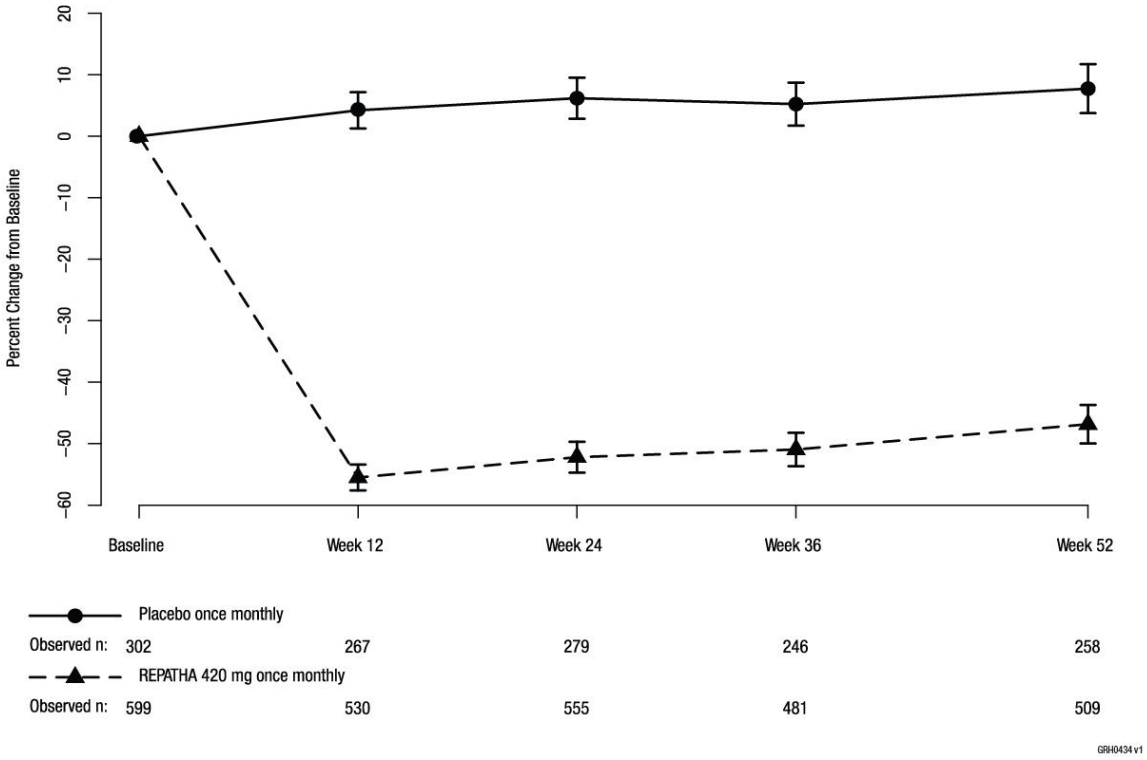
In these patients with hyperlipidemia on a protocol-determined background therapy, the difference between REPATHA 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was -55% (95% CI: -60%, -50%; $p < 0.0001$) (Table 5 and Figure 4). For additional results see Table 5.

Table 5. Effect of REPATHA on Lipid Parameters in Patients with Hyperlipidemia* (Mean % Change from Baseline to Week 52 in DESCARTES)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo once monthly (n = 302)	8	8	2	5
REPATHA 420 mg once monthly (n = 599)	-47	-39	-38	-26
Mean difference from placebo (95% CI)	-55 (-60, -50)	-46 (-50, -42)	-40 (-44, -37)	-31 (-34, -28)

Estimates based on a multiple imputation model that accounts for treatment adherence
* Prior to randomization, patients were stabilized on background therapy consisting of a cholesterol lowering diet either alone or in addition to atorvastatin (10 mg or 80 mg daily) or the combination of atorvastatin 80 mg daily with ezetimibe.

