

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125522Orig1s001

Trade Name: **Repatha injection**

Generic Name: **evolocumab**

Sponsor: **Amgen, Inc.**

Approval Date: **07/08/2016**

Indications: REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and:

- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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APPROVAL LETTER



BLA 125522/S-001, S-004

SUPPLEMENT APPROVAL

Amgen, Inc.
Attention: Adam Rupert
Senior Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-B
Thousand Oaks, CA 01320-1799

Dear Mr. Rupert:

Please refer to the following Supplemental Biologics License Applications (sBLAs) submitted under section 351(a) of the Public Health Service Act for Repatha (evolocumab) injection, 140 mg/mL:

1. Supplement -001 (S-001), dated and received September 10, 2015, proposes to market the Repatha Pushtronex system consisting of a Repatha (evolocumab) injection 420 mg/3.5 mL prefilled cartridge co-packaged with on-body infusion device, and associated labeling revisions.
2. Supplement -004 (S-004), dated and received February 29, 2016, submitted as a Changes Being Effected, as described under 21 CFR 601.12(f)(2), proposes to revise the Instructions for Use (IFU) for the approved SureClick® Autoinjector. Specifically, text and pictures have been added to convey that upon removal of the orange cap, the product should be injected within 5 minutes, and associated minor labeling revisions.

MANUFACTURING LOCATIONS

The final formulated prefilled cartridge drug product will be manufactured [REDACTED] (b) (4)

DATING PERIOD

The dating period for the Repatha Pushtronex system shall be 24 months from the date of manufacture when stored at 2-8C. The date of manufacture shall be defined as the date of sterile filtration of the formulated drug product. The expiration date for the Repatha Pushtronex system shall not exceed the shortest shelf life of any of the Repatha Pushtronex system components.

Results of ongoing stability studies should be submitted to the annual report.

We have approved the stability protocols in your supplemental application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, and Instructions for Use [IFU]) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in these supplemental applications.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125522/S-001.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 3105-1 Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the interim 1-year timepoint. These studies should use the methods equivalent to those used to evaluate device performance in the accelerated aging studies. The interim report must include results from the following shelf life tests: Device Function Test, Deliverable Volume Test, Injection Time Test, Sterile ^{(b) (4)} Integrity Test, ^{(b) (4)} Function Test, and Adhesive Function Test.

The timetable you submitted on July 6, 2016, states that you will conduct this study according to the following schedule:

Interim Report (1-year timepoint) Submission: July 2017

- 3105-2 Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the interim 2-year and 31-day timepoint. These studies should use methods equivalent to those used to evaluate device performance in the accelerated aging studies. The final report must include results from the following shelf life tests: Device Function Test, Deliverable Volume Test, Injection Time Test, Sterile ^{(b) (4)} Integrity Test, ^{(b) (4)} Function Test, and Adhesive Function Test.

The timetable you submitted on July 6, 2016, states that you will conduct this study according to the following schedule:

Interim Report (2-year and 31-day timepoint) Submission: July 2018

- 3105-3 Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the final 3-year and 31-day timepoint. These studies should use methods equivalent to those used to evaluate device performance in the accelerated aging studies. The final report must include results from the following shelf life tests: Device Function Test, Deliverable Volume Test, Injection Time Test, Sterile (b) (4) Integrity Test, (b) (4) Function Test, and Adhesive Function Test.

The timetable you submitted on July 6, 2016, states that you will conduct this study according to the following schedule:

Interim Report (3-year and 31-day timepoint) Submission: July 2019

Submit clinical protocols to your IND 105188 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Kati Johnson, Senior Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

James P. Smith, MD, MS
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Package Insert (S-001, S-004)

Patient Information (S-001)
Instructions for Use (S-001)
Instructions for Use (S-004)
Carton and Container Labeling (S-001)
Prefilled Cartridge Label
(b) (4) Lid Labeling
Carton (Trade)
Carton (Replacement)
Device Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
07/08/2016

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REPATHA® safely and effectively. See full prescribing information for REPATHA.

REPATHA (evolocumab) injection, for subcutaneous use
Initial U.S. Approval: 2015

-----RECENT MAJOR CHANGES-----
Dosage and Administration (2.2) 7/2016

-----INDICATIONS AND USAGE-----

REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and:

- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). (1.1)
- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. (1.2)

Limitations of Use

- The effect of REPATHA on cardiovascular morbidity and mortality has not been determined. (1.3)

-----DOSAGE AND ADMINISTRATION-----

- Administer subcutaneously. (2.1)
- Primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH: 140 mg every 2 weeks or 420 mg once monthly in abdomen, thigh, or upper arm. (2.1)
- HoFH: 420 mg once monthly. (2.1)
- The 420 mg dose of REPATHA can be administered:
 - over 9 minutes by using the single-use on-body infusor with prefilled cartridge, or
 - by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector or single-use prefilled syringe. (2.2)
- See Dosage and Administration for important administration instructions. (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

- Injection: 140 mg/mL solution in a single-use prefilled syringe (3)
- Injection: 140 mg/mL solution in a single-use prefilled SureClick® autoinjector (3)
- Injection: 420 mg/3.5 mL solution in a single-use Pushtronex™ system (on-body infusor with prefilled cartridge) (3)

-----CONTRAINDICATIONS-----

Patients with a history of a serious hypersensitivity reaction to REPATHA. (4)

-----WARNINGS AND PRECAUTIONS-----

Allergic Reactions: Rash and urticaria have occurred. 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. (5.1)

-----ADVERSE REACTIONS-----

Common adverse reactions in clinical trials (> 5% of patients treated with REPATHA and occurring more frequently than placebo): nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Primary Hyperlipidemia

REPATHA[®] is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

1.2 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.

1.3 Limitations of Use

The effect of REPATHA on cardiovascular morbidity and mortality has not been determined.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended subcutaneous dosage of REPATHA in patients with HeFH or patients with primary hyperlipidemia with established clinical atherosclerotic CVD is either 140 mg every 2 weeks OR 420 mg once monthly. When 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 patients 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.

If an every 2 week or once monthly dose is missed, instruct the patient to:

- Administer REPATHA as soon as possible if there are more than 7 days until the next scheduled dose, or,
- Omit the missed dose and administer the next dose according to the original schedule.

2.2 Important Administration Instructions

- The 420 mg dose of REPATHA can be administered:
 - over 9 minutes by using the single-use on-body infusor with prefilled cartridge, or
 - by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector or single-use prefilled 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 prefilled autoinjector or single-use prefilled syringe and for at least 45 minutes for the single-use on-body infusor with prefilled cartridge. Do not warm in any other

way. Alternatively, for patients and caregivers, REPATHA can be kept at room temperature at 68° F to 77°F (20°C to 25°C) in the original carton. However, under these conditions, REPATHA must be used within 30 days [see *How Supplied/Storage and Handling (16)*].

- 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 prefilled syringe, single-use prefilled autoinjector, or single-use on-body infusor with prefilled cartridge.
- 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 prefilled syringe
- Injection: 140 mg/mL solution in a single-use prefilled SureClick® autoinjector
- Injection: 420 mg/3.5 mL solution in a single-use Pushtronex™ system (on-body infusor with prefilled cartridge)

4 CONTRAINDICATIONS

REPATHA is contraindicated in patients with a history of a serious hypersensitivity reaction to REPATHA [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

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

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 Patients with Primary Hyperlipidemia and in Patients with Heterozygous Familial Hypercholesterolemia

REPATHA is not indicated for use in patients without familial hypercholesterolemia or atherosclerotic CVD [see *Indications and Usage (1.1)*].

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 2), 599 patients received 420 mg of REPATHA subcutaneously once monthly [see *Clinical Studies (14.1)*]. 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, and 6% Hispanic. Adverse reactions reported in at least 3% of REPATHA-treated patients, and more frequently than in placebo-treated patients in Study 2, 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 Study 2

	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% Hispanic. 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 (Study 2) 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%).

Neurocognitive Events

In placebo-controlled trials, neurocognitive events were reported in less than or equal to 0.2% in REPATHA-treated and placebo-treated patients.

Low LDL-C Levels

In a pool of placebo- and active-controlled trials, as well as open-label extension studies that followed them, a total of 1988 patients treated with REPATHA had at least one LDL-C value < 25 mg/dL. Changes to background lipid-altering therapy were not made in response to low LDL-C values, and REPATHA dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C

were not identified in these trials, the long-term effects of very low levels of LDL-C induced by REPATHA are unknown.

Musculoskeletal Events

Musculoskeletal adverse reactions were reported in 14.3% of REPATHA-treated patients and 12.8% of placebo-treated patients. The most common adverse reactions that occurred at a rate greater than placebo were back pain (3.2% versus 2.9% for REPATHA and placebo, respectively), arthralgia (2.3% versus 2.2%), and myalgia (2.0% versus 1.8%).

Adverse Reactions in Patients with Homozygous Familial Hypercholesterolemia

In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH (Study 4), 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 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, 0.1% of patients treated with at least one dose of REPATHA tested positive for binding antibody development. 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.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of 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 with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 studies, 1420 patients treated with REPATHA were ≥ 65 years old and 171 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 mild to moderate renal impairment. No data are available in patients with severe 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)*].

11 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 administration. Each 1 mL single-use prefilled syringe and single-use prefilled SureClick[®] 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. Each single-use Pushtronex[™] system (on-body infusor with prefilled cartridge) delivers a 3.5 mL solution containing 420 mg evolocumab, acetate (4.2 mg), polysorbate 80 (0.35 mg), proline (89 mg) in Water for Injection, USP. Sodium hydroxide may be used to adjust to a pH of 5.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Evolocumab is a human monoclonal IgG2 directed against human proprotein convertase subtilisin kexin 9 (PCSK9). Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the low density lipoprotein (LDL) receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. 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.

12.2 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.

12.3 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 (standard deviation [SD]) of 18.6 (7.3) $\mu\text{g/mL}$ and AUC_{last} mean (SD) of 188 (98.6) $\text{day}\cdot\mu\text{g/mL}$. Administration of the 420 mg dose in healthy volunteers resulted in a C_{max} mean (SD) of 59.0 (17.2) $\mu\text{g/mL}$ and AUC_{last} mean (SD) of 924 (346) $\text{day}\cdot\mu\text{g/mL}$. 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 (C_{min} [SD] 7.21 [6.6]) following 140 mg doses administered subcutaneously every 2 weeks or following 420 mg doses administered subcutaneously monthly (C_{min} [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.

Metabolism and 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 (8.5)*].

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. Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) have not been studied.

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; however, no dose adjustment is necessary in these patients.

Pregnancy

The effect of pregnancy on evolocumab pharmacokinetics has not been studied [*see Use in Specific Populations (8.1)*].

Drug Interaction Studies

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

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.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia in Patients with Clinical Atherosclerotic Cardiovascular Disease

Study 1 was a multicenter, double-blind, randomized controlled 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 296 patients with atherosclerotic CVD who received REPATHA or placebo as add-on therapy to daily doses of atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg. Among these patients, the mean age at baseline was 63 years (range: 32 to 80 years), 45% were ≥ 65 years old, 33% women, 98% White, 2% were Black, < 1% Asian and 5% Hispanic or Latino. After 4 weeks of statin therapy, the mean baseline LDL-C was 108 mg/dL.

In these patients with atherosclerotic CVD who were on maximum-dose statin therapy, the difference between REPATHA and placebo in mean percent change in LDL-C from baseline to Week 12 was -71%

(95% CI: -81%, -61%; $p < 0.0001$) and -63% (95% CI: -76%, -50%; $p < 0.0001$) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively. For additional results see Table 3 and Figure 1.

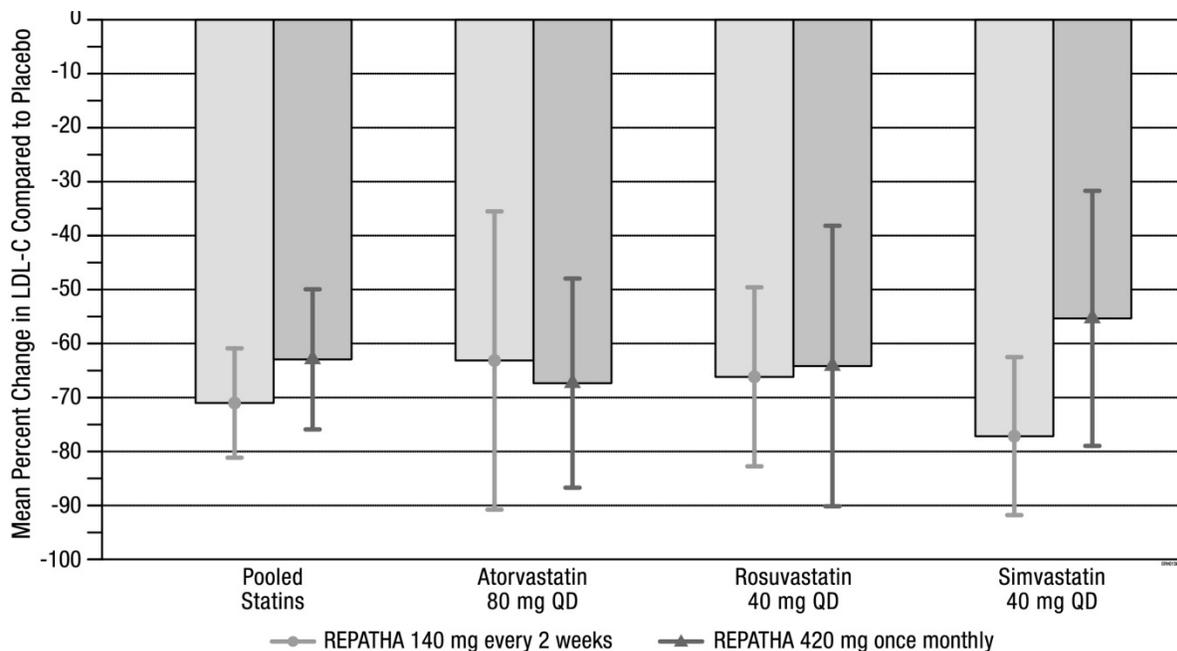
Table 3. Effect of REPATHA on Lipid Parameters in Patients with Atherosclerotic CVD on Atorvastatin 80 mg, Rosuvastatin 40 mg, or Simvastatin 40 mg (Mean % Change from Baseline to Week 12 in Study 1)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo every 2 weeks (n = 42)	7	2	5	4
REPATHA 140 mg every 2 weeks [†] (n = 105)	-64	-56	-49	-38
Mean difference from placebo (95% CI)	-71 (-81, -61)	-58 (-67, -49)	-55 (-62, -47)	-42 (-48, -36)
Placebo once monthly (n = 44)	5	5	3	3
REPATHA 420 mg once monthly [†] (n = 105)	-58	-47	-46	-32
Mean difference from placebo (95% CI)	-63 (-76, -50)	-52 (-63, -41)	-49 (-58, -39)	-36 (-43, -28)

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 1. Effect of REPATHA on LDL-C in Patients with Atherosclerotic CVD when Combined with Statins (Mean % Change from Baseline to Week 12 in Study 1)



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

Error bars indicate 95% confidence intervals

Study 2 was a multicenter, double-blind, randomized, placebo-controlled, 52-week trial that included 139 patients with atherosclerotic CVD who received protocol-determined background lipid-lowering therapy of atorvastatin 80 mg daily with or without ezetimibe 10 mg daily. After stabilization on

background therapy, patients were randomly assigned to the addition of placebo or REPATHA 420 mg administered subcutaneously once monthly. Among these patients, the mean age at baseline was 59 years (range: 35 to 75 years), 25% were ≥ 65 years, 40% women, 80% White, 3% Black, 5% Asian, and $< 1\%$ Hispanic or Latino. After stabilization on the assigned background therapy, the mean baseline LDL-C was 105 mg/dL.

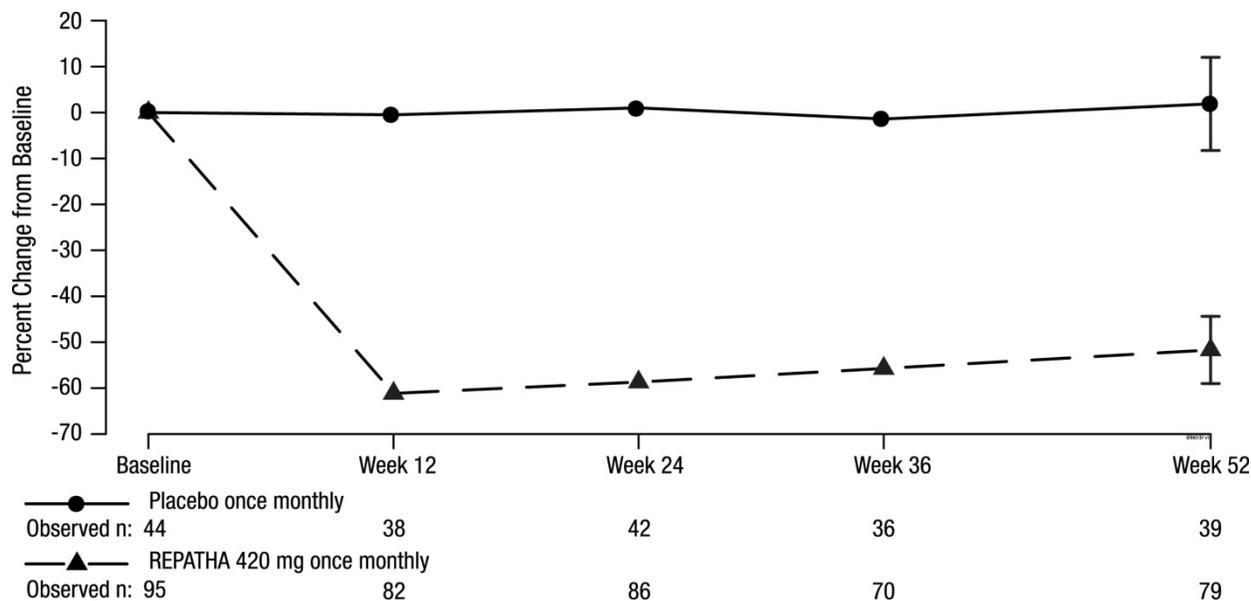
In these patients with atherosclerotic CVD on maximum-dose atorvastatin therapy with or without ezetimibe, the difference between REPATHA 420 mg once monthly and placebo in mean percent change in LDL-C from baseline to Week 52 was -54% (95% CI: -65% , -42% ; $p < 0.0001$) (Table 4 and Figure 2). For additional results see Table 4.

Table 4. Effect of REPATHA on Lipid Parameters in Patients with Atherosclerotic CVD on Atorvastatin 80 mg with or without Ezetimibe 10 mg daily (Mean % Change from Baseline to Week 52 in Study 2)

Treatment Group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Placebo once monthly (n = 44)	2	3	0	3
REPATHA 420 mg once monthly (n = 95)	-52	-41	-40	-28
Mean difference from placebo (95% CI)	-54 (-65, -42)	-44 (-56, -32)	-40 (-50, -30)	-31 (-39, -24)

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

Figure 2. Effect of REPATHA 420 mg Once Monthly on LDL-C in Patients with Atherosclerotic CVD on Atorvastatin 80 mg with or without Ezetimibe 10 mg Daily



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

14.2 Heterozygous Familial Hypercholesterolemia (HeFH)

Study 3 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). In Study 3, 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.

In these patients with HeFH on statins with or without other lipid lowering therapies, 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 5.

Table 5. Effect of REPATHA on Lipid Parameters in Patients with HeFH (Mean % Change from Baseline to Week 12 in Study 3)

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)
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

14.3 Homozygous Familial Hypercholesterolemia (HoFH)

Study 4 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.

In these patients with HoFH, 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 6.

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

Table 6. Effect of REPATHA on Lipid Parameters in Patients with HoFH (Mean % Change from Baseline to Week 12 in Study 4)

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	-31	-28	-21	-25
95% CI	(-44, -18)	(-41, -16)	(-33, -9)	(-36, -14)

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

16 HOW SUPPLIED/STORAGE AND HANDLING

REPATHA is a sterile, clear to opalescent, colorless to pale yellow solution for subcutaneous administration supplied in a single-use prefilled syringe, a single-use prefilled SureClick® autoinjector, or a single-use Pushtronex™ system (on-body infusor with prefilled cartridge). Each single-use prefilled syringe or single-use prefilled SureClick® autoinjector of REPATHA is designed to deliver 1 mL of 140 mg/mL solution. Each single-use Pushtronex™ system (on-body infusor with prefilled cartridge) is designed to deliver 420 mg evolocumab in 3.5 mL solution.

140 mg/mL single-use prefilled syringe	1 pack	NDC 55513-750-01
140 mg/mL single-use prefilled SureClick® autoinjector	1 pack	NDC 55513-760-01
140 mg/mL single-use prefilled SureClick® autoinjector	2 pack	NDC 55513-760-02
140 mg/mL single-use prefilled SureClick® autoinjector	3 pack	NDC 55513-760-03
420 mg/3.5 mL single-use Pushtronex™ system (on-body infusor with prefilled cartridge)	1 pack	NDC 55513-770-01

Pharmacy

Store refrigerated at 2° to 8°C (36° to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

For Patients/Caregivers

Store refrigerated at 2° to 8°C (36° to 46°F) in the original carton. Alternatively, REPATHA can be kept at room temperature at 68° F to 77°F (20°C to 25°C) in the original carton; however, under these conditions, REPATHA must be used within 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 (77°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved 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.

Provide guidance to patients and caregivers on proper subcutaneous administration technique, including aseptic technique, and how to use the single-use prefilled autoinjector, single-use prefilled syringe, or single-use on-body infusor with prefilled cartridge correctly (see **Instructions for Use** leaflet). Inform patients that it may take up to 15 seconds to administer REPATHA using the single-use prefilled autoinjector or single-use prefilled syringe and about 9 minutes to administer REPATHA using the single-use on-body infusor with prefilled cartridge.

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

The single-use on-body infusor with prefilled cartridge is not made with natural rubber latex.

For more information about REPATHA, go to www.REPATHA.com or call 1-844-REPATHA (1-844-737-2842).

AMGEN[®]

REPATHA[®] (evolocumab)

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

U.S. License Number 1080

Patent: <http://pat.amgen.com/repatha/>

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Patient Information
REPATHA® (ri-PAth-a)
(evolocumab)
Injection, for Subcutaneous Use

What is REPATHA?

REPATHA is an injectable prescription medicine called a PCSK9 inhibitor. REPATHA is used:

- along with diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia (an inherited condition that causes high levels of LDL) or atherosclerotic heart or blood vessel problems, who need additional lowering of LDL cholesterol.
- along with diet and other LDL lowering therapies in people with homozygous familial hypercholesterolemia (an inherited condition that causes high levels of LDL), who need additional lowering of LDL cholesterol.

The effect of REPATHA on heart problems such as heart attacks, stroke, or death is not known.

It is not known if REPATHA is safe and effective in children with homozygous familial hypercholesterolemia (HoFH) who are younger than 13 years of age or in children who do not have HoFH.

Who should not use REPATHA?

Do not use REPATHA if you are allergic to evolocumab or to any of the ingredients in REPATHA. See the end of this leaflet for a complete list of ingredients in REPATHA.

What should I tell my healthcare provider before using REPATHA?

Before you start using REPATHA, tell your healthcare provider about all your medical conditions, including allergies, and if you:

- are allergic to rubber or latex. The needle covers on the single-use prefilled syringes and within the needle caps on the single-use prefilled SureClick® autoinjectors contain dry natural rubber. The single-use Pushtronex™ system (on-body infusor with prefilled cartridge) is not made with natural rubber latex.
- are pregnant or plan to become pregnant. It is not known if REPATHA will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking REPATHA.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take REPATHA or breastfeed. You should not do both without talking to your healthcare provider first.

Tell your healthcare provider or pharmacist about any prescription and over-the-counter medicines you are taking or plan to take, including natural or herbal remedies.

How should I use REPATHA?

- **See the detailed “Instructions for Use” that comes with this patient information about the right way to prepare and administer REPATHA.**
- Use REPATHA exactly as your healthcare provider tells you to use it.
- REPATHA is administered under the skin (subcutaneously), every 2 weeks or 1 time each month.
- REPATHA comes as a single-use (1 time) prefilled autoinjector (SureClick® autoinjector), as a single-use prefilled syringe or as a single-use Pushtronex™ system (on-body infusor with prefilled cartridge). Your healthcare provider will prescribe the type and dose that is best for you.
- If your healthcare provider prescribes you the monthly dose, you may use:
 - a single-use on-body infusor with prefilled cartridge over 9 minutes, or
 - 3 separate injections in a row, using a different single-use prefilled syringe or single-use prefilled autoinjector for each injection. Give all of these injections within 30 minutes.
- If your healthcare provider decides that you or a caregiver can administer REPATHA, you or your caregiver should receive training on the right way to prepare and administer REPATHA. **Do not** try to administer REPATHA until you have been shown the right way by your healthcare provider or nurse.
- **Do not** administer REPATHA together with other injectable medicines at the same injection site.
- Always check the label of your single-use prefilled autoinjector, single-use prefilled syringe, or single-use on-body infusor with prefilled cartridge to make sure you have the correct medicine and the correct dose of REPATHA before each administration.
- If you forget to use REPATHA or are not able to take the dose at the regular time, administer your missed dose as soon as you remember, as long as there are more than 7 days until the next scheduled dose. If there are 7 days or less until your next scheduled dose, administer the next dose according to the original schedule. This will put you back on your original schedule. If you are not sure when to take REPATHA after a missed dose, ask your healthcare provider or pharmacist.
- If you use more REPATHA than you should, talk to your healthcare provider or pharmacist.
- **Do not** stop using REPATHA without talking with your healthcare provider. If you stop using REPATHA, your cholesterol levels can increase.

What are possible side effects of REPATHA?

