# Office of Clinical Pharmacology Review

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| **BLA Number** | 125522; SDN1631; Supplement 29 |
| **Link to EDR** | \\CDSESUB1\evsprod\BLA125522\0297\ |
| **Submission Date** | 11/24/2020 |
| **Submission Type** | Standard |
| **Brand Name** | Repatha |
| **Generic Name** | Evolocumab |
| **Dosage Form and Strength** | 1. 140mg/mL solution as single-use prefilled syringe or single-use prefilled SureClick autoinjector<br>2. 420mg/3.5mL as single-use Pushtronex system (on-body infusor with prefilled cartridge) |
| **Route of Administration** | Subcutaneous Injection |
| **Proposed Indication** | As an adjunct to diet, alone or in combination with other lipid-lowering therapy, for the treatment of pediatric patients aged 10 years and older with HeFH to reduce LDL-C |
| **Applicant** | Amgen |
| **Associated IND** | IND 105188 |
| **OCP Review Team** | Mohamad Kronfol, PhD |
| **OCP Final Signatory** | Jayabharathi Vaidyanathan, PhD |

# Table of Contents

1. EXECUTIVE SUMMARY ..... 3
1.1 Recommendations ..... 3
1.2 Post-Marketing Requirements and Commitments ..... 4
2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT ..... 4
2.1. Clinical Pharmacology information from Study 20120123 and 20120124 ..... 4
2.2. Dosing and Therapeutic Individualization ..... 5
2.2.1. General dosing ..... 5
2.3. Outstanding Issues ..... 5
2.4. Summary of Labeling Recommendations ..... 5
3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW ..... 6
3.1 Overview of the Product and Regulatory Background ..... 6
3.2 General Pharmacology and Pharmacokinetic Characteristics ..... 6
3.3 Clinical Pharmacology Review Questions ..... 8
3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness? ..... 8
3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought? ..... 10
4. APPENDICES ..... 10
4.1 Summary of Bioanalytical Method Validation and Performance ..... 10

# 1. EXECUTIVE SUMMARY

Repatha (evolocumab) is a human monoclonal IgG2 antibody directed against proprotein convertase subtilisin kexin 9 (PCSK9) and indicated to:

(1) reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease

(2) as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C)

(3) as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

Upon approval of Repatha (BLA125522) in 2015, FDA required that pediatric studies for HeFH patients 10 to less than 18 years to be conducted under PMR 2946-1. PMR 2946-1 required the Applicant to conduct an efficacy and safety study evaluating Repatha (evolocumab) in patients with HeFH ages 10 years to less than 18 years. The study would be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study (Part A) followed by an 18-month open-label extension in patients 10 years to less than 18 years with HeFH on stable lipid modifying therapy with LDL-C ≥ 130 mg/dL (Part B). The FDA agreed upon the Applicant's pediatric plan that included two protocols for study number 20120123 (fulfills Part A) and 20120124 (fulfills Part B). The Sponsor has submitted a pediatric efficacy supplement on 11/24/2020 and is seeking approval for a pediatric indication as follows "an adjunct to diet, alone or in combination with other lipid lowering therapy, for the treatment of pediatric patients aged 10 years and older with HeFH to reduce LDL-C".

The Applicant have submitted the final results of 20120123 and the interim results of 20120124 in this application. The Sponsor made labeling changes to the Clinical Pharmacology section 12.3 of the PI to reflect the new pharmacokinetic measures in the pediatric population.

## 1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology has reviewed BLA125522 Supplement 29 and the Clinical Pharmacology data submitted on November 24, 2020 and found the data acceptable and recommends approval of BLA125522 Supplement 29.

| Review Issue | Recommendations and Comments |
|---|---|
| **Pivotal or supportive evidence of effectiveness** | The applicant completed study number 20120123 while 20120124 is ongoing at the time of this submission. The difference between evolocumab 420 mg once monthly and placebo in mean percent change in LDL C from baseline to Week 24 was −38% in study 20120123. |
| **General dosing instructions** | The proposed dosing is acceptable (see section 2.2.1) |