Figure 4. Effect of REPATHA 420 mg Once Monthly on LDL-C in Patients with Hyperlipidemia in DESCARTES



Estimates based on a multiple imputation model that accounts for treatment adherence
Error bars indicate 95% confidence intervals

MENDEL-2 (NCT01763827) was a multicenter, double-blind, randomized, placebo- and active-controlled, 12-week trial that included 614 patients with hyperlipidemia who were not taking lipid-lowering therapy at baseline. Patients were randomly assigned to receive subcutaneous injections of REPATHA 140 mg every 2 weeks, REPATHA 420 mg once monthly, or placebo for 12 weeks. Blinded administration of ezetimibe was also included as an active control. Overall, the mean age at baseline was 53 years (range: 20 to 80 years), 18% were ≥ 65 years old, 66% were women, 83% White, 7% Black, and 9% Asian; 11% identified as Hispanic or Latino ethnicity. The mean baseline LDL-C was 143 mg/dL.

The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -55% (95% CI: -60%, -50%; $p < 0.0001$) and -57% (95% CI: -61%, -52%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. The difference between REPATHA and ezetimibe in mean percent change in LDL-C from baseline to Week 12 was -37% (95% CI: -42%, -32%; $p < 0.0001$) and -38% (95% CI: -42%, -34%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 6.

Table 6. Effect of REPATHA on Lipid Parameters in Patients with Hyperlipidemia (Mean % Change from Baseline to Week 12 in MENDEL-2)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo every 2 weeks (n = 76)	1	0	1	0
Ezetimibe 10 mg daily (n = 77)	-17	-14	-13	-10
REPATHA 140 mg every 2 weeks† (n = 153)	-54	-47	-44	-34
Mean difference from placebo (95% CI)	-55 (-60, -50)	-47 (-52, -43)	-45 (-50, -41)	-34 (-37, -30)
Mean difference from Ezetimibe (95% CI)	-37 (-42, -32)	-33 (-37, -29)	-32 (-36, -27)	-23 (-27, -20)
Placebo once monthly (n = 78)	1	2	2	0
Ezetimibe 10 mg daily (n = 77)	-18	-16	-13	-12
REPATHA 420 mg once monthly (n = 153)	-56	-49	-46	-35
Mean difference from placebo (95% CI)	-57 (-61, -52)	-51 (-54, -47)	-48 (-52, -44)	-35 (-38, -32)
Mean difference from Ezetimibe (95% CI)	-38 (-42, -34)	-32 (-36, -29)	-33 (-36, -29)	-23 (-26, -20)

Estimates based on a multiple imputation model that accounts for treatment adherence
† 140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C

RUTHERFORD-2 (NCT01763918) was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 329 patients with heterozygous familial hypercholesterolemia (HeFH) on statins with or without other lipid-lowering therapies. Patients were randomized to receive subcutaneous injections of REPATHA 140 mg every two weeks, 420 mg once monthly, or placebo. HeFH was diagnosed by the Simon Broome criteria (1991). 38% of patients had clinical atherosclerotic cardiovascular disease. The mean age at baseline was 51 years (range: 19 to 79 years), 15% of the patients were ≥ 65 years old, 42% were women, 90% were White, 5% were Asian, and 1% were Black. The average LDL-C at baseline was 156 mg/dL with 76% of the patients on high-intensity statin therapy.

The differences between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -61% (95% CI: -67%, -55%; $p < 0.0001$) and -60% (95% CI: -68%, -52%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 7 and Figure 5.