REPATHA can cause side effects including:

- **allergic reactions.** REPATHA may cause allergic reactions. Call your healthcare provider or go to the nearest hospital emergency room right away if you have any symptoms of an allergic reaction including a severe rash, redness, severe itching, a swollen face, or trouble breathing.

The most common side effects of REPATHA include: runny nose, sore throat, symptoms of the common cold, flu or flu-like symptoms, back pain, and redness, pain, or bruising at the injection site.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of REPATHA. Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of REPATHA.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. **Do not** use REPATHA for a condition for which it was not prescribed. **Do not** give REPATHA to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about REPATHA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about REPATHA that is written for healthcare professionals.

For more information about REPATHA, go to www.REPATHA.com or call 1-844-REPATHA (1-844-737-2842).

What are the ingredients in REPATHA?

- Active Ingredient: evolocumab
- Inactive Ingredients: proline, glacial acetic acid, polysorbate 80, water for injection, and sodium hydroxide.

Manufactured by: Amgen Inc. One Amgen Center Drive, Thousand Oaks, California 91320-1799.

U.S. License Number 1080

Patent: <http://pat.amgen.com/repatha/>

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This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised:

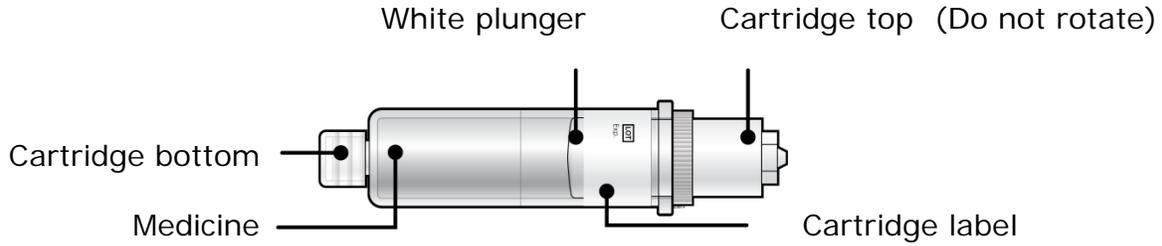
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**Instructions for use:
Pushtronex™ System for
Repatha® (ri-PAth-a)
(evolocumab)**

Single-Use On-Body Infusor and Prefilled Cartridge

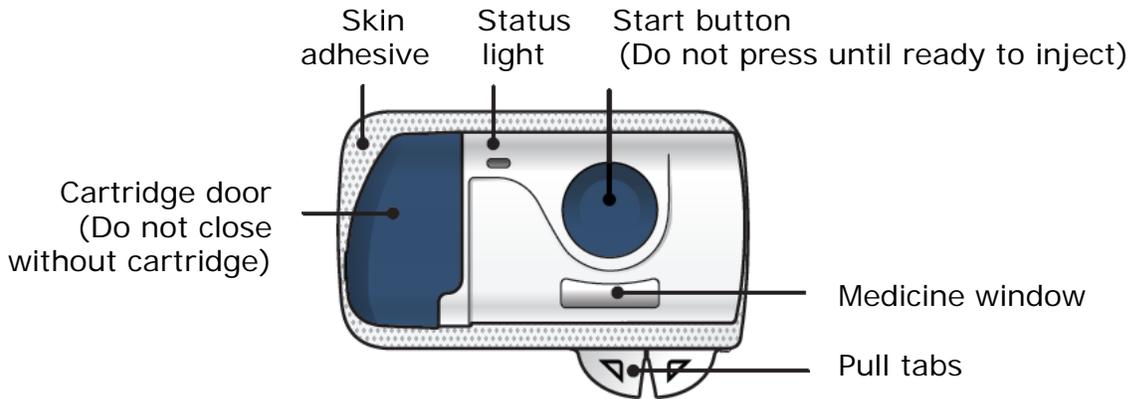
Guide to parts

Prefilled Cartridge

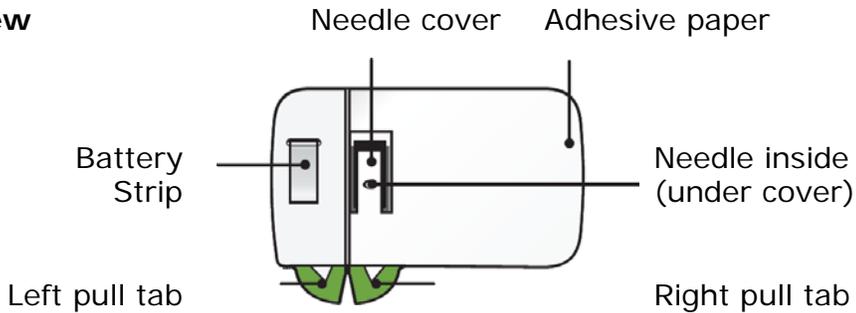


On-Body Infusor

Front view



Back view



Important: Needle is inside.

Important

Before you use the on-body infusor and prefilled cartridge for use with Repatha (evolocumab), read this important information:

- It is important that you do not try to give yourself the injection unless you have received training from your healthcare provider.

Storing your on-body infusor and prefilled cartridge

- Keep the on-body infusor and prefilled cartridge in the original carton to protect from light or physical damage.
- The on-body infusor and prefilled cartridge must be kept in the refrigerator 36 °F to 46 °F (2 °C to 8 °C).
- If removed from the refrigerator, the on-body infusor should be kept at room temperature at 68° F to 77°F (20° C to 25°C) in the original carton and must be used within 30 days.
- **Do not** store the on-body infusor and prefilled cartridge in temperatures above 77°F (25°C) such as in your vehicle's glove box or trunk. **Do not** freeze.

Using your on-body infusor and prefilled cartridge

- **Do not** shake the on-body infusor or prefilled cartridge.
- **Do not** remove the on-body infusor and prefilled cartridge from the box or clear tray until you are ready to inject.
- **Do not** touch the start button until you place the loaded on-body infusor and prefilled cartridge onto your skin and are ready to inject.
- You can only press the start button 1 time. If an error occurs, the on-body infusor cannot be used.
- **Do not** use the on-body infusor and prefilled cartridge if either has been dropped onto a hard surface. Part of the on-body infusor and prefilled cartridge may be broken even if you cannot see the break. Use a new on-body infusor and prefilled cartridge.
- **Do not** reuse the on-body infusor and prefilled cartridge. The on-body infusor and prefilled cartridge are for single use only.
- **Do not** let the on-body infusor get wet from water or any other liquids. It contains electronics that should not get wet.
- The single use on-body infusor for subcutaneous injection is made to only be used with the prefilled cartridge.
- Moderate physical activities can be done during the injection process, such as walking, reaching and bending.
- **Do not** use the on-body infusor and prefilled cartridge after the expiration date on the carton.
- The on-body infusor and prefilled cartridge are not made with natural rubber latex.

A healthcare provider who knows how to use the on-body infusor should be able to answer your questions. For more information, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

Keep the on-body infusor and prefilled cartridge out of the reach of children.

Step 1: Prepare

- 1A** Remove the on-body infusor and prefilled cartridge carton from the refrigerator. Wait 45 minutes.

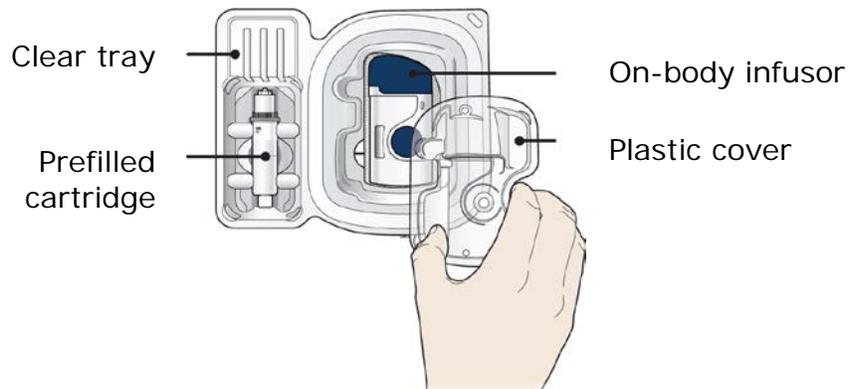


Important: Wait at least 45 minutes for the on-body infusor and prefilled cartridge to naturally reach room temperature in the carton.

- **Do not** try to warm the prefilled cartridge by using a heat source such as hot water or a microwave.

In any above cases, use a new on-body infusor and prefilled cartridge and call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

- 1B** Open the carton and peel away the white paper cover. Remove the plastic cover from the clear tray.



Leave the on-body infusor and prefilled cartridge in the clear tray until you are ready to inject.

- **Do not** touch the start button until the on-body infusor is on skin and you are ready to inject
- **Do not** use if the white paper cover is missing or damaged

1C Gather all materials needed for your injection and then wash your hands well with soap and water.

On a clean, well-lit work surface, place the:

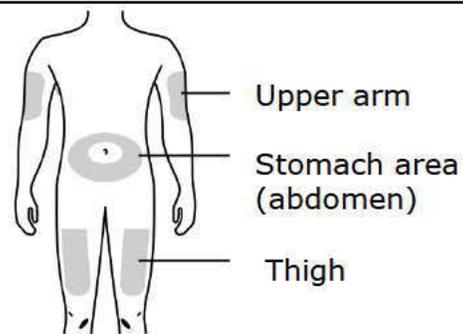
- Clear tray containing the on-body infusor and prefilled cartridge
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container



1D To securely attach the on-body infusor, prepare and clean an injection site that is less likely to have body hair, or you can trim the area. Use a firm and flat skin surface.

You can use:

- Your thigh
- Stomach area (abdomen), except for a **two**-inch area right around your navel
- Outer area of upper arm (only if someone else is giving the injection)



Clean your injection site with an alcohol wipe. Let your skin dry.

- **Do not** touch this area again before injecting.
- **Do not** inject into areas where the skin is tender, bruised, red or hard. Avoid injecting into areas with wrinkles, skin folds, scars, stretch marks, moles and excessive hair.

Important: To attach the on-body infusor securely, it is important to use a firm and flat skin surface.

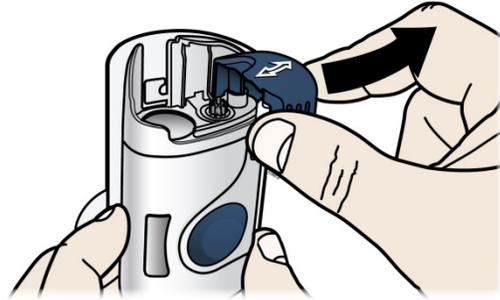
Step 2: Get ready

- 2A** Open the on-body infusor by swinging the cartridge door to the right. Then, **leave the door open**. **Do not** close the cartridge door before the cartridge is loaded.

If you accidentally close the cartridge door, press on the left side of the door to release the door latch.

If you are still unable to open the door, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

Do not press the start button until you are ready to inject.



- 2B** Inspect the cartridge.

Cartridge bottom

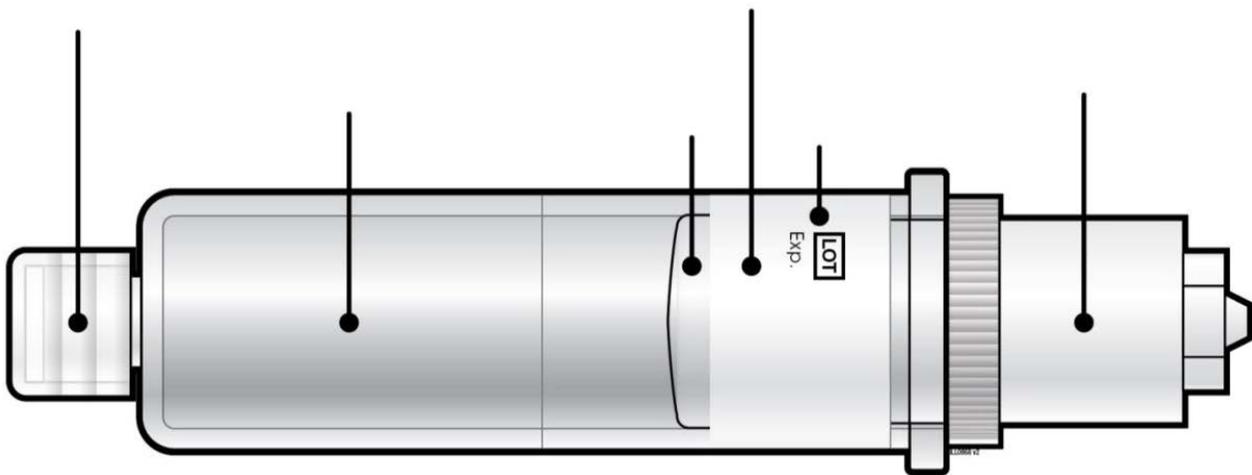
Medicine

White plunger

Cartridge label

Expiration date

Cartridge top (Do not rotate)



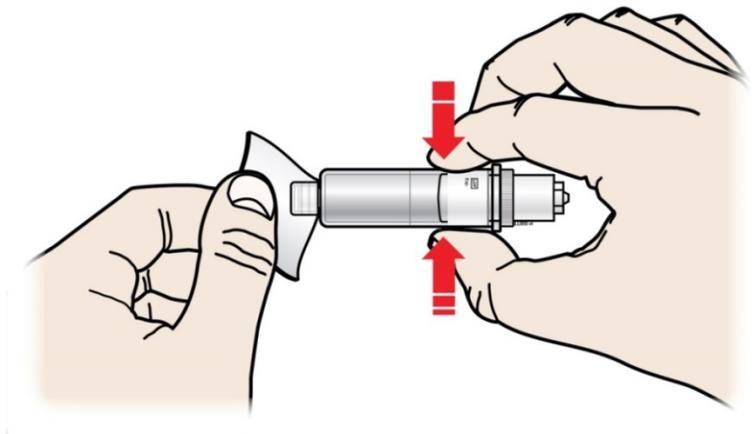
Check the expiration date: **do not** use if this date has passed.

Make sure the medicine in the cartridge is clear and colorless to slightly yellow.

- **Do not** use if the medicine is cloudy or discolored or contains flakes or particles.
- **Do not** use if any part of the cartridge looks cracked or broken.
- **Do not** use if pieces of the cartridge are missing or not securely attached.

In any above cases, use a new on-body infusor and prefilled cartridge and call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

2C Clean the cartridge bottom.



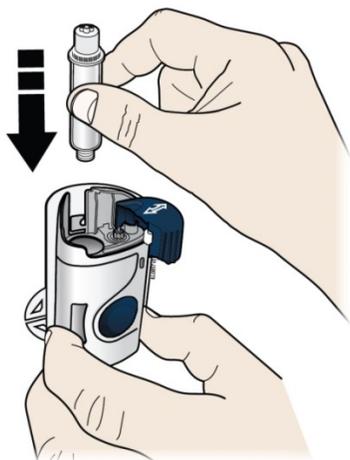
Grab Here

With 1 hand, hold the cartridge barrel and clean the cartridge bottom with an alcohol wipe.

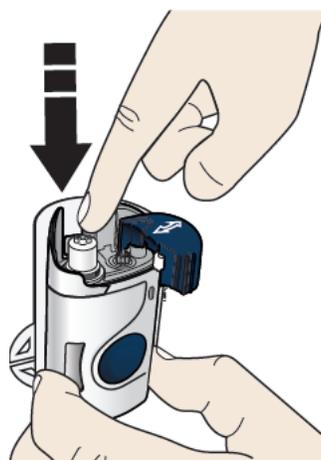
- **Do not** remove or rotate the cartridge top or bottom.
- **Do not** touch the bottom of the cartridge after cleaning with alcohol wipe.

2D Load the cleaned cartridge into the on-body infusor and firmly press on the top until it is secured in place.

Load cartridge straight



Press down firmly

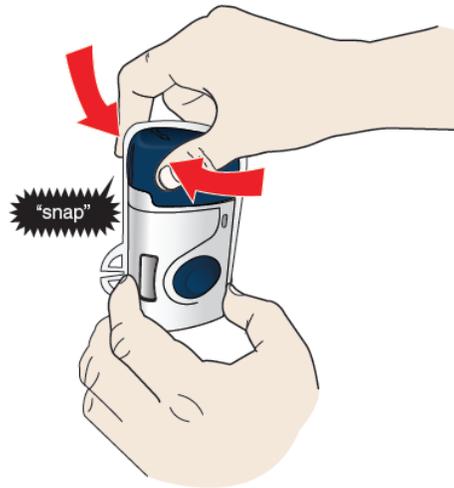


Insert the cartridge bottom first.

- **Do not** touch the start button until you have placed the loaded on-body infusor on your skin.

2E Swing the door to the left. Then, squeeze firmly until it snaps shut. Apply enough pressure when closing the door and make sure there is a “snap” before going to the next step.

Squeeze
Tight



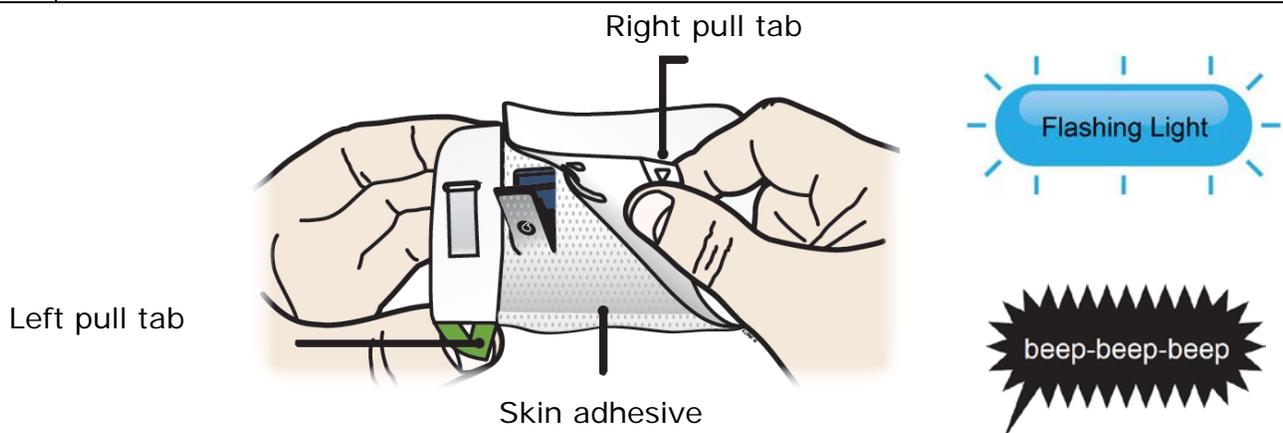
Make sure the cartridge fits securely in the on-body infusor before you close the door.

- **Do not** close the door if the cartridge is missing or not fully inserted.
- **Do not** touch the start button until you have placed the loaded on-body infusor on your skin.

Important: After you load the on-body infusor, go to the next step right away.

Step 3: Inject

3A Peel away **both** green pull tabs to show the adhesive. The on-body infusor is on when the blue status light flashes.



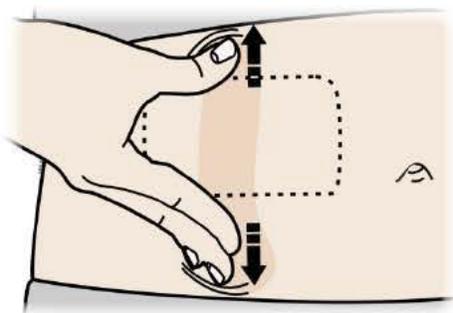
You must remove **both** green pull tabs to turn the loaded on-body infusor on. You will

hear beeping and see a flashing blue status light.

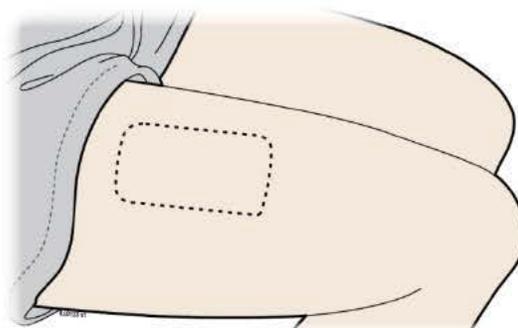
- **Do not** pull the skin adhesive backing off of the On-Body Infusor.
- **Do not** touch the skin adhesive.
- **Do not** touch the start button until you have placed the loaded on-body infusor on your skin.
- **Do not** touch the needle cover area.
- **Do not** place the loaded on-body infusor on your body if the red status light flashes continuously.
- **Do not** fold the skin adhesive over onto itself.

3B Choose your on-body infusor injection site. Only use the outer arm if someone else is giving the injection.

Stomach area placement



Thigh placement



or

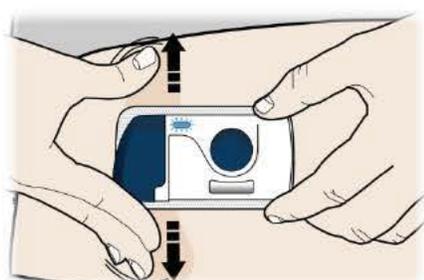
Stretch method for stomach

Do not stretch for thigh

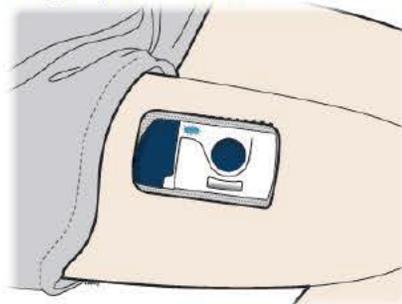
Important: Adjust your body posture to avoid skin folds and bulges.

3C When the blue light flashes, the on-body infusor is ready. Keep the stretch (stomach area method only). Hold the loaded on-body infusor with the blue light visible, and place it on your skin. You may hear beeps.

Stomach area placement



Thigh placement



or

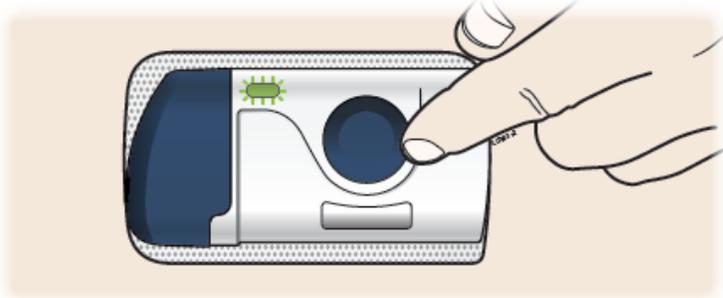


The loaded on-body infusor will lay flat on your body. Make sure all of the adhesive is attached to your skin. Run a finger around the adhesive edges to secure it.

Make sure clothing does not get in the way of the loaded on-body infusor, and you can see the blue light at all times.

- **Do not** move the loaded on-body infusor after it has been placed onto your skin.

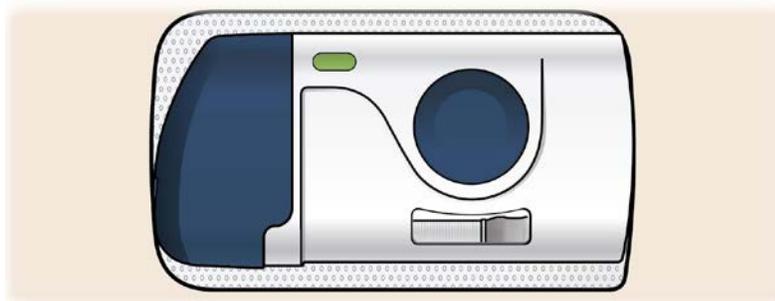
3D Firmly **press and release** the start button. A flashing green light and a click signals the injection has started.



- You may hear a pumping sound.
- You may feel a pinch.
- Make sure you see a green, flashing status light.
- You may hear beeps that mean your injection has started.

Important: If medication leaks from the on-body infusor, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

3E The injection takes about **nine** minutes to finish. The status light turns **solid green**, and the device beeps, when done.



It is okay to hear a pumping sound start and stop during injection.

Solid Light

Injection is finished when:

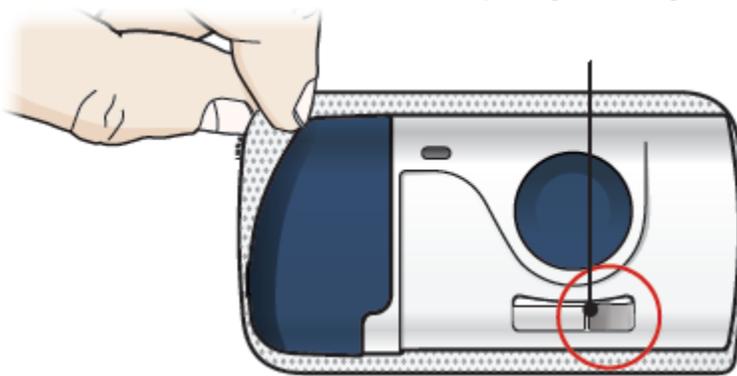
- The status light changes to **solid green**.
- You hear several beeps.
- The plunger fills medicine window all the way.

beep-beep-beep

Step 4: Finish

- 4A** When the injection is done, grab the skin adhesive to carefully peel the on-body infusor off skin. After removal, check the medicine window. The green light should now be off.

Used plunger filling medicine window



Light Off

beep-beep-beep

Check to see that the used plunger fills the medicine window all the way, and the green solid light turns off, letting you know all medicine has been injected. If the plunger did not fill the window, call 1-844-REPATHA (1-844-737-2842) or visit [www. REPATHA.com](http://www.REPATHA.com)

- The used on-body infusor will beep when removed from your skin.
- It is normal to see a few drops of fluid on your skin after you remove the used on-body infusor.

4B Throw away the used on-body infusor in a sharps container.

- The on-body infusor contains batteries, electronics, and a needle.
- Put the used on-body infusor in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the on-body infusor in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.



Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

- **Do not** recycle the on-body infusor or sharps disposal container or throw them into household trash.