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|---|---|
| **Dosing in patient subgroups (intrinsic and extrinsic factors)** | Not applicable |
| **Labeling** | See section 2.4 for labeling recommendation |
| **Bridge between the to-be-marketed and clinical trial formulations** | The formulation used in the phase 3 Study 20120123 is the prefilled autoinjector pen (140 mg / mL) and in Study 20120124 the prefilled autoinjector pen was used or if available the automated mini-doser (420 mg /3.5 mL). |

### 1.2 Post-Marketing Requirements and Commitments

FDA communicated with applicant that it would accept this supplement prior to the completion of Study 20120124. PMR 2946-1 will not be fulfilled until that final study report is submitted and reviewed.

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

## 2.1. Clinical Pharmacology information from Study 20120123 and 20120124

In Study 20120123, following SC administration of 420 mg evolocumab once monthly (QM) in pediatric patients with HeFH, mean (SD) serum concentrations of evolocumab were 22.4 (14.7) µg/mL, 64.9 (34.4) µg/mL and 25.8 (19.2) µg/mL over week 12, week 22, and week 24, respectively, where week 12 and week 24 represent the end of the dosing interval (trough) and week 22 represents the middle of the dosing interval (Table 1).

**Table 1. Descriptive Statistics of Serum Evolocumab Concentration (µg/mL) After SC Administration of 420 mg QM Evolocumab to Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)** (Source: Table 11-1 of Study 20120123 CSR)

| Descriptive Statistics | Study Visit | | |
|---|---|---|---|
| | Week 12 (trough) | Week 22 | Week 24 (trough) |
| **N** | 99 | 81 | 96 |
| **Mean (µg/mL)** | 22.4 | 64.9 | 25.8 |
| **SD** | 14.7 | 34.4 | 19.2 |
| **Min (µg/mL)** | 0 | 6.23 | 1.44 |
| **Median (µg/mL)** | 20.6 | 65.1 | 22.1 |
| **Max (µg/mL)** | 78.1 | 143 | 112 |
| **CV%** | 65 | 53 | 74 |

In Study 20120124, for de novo pediatric HoFH patients, pharmacokinetic analysis showed mean (SD) trough serum evolocumab concentrations after 420 mg QM dosing were 20.3 (14.6) µg /mL and 17.6 (28.6) µg /mL at week 12 and week 80, respectively.

**Table 2. Descriptive Statistics of Serum Evolocumab Concentration (µg/mL) After SC Administration of 420 mg QM Evolocumab to Pediatric Subjects With Homozygous Familial Hypercholesterolemia (HoFH) (Source: Table 11-1 of Study 20120124 CSR)**

| Descriptive Statistics | Study Visit | |
|---|---|---|
| | Week 12 (trough) | Week 80 (trough) |
| **N** | 12 | 10 |
| **Mean (µg/mL)** | 20.3 | 17.6 |
| **SD** | 14.6 | 28.6 |
| **Min (µg/mL)** | 3.53 | 0 |
| **Median (µg/mL)** | 16.6 | 9.87 |
| **Max (µg/mL)** | 46.6 | 97.9 |
| **CV%** | 72 | 163 |

## 2.2. Dosing and Therapeutic Individualization

### 2.2.1. General dosing

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.

## 2.3. Outstanding Issues

None

## 2.4. Summary of Labeling Recommendations

*Note: Strikethrough stands for the language deleted by the reviewer and red font represents new labeling language proposed by the reviewer.*

Section 12.3:

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Pediatric Patients

The pharmacokinetics of REPATHA were evaluated in 103 pediatric patients aged 10 to 17 years with HeFH (Study 6) *[see Use in Specific Populations (8.4), Clinical Studies (14)].* Following subcutaneous administration of 420 mg REPATHA once monthly, mean (SD) trough serum concentrations were 22.4 (14.7) mcg/mL, (b) (4) and 25.8 (19.2) mcg/mL over the Week 12 (b) (4) and Week 24 time points, respectively. The pharmacokinetics of REPATHA were evaluated in 12 pediatric patients aged 11 to 17 years with HoFH (Study 9) *[see Use in Specific Populations (8.4), Clinical Studies (14)].* Following subcutaneous administration of 420 mg Repatha once monthly, mean (SD) serum trough concentrations were 20.3 (14.6) mcg/mL and 17.6 (28.6) mcg/mL at Week 12 and Week 80, respectively.