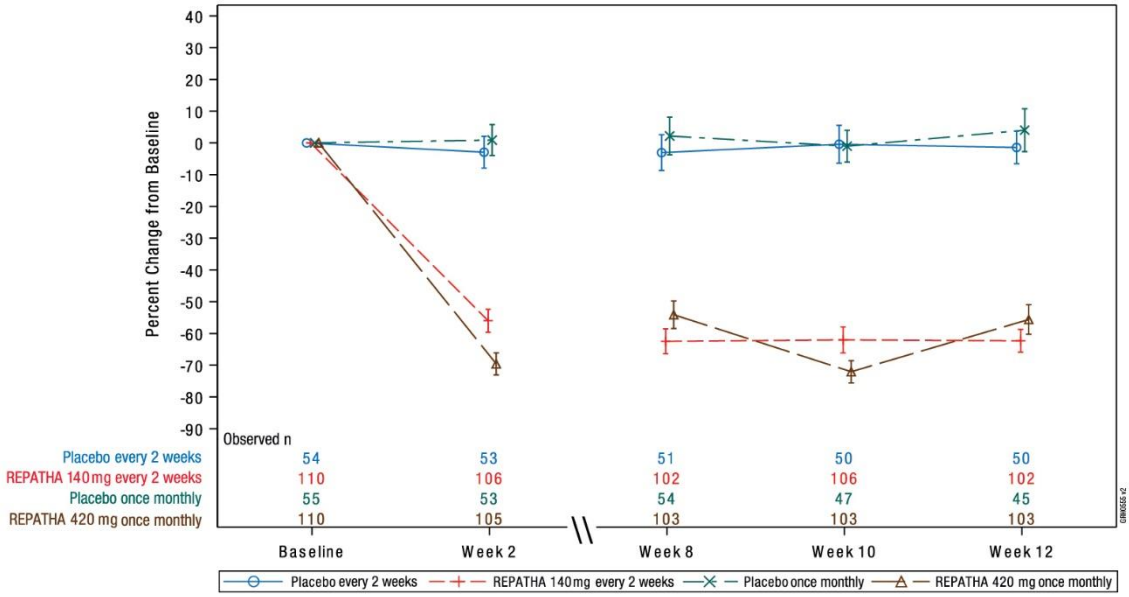
Table 7. Effect of REPATHA on Lipid Parameters in Patients with HeFH (Mean % Change from Baseline to Week 12 in RUTHERFORD-2)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo every 2 weeks (n = 54)	-1	-1	-1	-2
REPATHA 140 mg every 2 weeks† (n = 110)	-62	-56	-49	-42
Mean difference from placebo (95% CI)	-61 (-67, -55)	-54 (-60, -49)	-49 (-54, -43)	-40 (-45, -36)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo once monthly (n = 55)	4	4	4	2
REPATHA 420 mg once monthly† (n = 110)	-56	-49	-44	-37
Mean difference from placebo (95% CI)	-60 (-68, -52)	-53 (-60, -46)	-48 (-55, -41)	-39 (-45, -33)

Estimates based on a multiple imputation model that accounts for treatment adherence
† 140 mg every 2 weeks or 420 mg once monthly yield similar reductions in LDL-C

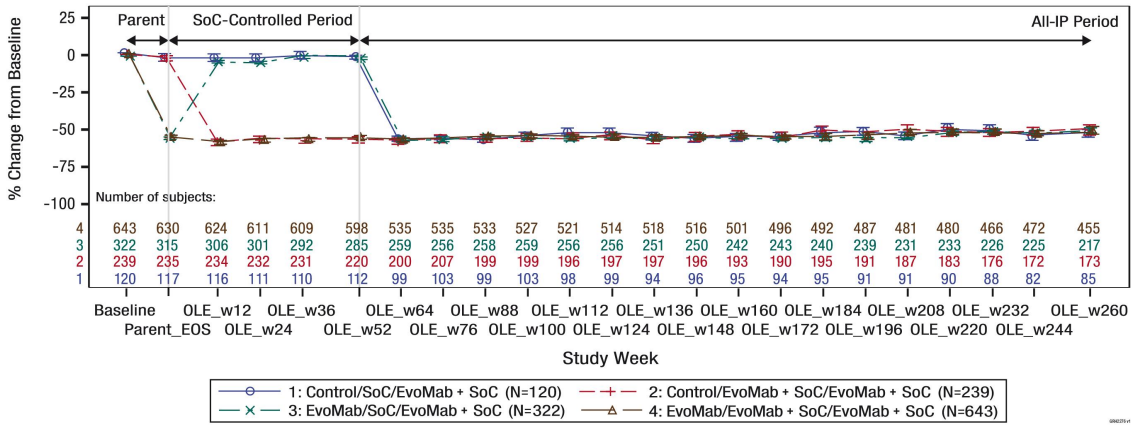
Figure 5. Effect of REPATHA on LDL-C in Patients with HeFH (Mean % Change from Baseline to Week 12 in RUTHERFORD-2)