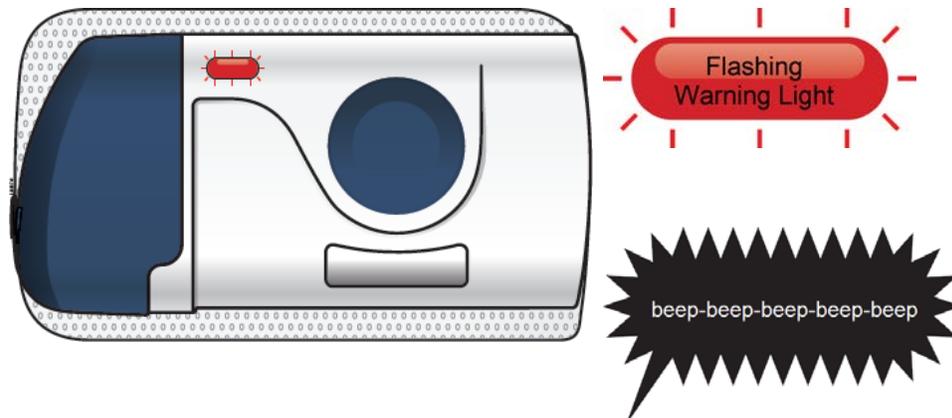
Important: Always keep the sharps disposal container out of the reach of children.

4C Check the injection site.

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

Troubleshooting

What do I do if the loaded on-body infusor status light continuously flashes red and you hear beeps?



Stop using the loaded on-body infusor. If the on-body infusor is attached to your body, carefully remove it. Call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

Commonly Asked Questions

What if I hear the on-body infusor beep and see a red blinking light when it is on my body?

This means that an error has happened. When this happens, the injection will stop by itself. Remove the on-body infusor from your body by slowly and carefully peeling it off of your skin, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

What should I do if the on-body infusor comes off my body during the injection?

Though unlikely, if the on-body infusor comes off during the injection, the on-body infusor will make a beeping sound, you will see the blinking red light, and the on-body infusor will stop. The loaded on-body infusor can no longer be used, and do not reapply to your body. Call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

What if I push the start button before I place the on-body infusor on my skin?

If you have removed the adhesive backing and pressed the start button, the on-body infusor will make a beeping sound and you will see the blinking red light. The on-body infusor will stop. Stop using the on-body infusor, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

What if the on-body infusor does not beep and the blue status light does not blink when I remove the pull tabs?

Check to see if both green pull tabs have been fully removed from the on-body infusor, including the adhesive paper over the battery strip and needle cover. If both green pull tabs have been fully removed and the on-body infusor still does not turn on, use a new on-body infusor and prefilled cartridge. Call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com

What if I push the start button and nothing happens?

Remove the on-body infusor by slowly and carefully peeling it away from your skin.

Do not reapply the same on-body infusor that you have already placed on your skin. Call 1-844-REPATHA (1-844-737-2842) or visit [www. REPATHA.com](http://www.REPATHA.com)

What if I cannot open the cartridge door to insert the cartridge?

To open the On-Body Infusor door, press on the left side of the door to release the door latch. If you are still unable to open the door, call 1-844-REPATHA (1-844-737-2842) or visit www. REPATHA.com

This Instructions for Use has been approved by the U.S. Food and Drug Administration.



Manufactured by:
 Amgen Inc.
 Thousand Oaks, CA 91320-1799
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 <part number> Revised: XX/XXXX vX

U.S. License Number 1080

Additional environmental conditions

Relative humidity range is 15% to 85%.

Altitude range is -984 feet to 11483 feet (-300 meters to 3500 meters).

During injection, keep the on-body infusor a minimum of 4 inches (10cm) away from other electronics such as cellular phones.

Warning: Do not modify the device.

On-body infusor operating temperature range is 59°F to 104°F (15°C to 40°C).

www.devicepatents.com

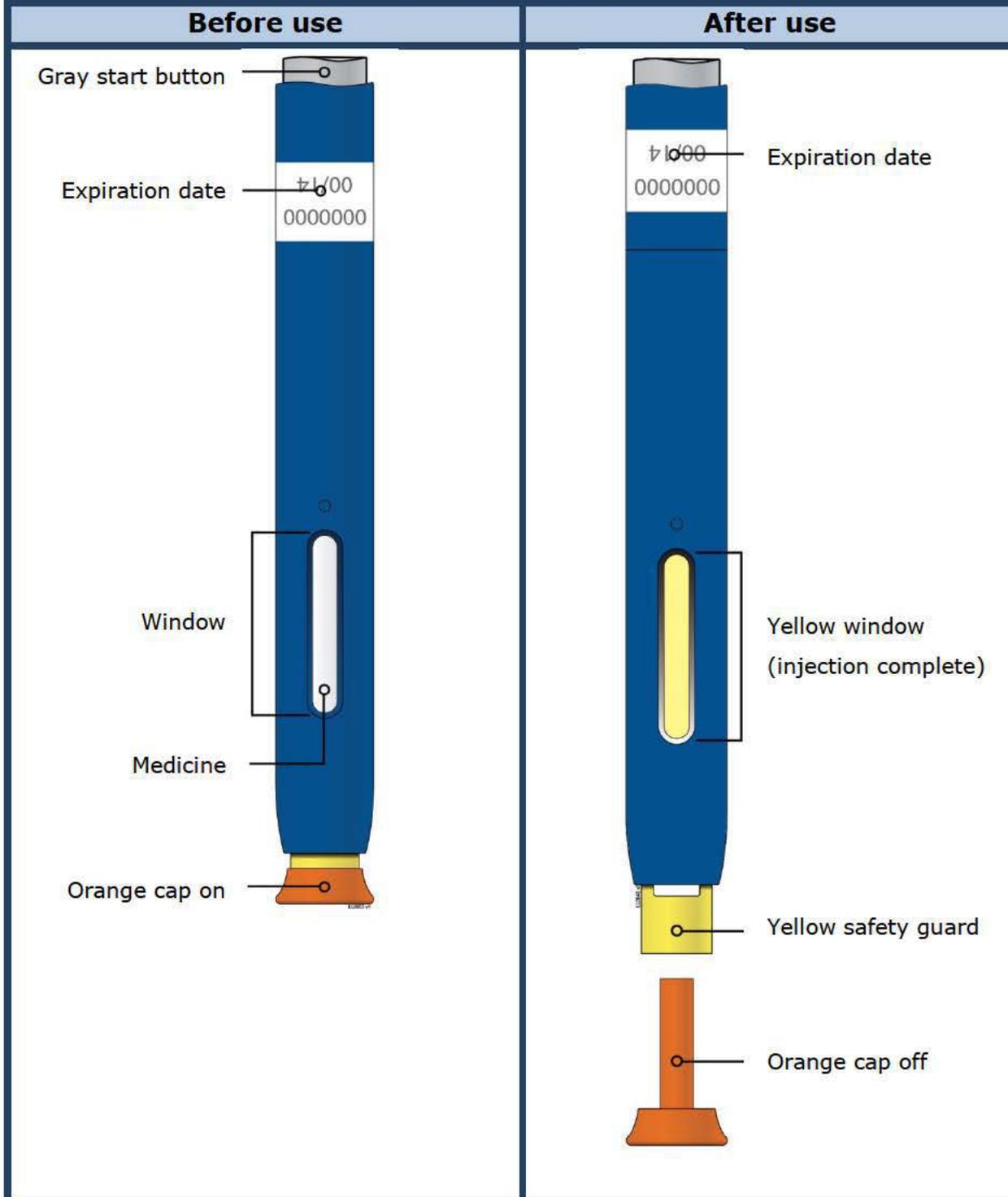
SYMBOL TABLE

				
Do not re-use	Serial number	Type BF Applied Part	Do not use if packaging is	On-Body Infusor

			damaged	containing 420 mg/3.5 mL (120 mg/mL)
 <p>Sterilized using ethylene oxide</p>	 <p>Refer to Instructions for Use</p>	 <p>Lot number</p>	 <p>Keep dry</p>	 <p>Open here</p>

Instructions for Use
Repatha® (ri-Path-a)
(evolocumab)
Single-Use Prefilled SureClick® Autoinjector

Guide to parts



Important: Needle is inside

Important

Before you use a Single-Use Repatha SureClick autoinjector, read this important information:

- It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.
- The orange cap on the Repatha SureClick autoinjector contains a needle cover (located inside the cap) that contains dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.

Storage of Repatha:

- Keep the Repatha SureClick autoinjector in the original carton to protect from light during storage.
- Keep the Repatha SureClick autoinjector in the refrigerator between 36°F to 46°F (2°C to 8°C).
- If removed from the refrigerator, the Repatha SureClick autoinjector should be kept at room temperature at 68°F to 77°F (20°C to 25°C) in the original carton and must be used within **30** days.
- **Do not** freeze the Repatha SureClick autoinjector or use a Repatha SureClick autoinjector that has been frozen.

Using Repatha:

- **Do not** shake the Repatha SureClick autoinjector.
- **Do not** remove the orange cap from the Repatha SureClick autoinjector until you are ready to inject.
- **Do not** use the Repatha SureClick autoinjector if it has been dropped on a hard surface. Part of the Repatha SureClick autoinjector may be broken even if you cannot see the break. Use a new Repatha SureClick autoinjector, and call 1-844-REPATHA (1-844-737-2842).
- **Do not** use the Repatha SureClick autoinjector after the expiration date.

A healthcare provider who knows how to use the Repatha SureClick autoinjector should be able to answer your questions. For more information, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

Keep the Repatha SureClick autoinjector out of the sight and reach of children.

Step 1: Prepare

1A Remove 1 Repatha SureClick autoinjector from the package.

Carefully lift the autoinjector straight up out of the box.

Put the original package with any unused autoinjectors back in the refrigerator.

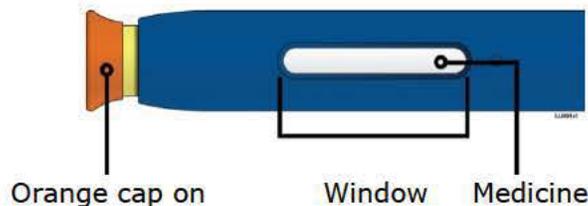
Wait at least **30 minutes** for the autoinjector to reach room temperature before injecting.



This is important for administering the entire dose and helps minimize discomfort. Repatha may take longer to inject if it has not reached room temperature. **Do not** heat the autoinjector. Let it warm up on its own.

- **Do not** try to warm the autoinjector by using a heat source such as hot water or microwave
- **Do not** leave the autoinjector in direct sunlight
- **Do not** shake the autoinjector
- **Do not** remove the orange cap from the autoinjector yet

1B Inspect the Repatha SureClick autoinjector.



Check the expiration date. **Do not** use the Repatha SureClick autoinjector past the expiration date printed on the label.

Make sure the medicine in the window is clear and colorless to slightly yellow.

- **Do not** use the autoinjector if the medicine is cloudy or discolored or contains particles.
- **Do not** use the autoinjector if any part appears cracked or broken.
- **Do not** use the autoinjector if the autoinjector has been dropped.
- **Do not** use the autoinjector if the orange cap is missing or not securely attached.

In all cases, use a new autoinjector, and call 1-844-REPATHA (1-844-737-2842).

1C Gather all materials needed for your injection.

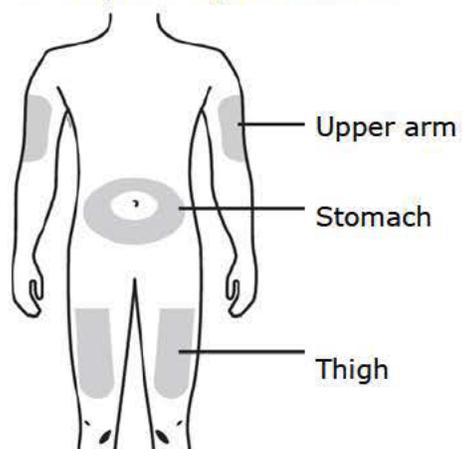
Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the:

- New autoinjector
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container (see Step 4: Finish)



1D Prepare and clean your injection site.



You can use:

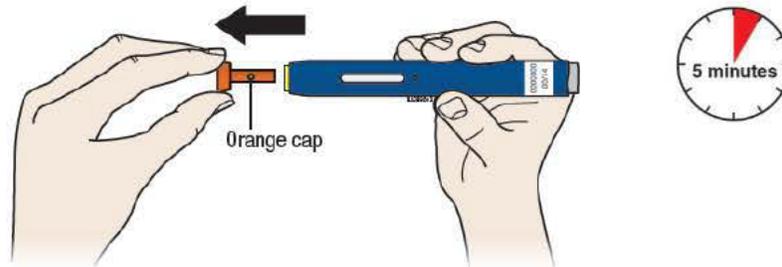
- Thigh
- Stomach (abdomen), except for a **two** inch area around your belly button
- Outer area of upper arm (only if someone else is giving you the injection)

Clean your injection site with an alcohol wipe. Let your skin dry.

- **Do not** touch this area again before injecting.
- Choose a different site each time you give yourself an injection. If you want to use the same injection site, make sure it is not the same spot you used for the last injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard.

Step 2: Get ready

2A Pull the orange cap off only when you are ready to inject. **Do not** leave the orange cap off for more than **five minutes**. This can dry out the medicine.



It is normal to see a drop of liquid at the end of the needle or yellow safety guard

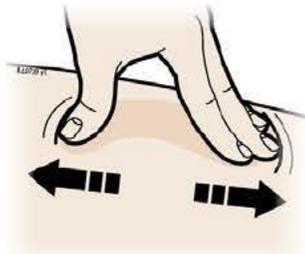
- **Do not** twist, bend, or wiggle the orange cap.
- **Do not** put the orange cap back onto the autoinjector.
- **Do not** put fingers into the yellow safety guard.
- **Do not** remove the orange cap from the autoinjector until you are ready to inject.

If you are unable to inject, please contact your healthcare provider.

2B Stretch or pinch your injection site to create a firm surface.

Thigh:

Stretch method

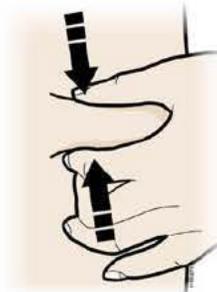


Stretch the skin firmly by moving your thumb and fingers in opposite directions, creating an area about **two** inches wide.

or

Stomach or upper arm:

Pinch method

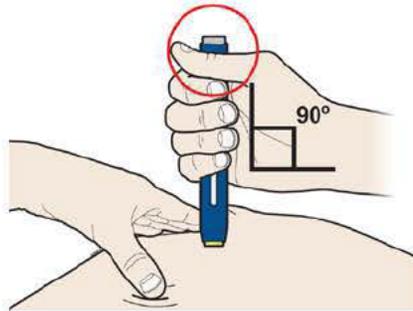


Pinch the skin firmly between your thumb and fingers, creating an area about **two** inches wide.

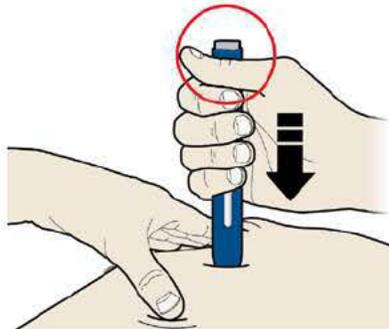
Important: It is important to keep skin stretched or pinched while injecting.

Step 3: Inject

3A Hold the stretch or pinched skin. With the orange cap off, **place** autoinjector on the skin at 90 degrees. Do not touch the gray start button yet.

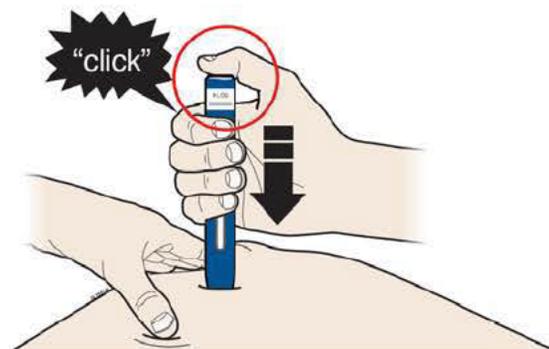


3B Firmly **push** down the autoinjector onto the skin until it stops moving.

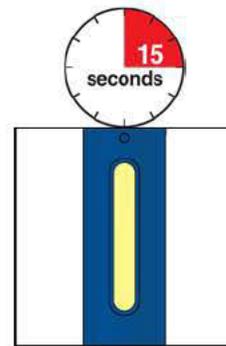
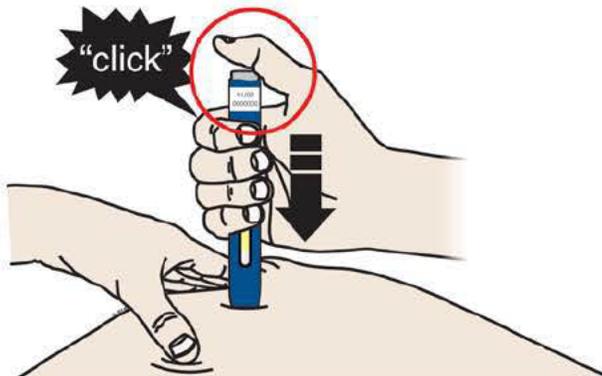


Important: You must push all the way down but **do not** touch the gray start button until you are ready to inject.

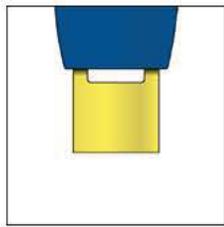
3C When you are ready to inject, **press** the gray start button. You will hear a click.



3D Keep **pushing** the autoinjector down on your skin. Then **lift** your thumb while still holding the autoinjector on your skin. Your injection could take about 15 seconds.



Window turns from clear to yellow when the injection is done. You may hear a second click.



NOTE: After you remove the autoinjector from your skin, the needle will be automatically covered.

Important: When you remove the autoinjector, if the window has not turned yellow, or if it looks like the medicine is still injecting, this means you have not received a full dose. Call your healthcare provider immediately.

Step 4: Finish

4A Throw away the used autoinjector and orange needle cap.



Put the used autoinjector and orange needle cap in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the autoinjector or orange cap in your household trash.

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

- **Do not** reuse the autoinjector.
- **Do not** recap the autoinjector or put fingers into the yellow safety guard.

Important: Always keep the sharps disposal container out of reach of children.

4B Check the injection site.

If there is blood, press a cotton ball or gauze pad on your injection site. Apply an adhesive bandage if needed.

Do not rub the injection site.

Commonly Asked Questions

What will happen if I press the gray start button before I am ready to do the injection on my skin?

You can lift your finger up off the gray start button and place the prefilled autoinjector back on your injection site. Then, you can push the gray start button again.

Can I move the autoinjector around on my skin while I am choosing an injection site?

It is okay to move the autoinjector around on the injection site as long as you do not press the gray start button. However, if you press the gray start button and the yellow safety guard is pushed into the autoinjector, the injection will begin.

Can I release the gray start button after I start my injection?

You can release the gray start button, but continue to hold the autoinjector firmly against your skin during the injection.

Will the gray start button pop up after I release my thumb?

The gray start button may not pop up after you release your thumb if you held your thumb down during the injection. This is okay.

What do I do if I did not hear a second click?

If you did not hear a second click, you can confirm a complete injection by checking that the window has turned yellow.

Whom do I contact if I need help with the autoinjector or my injection?

A healthcare provider familiar with Repatha should be able to answer your questions. For more information, call 1-844-REPATHA (1-844-737-2842) or visit www.REPATHA.com.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

AMGEN®

Manufactured by:

Amgen Inc.

Thousand Oaks, CA 91320-1799

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<part number> Revised: XX/XXXX vX

Repatha[®]

(evolocumab)

Injection

Rx Only

420 mg/3.5 mL (120 mg/mL)

For Subcutaneous Use Only

Single-Use Only

Amgen Inc

Databar

LOT

Exp.

MCK4105

Reference ID: 3956545

1 On-Body Infusor

AMGEN®

On-Body Infusor for
Repatha®
(evolocumab)

420 mg/3.5 mL

For Subcutaneous
Use Only

Mfd for Amgen Inc.
Thousand Oaks, CA 91320-1799 U.S.A.

 **Rx Only**

MCK4103



STERILE EO



Carton contents (1 Prefilled Cartridge, 1 On-Body Infusor, 1 Package Insert and 1 Instructions for Use) are intended to be dispensed and used as a unit. Each single-use Pushtronex system (On-Body Infusor with prefilled cartridge) delivers a 3.5 mL sterile, preservative-free solution containing 420 mg evolocumab, acetate (4.2 mg), polysorbate 80 (0.35 mg), proline (89 mg) in Water for Injection, USP, Sodium hydroxide may be used to adjust to a pH of 5.0. No U.S. standard of potency. See package insert for full drug prescribing information.

420 mg/3.5 mL

420 mg/
3.5 mL



Repatha® Pushtronex™ system
(evolocumab)
On-Body Infusor and Prefilled Cartridge



AMGEN®

1 x 3.5 mL Prefilled Cartridge
1 On-Body Infusor
NDC 55513-770-01

Patent/Caregiver
Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. If needed, Repatha® may be kept at room temperature (up to 25°C (77°F)) in the original carton and must be used within 30 days. Discard after 30 days. Write the date removed from the refrigerator.



Exp.
LOT
GTIN

MCK4104

1 x 3.5 mL Prefilled Cartridge
1 On-Body Infusor

NDC 55513-770-01

AMGEN®



Repatha® Pushtronex™ system
(evolocumab)
On-Body Infusor and Prefilled Cartridge

420 mg/3.5 mL

For Subcutaneous Use Only

Single-Use Only

Sterile Solution – No Preservative

Store refrigerated at 2°C to 8°C (36°F to 46°F).

Do Not Freeze or Shake.

Store in Carton to Protect from Light.

(see side panel for additional storage information)

Keep out of the sight and reach of children.

Refer to Instructions for Use

Do Not Use if Package is Damaged

On-Body Infusor Sterilized Using Ethylene Oxide

Keep Dry

Single Use

Type BF Applied Part

Relative Humidity Range is 15% to 85%

Rx Only



420 mg/
3.5 mL

Repatha® Pushtronex™ system
(evolocumab)

420 mg/3.5 mL

On-Body Infusor and Prefilled Cartridge



AMGEN®



Repatha® Pushtronex™ system
(evolocumab)

On-Body Infusor and Prefilled Cartridge



Manufactured by Amgen Inc.
Thousand Oaks, CA 91320-1799 U.S.A.
U.S. License No. 1080
Made in the U.S. with components from the U.S., Japan and Israel
© 2016 Amgen Inc. All rights reserved.
Patent: <http://amgen.com/Trade Name/>

Carton contents (1 Prefilled Cartridge, 1 On-Body Infusor, 1 Package Insert and 1 Instructions for Use) are intended to be dispensed and used as a unit. Each single-use Pushtronex system (On-Body Infusor with prefilled cartridge) delivers a 3.5 mL sterile, preservative-free solution containing 420 mg evolocumab, acetate (4.2 mg), polysorbate 80 (0.35 mg), proline (89 mg) in Water for Injection, USP, Sodium hydroxide may be used to adjust to a pH of 5.0. No U.S. standard of potency. See package insert for full drug prescribing information.

420 mg/
3.5 mL



420 mg/3.5 mL

Repatha® Pushtronex™ system
(evolocumab)
On-Body Infusor and Prefilled Cartridge
Not for Sale



AMGEN®

1 x 3.5 mL Prefilled Cartridge
1 On-Body Infusor
NDC 55513-770-91

Patent/Caregiver
Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. If needed, Repatha® may be kept at room temperature (up to 25°C (77°F)) in the original carton and must be used within 30 days. Discard after 30 days. Write the date removed from the refrigerator.



MCK4106

Exp.
LOT
GTIN

1 x 3.5 mL Prefilled Cartridge
1 On-Body Infusor

NDC 55513-770-91

AMGEN®



Repatha® Pushtronex™ system
(evolocumab)
Not for Sale

On-Body Infusor and Prefilled Cartridge

420 mg/3.5 mL



420 mg/
3.5 mL

For Subcutaneous Use Only
Single-Use Only
Sterile Solution – No Preservative
Store refrigerated at 2°C to 8°C (36°F to 46°F).
Do Not Freeze or Shake.
Store in Carton to Protect from Light.
(see side panel for additional storage information)
Keep out of the sight and reach of children.