# 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

## 3.1 Overview of the Product and Regulatory Background

Evolocumab injection for subcutaneous use is marketed in the US as Repatha (BLA 125522) by Amgen Inc. The Applicant submitted supplement 29 under this BLA 125522 application on November 24, 2020 for approval to market its Repatha (evolocumab) Injection, 140mg/mL solution as single-use prefilled syringe or single-use prefilled SureClick® autoinjector 420mg/3.5mL as single-use Pushtronex® system (on-body infusor with prefilled cartridge) in pediatric HeFH patients aged 10 to 17 years based on complete study results from Study 20120123 and interim result from Study 20120124. The Applicant is providing findings of safety and effectiveness for Repatha in pediatric HeFH subjects to support this BLA.

## 3.2 General Pharmacology and Pharmacokinetic Characteristics

*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 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.

*Summary of General Clinical Pharmacology and 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 Cmax mean (standard deviation [SD]) of 18.6 (7.3) µg/mL and AUClast mean (SD) of 188 (98.6) day•µg/mL. Administration of the 420 mg dose in healthy volunteers resulted in a Cmax mean (SD) of 59.0 (17.2) µg/mL and AUClast mean (SD) of 924 (346) day•µg/mL. Following a single 420 mg intravenous dose, the mean (SD) systemic clearance was estimated to be 12 (2) mL/hr. An approximate 2 to 3 fold accumulation was observed in trough serum concentrations (Cmin [SD] 7.21 [6.6]) following 140 mg doses administered subcutaneously every 2 weeks or following 420 mg doses administered

subcutaneously monthly (Cmin [SD] 11.2 [10.8]), 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 (SD) steady state volume of distribution was estimated to be 3.3 (0.5) 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.

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

*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] ≥ 90 mL/min/1.73 m2, n = 6), severe renal impairment (eGFR < 30 mL/min/1.73 m2, 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

*Hepatic Impairment*

Following a single 140 mg subcutaneous dose of evolocumab in patients with mild or moderate hepatic impairment, a 20 30% lower mean Cmax and 40 50% lower mean AUC were observed as compared to healthy patients.

*Drug Interaction Studies*

An approximately 20% decrease in the Cmax and AUC of evolocumab was observed in adult patients co administered with a high intensity statin regimen. This difference is not clinically meaningful.

## 3.3 Clinical Pharmacology Review Questions

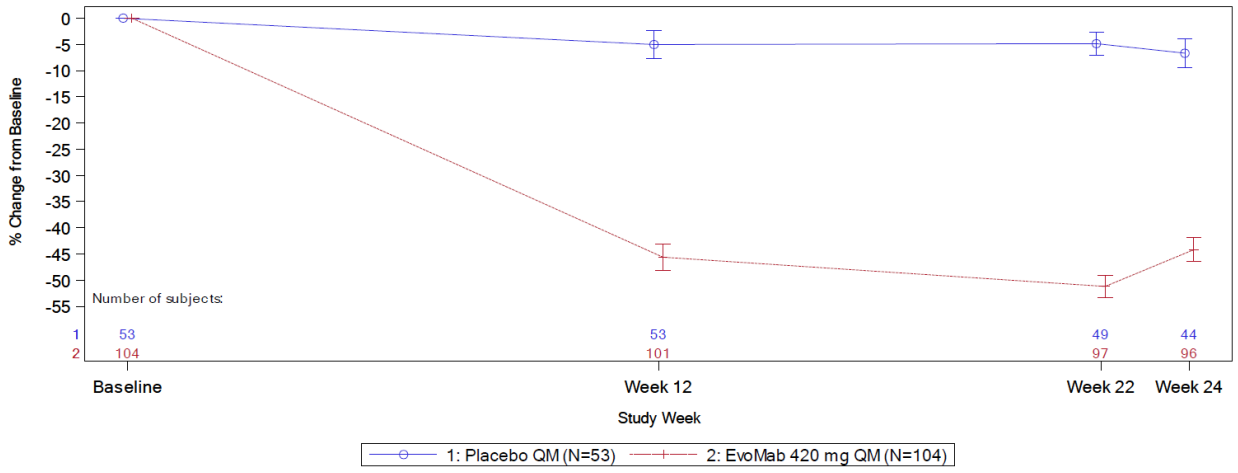
### *3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?*