N = number of patients randomized and dosed in the full analysis set
Estimates based on a multiple imputation model that accounts for treatment adherence
Error bars indicate 95% confidence intervals

OSLER-1 was a multicenter, randomized, controlled, open-label, 5-year extension study to assess the long-term safety and efficacy of Repatha in patients with hyperlipidemia. A total of 1324 patients who completed treatment in 1 of 5 parent (Phase 2) studies enrolled in the study. Patients were randomized 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 approximately additional 4 years. 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 (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 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 beginning of OSLER-1 without evidence of rebound (Figure 6).

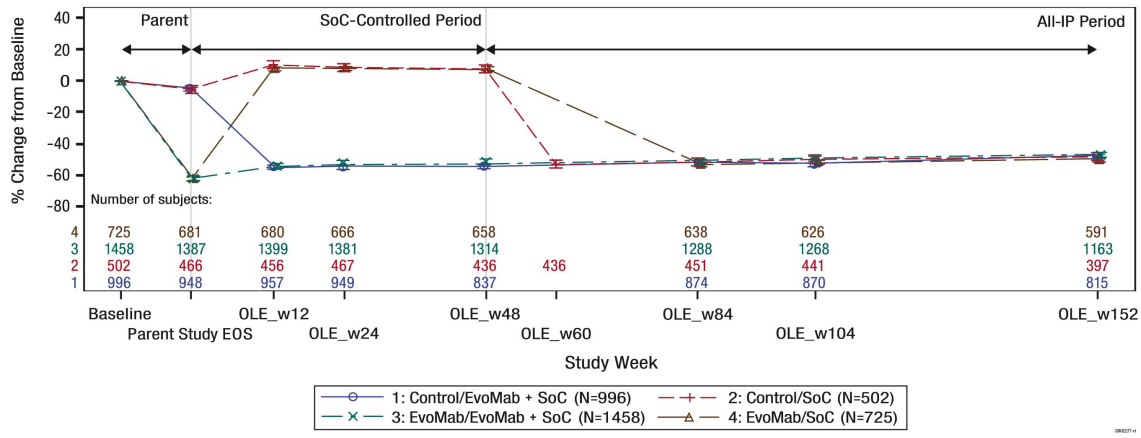
Figure 6. Effect of Repatha on LDL-C in Patients with Hyperlipidemia – Mean Percent Change from Baseline by Scheduled Visit and Treatment Group (OSLER-1)



Study - Final Analysis, Full Analysis Set and All-IP Period Analysis Set
N = number of patients that were randomized in Study; EvoMab = Evolocumab; SoC = standard of care; OLE = open-label extension. EOS = end of study; IP = investigational product.
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 remained 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 multicenter, randomized, controlled, open-label, 3-year extension study designed to assess the long-term safety and efficacy of Repatha in patients with hypercholesterolemia. A total of 3681 patients who completed treatment in 1 of 9 parent (Phase 3) studies enrolled in the study. Patients were randomized 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 up to two more years. 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 (Figure 6). 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 48 compared with control (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 7).