- Refer to Instructions for Use
- Do Not Use if Package is Damaged
- On-Body Infusor Sterilized Using Ethylene Oxide

- Keep Dry
- Single Use
- Type BF Applied Part
- Relative Humidity Range is 15% to 85%

Rx Only

Repatha® Pushtronex™ system
(evolocumab)
Not for Sale

420 mg/3.5 mL
On-Body Infusor
and Prefilled Cartridge



AMGEN®

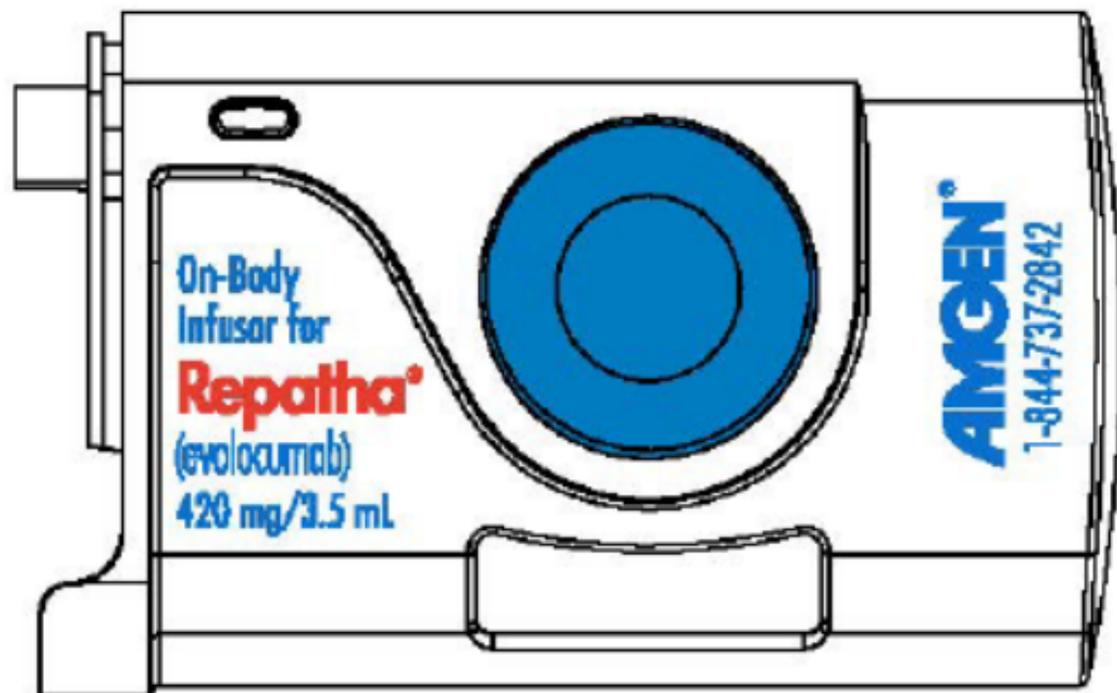


Repatha® Pushtronex™ system
(evolocumab)
On-Body Infusor and
Prefilled Cartridge
Not for Sale



Manufactured by Amgen Inc.
Thousand Oaks, CA 91320-1799 U.S.A.
U.S. License No. 1080
Made in the U.S. with components from
the U.S., Japan and Israel
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TEST967



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/s/

JAMES P SMITH
07/08/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125522Orig1s001

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type BLA
Application Number(s) 125522 S-001
Priority or Standard Standard

Submit Date(s) 10 September 2015
Received Date(s) 10 September 2015
PDUFA Goal Date 10 July 2016
Division / Office DMEP/ODE II/OND

Reviewer Name(s) Eileen Craig, MD
Review Completion Date 07 July 2016

Established Name Evolocumab injection
(Proposed) Trade Name Repatha ®
Therapeutic Class proprotein convertase
subtilisin/kexin type 9 (PCSK9)
inhibitor
Applicant Amgen, Inc.

Formulation(s) Subcutaneous (SC) injection
Dosing Regimen 420 mg once monthly
Indication(s) LDL-C reduction
Intended Population(s) HoFH; HeFH and clinical
atherosclerotic cardiovascular
disease on maximally tolerated
statin therapy who require
additional LDL-C reduction

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In this Prior Approval Supplement, Amgen is seeking approval of a new drug product presentation comprising a 120 mg/mL prefilled cartridge co-packaged with an automated mini-doser (AMD)¹ administration device, referred to as the 120 mg/mL AMD.

The 120 mg/mL AMD is intended to provide a single use, fixed dose for subcutaneous (SC) injection by a health care professional, a caregiver or by the patient. Administration is once a month and may be given either in the clinic or the home environment. (b) (4)

The AMD utilizes an electromechanical system to inject the drug product. When the user presses the activation button, the needle inserts and the motor is activated, which injects the drug product into the patient's tissue over the course of approximately 9 minutes. The applicant notes that the AMD is designed to administer the entire dose without user intervention. The use of the single AMD device once a month may be preferable to some patients compared to the use of three autoinjectors once monthly.

The applicant was able to establish pharmacokinetic (PK) and pharmacodynamic (PD) bioequivalence between administration of evolocumab using the marketed autoinjector (AI/pen) (3 x 1 mL at 140 mg/mL) to the AMD (3.5 mL at 120 mg/mL). The safety of the modified base device, which is similar to the commercial device, is adequate for approval. This device can be approved based on the efficacy and safety data submitted in this application.

1.2 Risk Benefit Assessment

Efficacy Assessment:

The primary clinical study supporting the 120 mg/mL AMD is a phase 1 pharmacokinetic bioequivalence study (study 20110168) conducted to bridge the phase 3 data obtained using the marketed autoinjector (AI/pen) (3 x 1 mL at 140 mg/mL) to the AMD (3.5 mL

¹ (b) (4)
It should be noted, however, that the CDRH considers the device constituent part of this combination product to be an "on-body infusion pump," and labeling will reflect this classification.

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at 120 mg/mL). Similar mean unbound evolocumab serum concentration time profiles were observed after a 420 mg subcutaneous (SC) dose of evolocumab when delivered using the AMD or 3 AI/pens, indicating bioequivalence between the formulations from the two devices. Analysis of LDL-C and PCSK9 data indicated that the reductions over time in LDL-C and PCSK9 were nearly identical between groups, indicating pharmacodynamic (PD) comparability.

Safety Assessment:

The duration of exposure (as of 02 April 2015) to AMD device (b) (4) which is similar to the commercial device (refer to Table 14 for additional information on the (b) (4) versions of the device), includes a total of 255 unique subjects with 133 patient-years of exposure with the AMD (b) (4) in Study 20120138. The median (min, max) exposure to evolocumab using the AMD (b) (4) was 5.5 months (2.1, 9.0) in year 1 and 5.6 months (0.3, 11.8) in year 2+, with a maximum exposure of approximately 12 months for any unique subject. This reviewer concludes that the subject exposure to AMD (b) (4) is sufficient to assess the device in an appropriate patient population.

Out of 3678 injections using AMD device (b) (4) there were 181 complaint issues reported for the AMD device during clinical use and 23 device failures. Thus, 4.9% of injection attempts resulted in a device complaint and 0.6% of injection attempts resulted in reported device failures/device malfunctions.

The most likely clinical effect following an instance of the reported failures for the AMD device would be under-dosing due to a missed or partial dose of evolocumab. With the AMD device, one missed dose is equivalent to missing one month of lipid lowering therapy. While it is a low likelihood that one missed dose would lead to a significant safety or efficacy risk to the patient, multiple missed or partial doses could be more problematic as the LDL-C level would not be optimally lowered.

The approvability of the AMD device is also supported by Study 20120356, which assessed the efficacy and safety of evolocumab during home-use with either the AMD (b) (4) or the commercially approved prefilled autoinjector. After training, the majority of subjects were able to successfully self-administer two full doses of evolocumab (420 mg) in a home-use setting using either the AMD (one 3.5 mL dose administered over 9 minutes) or AI/pen (3 separate 1.0 mL injections administered within 30 minutes). Similar reductions from baseline in LDL-C at week 12 were observed for evolocumab delivered via AMD or AI/pen in the home-use setting. Adverse events (AEs) and device-related AEs were similar among subjects who used either the AMD or AI/pen.

Given the entirety of evidence submitted for this application and the assessments from the other FDA teams involved in this review, especially the input from CDRH, this reviewer concludes that the safety of AMD (b) (4) as compared to the use of the 3 AI/pens, is adequate to support approval of this device as an alternative to the AI/pen.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

No requests from the clinical team. There may be PMC requests regarding real time aging/shelf-life studies for device performance from the CMC and CDRH review teams.

2 Introduction and Regulatory Background

2.1 Product Information

The non-proprietary name of this product is evolocumab (previously referred to as AMG 145) and the approved tradename is Repatha™. The proposed proprietary name for the drug/device combination is Repatha Pushtonex. A review from the Division of Medication Error Prevention and Analysis (DMEPA), dated 17 May 2016, concluded that the proposed proprietary name is acceptable.

Evolocumab, a human monoclonal immunoglobulin G2 (IgG2) directed against PCSK9, binds selectively to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface. This action prevents PCSK9-mediated LDLR degradation, which leads to increases in LDLR, and results in decreases in serum LDL-C.

Evolocumab was approved for the following indications on 27 August 2015:

Primary Hyperlipidemia

Evolocumab is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

Homozygous Familial Hypercholesterolemia

Evolocumab 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.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following drugs are currently approved for patients with primary hyperlipidemia to reduce LDL-C:

- rosuvastatin, atorvastatin, simvastatin, pitavastatin, lovastatin, fluvastatin, pravastatin, atorvastatin/ezetimibe, simvastatin/ezetimibe, ezetimibe, niacin extended-release and fenofibrate.
- Evolocumab and alirocumab, both PCSK9 inhibitors, are both approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.

The following drugs are currently approved for the reduction of elevated LDL-C specifically for patients with HoFH: lomitapide, mipomersen, simvastatin, atorvastatin, rosuvastatin, ezetimibe, atorvastatin/ezetimibe, simvastatin/ezetimibe and evolocumab.

2.3 Availability of Proposed Active Ingredient in the United States

Evolocumab is currently available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Evolocumab is the second drug in this class. Alirocumab (Praluent™), approved on 24 July 2015, is the first PCSK9 inhibitor to be approved in the US. Safety concerns include hypersensitivity/allergic reactions and injection site reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1. Relevant Regulatory History

Meeting Date/ Type	Meeting Purpose	Event/Notes
10 July 2012 End of Phase 2 (Clinical)	To discuss the proposed clinical development program and the device clinical study strategy from pivotal studies to commercial launch for the two indications of (1) hyperlipidemia and mixed dyslipidemia and (2) secondary prevention of heart disease.	<p>Issues related to the AMD device:</p> <ul style="list-style-type: none"> • Although you plan to collect data on the usability of your product presentations during the clinical trial, a well-designed human factors (HF) study is required. The results from the clinical trials can be used as part of a formative study to improve the product design and the instructions for use (IFU). You should also collect subjective data during the clinical trials which may inform how to improve your product design and IFU. • You stated in your End of Phase 2 Meeting Request that you will conduct design verification and validation Human Factor Engineering (HFE) study that includes simulated use studies. We require you to conduct validation Human Factors usability study for the autoinjector (AI) and large volume injector (LVI). You may also consider conducting validation Human Factors usability study for the prefilled syringe, since this is a new user population. • Consider the following for your user groups and study methodology: <ul style="list-style-type: none"> <input type="checkbox"/> If your device requires special training prior to the use of the devices, then your study should include at least a total of 90 participants equally divided between trained and untrained arms as follows: <ul style="list-style-type: none"> o 30 representative patients with injection experience (i.e., 15 participants trained and 15 participants untrained). o 30 representative patients without injection experience (i.e., 15 participants trained and 15 participants untrained). Since representative patients may have concomitant health conditions (e.g., diabetes), ensure you include participants with vision and dexterity issues. <ul style="list-style-type: none"> o 30 health care practitioners that will be using the device: nurses and physicians (i.e. 15 participants trained and 15 participants untrained). <input type="checkbox"/> If training will not be required as part of the labeling, then study should only have the untrained arm as described above. • In your Human Factors study, we recommend including a task to simulate complete device failure. • The feedback mechanism regarding dose delivery may also be insufficient. Consider color-blind patients who may not be able to distinguish between the blue, green, and red lights. The beeps may not be helpful if the patient is distracted or loses track of the count or has trouble hearing. You may want to consider simplifying this aspect of your device. • Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. We expect you to collect both empirical and qualitative data in a design validation study. • Performance Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test

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Meeting Date/ Type	Meeting Purpose	Event/Notes
		facilitator/moderator. •Subjective Data – We expect you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" •Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. •The currently proposed phase 3 lipid-lowering trials do not use the proposed devices (AI and LVI), and we are not confident that the substudies within an open-label extension study will provide sufficient data to demonstrate whether the home use of these devices affects their clinical effectiveness (i.e., LDL-C). We will require you to provide sufficient phase 3 data using these devices in controlled clinical trials that have LDL-C as an outcome.

2.6 Other Relevant Background Information

Device Information

In this Prior Approval Supplement, Amgen is seeking approval of a new drug product presentation comprising a 120 mg/mL prefilled cartridge co-packaged with an automated mini-doser (AMD) administration device, referred to as the 120 mg/mL AMD. The 120 mg/mL AMD is intended to provide a single use, fixed dose for SC injection by a health care professional, a caregiver or by the patient. Administration may be either in the clinic or in a non-clinical environment. (b) (4)

and consists of 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The cartridge for use with the AMD contains a 3.5 mL deliverable volume (420 mg), which enables once monthly dosing.

The AMD is a compact, sterile, single-use, disposable, electro-mechanical (battery powered, micro-processor controlled), on-body infusion device. The 120 mg/mL AMD presentation was developed to reduce the number of injections required for the once monthly dose to a single injection. The prefilled cartridge assembly is co-packaged with the AMD. The prefilled cartridge assembly is loaded into the AMD immediately prior to use (see figure below).

Figure 1. Prefilled Cartridge Assembly and AMD



Source: Applicant's Figure 6 from Module 2.3.P, page 56

The AMD utilizes an electromechanical system to inject the drug product. When the user presses the activation button, the needle inserts and the motor is activated, which injects the drug product into the patient's tissue over the course of approximately 9 minutes.

According to the applicant, following removal of the AMD from the packaging, the user opens the door of the AMD, inserts the prefilled cartridge assembly, and closes the door. The AMD has an adhesive which attaches the device to the skin for dose administration. After removing the adhesive liner and adhering to the body, the injection is initiated by the user upon depressing the activation button, (b) (4). Once the user presses the button, the needle is inserted into subcutaneous tissue, and the loaded AMD subsequently initiates drug administration. The drug is automatically injected (b) (4). The loaded AMD provides visual and auditory notifications to the user to signal the completion of injection. The loaded AMD is then removed from the skin following completion of the injection. When the device is removed from the body, the (b) (4) returns to the open position to prevent needle-stick injury. The empty cartridge assembly cannot be removed from the loaded AMD after administration of the drug product; the AMD system is disposed of together.

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The applicant notes that the AMD is designed to administer the entire dose without user intervention. The dose volume and dose administration duration cannot be changed by the user. Both visual and auditory notifications provide feedback on the progress of drug administration. In the event of a drug delivery error, visual and auditory alarms will notify the user. Additionally, a viewing window that allows the user to see the prefilled cartridge allows inspection to confirm dose completion. Per device design, the needle will not retract from the patient's subcutaneous tissue until physically removed by the patient. The presence of audible and visible notifications for the dose initiation and dose completion, combined with the viewing window are measures to avoid premature removal by the user.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The eCTD format of the submission was navigable and well organized. The submission quality and integrity was acceptable. The applicant was asked to provide additional information throughout the course of the review and did so in a timely fashion.

3.2 Compliance with Good Clinical Practices

The applicant asserts that the clinical trials were conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312. The applicant states that all clinical trials were conducted with the approval of Ethics Committees or Institutional Review Boards and that all subjects were asked to provide written informed consent before undergoing any study-related procedures. This information was included in each clinical study report located in Module 5 of original BLA submission (submitted 27 August 2014).

Lakshmi Narasimhan and Patricia Hughes from the Office of Combination Products, OMPT/CDER/OPQ/OPF/DMA/MABIV, recommended the inspection of the following manufacturing sites:

 (b) (4)



3.3 Financial Disclosures

The applicant submitted in the original BLA submission (submitted 27 August 2014) a completed Form FDA 3454 attesting to the absence of financial interests and arrangements for all investigators that submitted financial information, with the exception of one clinical investigator.

The applicant certifies that it has acted with due diligence to obtain the financial information described in 21 CFR 54.4(a)(3), but was unable to do so for thirteen (13) sub-investigators who participated in covered clinical studies for evolocumab in the original BLA.

The covered clinical trials for this submission include the following protocols: 20110168, 20120138, 20120135 and 20120356.

Table 2. Financial Disclosures of Covered Clinical Trials for the Original BLA

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: _____		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>		
Significant payments of other sorts: <u>0</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator in sponsor of covered study: <u>1</u>		
Is an attachment provided with details	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from

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of the disclosable financial interests/arrangements:		applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>13</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. The 13 subinvestigators with a certification of due diligence because they either departed the site shortly after study initiation and are no longer affiliated with the facility or the facility has been closed do not raise questions about the integrity of the data. No investigators were also sponsor employees. Only one Primary Investigator had any financial interests or arrangements to disclose.

One clinical investigator (b) (6) had a significant equity interest, as defined in 21 CFR 54.2(b), which consisted of approximately 2000 shares purchased decades ago. (b) (6) enrolled a total of (b) (6) subjects: (b) (6) subjects in Study (b) (6), (b) (6) subjects in Study (b) (6) and (b) (6) subject in Study (b) (6).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The 120 mg/mL AMD is intended to provide a single use, fixed dose for SC injection by a health care professional, a caregiver or by the patient. (b) (4)

and consists of 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The cartridge for use with the AMD contains a 3.5 mL deliverable volume (420 mg), which enables once monthly dosing.

The evolocumab drug product manufacturing process consists of (b) (4). Filling of the cartridge occurs at (b) (4). Assembly of the prefilled cartridge with a (b) (4), co-packaging of the cartridge with (b) (4).

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the pre-sterilized AMD, and labeling occurs at (b) (4). The sterilized AMD administration device is manufactured by (b) (4).

As per the review dated 30 June 2016 by Sang Bong Lee, Ph.D., the Product Quality Review by Office of Biotechnology Products (OBP) recommended that the new drug product presentation comprising a 120 mg/mL evolocumab prefilled cartridge co-packaged with an automated mini-doser (AMD) administration device be approved for human use (under conditions specified in the package insert). The data submitted in this sBLA support the conclusion that the manufacture of the 120 mg/mL evolocumab prefilled cartridge at (b) (4) and co-packaging with AMD at (b) (4) are well controlled and leads to a product that is pure and potent. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. Stability data for the 120 mg/mL evolocumab AMD submitted support 24 months of expiry from the date of manufacture when stored at 2-8°C under light protection.

4.2 Office of Process and Facilities (OPF)/ Division of Microbiology Assessment (DMA)

As per the review dated 21 June 2016 by Lakshmi Narasimhan, Ph.D., this efficacy supplement, as amended, is recommended for approval from a product quality microbiology perspective. The inspection of the drug product manufacturing site, (b) (4) was waived.

4.3 Preclinical Pharmacology/Toxicology

Not applicable for this submission which is only seeking approval for a new drug product device.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

This information was submitted in the original BLA (Sequence: 0000; see Clinical Pharmacology review dated 01 Jun 2015 in DARRTS, document ID 3772601). In brief, when PCSK9 binds to low-density lipoprotein receptor (LDLR), the LDLR is targeted for destruction rather than being recycled back to the cell surface, thereby reducing the levels of LDLR available for low-density lipoprotein cholesterol (LDL-C) clearance from

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the bloodstream. Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

4.4.2 Pharmacodynamics

This information was submitted in the original BLA (Sequence: 0000; see Clinical Pharmacology review dated 01 Jun 2015 in DARRTS, document ID 3772601). In brief, in the primary hyperlipidemia population, LDL-C reduction of approximately 55% to 75% was achieved as early as 1 week after dosing initiation. Maximal response was generally achieved within 2 weeks after dosing with 140 mg every 2 weeks and 420 mg once monthly, respectively, and maintained during long-term therapy. In patients with homozygous familial hypercholesterolemia (HoFH) not on apheresis, evolocumab 420 mg QM, compared to placebo, significantly reduced LDL-C from baseline to Week 12 by 31%. The mean change from baseline to Week 12 within the evolocumab arm alone was -23% and within the placebo arm alone was +8%.

4.4.3 Pharmacokinetics

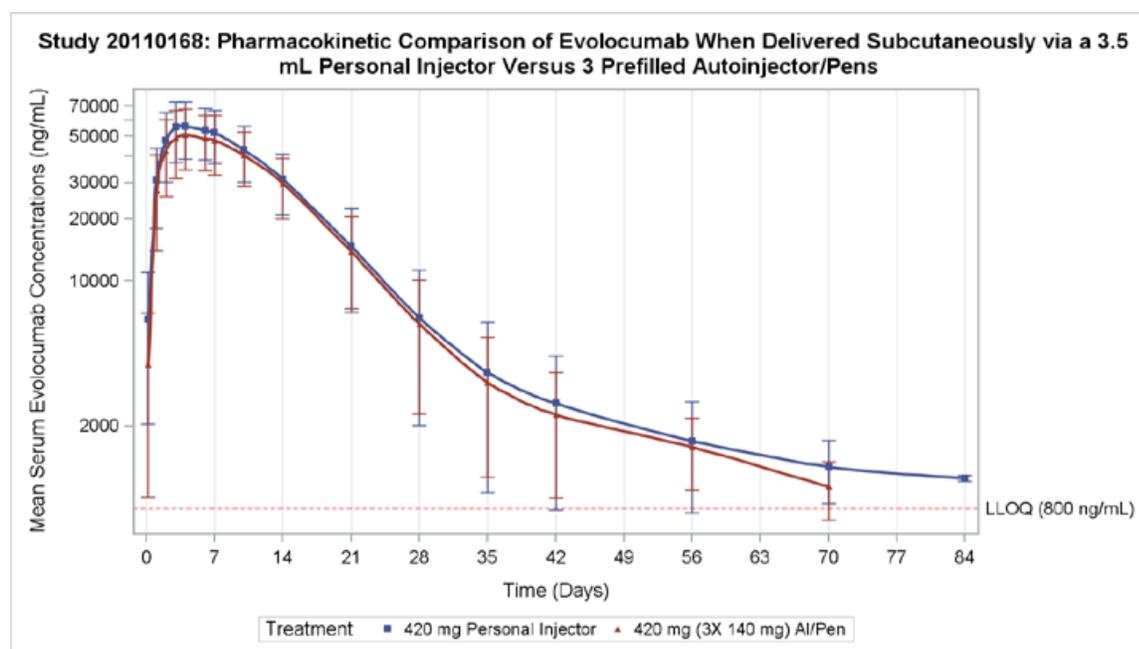
The primary clinical study supporting the 120 mg/mL AMD is a phase 1 pharmacokinetic bioequivalence study (study 20110168) conducted to bridge the phase 3 data obtained using the AI/pen (3 x 1 mL at 140 mg/mL) to the AMD (3.5 mL at 120 mg/mL). The comparability data supporting this new device was previously submitted to the original BLA and cross-referenced within this supplement, and was reviewed in the original BLA (Document ID: 3772601 dated 01 June 2015, in DARRTS).

It is important to note that this bridging study was conducted using a “base device” (b) (4) that then underwent various design changes. One of our concerns was whether the design changes that the applicant made since conducting their clinical studies (including the bridge to the autoinjector) preclude us from relying on these studies. We have consulted with the appropriate review team in the Center for Devices and Radiological Health (CDRH) and while there were notable differences in the original first iteration of the device as compared to the version of the device (b) (4) used in the open-label extension study 20120138 and the to-be-marketed device (b) (4) those modifications should not invalidate the PK/PD bridge data using device (b) (4). The safety of the device, discussed primarily in Section 7, is based on the modified base device (b) (4).

A summary of the clinical pharmacology team’s assessment, based on a memorandum dated 5/19/2016 in DARRTS (Reference ID: 3933745), is shown below:

As seen from the following figure, similar mean unbound evolocumab serum concentration time profiles were observed after a 420 mg SC dose of evolocumab when delivered using the AMD or 3 AI/pens. Median t_{max} was 4.0 days for both AMD (range = 2.0 to 9.9 days) and 3 AI/pens (range = 1.9 to 10 days). The geometric least square mean ratios (90% CI) of the AMD to 3 AI/pens for C_{max} and AUC_{last} were 1.10 (1.03 - 1.18) and 1.06 (0.97 - 1.14), respectively, indicating bioequivalence between the formulations from the two devices.

Figure 2. Mean unbound serum evolocumab concentration following subcutaneous administration of a 420 mg dose delivered either via one 3.5 mL AMD or three AI/Pens



A statistical comparison of pharmacokinetic parameters is shown in the table below:

Table 3. Summary of Statistical Evaluation of Pharmacokinetic Parameter Estimates of Evolocumab After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects

Parameter(unit)	n	AMD (Test) (N = 130)		3 AI/pens (Reference) (N = 135)		Ratio of Test/Reference ^a		
		LSMean	90% CI	n	LSMean	90% CI	LSMean	90% CI
AUC _{last} (day*ug/mL)	118	862.62	(815.31, 912.68)	122	817.55	(773.43, 864.18)	1.06	(0.96, 1.14)
C _{max} (ug/mL)	130	56.19	(53.59, 58.93)	135	51.07	(48.74, 53.51)	1.10	(1.03, 1.18)

CI = Confidence Interval.

LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.

AMD = automated mini-doser

^aRatio and CI are based on natural log scale data converted back to the original scale

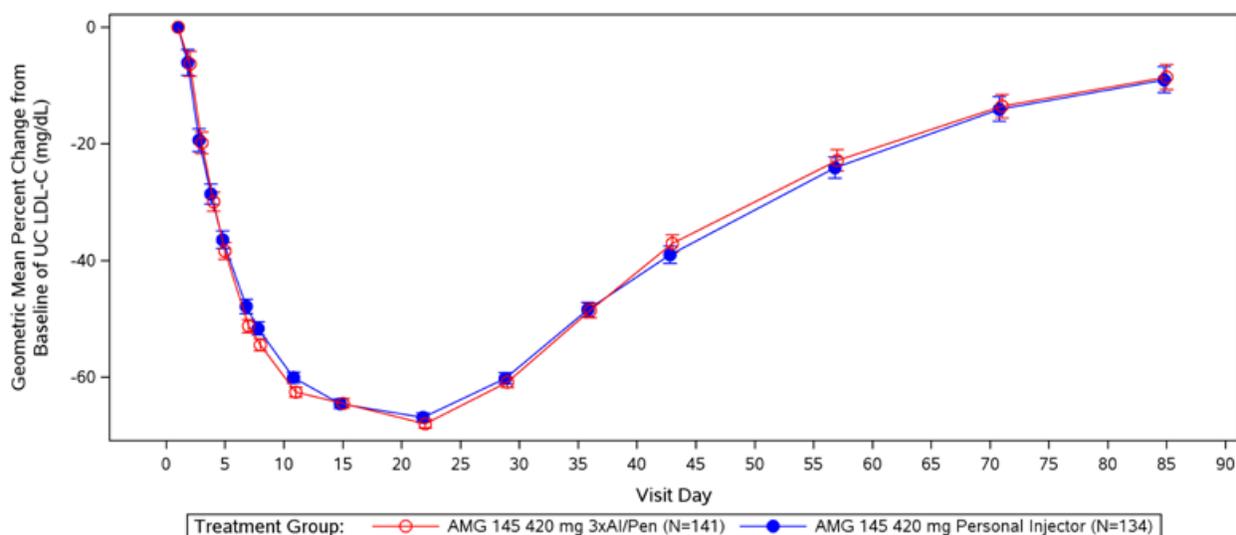
(source: report for study 20110168, table 11-1, page 43)

Analysis of LDL-C and PCSK9 data indicated that the reductions over time in LDL-C and PCSK9 were nearly identical between groups. The geometric LS mean ratio (90% CIs) of the AMD to 3 AI/pens for LDL-C AUEC_{day1-day85} was 1.00 (0.96 - 1.04), indicating pharmacodynamic (PD) comparability.