The Phase 3b study 20120123 was a double-blind, randomized, multicenter, placebo-controlled, parallel group study to characterize the efficacy, safety, and tolerability of 24 weeks of evolocumab for low density lipoprotein-cholesterol (LDL-C) reduction, as add-on to diet and lipid-lowering therapy, in pediatric subjects 10 to 17 years of age with HeFH. The primary objective was to evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab compared with placebo, when added to standard of care, on percent change from baseline in LDL-C. The LS mean (SE) reduction in LDL-C from baseline at week 24 was 44.5% (2.2%) in the evolocumab group and 6.2% (3.1%) in the placebo group with a statistically significant LS mean treatment difference (95% CI) of 38.3% (31.1, 45.5). Mean percent changes from baseline at week 12, 22, and 24 are reported in **Figure 1**.

Serum concertation of evolocumab was evaluated on week 12 and 24 (trough) and on week 22 (peak). Mean (SD) serum trough concentration values of evolocumab at week 12 and week 24 were similar and ranged from 22.4 (14.7) to 25.8 (19.2) µg/mL (**Table 1** and **Figure 2**). Mean (SD) serum concertation values of unbound PCSK9 at week 12, week 22, and week 24 were 137.3 (86), 19.9 (51.9) and 150.5 (104.2) ng/mL. The reviewer's analysis agrees with that of the applicant.

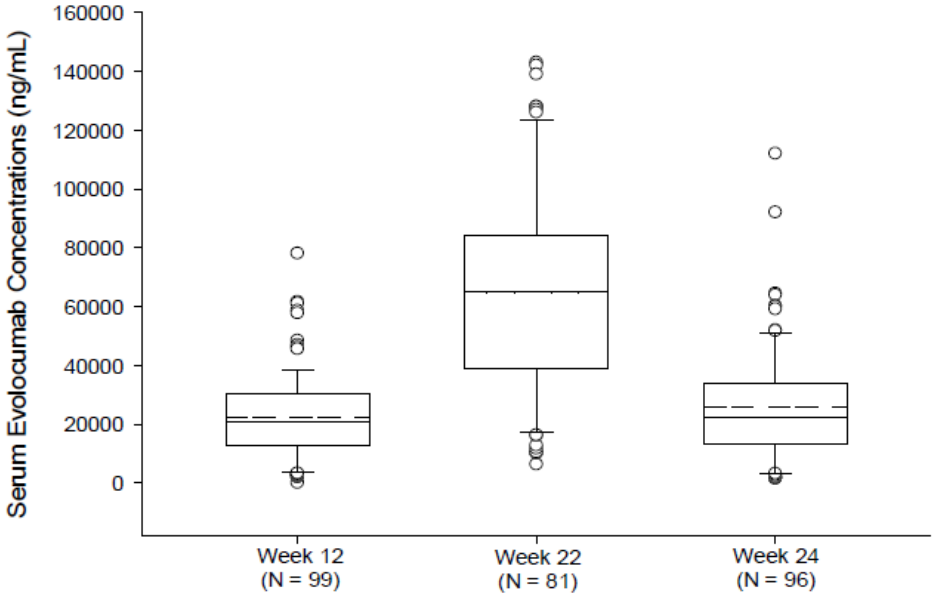
The development of anti-evolocumab antibodies was not detected at baseline or post-baseline in this study in pediatric patients treated with evolocumab and therefore there is no effect observed on PK.

**Figure 1. Mean Percent Change From Baseline in LDL-C by Scheduled Visit and Treatment Group Study 20120123 (**Source: Figure 10-1 page 66 of Study 20120123 CSR**)**



EvoMab = Evolocumab (AMG 145); LDL-C = low density lipoprotein cholesterol; QM = monthly (subcutaneous). N = number of subjects 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. When calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, the UC LDL-C value from the same blood sample was used instead, if available.