Figure 7. Effect of Repatha on LDL-C in Patients with Hyperlipidemia– Mean Percent Change from Baseline by Scheduled Visit and Treatment Group (OSLER-2)



Study - Final Analysis, Full Analysis Set and All-IP Period Analysis Set
N = number of patients that were randomized in Study and have at least 12 weeks of potential follow-up;
EvoMab = Evolocumab; SoC = standard of care; OLE = open-label extension; EOS = end of study; IP = investigational product
OLE visits prior to OLE_w48 are under SoC-Controlled period and OLE visits on or after OLE_w48 are under all-IP period. All patients remained 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.

TAUSSIG was a multicenter, open-label 5-year extension study to assess the long-term safety and efficacy of Repatha in patients with severe familial hypercholesterolemia (FH), including HoFH, who were treated with Repatha as an adjunct to other lipid-lowering therapies. A total of 194 severe FH (non-HoFH) patients and 106 HoFH 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 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 reduction of LDL-C in patients with severe FH (non-HoFH) (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 severe FH (non-HoFH).

Table 8. Effect of Repatha on LDL-C in Patients with Severe FH (non-HoFH) – Median Percent Change from Baseline to OLE Week 216

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)	-57.1	-57.1	-56.1	-59.7	-57.1	-56.5	-52.2	-50.6

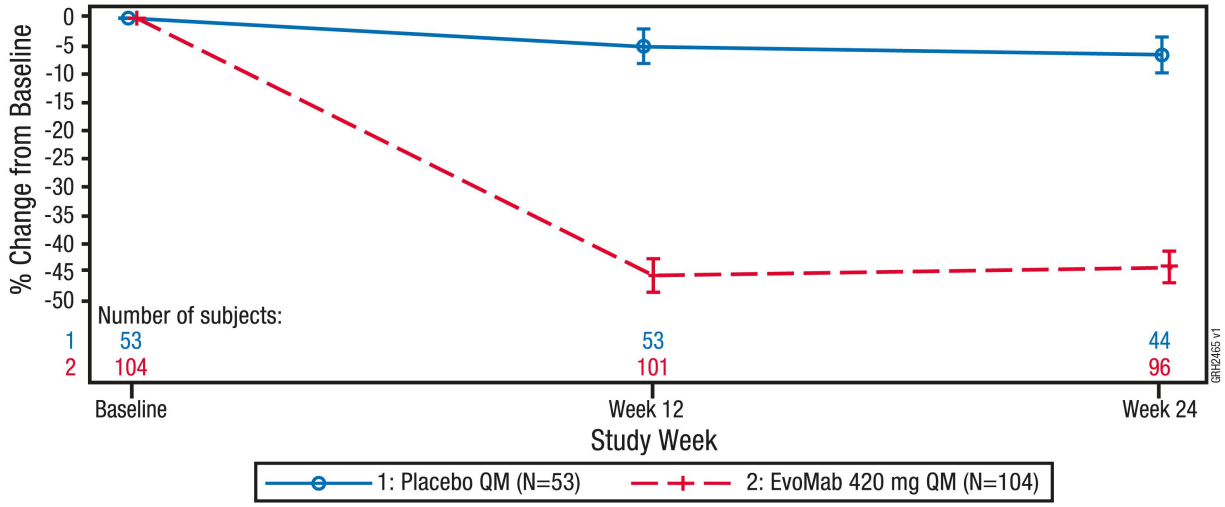
OLE = open-label extension
N (n) = Number of evaluable patients (N) and patients with observed LDL values at specific schedule visit (n) in the Severe FH (non-HoFH) Final Analysis Set

Pediatric Patients with HeFH

HAUSER-RCT (NCT02392559) was a randomized, multicenter, placebo-controlled, double-blind, 24-week trial in 157 pediatric patients aged 10 to 17 years with HeFH *[see Use in Specific Populations (7.3)]*. HeFH was diagnosed by diagnostic criteria for HeFH [Simon Broome Register Group (1991), the Dutch Lipid Clinic Network (1999), MEDPED (1993)] or by genetic testing. Patients were required to be on a low-fat diet and optimized background lipid-lowering therapy. Patients were randomly assigned 2:1 to receive 24 weeks of subcutaneous once monthly 420 mg REPATHA or placebo; 104 patients received REPATHA and 53 patients received placebo. The mean age was 14 years (range: 10 to 17 years), 56% were female, 85% White, 1% Black, 1% Asian, 13% Other, and 8% Hispanic. The mean LDL-C at baseline was 184 mg/dL; 17% of patients were on high-intensity statin, 62% on moderate-intensity statin, and 13% on ezetimibe.