Between days 1 to 11, unbound PCSK9 serum concentrations reached the lower limit of quantification (LLOQ) (15 ng/mL) of the assay (> 94% mean reductions from baseline) in both groups. By day 22, the mean percent reduction from baseline in unbound PCSK9 serum concentrations was approximately 85% for both groups; by end of the study, mean percent reductions from baseline were approximately 15% and 18% for the AMD and AI/pen groups, respectively.

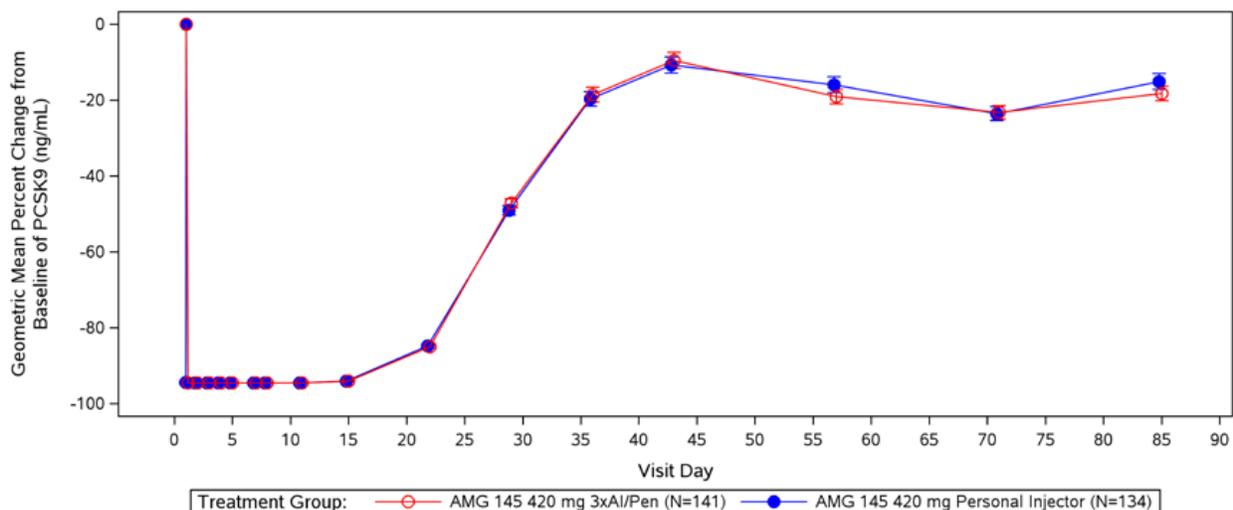
Mean LDL-C and PCSK9 profiles shown in the figures below show that profiles for LDL-C and PCSK9 were also similar between the two devices.

Figure 3. Geometric Mean Percent Change from Baseline (+/- Standard Error) of LDL-C (mg/dL) over Time After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects



Values on the x-axis have been shifted slightly for ease of reading.
Geometric mean percentage change is generated by $(\text{modeled based ratio to baseline} - 1) \times 100$
(source: report for study 20110168, Figure 11-2, page 48)

Figure 4. Geometric Mean Percent Change from Baseline (+/- Standard Error) of PCSK9 over Time After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects



Values on the x-axis have been shifted slightly for ease of reading.
Geometric mean percentage change is generated by (modeled based ratio to baseline - 1)*100
BQL of PCSK9 is set at low limit level of 15 ng/mL.

(source: report for study 20110168, Figure 11-3, page 50)

The Clinical Pharmacology team concludes that PK and PD comparability was demonstrated between the 420 mg dose of evolocumab delivered either via a single 3.5 mL unit AMD (120 mg/mL) or 3 AI/pens (1 mL, 140 mg/mL).

4.5 Center for Devices and Radiological Health (CDRH) Review of Device

Refer to the review in DARRTS by Carolyn Cochenour dated 30 June 2016, Reference ID: 3953619. CDRH performed a review of the device constituent of the combination product for BLA 125522/S001 for Amgen's Automated Mini-Doser for on-body subcutaneous infusion of Repatha. The focus of the CDRH review was on the risk assessment and performance testing of the device risk including design verification, design validation, biocompatibility testing and software validation. The device underwent extensive testing to verify the device against specifications. The commercial iteration of the device passed all testing requirements, biocompatibility tests, and software validation. The risk assessment identified the critical aspects of the device and linked to test reports used to reduce the residual risk to an acceptable level.

The CDRH reviewer states that while significant changes were made between device iterations (refer to Table 14 for additional information), the Sponsor has provided adequate evidence that these changes will not impact the effectiveness of the device. Additionally, this testing provides evidence that the differences between pump iterations

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made during the various clinical studies will not have an impact on the safety or effectiveness of the device. CDRH recommends that the device constituent part of the combination product for BLA 125522/S001 is appropriate for the intended use of subcutaneous infusion of Repatha. There are no device concerns that would prevent approval of BLA 125522/S001. Amgen will have to provide real time aging shelf-life testing as it becomes available for review. The accelerated aging tests simulated (b) (4) under refrigerated conditions as well as storage for a limited time (1 month) at room temperature. The labeled expiry date for the device constituent of the combination product is 24 months.

4.6 Office of Medication Error Prevention and Risk Management (OMEPRM)/ Division of Medication Error Prevention and Analysis (DMEPA)

There are two AMD Human Factor summative studies that are included in this submission. Both used placebo that mimics the appearance and viscosity of the evolocumab drug product. Both studies were simulated use with injections into skin pads. Changes between the first and second study included (b) (4)

Summative Study 1:

- The materials used for the first summative study were representative of the intended commercial configuration
 - The first summative study included a (b) (4)
- Placebo that mimics the appearance and viscosity of the evolocumab drug product

Summative Study 2:

- The following changes were made following the first summative study and were tested in the second summative study:
 - (b) (4)
 - Instructions for Use illustrations were modified to address the changes described above, as well as enhanced instructions for hand washing, cleaning of injection site, cartridge insertion and door closing
- Placebo that mimics the appearance and viscosity of the evolocumab drug product

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted to evaluate the results of the Human Factors Study (HFS), container label, carton labeling, Prescribing Information, Instructions for Use, and (b) (4) for Repatha

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(evolocumab) prefilled cartridge and automated mini-doser (refer to the review by Hina Mehta, PharmD., dated 6/8/2016 in DARRTS, Reference ID: 3943307). In summary, DMEPA expects that patients, caregivers, and health care professionals will be able to use Repatha pre-filled cartridge and automated mini-doser safely and effectively when training is provided and training materials [i.e., Instructions for Use (IFU)] are available for review.

DMEPA concludes that the results of the human factors validation study and the supplemental validation study indicate that there are several areas of improvements necessary with respect to the IFU. The improvements suggested are to enhance key information already in the IFU or add additional information for further clarity. In addition, the proposed container labels and carton labeling can be improved to increase the readability and prominence of important information. DMEPA recommends the removal of [REDACTED] (b) (4)

DMEPA also provided guidance to DMEP and Amgen regarding changes to the Instructions for Use and the Container Label and Carton Labeling.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Clinical information for the 120 mg/mL AMD was submitted to BLA 125522 in the original BLA (Sequence No. 0000); however, the 120 mg/mL AMD was still under development at the time of the original BLA submission, and thus was not part of the formal review and approval.

The table below provides a summary of the clinical studies using some version of the AMD device, but not the to-be-marketed/commercial version of the AMD device. The clinical studies were conducted using a “base device” that then underwent various design changes. The AMD device used in the ongoing study 20120138, introduced into the study in April 2014, has been modified from the base device used in studies 20120135, 20110168 and 20120356.

Table 4. Summary of Clinical Studies with AMD Devices Used in the Evolocumab Program

Study	Description	Device(s) Used
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Clinical Pharmacology Studies		
20120135	Assess the drug delivery performance of the AMD using a placebo buffer	AMD (b) (4)
20110168	Bioequivalence PK/PD study conducted to bridge data obtained using the currently approved prefilled autoinjector vs. AMD	AI/pen, AMD (b) (4)
Efficacy/Safety Studies for Hyperlipidemia		
20120138 (ongoing)	Controlled, Long-term, Open-label Phase 3 Extension Study: AI/pen self-administration (OSLER-2)	AI/pen, AMD (b) (4)
20120356	Phase 3 home-use study to assess the users' ability to administer a full dose (420 mg) of evolocumab by the patient during home-use (with primary LDL endpoint assessment) using either the AMD or the commercially approved prefilled autoinjector	AI/pen, AMD (b) (4)
AI/pen=autoinjector/pen; AMD= automated mini-doser; PD= pharmacodynamic; PK= pharmacokinetic.		

5.2 Review Strategy

Study 20110168 is the bioequivalence PK/PD study conducted to bridge data obtained using the currently approved prefilled autoinjector vs. AMD. This study is discussed in Section 4.4.3 Pharmacokinetics and Section 5.3.1 Study 20110168.

Study 20120135 Study is a phase 0, open-label, non-randomized study in healthy subjects. The primary objective was to assess the subcutaneous (SC) delivery performance of the AMD. This study is discussed in Section 5.3.2 Study 20120135.

Study 20120356 is the Phase 3 home-use study evaluating the users' ability to administer a full dose (420 mg) of evolocumab by the patient during home-use with either the AMD or the commercially approved prefilled autoinjector. Study 20120356 also assessed LDL reduction with evolocumab with either the AMD or the commercially approved prefilled autoinjector. This study is discussed in Section 6 Review of Efficacy.

The overall safety of the AMD device as assessed in several clinical trials is presented in Section 7 Review of Safety.

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5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study 20110168

Study 20110168: An Open-label, Randomized, Parallel Study in Healthy Volunteers to Compare the Pharmacokinetics of AMG 145 When Delivered Subcutaneously via a 3.5 mL Personal Injector versus 3 Prefilled Autoinjector/Pens

This was a phase 1 open-label, randomized, parallel study design in healthy volunteers to demonstrate pharmacokinetic equivalence of the AMD (test article) to 3 prefilled AI/pens (reference article).

Two hundred and ninety-two subjects were enrolled at 4 study centers in the United States and were randomized equally into 1 of 2 parallel treatments, where treatment group A received a 420 mg total dose of evolocumab via 3 prefilled AI/pens, and treatment group B received a 420 mg dose of evolocumab using a single AMD. Subjects were given a single administration of evolocumab by the clinic staff on Day 1. Subjects were followed through study day 85 for safety, tolerability, pharmacokinetic, and pharmacodynamic assessments. Two hundred and eighty-nine (99.0%) subjects received IP and 267 (91.4%) completed the study (ie, EOS procedures were performed).

Disposition

A total of 25 (8.6%) subjects discontinued the study either due to withdrawal of consent (16 subjects; 5.5%) or were lost to follow-up (9 subjects; 3.1%); this was balanced between the AMD and AI/pen device groups.

Demographics

The study population consisted of 81.7% men and 18.3% women with a mean (standard deviation [SD]) age of 37.3 (10.6) years. All subjects were \leq 55 years of age. The majority of subjects were white (69.9%), followed by black (22.1%) and Asian (6.6%). The baseline demographics were reasonably balanced between the AMD and AI/pen device groups. Mean (SD) LDL-C concentrations at baseline prior to each dose were similar: 112.2 (28.4) mg/dL and 119.0 (32.0) mg/dL in the AI/pen and AMD groups, respectively.

Pharmacodynamic/pharmacokinetic results are presented in Section 4.4.3
Pharmacokinetics.

Device Delivery Assessment

Of the 289 subjects in the safety analysis set, 14 (4 [2.8%] in AI/pen and 10 [6.9%] in

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AMD group) subjects received incomplete or partial doses due to device failures. Of note, the administration of evolocumab via either AI/pen or AMD was performed by the clinic site staff and not by the patient.

Complete delivery of the device was defined as: the entire window on AI/pen turning yellow, or the AMD device light turning solid green, no observed fluid leakage during delivery, and window on device showing complete delivery. Complete delivery of evolocumab was observed for 430/435 (98.9%) of the AI/pens used and for 134/144 (93.1%) AMDs used.

All Adverse Events

Treatment emergent adverse events were reported in 66 (45.5%) subjects in the AI/pen group and 102 (70.8%) subjects in the AMD group. Most adverse events in this study were reported as mild (Common Terminology Criteria for Adverse Events [CTCAE] grade 1) in severity. Nineteen (7 [4.8%] in AI/pen and 12 [8.3%] in AMD group) subjects experienced grade 2 adverse events. There were no treatment emergent adverse events \geq Grade 3.

Treatment emergent adverse events reported in $>5\%$ of subjects (for both groups combined) were erythema (19.0%), induration (12.1%), and upper respiratory tract infection (5.9%). As shown in the table below, the AEs of erythema, induration, complication of device insertion, abdominal pain (includes discomfort, distension, and tenderness), presyncope, pruritus, implant site erythema, implant site edema and medical device pain were more frequent in the AMD group. The AEs of injection site erythema, injection site pain and injection site hemorrhage were reported more often in the AI/Pen group. Of note, this study used (b) (4) of the AMD device; design changes were made in (b) (4) devices to improve the performance of the device.

No subject had an adverse event that led to discontinuation of evolocumab during this study, although there was only one administration of evolocumab in this study. No deaths and no non-fatal serious adverse events occurred during the study.

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Table 5. Treatment Emergent Adverse Events Occurring in > 2% of Subjects in Either Treatment Group in Descending Order of Preferred Term (Study 20110168: Safety Analysis Set)*

Preferred Term	AMG 145 420 mg		Total (N = 289) n (%)
	3xAl/Pen (N = 145) n (%)	AMD (N = 144) n (%)	
Number of subjects reporting treatment emergent adverse events	66 (45.5)	102 (70.8)	168 (58.1)
Erythema	18 (12.4)	37 (25.7)	55 (19.0)
Induration	2 (1.4)	33 (22.9)	35 (12.1)
Upper respiratory tract infection	10 (6.9)	7 (4.9)	17 (5.9)
Injection site erythema	14 (9.7)	0 (0.0)	14 (4.8)
Complication of device insertion	0 (0.0)	11 (7.6)	11 (3.8)
Abdominal pain upper	2 (1.4)	8 (5.6)	10 (3.5)
Injection site pain	7 (4.8)	2 (1.4)	9 (3.1)
Presyncope	1 (0.7)	8 (5.6)	9 (3.1)
Pruritus	1 (0.7)	8 (5.6)	9 (3.1)
Abdominal discomfort	1 (0.7)	7 (4.9)	8 (2.8)
Headache	4 (2.8)	4 (2.8)	8 (2.8)
Blood creatine phosphokinase increased	2 (1.4)	4 (2.8)	6 (2.1)
Abdominal distension	1 (0.7)	4 (2.8)	5 (1.7)
Implant site erythema ^a	0 (0.0)	5 (3.5)	5 (1.7)
Injection site hemorrhage	5 (3.4)	0 (0.0)	5 (1.7)
Nausea	3 (2.1)	2 (1.4)	5 (1.7)
Abdominal tenderness	0 (0.0)	4 (2.8)	4 (1.4)
Diarrhoea	1 (0.7)	3 (2.1)	4 (1.4)
Implant site edema ^a	0 (0.0)	4 (2.8)	4 (1.4)
Medical device pain	0 (0.0)	4 (2.8)	4 (1.4)
Nasal congestion	1 (0.7)	3 (2.1)	4 (1.4)
Oropharyngeal pain	0 (0.0)	4 (2.8)	4 (1.4)

*Using device (b) (4)

Al/pen = autoinjector/pen; AMD = automated mini-doser; MedDRA = Medical Dictionary for Regulatory Activities

^a Implant site refers to AMD device placement site.

Coded using MedDRA version 16.1

Source: CSR 20110168, Table 12-2, page 54.

Device-related Adverse Events

Device related adverse events were reported in 39 (26.9%) subjects in the Al/pen group and 70 (48.6%) subjects in the AMD group. Most adverse events in this study were reported as mild (CTCAE grade 1) in severity. No subjects in Al/pen and 4 [2.8%] in AMD group) subjects experienced grade 2 adverse events. There were no device-related adverse events ≥ Grade 3.

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All adverse events related to erythema, injection site erythema, implant site (refers to AMD device placement site) erythema, induration and implant site (AMD device placement site) induration were reported as mild (CTCAE grade 1) in severity. The duration of these adverse events in the AI/pen group ranged from 1 to 5 days with the majority of subjects (25/34; 73.5%) experiencing an event of 1 day duration. The duration of these adverse events in the AMD group ranged from 1 to 3 days with the majority of subjects (58/76; 76.3%) experiencing an event of 1 day duration.

Laboratory Evaluations

- No subject had ALT values > 3 x ULN or total bilirubin > 2 x ULN.
- One subject had an AST elevation > 3 x ULN.
- Nine subjects had postbaseline CK values > 5 x ULN. CK concentrations returned to < 5x ULN in 5 subjects and there were no follow up visits for the other 4 subjects. None of these subjects had muscle related adverse events reported.
- A total of 289 subjects in this study were tested for the presence of anti evolocumab antibodies (288 subjects had pre-dose results and 282 had postbaseline results). One subject tested positive for pre-existing anti-evolocumab binding antibodies: Subject 16866008109 (AI/pen group) tested positive for anti-evolocumab binding antibodies (negative for neutralizing antibodies) at day 1 (prior to receiving evolocumab), at day 29, and at day 85. The subject experienced 3 grade 1 adverse events (muscle pain and 2 incidents of headache) during the study. The C_{max} and AUC_{last} values for this subject after each treatment were within the range of values observed for other subjects in this study. The presence of anti-evolocumab binding antibodies did not appear to impact evolocumab pharmacokinetics for this subject.

Conclusions:

The study demonstrated that the AMD and AI/pen devices were pharmacokinetically equivalent based on the pre-defined 90% CI for the ratio (AMD to AI/pen) for both AUC_{last} and C_{max} . Changes in LDL-C and PCSK9 also showed a similar pharmacodynamic response for each device.

In this study, which involved only one administration of evolocumab given by the study site staff, more subjects received incomplete or partial doses due to device failures in the AMD group (6.9%) as compared to the AI/pen group (2.8%); more subjects reported adverse events in the AMD group (70.8%) as compared to the AI/pen group (45.5%); and more subjects reported device-related adverse events in the AMD group (48.6%) as compared to the AI/pen group (26.9%). Treatment emergent adverse events were mainly related to injection site reactions (erythema and induration events) and the majority were transient (1 to 5 days duration) and mild in severity.

5.3.2 Study 20120135

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Study 20120135 Study Title: An Open-Label, Non-Randomized Study in Healthy Volunteers to Assess Drug Delivery Performance of the 3.5 mL Personal Injector Using Placebo Buffer

Design: This was a phase 0, open-label, non-randomized study in healthy subjects. The primary objective was to assess the subcutaneous (SC) delivery performance of the AMD. The secondary objective was to assess safety and tolerability when using the AMD. Eligible subjects were healthy adults between the ages of 18 and 55 years. The investigational product was the AMD with 3.5 mL placebo buffer containing 0.7% sodium carboxymethylcellulose (CMC). The placebo buffer had comparable viscosity to the evolocumab 120 mg/mL formulation. Using the umbilicus as a center point, each subject's abdomen was divided into 4 quadrants. The first device application and placebo delivery was performed on the left upper quadrant, the second on the right upper quadrant, and the third on the right lower quadrant of the abdomen. Each administration delivered 3.5 mL of placebo buffer over approximately 9 minutes and each administration was separated by at least 15 minutes. Complete SC delivery of 3.5 mL of placebo buffer was defined by the device light-emitting diode turning solid green, no observed fluid leakage during delivery, and the window on the device showing complete delivery.

Disposition of Subjects and Baseline Characteristics: All 100 subjects received 3 applications of the placebo buffer in the AMD. No subject withdrew from the study. There were more men (54%) than women (46%); 52% of subjects were white, 31% were black, and 10% were Asian. At baseline, mean (SD) age was 34.6 (11.0) years.

Efficacy: Complete SC delivery of 3.5 mL placebo buffer was achieved in 94.7% (284 of 300) of AMD applications (95% CI: 91.5%, 96.7%). The percentage of AMD applications that resulted in complete delivery of placebo buffer increased from 86.0% (95% CI: 77.9%, 91.5%) in period 1, when the first of 3 AMDs was applied to each subject, to 99.0% (95% CI: 94.6%, 99.8%) in periods 2 and 3.

Safety: Treatment emergent adverse events were reported in 72 (72.0%) subjects. No serious adverse events, fatal adverse events, or adverse events leading to discontinuation were reported. No trends in vital signs or other observations related to safety were noted.

Treatment emergent adverse events reported in $\geq 5\%$ of subjects were erythema (56.0%), skin induration (43.0%), induration (23.0%), pruritus (20.0%), abdominal distension (17.0%), abdominal pain upper (16.0%), abdominal pain lower (7.0%), and localized edema (5.0%).

Table 6. Treatment-Emergent Adverse Events by Preferred Term, Study 20120135 Safety Analysis Set*

Preferred Term	Total (N=100) n (%)
Erythema	56 (56.0)
Skin induration	43 (43.0)
Induration	23 (23.0)
Pruritus	20 (20.0)
Abdominal distension	17 (17.0)
Abdominal pain upper	16 (16.0)
Abdominal pain lower	7 (7.0)
Localised oedema	5 (5.0)
Abdominal tenderness	4 (4.0)
Burning sensation	4 (4.0)
Pain of skin	4 (4.0)
Implant site swelling	3 (3.0)
Hypoaesthesia	2 (2.0)
Medical device pain	2 (2.0)
Abdominal discomfort	1 (1.0)
Catheter site pain	1 (1.0)
Headache	1 (1.0)
Incision site oedema	1 (1.0)
Skin irritation	1 (1.0)

*Using device (b) (4)

Coded using MedDRA version 16.0

Source: CSR 20120135, Table 12-1, page 27.

Adverse events were also analyzed by the derived abdominal location where the device was applied during each of the periods. The distribution of events was similar across the 3 abdominal quadrants where the device was applied (ie, LUQ, RUQ, RLQ).

Conclusions: Complete delivery of the placebo buffer was achieved for approximately 95% of applications overall, including 86% of the first applications and 99% of the second and third applications. The most common emergent adverse events reported in subjects using the AMD device with placebo were erythema, skin induration, induration, pruritus, and abdominal distension.

6 Review of Efficacy

Efficacy Summary

Study 20120356, entitled, “A Multicenter, Randomized Study in Subjects With Primary Hypercholesterolemia or Mixed Dyslipidemia to Assess Subjects’ Ability to Administer a Full Dose of AMG 145 in Home-use, Using Either a 3.5 mL Personal Injector or a Prefilled Autoinjector/Pen” assessed the efficacy and safety of evolocumab during home-use with either the AMD (b) (4) or the commercially approved prefilled autoinjector.

Conclusions:

After training, the majority of subjects were able to successfully self-administer two full doses of evolocumab (420 mg) in a home-use setting using either the AMD (one 3.5 mL dose administered over 9 minutes) or AI/pen (3 separate 1.0 mL injections administered within 30 minutes).

The ability to successfully administer evolocumab in the home-use setting was similar using the AMD or AI/pen.

Similar reductions from baseline in LDL-C at week 12 and at the mean of weeks 10 and 12 were observed for evolocumab delivered via AMD or AI/pen in the home-use setting.

Adverse events (AEs) and device-related AEs were similar among subjects who used either the AMD or AI/pen.

6.1 Indication

6.1.1 Methods

This phase 3, multicenter, open-label, randomized study was designed to assess subjects’ ability to administer a full dose of evolocumab in a home-use setting using either an automated mini-doser (AMD) (b) (4) or 3 autoinjector/pens (AI/pen).

Subjects who completed screening and met final eligibility criteria were randomized 1:1 to receive evolocumab for 8 weeks (day 1, week 4, and week 8) for a total of 3 administrations (one performed in the clinic and 2 self-administrations performed at home) using 1 of 2 devices:

- evolocumab, 420 mg QM SC using AI/pen (three 1.0 mL injections, each approximately 15 seconds)

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- evolocumab, 420 mg QM SC using an AMD (one 3.5 mL injection over approximately 9 minutes)

Randomization was stratified by baseline low-density lipoprotein cholesterol (< 130 mg/dL versus \geq 130 mg/dL).

After a subject was randomized to a device (AI/pen or AMD), the subject was trained by study site staff to prepare and self-administer evolocumab. Subjects self-administered evolocumab in the clinic on day 1 under supervision of site staff and then self-administered in a home setting at weeks 4 and 8. At each visit (i.e., in the clinic on day 1 and by telephone at weeks 4 and 8), site staff documented on the administration electronic case report form (eCRF) whether the subject was able to successfully administer a full dose of evolocumab, that is, the entire set of three 1.0 mL injections (AI/pen) or the entire 3.5 mL injection (AMD). If the subject was not able to successfully administer a full dose of evolocumab, the site staff documented the reason for a missed or partial injection based on the subject's assessment. The eCRF questionnaire captured the following information:

- The subject user was interviewed about all attempted injection(s) and if the injection was administered in part, full, or none at all.
- If the subject indicated that a full dose was not administered or was partially administered, the reason was recorded.