**Figure 2. Serum Evolocumab Concentrations by Week in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH).** (Source: Figure 11-1 page 76 of Study 2012013 CSR)




Y-axis is in linear scale. Note: Boxes display mean (dashed lines), median (solid lines), 25th (bottom) percentile), and 75th (top) percentile. Whiskers represent the 10th (bottom) and 90th (top) percentiles

The Phase 3b study 20120124 was open-label, single-arm, multicenter study to evaluate the safety, tolerability and efficacy of evolocumab for LDL-C reduction, as add-on to diet and lipid-lowering therapy, in pediatric subjects from 10 to 17 years of age with HeFH or HoFH (interim analysis). Since the applicant plans to use interim results of this study to support labeling changes to section 12.3 regarding pediatric HoFH population, we will focus on the PK assessment in this review.

Serum concertation of evolocumab was evaluated on week 12 and 80 (trough) before apheresis. Evolocumab was administered after the apheresis. Mean (SD) serum trough concentration values of evolocumab at week 12 and week 80 were similar and ranged from 20.3 (14.6) to 17.6 (28.6) µg/mL (**Table 2**). The reviewer's analysis agrees with that of the applicant.

The development of anti-evolocumab antibodies was not detected at baseline or post-baseline in this study in pediatric patients treated with evolocumab and therefore there is no effect observed on PK.

### *3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought because it is consistent with the dosing regimen of the US approved Repatha.

# 4. APPENDICES

## 4.1 Summary of Bioanalytical Method Validation and Performance

The Applicant used ELISA assay (BAL-II/MOA/026) to determine evolocumab concentration in human serum (Validation Report Study No. 12253/Amgen PKDM number: 117093). Briefly, microplates coated with Mu anti- evolocumab (Clone 1.18.1 Mab, Amgen Inc) captured evolocumab from serum samples. Unbound material was removed by washing the microplate wells. Following washing, Horseradish peroxidase (HRP) conjugated Mu anti-evolocumab (Clone 1.46.1 Mab, Amgen Inc.) was added to the microplate wells to bind the captured evolocumab. After another wash step, a one component 3,3',5,5'tetramethylbenzidine (TMB) substrate solution was added to the wells. The TMB substrate solution reacts with peroxide and in the presence of HRP, creates a colorimetric signal, which was proportional to the amount of evolocumab bound by the capture reagent. The reaction was stopped using 1N H2SO4 and the intensity of the color (OD) was measured at 450 nm with reference to 650 nm subtracted. The OD signal versus concentration relationship was regressed according to a logistic (auto-estimate) 4 PL regression model with a weighting factor of 1. The conversion of OD signals to concentrations was performed using Watson LIMS data reduction software. Summary of key descriptive parameters for the bioanalytical assay used is reported in **Table 3.** The bioanalytical assay for measuring evolocumab in serum samples is acceptable.

**Table 3. Bioanalytical method validation of serum evolocumab concentrations for Study 2012013.** (Source: sections 2.3, 2.4 pages 18 of the supportive PK information of Study 20120123 and validation report No. 12253)

| | |
|---|---|
| Validation Study Number: | 12253 |
| Method Type: | ELISA |
| Regression Model; Weighting Factor | Logistic (auto-estimate) (4-PL) with weighing factor of 1 |
| Test Article | evolocumab |
| Lower Limit of Quantitation (LLOQ): | 800 ng/mL |
| Upper Limit of Quantitation (ULOQ): | 10000 ng/mL |
| Inter-assay Accuracy (%Bias) Standard curve 800-10000 ng/mL | -4 to 4 |

| | |
|---|---|
| Inter-assay Precision (%CV)<br>Standard curve 800-10000 ng/mL | 1 to 2 |
| Freeze/Thaw Stability: | Up to 5 cycles |
| Room Temperature Stability: | Up to 24 hours |
| 2 to 8°C Stability: | Up to 24 hours |
| Long Term Stability: | Up to 394 days at -70 to -90 °C |
| Method Developed By: | Applicant, validated at (b) (4) |

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