The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 24 was −38% (95% CI: −45%, −31%; $p < 0.0001$). For additional results, see Table 9 and Figure 8.

Figure 8. Effect of REPATHA on LDL-C in Pediatric Patients with HeFH (Mean % Change from Baseline in HAUSER-RCT)



EvoMab = evolocumab; LDL-C = low density lipoprotein cholesterol; QM = monthly (subcutaneous)
N = number of patients randomized and dosed in the full analysis set.
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.

Table 9. Effect of REPATHA on Lipid Parameters in Pediatric Patients with HeFH (Mean % Change from Baseline to Week 24 in HAUSER-RCT)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo once monthly (n = 53)	-6	-6	-2	-5
REPATHA 420 mg once monthly (n = 104)	-44	-41	-35	-32
Mean difference from placebo (95% CI)	-38 (-45, -31)	-35 (-42, -28)	-32 (-39, -26)	-27 (-32, -21)

All adjusted p-values < 0.0001.
n = number of patients randomized and dosed in the full analysis set.

Adult and Pediatric Patients with HoFH

TESLA (NCT01588496) was a multicenter, double-blind, randomized, placebo-controlled, 12-week trial in 49 patients (not on lipid-apheresis therapy) with homozygous familial hypercholesterolemia (HoFH). In this trial, 33 patients received subcutaneous injections of 420 mg of REPATHA once monthly and 16 patients received placebo as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe). The mean age at baseline was 31 years, 49% were women, 90% White, 4% were Asian, and 6% other. The trial included 10 adolescents (ages 13 to 17 years), 7 of whom received REPATHA. The mean LDL-C at baseline was 349 mg/dL with all patients on statins (atorvastatin or rosuvastatin) and 92% on ezetimibe. The diagnosis of HoFH was made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of HeFH in both parents.

The difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -31% (95% CI: -44%, -18%; p < 0.0001). For additional results see Table 10.

Patients known to have two LDL-receptor negative alleles (little to no residual function) did not respond to REPATHA.

Table 10. Effect of REPATHA on Lipid Parameters in Patients with HoFH (Mean % Change from Baseline to Week 12 in TESLA)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo once monthly (n = 16)	9	8	4	8
REPATHA 420 mg once monthly (n = 33)	-22	-20	-17	-17
Mean difference from placebo (95% CI)	-31 (-44, -18)	-28 (-41, -16)	-21 (-33, -9)	-25 (-36, -14)

Estimates based on a multiple imputation model that accounts for treatment adherence

Long-term Efficacy in Homozygous Familial Hyperlipidemia

TAUSSIG (NCT01624142) was a multicenter, open-label 5-year extension study with REPATHA in 106 patients with HoFH, who were treated with REPATHA as an adjunct to other lipid-lowering therapies. The study included 14 pediatric patients (ages 13 to 17 years). All patients in the study were initially treated with REPATHA 420 mg once monthly except for those receiving lipid 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.

A total of 48 patients with HoFH received REPATHA 420 mg once monthly for at least 12 weeks followed by REPATHA 420 mg every 2 weeks for at least 12 weeks. Mean percent change from baseline in LDL-C were −20% at Week 12 of 420 mg once monthly treatment and −30% at Week 12 of 420 mg every 2 weeks treatment, based on available data.