Subjects returned to the clinical trial site at week 10 for fasting LDL-C, HDL-C, total cholesterol, triglycerides, VLDL-C and non-HDL-C measurements. For all analyses related to LDL-C, a reflexive approach was used, where the calculated LDL-C was employed unless the calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, in which case ultracentrifugation (UC) LDL-C was determined and utilized.

The end-of-study (EOS) visit was a site visit at week 12 (approximately 28 days after last evolocumab administration) for LDL-C measurement and adverse event follow-up.

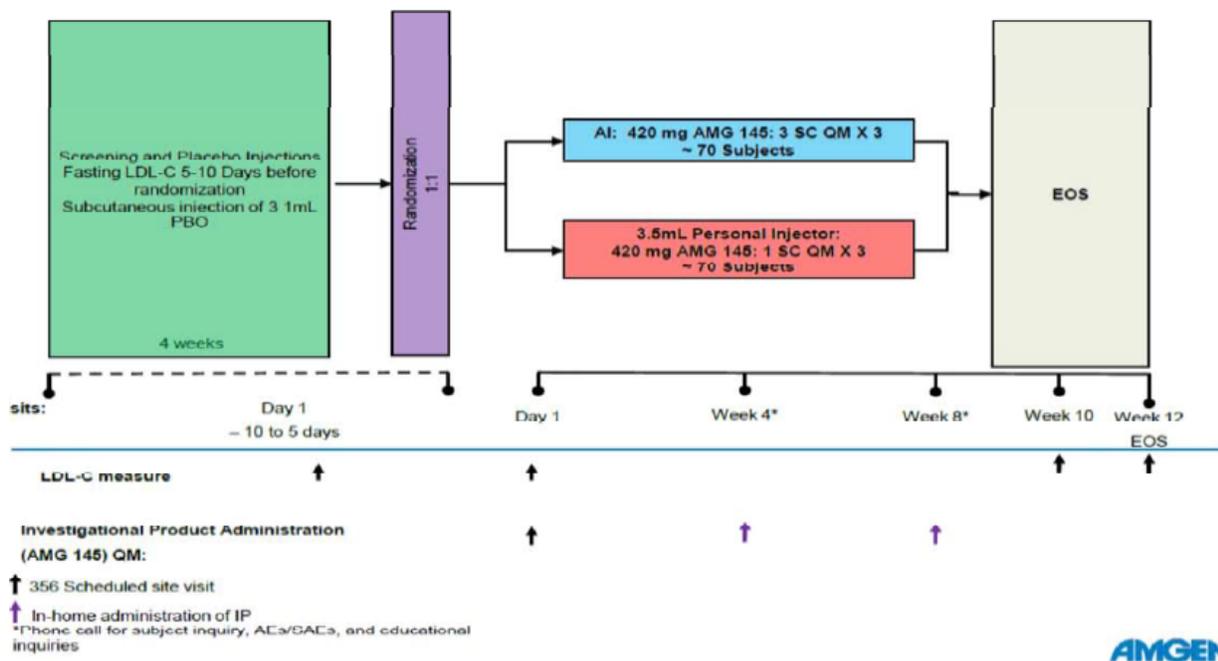
This study was conducted to support bridging between the use of the AI/pen that was used in phase 3 studies and the AMD. This study was conducted at 22 centers in the USA and Canada.

Study Initiation Date: 11 July 2013 (first subject enrolled)

Study Completion Date: 16 December 2013 (last subject completed follow-up)

The original protocol dated 29 January 2013 was not amended.

Figure 5. Study Design and Treatment Schema for Study 20120356



AE = adverse event; AI = autoinjector/pen; AMG 145 = evolocumab; EOS = end-of-study; IP = investigational product; LDL-C = low-density lipoprotein cholesterol; PBO = placebo; QM = once monthly; SAE = serious adverse event; SC = subcutaneously; X 3 = 3 times

Source: CSR 20120356, Figure 8-1, page 22.

6.1.2 Demographics

Eligible subjects were men and women ≥ 18 and ≤ 80 years of age with fasting LDL-C at screening of ≥ 85 mg/dL and fasting triglycerides ≤ 400 mg/dL. Subjects were required to be on a stable dose of a statin with or without ezetimibe for at least 4 weeks prior to randomization.

The study population consisted of 47.6% women; the mean (SD) age of study subjects was 59.7 (10.2) years. The majority (64.6%) of subjects were < 65 years old. Hispanic or Latino subjects comprised 6.1% of subjects. Races in the subject population were white (87.8%), black (4.9%), Asian (4.3%), American Indian or Alaska Native (1.2%), other (1.2%), and mixed race (0.6%). Characteristics of the 2 treatment groups were similar across these demographic variables.

Baseline risk factors were 40% of subjects were classified as high risk by National Cholesterol Education Program (NCEP) coronary heart disease criteria, 15% had a medical history of coronary artery disease, 12% had cerebrovascular or peripheral arterial disease, and 21% had type 2 diabetes mellitus. In the AMD group, there was approximately 10% higher percentage of subjects in the NCEP coronary heart disease

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high risk category and approximately 10% higher incidence of carotid or vertebral artery disease compared with subjects in the AI/pen group.

Baseline overall mean lipid parameters, including LDL-C (116.3 mg/dL), total cholesterol (195.3 mg/dL), HDL-C (50.3 mg/dL), triglycerides (143.7 mg/dL), VLDL-C (28.7 mg/dL), and non-HDL-C (145.0 mg/dL) were similar between groups.

Concomitant statins were reported by 163 subjects (99.4%) at baseline and included atorvastatin (40.2%), simvastatin (28.0%), rosuvastatin (15.9%), pravastatin (12.2%), as well as fluvastatin, lovastatin, and pitavastatin (1.2% each). Other non-statin lipid-modifying concomitant medications at baseline included ezetimibe (8.5%), fish oil (7.9%), and omega-3-acid ethyl ester (0.6%).

6.1.3 Subject Disposition

A total of 243 subjects were screened for the study at 22 centers in the US and Canada and 164 subjects were randomized (82 each to AMD and AI/pen). All 164 subjects received at least 1 of the 3 planned doses of evolocumab and were included in the full analysis set (FAS); 157 subjects completed IP and 7 subjects (35616005011, 35666002018, 35666006004, 35666010002, 35666010004, 35666026005, and 35666028016) discontinued evolocumab because of adverse event(s), subject request, or lost to follow-up. A total of 7 subjects (35666002018, 35666006004, 35666006017, 35666010002, 35666026003, 35666026005, and 35666032001) discontinued the study, including 3 subjects who completed evolocumab but were lost to follow-up between week 8 and week 12 (35666006017, 35666026003, and 35666032001). As shown in the following table, only 1 (1.2%) subject discontinued using the AMD device as compared to 6 (7.3%) subjects in the AI/pen group.

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Table 7. Subject Disposition With Discontinuation Reason Study 20120356 (All Randomized Subjects)

Subject status	EvoMab AMD (N = 82) n (%)	EvoMab 3 x AI/pen (N = 82) n (%)	Total (N = 164) n (%)
IP accounting			
Never received IP	0 (0.0)	0 (0.0)	0 (0.0)
Received IP	82 (100.0)	82 (100.0)	164 (100.0)
Completed IP	81 (98.8)	76 (92.7)	157 (95.7)
Discontinued IP	1 (1.2)	6 (7.3)	7 (4.3)
Adverse event	0 (0.0)	1 (1.2)	1 (0.6)
Subject request	1 (1.2)	2 (2.4)	3 (1.8)
Lost to follow-up	0 (0.0)	3 (3.7)	3 (1.8)
Study completion accounting			
Completed the study	80 (97.6)	77 (93.9)	157 (95.7)
Discontinued the study	2 (2.4)	5 (6.1)	7 (4.3)
Withdrawal of consent	1 (1.2)	0 (0.0)	1 (0.6)
Lost to follow-up	1 (1.2)	5 (6.1)	6 (3.7)

AI/pen = autoinjector/pen; AMD = automated mini-doser; EvoMab = evolocumab; IP = investigational product; N = number of subjects randomized; n = number of subjects with observed data
 Source: CSR 20120356, Table 9-1, page 42.

Exposure

All 164 subjects received at least 1 administration of IP and were included in the full analysis set (FAS). As shown in the table below, the mean and median exposure to evolocumab in months and the mean and median cumulative dose were similar between groups.

Table 8. Summary of Exposure to Evolocumab: Study 20120356 (Full Analysis Set)

	EvoMab AMD (N = 82)	EvoMab 3 x AI/pen (N = 82)
Duration of EvoMab exposure (months) ^a		
n	82	82
Mean	2.8	2.7
SD	0.2	0.4
Median	2.8	2.8
Q1, Q3	2.8, 2.8	2.8, 2.8
Min, max	0.9, 2.8	1.0, 2.9
Number of EvoMab doses received – n (%)		
0	0 (0.0)	0 (0.0)
1	1 (1.2)	3 (3.7)
2	1 (1.2)	3 (3.7)
3	80 (97.6)	76 (92.7)
Cumulative dose of EvoMab (mg) ^b		
n	82	82
Mean	1234.4	1212.2
SD	137.6	179.0
Median	1260.0	1260.0
Q1, Q3	1260.0, 1260.0	1260.0, 1260.0
Min, max	420, 1260	420, 1260

AI/pen = autoinjector/pen; AMD = automated mini-doser; EvoMab = evolocumab; IP = investigational product; max = maximum; min = minimum; N = number of subjects with an attempted IP administration; n = number of subjects with at least 1 dose; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
 a [min (end of IP date + 28 days, end-of-study date) – first investigational product administration date + 1] / 365.25 × 12

b Partial doses imputed as 0.

Source: CSR 20120356, Table 12-1, page 53.

6.1.4 Analysis of Primary Endpoint(s)

The primary objective of this study was to assess users' ability to administer a full dose of evolocumab in a home-use setting using either an AMD or AI/pen.

The primary endpoint of the study was the subject-reported outcome of attempted full-dose administration at each of weeks 4 and 8. Subjects who discontinued evolocumab had subsequent responses recorded as 'discontinued investigational product (IP) prior to administration time.' Therefore, each primary endpoint had 3 possible values (yes/ no/ discontinued IP prior to administration time).

Full home administrations of evolocumab at both week 4 and week 8 were reported by 93.9% of subjects in the AMD group (n = 77) and 91.5% of subjects in the AI/pen group (n = 75) (see table below). When full administrations that occurred outside the

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prespecified visit window were included (1 in each device group), the administration rate increased to 95.1% of subjects in the AMD group (n = 78) and 92.7% of subjects in the AI/pen group (n = 76). A total of 97.6% of subjects in the AMD group (n = 80) and 95.1% of subjects in the AI/pen group (n = 78) had at least 1 home administration of evolocumab (data not shown in table).

For reasons other than discontinuation, 4.9% and 2.4% of subjects in the AMD and AI/pen groups, respectively, did not administer a full dose of evolocumab at week 4, and 2.4% of subjects in each group did not administer a full dose at week 8.

By week 8, discontinuations were seen for 1.2% (n=1) of subjects in the AMD group and 4.9% (n=4) of subjects in the AI/pen group.

In an analysis of administration by week, 95.1% of subjects fully administered a dose of evolocumab by AMD at week 4 and 96.3% at week 8; one subject (1.2%) administered a full dose outside the planned visit window. In the AI/pen group, 93.9% of subjects fully administered evolocumab in a home-use setting at week 4 and 92.7% at week 8; one subject (1.2%) administered a full dose outside the planned visit window.

Table 9. Primary Analysis of the Primary Endpoint of Subject-reported Outcome of Attempted Full-dose Administration at Each of Weeks 4 and 8; Study 20120356 (Full Analysis Set)

	EvoMab AMD* (N = 82)	EvoMab 3 x AI/pen (N = 82)	Treatment Difference
Two full home administrations at any time – n (%), (95% CI)	78 (95.1) (88.1, 98.1)	76 (92.7) (84.9, 96.6)	-2.4 (-10.7, 5.6)
At planned weeks – n (%), (95% CI)	77 (93.9) (86.5, 97.4)	75 (91.5) (83.4, 95.8)	-2.4 (-11.2, 6.1)
At least one off planned week – n (%), (95% CI)	1 (1.2) (0.2, 6.6)	1 (1.2) (0.2, 6.6)	0.0 (-5.5, 5.5)
Week 4 Outcome			
Full home administration – n (%), (95% CI)	78 (95.1) (88.1, 98.1)	77 (93.9) (86.5, 97.4)	-1.2 (-9.2, 6.6)
Not full home administration – n (%), (95% CI)	4 (4.9) (1.9, 11.9)	2 (2.4) (0.7, 8.5)	-2.4 (-9.7, 4.3)
Discontinued IP, n (%), (95% CI)	0 (0.0) (0.0, 4.5)	3 (3.7) (1.3, 10.2)	3.7 (-1.4, 10.2)
Week 8 Outcome			
Full home administration – n (%), (95% CI)	79 (96.3) (89.8, 98.7)	76 (92.7) (84.9, 96.6)	-3.7 (-11.8, 4.0)
Not full home administration – n (%), (95% CI)	2 (2.4) (0.7, 8.5)	2 (2.4) (0.7, 8.5)	0.0 (-6.3, 6.3)
Discontinued IP, n (%), (95% CI)	1 (1.2) (0.2, 6.6)	4 (4.9) (1.9, 11.9)	3.7 (-2.5, 10.7)

*Using device (b) (4)

AI/pen = autoinjector/pen; AMD = automated mini-doser; CI = confidence interval; EvoMab = evolocumab; IP = investigational product; N = number of subjects randomized with an attempted IP administration; n = number of subjects with observed data
 Full administration occurred when there was a record for a full administration for the planned administration time. Not full administration occurred when there was not a record for full administration and the subject did not discontinue IP prior to the planned administration time. Discontinued IP occurred when there was documentation that the subject ended IP administration prior to the planned administration time. The 95% CIs for percentages were calculated using the Wilson score method. The 95% CIs for differences in percentages were calculated using the Newcombe hybrid score method.

Source: CSR 20120356, modified from Table 10-1, page 47.

Although this study is limited by a small number of subjects (approximately 80 in each group) and only 2 administration periods where the subjects were injecting evolocumab at home without health provider supervision, the subjects using the AMD device were able to administer a full dose of evolocumab in a home-use setting at least as well as the subjects using the AI/pen.

Prespecified subgroup analyses of the primary endpoint were performed for subjects with a screening LDL-C of < 130 mg/dL or ≥ 130 mg/dL; subjects < 65 years old; subjects ≥ 65 years old; women; and men. The results of these analyses did not suggest any major differences between subgroups in the ability to use either device. However, subjects that were 65 years or older seemed to perform slightly better using the AI/pen as compared to the AMD. In this subgroup, full home administrations of evolocumab at both week 4 and week 8 were reported by 90.9% of subjects ≥ 65 years old in the AMD group (n = 30) and 96.0% of subjects ≥ 65 years old in the AI/pen group (n = 24) (see table below). This trend was not seen in the other subgroup analyses.

Table 10. Subgroup Analysis (Age ≥ 65 Years) of the Primary Endpoint of Subject-reported Outcome of Attempted Full-dose Administration at each of Weeks 4 and 8. Study 20120356 (Full Analysis Set)

	EvoMab AMD* (N = 33)	EvoMab 3 x AI/pen (N = 25)	Treatment Difference
Two full home administrations at any time – n (%), (95% CI)	30 (90.9) (76.4, 96.9)	24 (96.0) (80.5, 99.3)	5.1 (-11.6, 19.9)
At planned weeks – n (%), (95% CI)	29 (87.9) (72.7, 95.2)	24 (96.0) (80.5, 99.3)	8.1 (-9.1, 23.7)
At least one off planned week – n (%), (95% CI)	1 (3.0) (0.5, 15.3)	0 (0.0) (0.0, 13.3)	0 (0.0) (-15.3, 10.5)

*Using device (b) (4)
 AI/pen = autoinjector/pen; AMD = automated mini-doser; CI = confidence interval; EvoMab = evolocumab; IP = investigational product; N = number of subjects randomized with an attempted IP administration; n = number of subjects with observed data
 Full administration occurred when there was a record for a full administration for the planned administration time. Not full administration occurred when there was not a record for full administration and the subject did not discontinue IP prior to the planned administration time. Discontinued IP occurred when there was documentation

that the subject ended IP administration prior to the planned administration time. The 95% CIs for percentages were calculated using the Wilson score method. The 95% CIs for differences in percentages were calculated using the Newcombe hybrid score method.

Source: CSR 20120356, modified from Table 14-4.3.4, page 102.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary objective of this study was to assess the effect of evolocumab on LDL-C.

The secondary endpoint of the study was the mean at weeks 10 and 12 for percent change from baseline in LDL-C.

The percent reduction from baseline in reflexive LDL-C at the mean of weeks 10 and 12 (least squares mean [SE]) was 67.9% (2.4%) in the AMD group and 64.5% (2.4%) in the AI/pen group, with an estimated treatment difference of 3.4% (95% CI, -2.9% to 9.7%) (see table below). For calculated LDL-C, the results were qualitatively similar.

Table 11. Analysis of Secondary Endpoint of Percent Change From Baseline in Reflexive LDL-C at the Mean of Weeks 10 and 12; Study 20120356 (Full Analysis Set)

Mean of Weeks 10 and 12	EvoMab AMD* (N = 82)	EvoMab 3 x AI/pen (N = 82)	Treatment Difference
Summary statistics			
N	79	78	
Mean	-67.7	-63.6	
SE	1.7	2.9	
Q1, Q3	(-77.2, -59.7)	(-75.9, -61.3)	
Min, max	(-93.0, 3.1)	(-97.2, 49.0)	
Least squares mean ^a			
Estimate	-67.9	-64.5	3.4
SE	2.4	2.4	3.2
95% CI)	(-72.6, -63.2)	(-69.2, -59.8)	(-2.9, 9.7)

*Using device (b) (4)

AI/pen = autoinjector/pen; AMD = automated mini-doser; CI = confidence interval; EvoMab = evolocumab; IVRS = interactive voice/web response system; max = maximum; min = minimum; N = number of subjects randomized with an attempted IP administration; n = number of subjects with observed data; Q1 = first quartile; Q3 = third quartile; SE = standard error

^a Least squares mean is from the repeated measures model which includes treatment group, stratification factor (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates.

Note: When the calculated low-density lipoprotein cholesterol (LDL-C) was < 40 mg/dL or triglycerides were > 400 mg/dL, calculated LDL-C was replaced with ultracentrifugation LDL-C from the same blood sample, if available.

Source: CSR 20120356, modified from Table 14-4.4.1, page 108.

Prespecified subgroup analyses of the secondary endpoint were performed for subjects with a screening LDL-C of < 130 mg/dL or ≥ 130 mg/dL. The percent reduction in LDL-C from baseline to the mean of weeks 10 and 12 (least squares mean) ranged from 62.6% (in the AI/Pen group with a screening LDL-C < 130 mg/dL) to 68.6% (in the AI/Pen group with a screening LDL-C ≥ 130 mg/dL) across both subgroups and both treatment groups.

Analysis of Other Lipid Parameters

The table below shows the percent change from baseline at week 12 and the percent change from baseline at the mean of weeks 10 and week 12 for lipid parameters (reflexive LDL-C, calculated LDL-C, total cholesterol, non-HDL-C, total cholesterol/HDL-C ratio, VLDL-C, HDL-C, triglycerides). All were ad hoc analyses except for the percent change from baseline to the mean of weeks 10 and 12 for reflexive LDL-C. The changes in these lipid parameters are consistent with what one would expect from the mechanism of action for evolocumab and the changes are similar for both devices.

Table 12. Summary of Mean Percent Changes From Baseline in Lipid Parameters at Week 12 and at the Mean of Weeks 10 and 12; Study 20120356 (Full Analysis Set)

Lipid Parameter	EvoMab AMD Mean (SE) (N = 82)		EvoMab 3 x AI/pen Mean (SE) (N = 82)	
	% Change From Baseline to Week 12	% Change From Baseline to the Mean of Weeks 10 and 12	% Change From Baseline to Week 12	% Change From Baseline to the Mean of Weeks 10 and 12
Reflexive LDL-C ^a (mg/dL)	-60.4 (1.9)	-67.7 (1.7)	-60.4 (2.7)	-63.6 (2.9)
Calculated LDL-C (mg/dL)	-62.0 (2.0)	-68.9 (1.8)	-62.6 (2.8)	-65.9 (3.1)
Total cholesterol (mg/dL)	-35.1 (1.4)	-40.5 (1.2)	-35.7 (1.9)	-38.3 (2.0)
Non-HDL-C (mg/dL)	-52.3 (1.8)	-59.3 (1.5)	-51.5 (2.5)	-54.8 (2.6)
Total cholesterol/ HDL-C ratio	-42.6 (1.5)	-47.0 (1.3)	-40.7 (2.1)	-43.0 (2.3)
VLDL-C (mg/dL)	-14.0 (2.7)	-19.5 (2.2)	-2.7 (4.1)	-6.2 (2.9)
HDL-C (mg/dL)	14.7 (1.6)	13.7 (1.4)	9.9 (1.5)	10.3 (1.3)
Triglycerides (mg/dL)	-13.8 (2.7)	-19.4 (2.2)	-2.4 (4.1)	-6.0 (2.9)

AI/pen = autoinjector/pen; AMD = automated mini-doser; EvoMab = evolocumab; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; N = number of subjects randomized with an attempted investigational product administration; PCSK9 = proprotein convertase subtilisin/kexin type 9; SE = standard error; VLDL-C = very-low-density lipoprotein cholesterol

^a When the calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, calculated LDL-C was replaced with ultracentrifugation LDL-C from the same blood sample, if available.

Source: CSR 20120356, modified from Table 10-3, page 50.

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6.1.6 Other Endpoints and Safety Evaluations

The exploratory endpoints of the study were the subject incidence of adjudicated events:

- death by any cause
- cardiovascular death
- myocardial infarction
- hospitalization for unstable angina
- coronary revascularization
- stroke
- TIA
- hospitalization for heart failure

There were no subjects with positively adjudicated events.

All Adverse Events

Treatment emergent adverse events were reported in 21 subjects (25.6%) in the AMD group and 27 subjects (32.9%) in the AI/pen group. Most adverse events in this study were reported as mild (CTCAE grade 1) in severity. Fifteen subjects (6 subjects [7.3%] in the AMD group; 9 subjects [11.0%] in the AI/pen group) experienced adverse events that were \geq grade 2, and 2 subjects (1 each [1.2%] in the AMD and AI/pen groups) experienced grade 3 adverse events. There were no treatment emergent adverse events \geq grade 4. The incidence of adverse events was low and generally similar between treatment groups. No preferred term was reported by $> 5\%$ of subjects (5 subjects) in either group. The 3 most commonly reported adverse events (AMD group; AI/pen group) were pain in extremity (0% [0 subjects]; 3.7% [3 subjects]), fatigue (2.4% [2 subjects]; 1.2% [1 subject]), and sinusitis (3.7% [3 subjects]; 0% [0 subjects]).

No fatal adverse events were reported. One subject (1.2%; AI/pen group) experienced a serious adverse event (deep vein thrombosis), and 1 subject (1.2%; AI/pen group, #35616005011) experienced an adverse event (injection-site hematoma) that led to discontinuation of IP.

Device-related Adverse Events

In the AMD group, where 82 participants received a dose of 420 mg evolocumab via a single 3.5 mL injection administered over approximately 9 minutes, 1 (1.2%) participant experienced 2 non-serious adverse events of injection site reaction that were considered related to the device by the investigator. Of note, subjects in this study used AMD device (b) (4) which was subsequently modified to improve performance.

In the AI/pen group, where 82 participants received a dose of 420 mg evolocumab via 3 separate 1.0 mL injections, 2 (2.4%) participants experienced a device-related adverse event. One participant (1.2%) experienced an adverse event of injection site hematoma,

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and 1 participant (1.2%) experienced an event of pain in extremity, and both events were non-serious and considered related to the device by the investigator.

Laboratory Evaluations

- No subject had AST or ALT values > 3 x ULN or total bilirubin > 2 x ULN.
- No subject had postbaseline CK values > 5 x ULN.
- In 1 subject (1.2%) in the AI/pen group, glucose increased from baseline grade 2 to grade 3.
- A total of 163 subjects in this study (163 at baseline and 152 postbaseline) were tested for the presence of anti-evolocumab antibodies, and no subjects tested positive for anti-evolocumab antibodies

6.1.7 Subpopulations

Discussed in Sections 6.1.4 and 6.1.5.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

As discussed throughout this document, clinical studies 20120356, 20110168 and 20120135 used the base device [REDACTED]^{(b) (4)} which the company maintains has the equivalent form, fit, and function as the to-be-marketed device. The clinical review team asked the applicant to provide their rationale on why the clinical studies can be relied on for approval consideration given that they were conducted using a “base device” that then underwent various design changes. The applicant was asked to specifically address whether the design changes that have been made since conducting the clinical studies (including the bridge to the autoinjector) could be expected to change or influence the patient’s experience with the AMD device.

The applicant responded that since the completion of the first three clinical studies, they made minor reliability improvements and one minor usability improvement to the base AMD device. The applicant believes that these changes are considered continuous improvements to the device as described in FDA’s Design Control Guidance for Medical

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Device Manufacturers (1997) in Section I, Design Changes. Inputs to these design changes included complaints from the clinical studies, design verification (bench testing), and human factors testing. Each change was evaluated for impact and verified and/or validated as appropriate and the results from design verification and/or validation of the to-be-marketed device (commercial configuration) are included in the applicant's submission. The applicant states that these changes did not alter critical drug delivery parameters such as drug-contacting materials, delivered volume, or injection time; all of these critical parameters remained the same throughout the clinical trials. Therefore, the applicant believes that the data collected in the clinical studies using the base AMD device demonstrate the actual performance of the to-be-marketed AMD device.

The CDRH review team agree that the effectiveness data (PK/PD bridge to the autoinjector) collected in the clinical studies using the base AMD device (b) (4) can be relied on to establish effectiveness of the to-be-marketed AMD device. The safety of the device, for the purposes of this review, primarily relies on the uncontrolled experience from Study 201201138, using AMD modified device (b) (4)

7 Review of Safety

Safety Summary

The duration of exposure (as of 02 April 2015) to AMD device (b) (4) which is similar to the commercial device, is as follows:

- A total of 255 unique subjects had a total of 133 patient-years of exposure with the AMD (b) (4) in Study 20120138.
 - A total of 206 subjects had ≥ 3 months exposure to evolocumab using the AMD, 151 subjects had ≥ 6 months, and 88 subjects had ≥ 9 months.
- Median (min, max) exposure to evolocumab using the AMD (b) (4) was 5.5 months (2.1, 9.0) in year 1 and 5.6 months (0.3, 11.8) in year 2+, with a maximum exposure of approximately 12 months for any unique subject.

This reviewer concludes that the subject exposure to AMD (b) (4) is adequate to assess the device in an appropriate patient population.

Complaint Issues and Device Failures using AMD Device (b) (4)

Out of 3678 injections using AMD device (b) (4), there were 181 complaint issues reported for the AMD device during clinical use and 23 device failures. Thus, 4.9% of injection attempts resulted in a device complaint and 0.6% of injection attempts resulted in reported device failures/device malfunctions. The majority (57%) of the complaint codes with device failures were "delivery device not functioning (e.g. no beep after liner removal, no (b) (4) beeps upon injection start, no (b) (4) beeps upon injection completion, no pumping sound during injection, no blue blinking light upon liner removal, no blinking green light during injection or no solid green light after completed injection)".

The most likely clinical effect following an instance of the reported failures for the AMD device would be under-dosing due to a missed or partial dose of evolocumab. With the AMD device, one missed dose is equivalent to missing one month of lipid lowering therapy. While it is a low likelihood that one missed dose would lead to a significant safety or efficacy risk to the patient, multiple missed or partial doses could be more problematic as the LDL-C level would not be optimally lowered.

The approvability of the AMD device is also supported by Study 20120356, entitled, “A Multicenter, Randomized Study in Subjects With Primary Hypercholesterolemia or Mixed Dyslipidemia to Assess Subjects’ Ability to Administer a Full Dose of AMG 145 in Home-use, Using Either a 3.5 mL Personal Injector or a Prefilled Autoinjector/Pen”, which was discussed in Section 6 and assessed the efficacy and safety of evolocumab during home-use with either the AMD (b) (4) or the commercially approved prefilled autoinjector. After training, the majority of subjects were able to successfully self-administer two full doses of evolocumab (420 mg) in a home-use setting using either the AMD (one 3.5 mL dose administered over 9 minutes) or AI/pen (3 separate 1.0 mL injections administered within 30 minutes). The ability to successfully administer evolocumab in the home-use setting was similar using the AMD or AI/pen. Similar reductions from baseline in LDL-C at week 12 were observed for evolocumab delivered via AMD or AI/pen in the home-use setting. Adverse events (AEs) and device-related AEs were similar among subjects who used either the AMD or AI/pen.

Given the entirety of evidence submitted for this application, this reviewer concludes that the safety of AMD (b) (4) as compared to the use of the 3 AI/pens, is adequate to support approval of this device as an alternative to the AI/pen.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following studies used the “base” device (b) (4) or a modified device (b) (4); the commercial device (b) (4) was not used.

Table 13. Clinical Studies Using the AMD “Base” Device in the Evolocumab Program

Study	Description	Device(s) Used
Clinical Pharmacology Studies		
20120135	Assess the drug delivery performance of the	AMD

	AMD using a placebo buffer	
20110168	Bioequivalence PK/PD study conducted to bridge data obtained using the currently approved prefilled autoinjector vs. AMD	AI/pen, AMD
Efficacy/Safety Studies for Hyperlipidemia		
20120138 (ongoing)	Controlled, Long-term, Open-label Phase 3 Extension Study: AI/pen self-administration (OSLER-2)	AI/pen, AMD*
20120356	Phase 3 home-use study to assess the users' ability to administer a full dose (420 mg) of evolocumab by the patient during home-use (with primary LDL endpoint assessment) using either the AMD or the commercially approved prefilled autoinjector	AI/pen, AMD
AI/pen=autoinjector/pen; AMD= automated mini-doser; PD= pharmacodynamic; PK= pharmacokinetic. * The AMD device (b) (4) used in the ongoing study 20120138, introduced into the study in April 2014, has been modified from the base device used in studies 20120135, 20110168 and 20120356.		

The applicant maintains that there are no important differences in the usability and functionality of the base device and to-be-marketed device. Since the completion of the first three clinical studies, Amgen states that they made minor reliability improvements and one minor usability improvement to the base AMD device. Inputs to these design changes included complaints from the clinical studies, design verification (bench testing), and human factors testing. The applicant states that these changes did not alter critical drug delivery parameters such as drug-contacting materials, delivered volume, or injection time. The reliability improvements reportedly are internal to the device and do not affect the normal sequence or timing of operation; they are not observable by the user during normal use. Thus, the applicant believes that the data collected in the clinical studies using the base AMD device demonstrate the actual performance of the to-be-marketed AMD device.

The table below identifies which design changes are reliability improvements and which change is the single usability improvement.

Table 14. Chronological Summary of Device Design Subsystem Changes

(b) (4)

7.1.2 Categorization of Adverse Events

As described in the applicant's Module 5.3.5.3 – Clinical Device Safety Summary, a product complaint is defined by Amgen as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released by either Amgen or by distributors and partners for whom Amgen manufactures the material. Once a complaint is reported, Amgen is responsible for investigation to identify and/or confirm

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failures. A product failure is defined by Amgen as an event or defect Amgen has the capacity to control that has potential to affect quality attributes such as safety, purity, identity, potency, reliability, effectiveness, durability, or performance of the product under specified conditions.

The definition for adverse device effect (ADE) as defined in the evolocumab clinical program is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use resulting from any malfunction of the device or adverse events resulting from use error or from intentional misuse of the device.

Device-related adverse events were captured in the clinical trial database via the electronic case report form (eCRF) which included a field for investigator assessment of relationship of the AMD device to reported adverse events.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The applicant provided a summary of clinical device safety data collected during use of the Automated Mini-Doser (AMD) in the clinical development program for evolocumab. This consisted of the three completed clinical studies (20120135, 20110168 and 20120356) and the ongoing clinical study 20120138, all with a data cutoff of 01 July 2014.

One of the issues with the pooling is that the original base device (b) (4) underwent significant design changes in the production of the modified base device (b) (4). So it is somewhat problematic to pool the device adverse events from these 2 devices as device (b) (4) included modifications intended to improve performance. The applicant did confirm that all subjects using the AMD device in Clinical Study 20120138 were using the modified base device (b) (4). There were no 20120138 subjects using the original base device (b) (4) that was used in Clinical Studies 20120356, 20110168 and 20120135.

Of note, the CDRH reviewer notes that (b) (4) and the commercial device (b) (4) are quite similar.

Another issue was that the data cutoff for this application, 01 July 2014, was more than 14 months prior to submission. During the review, we asked for updated safety data with more recent data cutoff points. Some of the safety data will represent different data cut points which I will try and make clear throughout the safety portion of this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Duration of exposures to the AMD device (b) (4) and the demographics of the study population are discussed in the individual study reviews in Sections 5.3 and 6.

The duration of exposure to AMD device (b) (4) which is similar to the commercial device, is described below:

As of the 02 April 2015 data cutoff date, a total of 255 unique subjects had a total of 133 patient-years of exposure with the AMD (b) (4) in Study 20120138. A total of 206 (81%) subjects had ≥ 3 months exposure to evolocumab using the AMD, 151 (59%) subjects had ≥ 6 months, and 88 (35%) subjects had ≥ 9 months. Median (min, max) exposure to evolocumab using the AMD (b) (4) was 5.5 months (2.1, 9.0) in year 1 and 5.6 months (0.3, 11.8) in year 2+, with a maximum exposure of approximately 12 months for any unique subject.

This reviewer concludes that the subject exposure to AMD (b) (4) is sufficient to assess the device in an appropriate patient population.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

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7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

7.3.1 Deaths

There were no fatal device-related adverse events reported during use of the AMD device in the clinical trials.

7.3.2 Nonfatal Serious Adverse Events

There were no serious device-related adverse events reported during use of the AMD device in the clinical trials.

7.3.3 Dropouts and/or Discontinuations

In Study 20120135, subjects were given 3 subcutaneous administrations of placebo in 3 different abdominal locations on Day 1. No subject had an adverse event that led to discontinuation from the study.

In Study 20110168, subjects were given a single administration of evolocumab by the clinic staff on Day 1. Subjects were followed through study day 85 for safety, tolerability, pharmacokinetic, and pharmacodynamic assessments. No subject had an adverse event that led to discontinuation of evolocumab during this study.

In Study 20120356, subjects self-administered evolocumab in the clinic on day 1 under supervision of site staff and then self-administered in a home setting at Weeks 4 and 8. One subject (35616005011) in the AI/pen group experienced an adverse event of injection site hematoma leading to discontinuation of evolocumab.

In Study 20120138, at the time of the data cutoff of 01 April 2014, only the AI/pen device was in use. The AMD (b) (4) was introduced into this ongoing, phase 3, long-term, open-label extension in April 2014.

Year 2 [After week 48 (year 2), all subjects received open-label evolocumab for approximately 1 year]

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No AI/Pen device related adverse events or withdrawal from device-related AEs were reported for the 17 subjects in the Year 2 group at the time of the data cutoff date.

7.3.4 Significant Adverse Events

Not applicable.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In response to an FDA information request, the applicant provided on 4 April 2016 updated device-related adverse events and device failures for the ongoing use of the AMD in the OLE Study 20120138 with a data cutoff date of 17 January 2016. The following table summarizes the complaints/failures and adverse device effects as reported for 3 completed clinical trials (20110135, 20110168 and 20120356) and an ongoing clinical trial (20120138) with an original data cutoff of 01 July 2014 and an updated data cutoff of 17 January 2016. The additional information provided following the original data cutoff of 01 July 2014 is from the ongoing Study 20120138 only, as the other 3 studies were already completed. The AMD device used in Study 20120138 has been modified from the base device used in the other 3 studies.

Table 15. Total Complaint Issues and Failures Received for the Evolocumab Clinical Program (AMD)

	Original AMD submission (data cutoff 01 July 2014) ¹	Cumulative AMD data through 17 January 2016 ²	AMD (b) (4) data from April 2014 through 17 January 2016 in Study 20120138
Total Device Injection Attempts	828	4506	3678
Number of Device Complaint Issues	70 (8.5%)	251 (5.6%)	181 (4.9%)
Number of Device Failures	53 (6.4%)	76 (1.7%)	23 (0.6%)

¹Original AMD submission includes aggregated data from clinical studies 20110168, 20120138, 20120356 and

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20120135 using device (b) (4)
²Cumulative AMD Data includes aggregate data from clinical studies listed above. New reported complaints and device failures are associated with study 20120138. This represents cumulative data using device (b) (4) and (b) (4)
 AMD = automated mini-doser.
 Source: modified from Applicant's Table 1 from 4/4/2016 IR response: 5.3.5.3 – Clinical Device Safety Summary

As of 01 July 2014, out of 828 injections using the AMD device, there were 70 complaint issues reported for the AMD device during clinical use and 53 product failures. Thus, 8.5% of injection attempts resulted in a device complaint and 6.4% of injection attempts resulted in reported device failures/device malfunctions.

Since the original submission (data cutoff 01 July 2014), there were a total of 3678 new injection attempts and 23 newly reported device failures. As of 17 January 2016, out of 4506 injections using the AMD device, there were 251 complaint issues reported for the AMD device during clinical use and 76 product failures. Thus, 5.6% of injection attempts resulted in a device complaint and 1.7% of injection attempts resulted in reported device failures/device malfunctions.

When we just look at complaint issues and device failures using device (b) (4) which is quite similar to the commercial/to-be-marketed version, out of 3678 injections using AMD device (b) (4) there were 181 complaint issues reported for the AMD device during clinical use and 23 product failures. Thus, 4.9% of injection attempts resulted in a device complaint and 0.6% of injection attempts resulted in reported device failures/device malfunctions.

The applicant believes that the reduction in the rate of complaint issues and device failures in the updated dataset provided is likely due to design changes in the AMD device used only in Study 20120138. The following table provides a description of the complaint codes and the corresponding number of AMD device failures.

Table 16. AMD Complaint Codes with Failures Reported in the Evolocumab Clinical Program (in descending order of frequency)

Complaint Code	Description	Device (b) (4) Failures as of 01Jul2014 ¹ (n=53)	Device (b) (4) Failures as of 17Jan2016 ² (n=76)	Device (b) (4) Failures from April 2014 through 17 January 2016 in Study 20120138 ³ (n=23)
Device Not Functioning/ Activation Failed	Delivery device not functioning (e.g. no beep after liner removal, no (b) (4))			

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	beeps upon injection start, no (b)(4) beeps upon injection completion, no pumping sound during injection, no blue blinking light upon liner removal, no blinking green light during injection or no solid green light after completed injection).	33 (62.3%)	46 (60.5%)	13 (56.5%)
Drug Injection Failed/ Leakage	Delivery device stalls and/or fails to complete injection	11 (20.7%)	14 (18.4%)	3 (13.0%)
Cartridge other	Any event or condition applicable to this item that is not covered by any other Event/Cause Code.	5 (9.4%)	7 (9.2%)	2 (8.7%)
Device Cartridge Door Broken	Delivery device door is broken, not functioning properly or cartridge not able to be loaded during or after handling.	3 (5.7%)	3 (3.9%)	0
Needle Other	Any event or condition applicable to this item that is not covered by any other Event/Cause Code.	0	2 (2.6%)	2 (8.7%)
Drug Particles Fibers / Cartridge Foreign Object External	Fibrous particles in the drug or foreign object, including dirt, attached to external surface of the cartridge.	0	2 (2.6%)	2 (8.7%)
Device Application Adhesive Does Not Function as Expected	Delivery device application adhesive did not function as expected, including not adhering to skin or partially adhering to skin.	1 (1.9%)	1 (1.3%)	0
Needle Bent During Use	Needle appears deviated from a straight line; appears bowed, or crooked. Needle shows deflection starting anywhere from the base, in the needle cannula or anywhere from the base of the device needle.	0	1 (1.3%)	1 (4.4%)

Source: modified from Applicant's Table 2 from 4/4/2016 IR response: 5.3.5.3 – Clinical Device Safety Summary

¹Complaint failures (using device (b)(4)) originated from clinical studies 20120135, 20110168, and 20120356

²Additional complaint failures (using device (b)(4)) occurring after 01Jul2014 originated from clinical study 20120138

³Represents AMD Data from device (b)(4) used in study 20120138 (data cutoff 17Jan2016).

Clinical Effect of Failures Reported for the AMD Device

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I agree with the applicant that the most likely clinical effect following an instance of the reported failures listed in Table 16 for the AMD device would be under-dosing due to a missed or partial dose of evolocumab. With the AMD device, one missed dose is equivalent to missing one month of lipid lowering therapy. While it is a low likelihood that one missed dose would lead to a significant safety or efficacy risk to the patient, multiple missed or partial doses could be more problematic as the LDL-C level would not be optimally lowered. This situation could potentially be noticed if the health care provider is periodically assessing the LDL-C level but it could lead to reduced effectiveness in LDL-C lowering and, in the worst case scenario, reduced cardiovascular risk reduction.

Most device-related adverse events were mild in severity and were associated with the injection site. The applicant made design changes to the AMD device as a response to these failures, as summarized in Table 14. Chronological Summary of Device Design Subsystem Changes.

In Study 20120138, the incidence of device-related events for the AMD was 3.0% in the year 1 SoC-controlled period (evolocumab plus SoC vs SoC alone; SoC alone did not receive injections) and 3.8% for the year 2+ open-label extension. The events were primarily injection site reactions, and all events were nonserious and CTCAE grade 1 and 2 (mild to moderate severity). A direct comparison of incidence rates between the AMD and autoinjector is not possible due to different exposure counts, sample sizes, and dosing schedules. The following two tables provide subject incidence of device-related adverse events by preferred term reported during the year 1 SOC-controlled period as well as during the year 2+ OLE.

Table 17. AMD Related Adverse Events During the Extension Studies SoC-Controlled Period by Preferred Term in Descending Order of Frequency Study 20120138 (Interim SoC-Controlled Period Analysis Set)

Preferred Term	SoC ² (N = 0) n (%)	EvoMab + SoC (N = 99) n (%)
Number of subjects reporting AMD device-related adverse events¹	-	3 (3.0)
Dermatitis Contact	-	1 (1.0)
Injection Site Erythema	-	1 (1.0)
Injection Site Pain	-	1 (1.0)
Medical Device Site Reaction	-	1 (1.0)
Data cutoff date 17JAN2016.		
¹ Adverse events reported by the investigator to be possibly related to the AMD device.		
² No AMD injections for the subjects randomized to SoC arm.		
N = number of subjects randomized in the integrated extension SoC-controlled period analysis set exposed to the 3.5 mL AMD. EvoMab = Evolocumab (AMG 145); SoC = Standard of Care. Coded using MedDRA version 18.1.		
Source: Applicant's Table 3 from 4/4/2016 IR response: 5.3.5.3 – Clinical Device Safety Summary		

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Table 18. AMD Related Adverse Events by Preferred Term in Descending Order of Frequency Study 20120138 (Interim All-IP Period Analysis Set)

Preferred Term	EvoMab + SoC (N = 343) n (%)
Number of subjects reporting AMD device-related adverse events¹	13 (3.8)
Injection Site Pain	4 (1.2)
Injection Site Reaction	3 (0.9)
Injection Site Urticaria	2 (0.6)
Injection Site Erythema	1 (0.3)
Injection Site Bruising	1 (0.3)
Injection Site Mass	1 (0.3)
Injection Site Pruritus	1 (0.3)
Injection Site Vesicles	1 (0.3)
Data cutoff date 17JAN2016. ¹ Adverse events reported by the investigator to be possibly related to the AMD device. N = number of subjects randomized in the integrated extension SoC-controlled period analysis set exposed to the 3.5 mL AMD. EvoMab = Evolocumab (AMG 145); SoC = Standard of Care. Coded using MedDRA version 18.1. Source: Applicant's Table 4 from 4/4/2016 IR response: 5.3.5.3 – Clinical Device Safety Summary	

7.4.2 Laboratory Findings

Not applicable.

7.4.3 Vital Signs

Not applicable.

7.4.4 Electrocardiograms (ECGs)

Not applicable.

7.4.5 Special Safety Studies/Clinical Trials

None.

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7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

In the applicant's submission, they provided a report that summarizes complaints and adverse device effects as reported for the three completed clinical trials and the ongoing clinical trial 20120138 with a data cutoff of 01 July 2014. We requested the following updated data from the OLE studies:

- a) Adverse events related to immunogenicity, skin-related adverse events, injection-site reactions, hypersensitivity, and other relevant adverse events for the patients who used the AMD.
- b) Any information regarding patients switching from the AMD back to the AI and, if they did, why?
- c) Clarify if the patients in the OLE studies are using the to-be-marketed AMD device.
- d) Provide information on the number of patients using the AMD device and the duration of use.

The applicant responded that the AMD (b) (4) was introduced into the ongoing, phase 3, long-term, open-label extension Study 20120138 in April 2014. They have provided updated data from Study 20120138 with a data cut-off date of 02 April 2015. As of the data cutoff date, a total of 255 unique subjects have used the AMD in Study 20120138 to administer evolocumab; 95 subjects used the AMD during year 1 and 196 subjects during year 2+. It should be noted that some subjects may have used the AMD in both year 1 and year 2+, and therefore, the total number of subjects is not additive. Median (min, max) exposure to evolocumab using the AMD was 5.5 months (2.1, 9.0) in year 1 and 5.6 months (0.3, 11.8) in year 2+ of Study 20120138.

An updated summary of adverse events that occurred in subjects while using the AMD (b) (4) during the standard of care (SoC)-controlled period (year 1) or all-investigational product (all-IP; year 2+ period) of Study 20120138, as of the 02 April 2015 data cut-off date, is summarized in the table below. Overall, the incidences of any adverse event while using the AMD were 42.1% in year 1 and 37.8% in year 2+. The incidences (year 1 and year 2+) of adverse events while using the AMD were

- National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grade \geq 3: 4.2% and 3.1%²

² The following is a list of the Grade 3 and/or serious AEs. None of these grade 3 or serious adverse events were considered related to the AMD device. These AEs included sensorineural hearing loss (grade 3, serious); anemia secondary to acute gastric ulcer hemorrhage (grade 3, serious); 2 cases of osteoarthritis requiring surgical repair (grade 3, serious); oral papilloma (grade 2, serious); arthritis (grade

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- serious adverse events: 3.2% and 3.1%
- adverse events leading to discontinuation of investigational product: 0% and 0.5%
- device related adverse events: 2.1% and 1.5%

There were no CTCAE grade 4 adverse events, fatal adverse events, device related adverse events of CTCAE grade ≥ 3 , or serious device related adverse events reported for subjects during AMD use in year 1 or year 2+ of the study.

Table 19. Summary of Subject Incidence of Adverse Events Reported While Using the AMD* in Year 1 or Year 2+ of Study 20120138 (Interim SoC-Controlled Period and Interim All-IP Period Analysis Set)

	EvoMab	
	Year 1 (SoC-controlled period)	Year 2+ (All-IP period)
	(N = 95) n (%)	(N = 196) n (%)
All adverse events	40 (42.1)	74 (37.8)
Grade ≥ 2	35 (36.8)	51 (26.0)
Grade ≥ 3	4 (4.2)	6 (3.1)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious adverse events	3 (3.2)	6 (3.1)
Leading to discontinuation of investigational product	0 (0.0)	1 (0.5)
Serious	0 (0.0)	0 (0.0)
Non-serious	0 (0.0)	1 (0.5)
Fatal adverse events	0 (0.0)	0 (0.0)
Device related adverse events	2 (2.1)	3 (1.5)
Grade ≥ 2	1 (1.1)	1 (0.5)
Grade ≥ 3	0 (0.0)	0 (0.0)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious	0 (0.0)	0 (0.0)

*device (b) (4)

Data cutoff date of 02APR2015.

AMD = automated mini-doser or 3.5 mL Personal Injector; EvoMab = Evolocumab (AMG 145);
 IP = investigational product; SoC = standard of care.

Source: Applicant's response to FDA IR 15Oct15, Table 2, page 9 of 18.

3, nonserious); gallbladder pain (grade 3, nonserious); pulmonary hypertension (grade 3, serious); large intestine polyp (grade 3, nonserious) and colon adenoma (grade 3, serious); in one subject: abdominal pain (grade 3, serious)/ureteral spasms (grade 3, serious)/renal cell carcinoma (grade 2, serious)/renal cell carcinoma (grade 3, serious); carotid artery stenosis (grade 3, serious) and syncope (grade 3, nonserious); and diverticulitis (grade 3, serious).

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a) *Adverse events related to immunogenicity, skin-related adverse events, injection-site reactions, hypersensitivity, and other relevant adverse events for the patients who used the AMD:*

The incidence of skin-related adverse events, injection-site reactions, and hypersensitivity while using the AMD was assessed using narrow and broad Standard MedDRA Query (SMQ) searches of potential hypersensitivity events and potential injection site reaction events, as well as adverse events in the skin and subcutaneous disorders system organ class in year 1 and year 2+ of Study 20120138. For both narrow and broad search strategies, the subject incidences of potential hypersensitivity events and potential injection site reaction events were low in year 1 and year 2+ while using the AMD (refer to the 2 tables below for the narrow search results). All of the potential hypersensitivity events, potential injection site reactions, and skin-related adverse events reported for subjects using the AMD were CTCAE grade 1 or grade 2 in severity and none were reported as serious adverse events.

Table 20. Adverse Events Associated with Injectable Protein Therapies Reported With AMD* Use by Category and Preferred Term Using Narrow Search Strategies for Year 1 of Study 20120138 (Interim SoC-Controlled Period Analysis Set)

Category High Level Term Preferred Term	EvoMab (N = 95) n (%)
Number of subjects reporting adverse events of interest	5 (5.3)
POTENTIAL HYPERSENSITIVITY EVENTS	3 (3.2)
Dermatitis and eczema	3 (3.2)
Eczema	1 (1.1)
Dermatitis Contact	1 (1.1)
Hand Dermatitis	1 (1.1)
POTENTIAL INJECTION SITE REACTION EVENTS	2 (2.1)
Injection site reactions	2 (2.1)
Injection Site Erythema	1 (1.1)
Injection Site Swelling	1 (1.1)

*device (b) (4)

Data cutoff date 02APR2015. AMD = automated mini-doser or 3.5 mL Personal Injector; EvoMab = Evolocumab (AMG 145); SoC = standard of care.

Source: Applicant's response to FDA IR 15Oct15, Table 3, page 11 of 18.

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Table 21. Adverse Events Associated with Injectable Protein Therapies Reported With AMD* Use by Category and Preferred Term Using Narrow Search Strategies for Year 2+ of Study 20120138 (All-IP Period Analysis Set)

Category High Level Term Preferred Term	EvoMab (N = 196) n (%)
Number of subjects reporting adverse events of interest	10 (5.1)
POTENTIAL HYPERSENSITIVITY EVENTS	5 (2.6)
Allergies to foods, food additives, drugs and other chemicals	1 (0.5)
Drug Hypersensitivity	1 (0.5)
Rashes, eruptions and exanthems NEC	1 (0.5)
Rash	1 (0.5)
Urticarias	3 (1.5)
Urticaria	3 (1.5)
POTENTIAL INJECTION SITE REACTION EVENTS	5 (2.6)
Injection site reactions	5 (2.6)
Injection Site Pain	2 (1.0)
Injection Site Reaction	2 (1.0)
Injection Site Pruritus	1 (0.5)

*device (b) (4)

Data cutoff date 02APR2015. AMD = automated mini-doser or 3.5 mL Personal Injector; EvoMab = Evolocumab (AMG 145); SoC = standard of care.