HAUSER-OLE, NCT02624869 was an open-label, single-arm, multicenter, 80-week study to evaluate the safety, tolerability, and efficacy of REPATHA for LDL-C reduction in pediatric patients aged 10 to 17 years with HoFH *[see Use in Specific Populations (7.3)]*. Patients were on a low-fat diet and receiving background lipid-lowering therapy. Overall, 12 patients with HoFH received 420 mg REPATHA subcutaneously once monthly. The mean age was 12 years (range 11 to 17 years), 17% were female, 75% White, 17% Asian, and 8% Other. Median (Q1, Q3) LDL-C at baseline was 398 (343, 475) mg/dL, and all patients were on statins (atorvastatin or rosuvastatin) and ezetimibe. No patients were receiving lipid apheresis. The diagnosis of HoFH was made by genetic confirmation in all patients but enrollment by a clinical diagnosis was permitted. The median (Q1, Q3) percent change in LDL-C from baseline to Week 80 was −14% (−41, 4). Two of the 3 subjects with < 5% LDLR activity responded to evolocumab treatment.

Regression of Atherosclerosis

GLAGOV was a phase 3, double-blind, randomized, 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 stable background lipid-lowering therapy and to have a LDL-C ≥ 80 mg/dL (2.07 mmol/L) or LDL-C ≥ 60 to < 80 mg/dL (1.55 to 2.07 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 randomized 1:1 into two treatment groups to either receive Repatha 420 mg once monthly or placebo once monthly 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 92.6 (27.3) mg/dL (2.4 [0.7] mmol/L).

Repatha reduced 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 11 below:

Table 11. Treatment Effects of Repatha Compared with Placebo in Patients with Hyperlipidemia – 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 29.2 (27.6) mg/dL 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 reduction in PAV.

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).

Effect on LDL-C During Acute Phase of Acute Coronary Syndrome (ACS)

EVOPACS was an investigator-sponsored, multicenter, double-blind, randomized, placebo-controlled, 8-week study conducted in Switzerland of Repatha in 308 patients admitted to the hospital within 24 to 72 hours of an ACS event who received concomitant atorvastatin. Repatha 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 the evolocumab clinical development program and no new safety concerns were noted.

12 HOW SUPPLIED/STORAGE AND HANDLING

REPATHA is a clear to opalescent, colorless to pale yellow solution supplied in a single-use pre-filled syringe or a single-use pre-filled autoinjector. Each single-use pre-filled syringe or single-use pre-filled autoinjector of REPATHA is designed to deliver 1 mL of 140 mg/mL solution.

The needle cover of the glass single-use pre-filled syringe and the single-use pre-filled autoinjector contain dry natural rubber (a derivative of latex).

Store refrigerated at 2°C to 8°C in the original carton to protect from light. Do not freeze. Do not shake.

REPATHA may be kept at room temperature (up to 25°C) in the original carton for 30 days. If not used within the 30 days, discard REPATHA.

Protect REPATHA from direct light and do not expose to temperatures above 25°C.

13 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the patient labeling [**Patient Information** and **Instructions for Use** (IFU)] before the patient starts using REPATHA, and each time the patient gets a refill as there may be new information they need to know.

Hypersensitivity
Inform patients that serious hypersensitivity reactions (e.g., angioedema) have been reported in patients treated with REPATHA. Advise patients on the symptoms of hypersensitivity reactions and instruct them to discontinue REPATHA and seek medical attention promptly, if such symptoms occur.

Administration
Provide guidance to patients and caregivers on proper subcutaneous administration technique, including aseptic technique, and how to use the single-use pre-filled autoinjector or single-use pre-filled syringe correctly (see **Instructions for Use** leaflet). Inform patients that it may take up to 15 seconds to administer REPATHA using the single-use pre-filled autoinjector or single-use pre-filled syringe.

Latex-Sensitivity
Advise latex-sensitive patients that the needle cover of the glass single-use pre-filled syringe and the single-use pre-filled autoinjector contain dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex.

REPATHA® (evolocumab)

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