Source: Applicant's response to FDA IR 15Oct15, Table 4, page 12 of 18.

To assess immunogenicity, incidence of anti-evolocumab antibodies with AMD use was reviewed. No subject who used the AMD tested positive for anti-evolocumab antibodies during year 1 or year 2+ of Study 20120138.

b) Any information regarding patients switching from the AMD back to the AI and, if they did, why?

Subjects randomized to the evolocumab group during year 1 of Study 20120138, and all subjects in year 2+, were allowed to choose between 2 dosing regimens (evolocumab 140 mg SC Q2W plus standard of care or evolocumab 420 mg SC QM plus standard of care) and could switch between dosing regimens at quarterly study visits. Each Q2W dose of evolocumab was administered using a single autoinjector/pen (AI/pen) that delivered a 140 mg dose; each QM dose was initially administered using 3 AI/pens for a total evolocumab dose of 420 mg. The AMD (b) (4) was introduced into the study in April 2014, approximately 1 year after study start, at a select number of sites. However,

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the availability of the AMD varied by region/study site. Nearly all subjects randomized to the evolocumab plus standard of care group during year 1 of Study 20120138 received study drug via the AI pen at the outset of the study.

As of 02 April 2015, 804 subjects had access to or were eligible for the AMD in Study 20120138. A total of 255 (32%) of the 804 subjects with access to the AMD chose it to administer evolocumab, and 207 (81%) of the 255 subjects who used the AMD chose to remain on it. The other 19% of subjects switched back to the AI/pen at some time point after using the AMD (see table below). While the device used was collected on the electronic case report form (eCRF) for each subject, investigators were not required to record the reason that the subject switched in the CRF so that information is not known.

Table 22. Use of AMD* in Study 20120138

Total Number of subjects randomized to evolocumab during year 1 or received evolocumab during year 2+	3395
Number of subjects who had access and could choose the AMD during year 1 or year 2+	804
Number of subjects who used AMD during year 1 or year 2+	255
Number of subjects remained on AMD after 1st use	207 (81%)
Number of subjects who ever switched back to AI after using the AMD	48 (19%)

*device (b) (4)

Data cutoff date: 02 APR 2015

AMD = automated mini-doser

Source: Applicant's response to FDA IR 15Oct15, Table 6, page 14 of 18.

c) *Clarify if the patients in the OLE studies are using the to-be-marketed AMD device.*

No. The applicant states that the device configuration used in Study 20120138 and the to-be-marketed AMD device share the same technological characteristics and intended use.

d) *Provide information on the number of patients using the AMD device and the duration of use.*

Overall exposure and duration of exposure for the AMD are provided in the following table. The AMD was not available at the start of Study 20120138, therefore AMD exposure reported below is not reflective of overall study exposure or exposure to evolocumab in this study. As of the 02 April 2015 data cutoff date, a total of 255 unique subjects had a total of 133 patient-years of exposure with the AMD in Study 20120138. A total of 206 (81%) subjects had ≥ 3 months exposure to evolocumab using the AMD, 151 (59%) subjects had ≥ 6 months, and 88 (35%) subjects had ≥ 9 months. Median (min, max) exposure to evolocumab using the AMD was 5.5 months (2.1, 9.0) in year 1

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and 5.6 months (0.3, 11.8) in year 2+, with a maximum exposure of approximately 12 months for any unique subject.

Table 23. Summary of AMD* Exposure in Study 20120138 (Interim SoC-Controlled Period and Interim All-IP Period Analysis Set)

	EvoMab
Number of Subjects Used AMD	255
Total patient-year exposure	133
Number of Subjects Used AMD	
≥ 3 months	206
≥ 6 months	151
≥ 9 months	88
≥ 12 months	7

*device (b) (4)

Data cutoff date 02APR2015. EvoMab = Evolocumab (AMG 145); AMD = automated mini-doser or 3.5 mL Personal Injector). pt-year = patients years, where years are calculated as the sum of period durations for the treatment group across subjects divided by 365.25. Months are calculated by multiplying the patient years by 12 and rounding to the nearest whole month. For periods with only a single device option for subjects, the device exposure duration is set to the period duration. For studies with multiple device options, device exposure duration is the sum of time from being exposed to a device until switching to another device, ending the study, or the data cutoff date.

Source: Applicant's response to FDA IR 15Oct15, Table 7, page 16 of 18.

7.6 Additional Safety Evaluations

None

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Not applicable as this AMD device has not been approved for marketing.

9 Appendices

9.1 Literature Review/References

Literature references were made throughout this document when relevant.

9.2 Labeling Recommendations

9.2.1 Applicant's Proposed Changes to the Package Insert (PI)

 (b) (4)
This device is an infusion pump; thus, FDA suggested 'on-body infusor' for the device name (refer to Section 12 of the CDRH review for additional details).

The applicant submitted a revised PI and PPI on 5/27/2016 based on FDA feedback. Deleted text denoted by strike-through and additional text by underline. Minor editorial changes are not displayed.

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Comments:

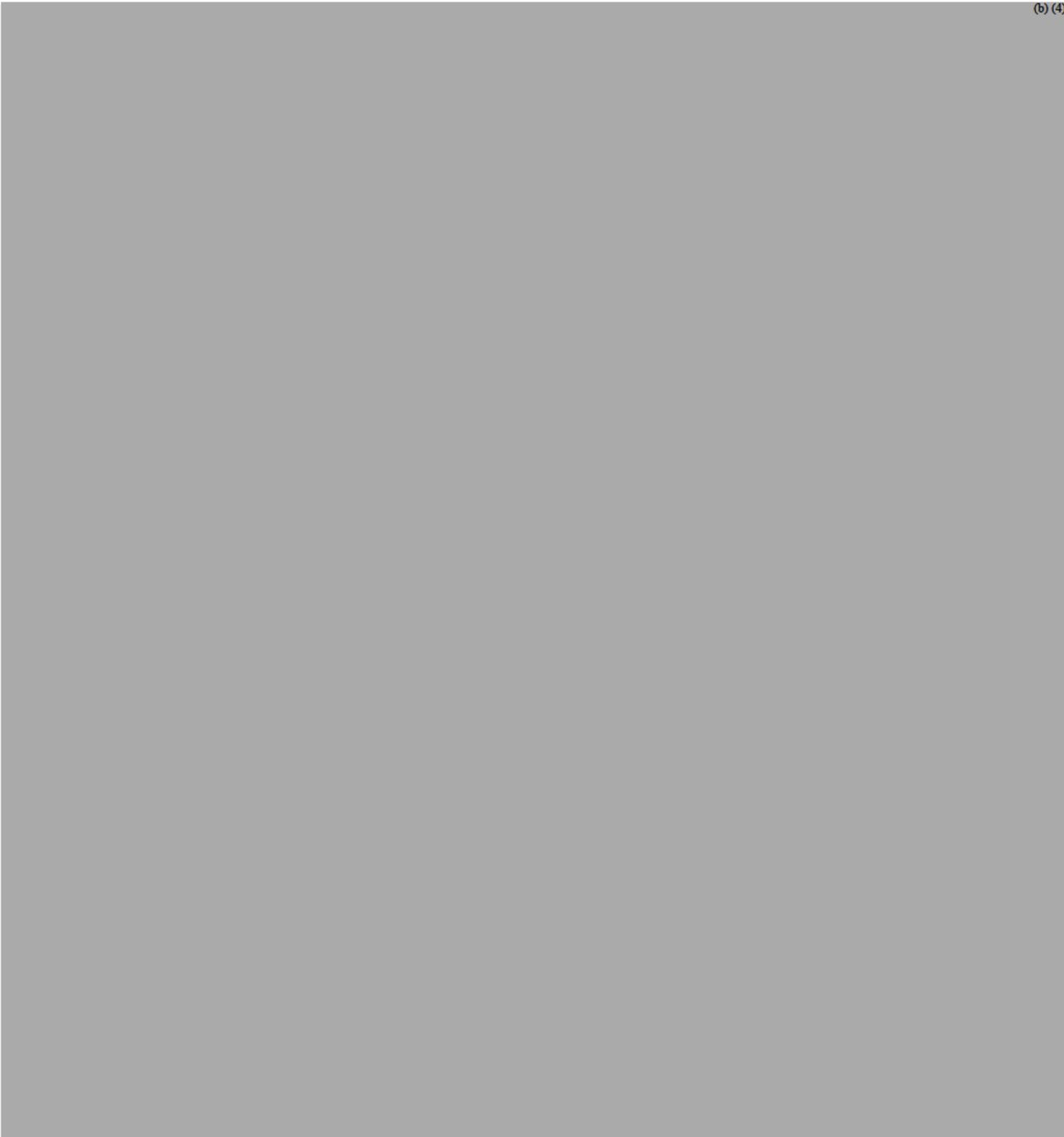
1. DMEPA provides the following comment for consideration by the review Division prior to the approval of this supplement.
 - Highlights of Prescribing Information, Dosage and Administration
 - i. The ability to administer the 420 mg dose via the automated mini-doser needs to be added to the bullet on administering this dose.
For example:
 1. “To administer the 420 mg dose, give 1 Repatha injection using the automated mini-doser with the pre-filled cartridge. Alternatively give 3 Repatha injections using the autoinjector or pre-filled syringe consecutively within 30 minutes.”
 - *Of note, Amgen addressed this concern in their revised label submitted 5/27/2016.*
2. OPQ/OBP had several labeling comments which will be conveyed to the applicant.

9.2.2. Applicant’s Proposed Changes to the Patient Package Insert (PPI)

Deleted text denoted by strike-through and additional text by underline.

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(b) (4)



Comments:

1. OPQ/OBP had several labeling comments which will be conveyed to the applicant.

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9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EILEEN M CRAIG
07/07/2016

JAMES P SMITH
07/07/2016

CLINICAL FILING CHECKLIST FOR BLA 125522/S-001

BLA Number: 125522/S-001

Applicant: Amgen

Stamp Date: 9/10/15

SD: 107/eCTD 0082

**Drug Name:
evolocumab/Repatha**

PDUFA Date: 7/10/16 (STD)

Filing Meeting: Wed 11/05/15; 1-2p; WO 6201 Bldg 22

Filing Date: 11/09/15

Mid-cycle Review Meeting: date pending

Wrap-up Meeting: date pending

Reviews signed-off in DARRTS: 15 May 2016

Action Goal Date: PDUFA Date: 7/10/16

The network location is: \\CDSESUB1\evsprod\BLA125522\0082

Reviewers

Clinical:	Eileen Craig/James Smith
Clin Pharm:	Suryanarayana Sista/Jaya Vaidyanathan
Pharmacometrics:	Justin Earp/ Nitin Mehrotra
Biometrics:	Shuxian (Susie) Sinks /Mark Rothmann
CMC/Product Quality Reviewers (OBP):	Sang Bong Lee/Chana Fuchs
Product Quality Microbiology	
Reviewers:	Lakshmi Narasimhan/Patricia Hughes
Facility	Laura Fontan
CDRH (devices):	Alan Stevens
CDRH OC	Crystal Lewis/Bleta Vuniqi
Patient Labeling (DMPP):	Sharon Williams/Marcia Britt Williams
OSE/DMEPA (labeling/HF/REMS):	Mishale Mistry/Lena Maslov/Deveonne
Hamilton-Stokes	
Project Manager:	Kati Johnson

Background:

Evolocumab (AMG 145) is a human monoclonal immunoglobulin G2 directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9).

Mode of Action

When PCSK9 binds to low-density lipoprotein receptor (LDLR), the LDLR is targeted for destruction rather than being recycled back to the cell surface, thereby reducing the levels of LDLR available for low-density lipoprotein cholesterol (LDL-C) clearance from the bloodstream. Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

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The clinical development of evolocumab included evaluation of the following 4 SC presentations:

- vial and syringe
- prefilled syringe (PFS)
- prefilled autoinjector/pen (AI/pen)
- automated mini-doser (AMD) – also referred to as 3.5 mL personal injector and large volume injector

The PFS and the prefilled AI/pen provide a single SC administration of 140 mg evolocumab. The prefilled AI/pen was used in the majority of the phase 3 studies, and 3 consecutively administered prefilled AI/pens were used within 30 minutes to deliver the 420 mg dose. The prefilled AI/pen and the PFS were included in the initial BLA filing for approval.

Supplement S-001

In this Prior Approval Supplement, Amgen is seeking approval of a new drug product presentation comprising a 120 mg/mL prefilled cartridge co-packaged with an automated mini-doser (AMD) administration device, referred to as the 120 mg/mL AMD, according to the approved dosing. The AMD is a compact, sterile, single-use, disposable, electro-mechanical (battery powered, micro-processor controlled), on-body injection device. The prefilled cartridge assembly is co-packaged with the AMD. The prefilled cartridge assembly is loaded into the AMD immediately prior to use. The 120 mg/mL AMD presentation was developed to reduce the number of injections required for the once monthly dose to a single injection.

The AMD utilizes an electromechanical system to inject the drug product. When the user presses the activation button, the needle inserts and the motor is activated, which injects the drug product into the patient's tissue over the course of approximately 9 minutes.

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Following removal of the AMD from the packaging, the user opens the door of the AMD, inserts the prefilled cartridge assembly, and closes the door. The AMD has an adhesive which attaches the device to the skin for dose administration. After removing the adhesive liner and adhering to the body, the injection is initiated by the user upon depressing the activation button, (b) (4). Once the user presses the button, the needle is inserted into subcutaneous tissue, and the loaded AMD subsequently initiates drug administration. The drug is automatically injected (b) (4)

(b) (4) The loaded AMD provides visual and auditory notifications to the user to signal the completion of injection. The loaded AMD is then removed from the skin following completion of the injection. When the device is removed from the body, the (b) (4) returns to the open position to prevent needle-stick injury. The empty cartridge assembly cannot be removed from the loaded AMD after administration of the drug product, the AMD system is disposed of together.

The applicant notes that the AMD is designed to administer the entire dose without user intervention. The dose volume and dose administration duration cannot be changed by the user. Both visual and auditory notifications provide feedback on the progress of drug administration. In the event of a drug delivery error, visual and auditory alarms will notify the user. Additionally, a viewing window that allows the user to see the prefilled cartridge allows inspection to confirm dose completion. Per device design, the needle will not retract from the patient's subcutaneous tissue until physically removed by the patient. The presence of audible and visible notifications for the dose initiation and dose completion, combined with the viewing window are measures to avoid premature removal by the user.

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Clinical information for the 120 mg/mL AMD was submitted to BLA 125522 in the original BLA (Sequence No. 0000); however, the 120 mg/mL AMD was still under development at the time of the original BLA submission, and thus was not part of the formal review and approval. The primary clinical study supporting the new presentation is a bioequivalence PK study (**study 20110168**) conducted to bridge data obtained using the currently approved prefilled autoinjector. Also referenced is a phase 0 study (**20120135**) to assess the drug delivery performance of the AMD using a placebo buffer and a phase 3 home-use study (**20120356**) to assess the users' ability to administer a full dose (420 mg) of evolocumab by the patient during home-use (with primary LDL endpoint assessment) using either the AMD or the commercially approved prefilled autoinjector. All bioequivalence data and other supporting studies have been previously submitted to the BLA and are cross-referenced within this supplement.

The applicant's table below provides a summary of the clinical studies using some version of the AMD device, but not necessarily the *to-be-marketed* version of the AMD device.

Table 1. Summary of Clinical Studies with AMD Devices Used in the Evolocumab Program

Study	Brief Description	Device(s) Used
<u>Clinical Pharmacology Studies (Phase 1)</u>		
20120135	Drug delivery performance of the 3.5 mL personal injector (AMD) using placebo buffer	AMD
20110168	PK/PD equivalence of AI/pen vs. AMD	AI/pen, AMD
<u>Efficacy and Safety Studies for Hyperlipidemia and Mixed Dyslipidemia</u>		
20120138 (ongoing)	<i>Controlled, Long-term Study (Phase 3)</i> Long-term, controlled, open-label extension; AI/pen self-administration (OSLER-2)	AI/pen, AMD
20120356	<i>Device Home-Use Study with Self Administration (Phase 3)</i> <i>Clinical home use of evolocumab with AI/Pen vs. AMD</i>	AI/Pen, AMD

AI/pen = autoinjector/pen; AMD = automated mini-doser; PD = Pharmacodynamic; PK = Pharmacokinetic. All studies are completed unless indicated as ongoing. The data cutoff for ongoing studies is 1 July 2014.

In addition, there are two AMD Human Factor summative studies that are included in this submission. Both used placebo that mimics the appearance and viscosity of the evolocumab drug product. Both studies were simulated use with injections into skin pads. Changes between the first and second study included (b) (4)

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CLINICAL FILING CHECKLIST FOR BLA 125522/S-001

Summative Study 1:

- The materials used for the first summative study were representative of the intended commercial configuration
 - Please note that the first summative study included a (b) (4)
- Placebo that mimics the appearance and viscosity of the evolocumab drug product

Summative Study 2:

- The following changes were made following the first summative study and were tested in the second summative study:
 - (b) (4)
 - Instructions for Use illustrations were modified to address the changes described above, as well as enhanced instructions for hand washing, cleaning of injection site, cartridge insertion and door closing
- Placebo that mimics the appearance and viscosity of the evolocumab drug product

The 120 mg/mL AMD is intended to provide a single use, fixed dose for SC injection by a health care professional, a caregiver or by the patient. Administration may be either in the clinic or in a non-clinical environment. (b) (4) and consists of 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The cartridge for use with the AMD contains a 3.5 mL deliverable volume (420 mg), which enables once monthly dosing.

The evolocumab drug product manufacturing process consists of (b) (4). Filling of the cartridge occurs at (b) (4). Assembly of the prefilled cartridge with a (b) (4), co-packaging of the cartridge with the pre-sterilized AMD, and labeling occurs at (b) (4). The sterilized AMD administration device is manufactured by (b) (4).

The following table from the sponsor compares the currently approved devices with the proposed device.

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Table 2. Comparison of the Currently Approved 140 mg/mL PFS and AI/Pen Presentations and the Proposed 120 mg/mL AMD Presentation

Presentation	140 mg/mL PFS	140 mg/mL AI/Pen	120 mg/mL AMD
Approval status	Approved	Approved	Proposed
Formulation	140 mg/mL evolocumab 220 mM proline 20 mM acetate 0.01%(w/v) polysorbate 80 pH 5.0	140 mg/mL evolocumab 220 mM proline 20 mM acetate 0.01%(w/v) polysorbate 80 pH 5.0	120 mg/mL evolocumab 220 mM proline 20 mM acetate 0.01%(w/v) polysorbate 80 pH 5.0
Container closure	(b) (4)		
Quantity delivered per container	1.0 mL	1.0 mL	3.5 mL
Number of injections for monthly dosing	3	3	1
Dose per container	140 mg	140 mg	420 mg
Delivery device	Single-use, disposable, handheld syringe	Single-use, disposable, mechanical (spring-based) injection device	Single-use, disposable, electro-mechanical (battery powered, micro-processor controlled), on-body injection device
Route of administration	SC injection	SC injection	SC injection
Administration method	Health care professional Caregiver Patient	Health care professional Caregiver Patient	Health care professional Caregiver Patient
Drug product manufacturing	AML, USA	AML, USA	(b) (4)
Assembly, packaging, and labeling	AML, USA	AML, USA	(b) (4)
Device manufacturer location	(b) (4)		

AML = Amgen Manufacturing Limited

As shown in the applicant's table below, the clinical studies were conducted using a "Base device" that then underwent various design changes. In the clinical reviewer guide for the current submission it states, "Clinical information for the 120 mg/mL AMD was also submitted to BLA 125522 in the original BLA; however, the 120 mg/mL AMD was still under development at the time of the original BLA submission, and thus was not part of the formal review and approval." It will be a review issue whether the design changes that they made since conducting their clinical studies (including the bridge to the

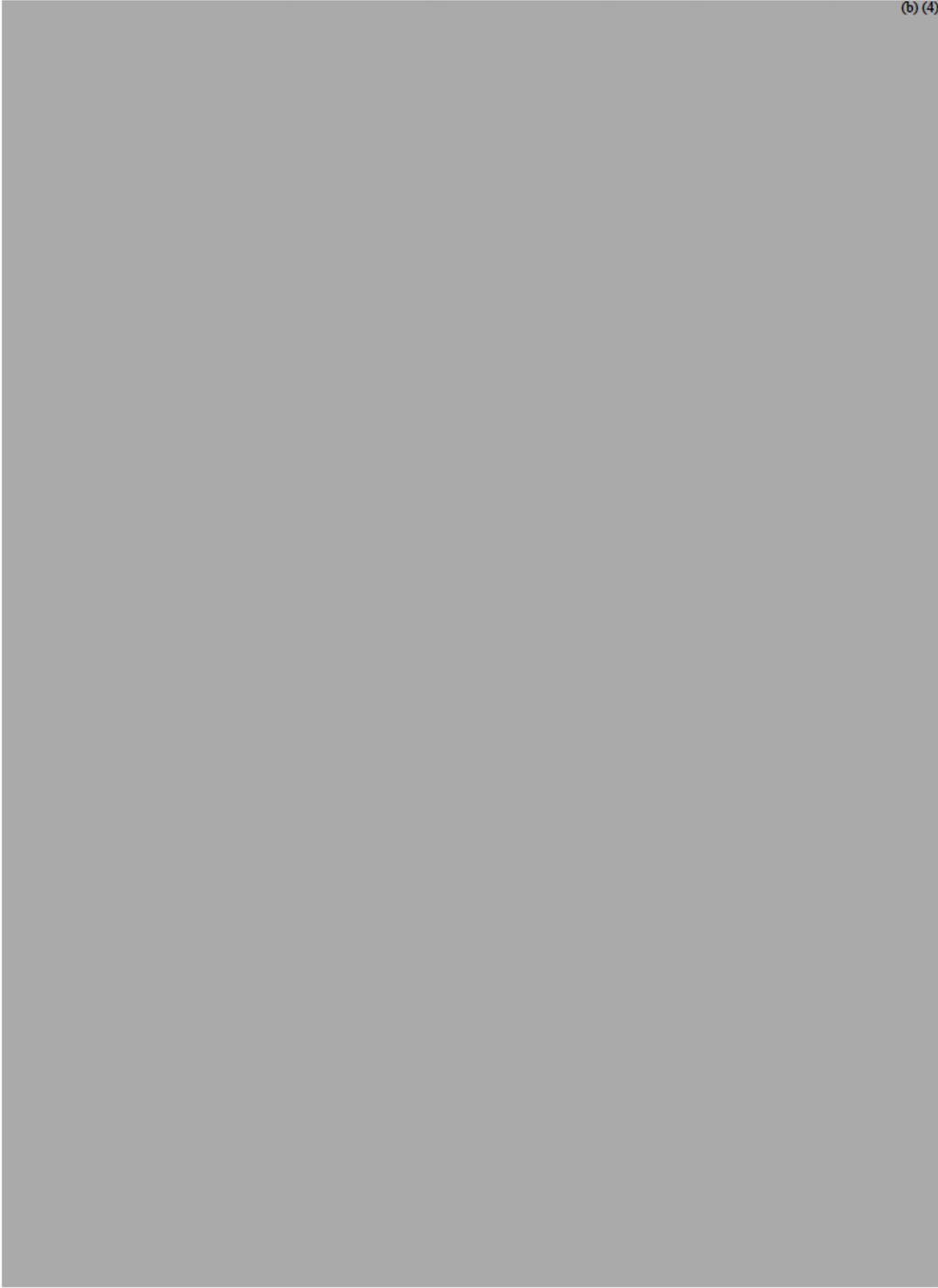
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autoinjector) preclude us from relying on those studies.

Table 48. Chronological Summary of Device Design Subsystem Changes

(b) (4)



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Excerpts of Regulatory History:

Meeting Date/ Type	Meeting Purpose	Event/Notes
10 July 2012 End of Phase 2 (Clinical)	To discuss the proposed clinical development program and the device clinical study strategy from pivotal studies to commercial launch for the two indications of (1) hyperlipidemia and mixed dyslipidemia and (2) secondary prevention of heart disease.	<p>Issues related to the AMD device:</p> <ul style="list-style-type: none"> • Although you plan to collect data on the usability of your product presentations during the clinical trial, a well-designed human factors (HF) study is required. The results from the clinical trials can be used as part of a formative study to improve the product design and the instructions for use (IFU). You should also collect subjective data during the clinical trials which may inform how to improve your product design and IFU. • You stated in your End of Phase 2 Meeting Request that you will conduct design verification and validation Human Factor Engineering (HFE) study that includes simulated use studies. We require you to conduct validation Human Factors usability study for the autoinjector (AI) and large volume injector (LVI). You may also consider conducting validation Human Factors usability study for the prefilled syringe, since this is a new user population. • Consider the following for your user groups and study methodology: <ul style="list-style-type: none"> <input type="checkbox"/> If your device requires special training prior to the use of the devices, then your study should include at least a total of 90 participants equally divided between trained and untrained arms as follows: <ul style="list-style-type: none"> o 30 representative patients with injection experience (i.e., 15 participants trained and 15 participants untrained). o 30 representative patients without injection experience (i.e., 15 participants trained and 15 participants untrained). <p>Since representative patients may have concomitant health conditions (e.g., diabetes), ensure you include participants with vision and dexterity issues.</p> <ul style="list-style-type: none"> o 30 health care practitioners that will be using the device: nurses and physicians (i.e. 15 participants trained and 15 participants untrained). <input type="checkbox"/> If training will not be required as part of the labeling, then study should only have the untrained arm as described above. <ul style="list-style-type: none"> • In your Human Factors study, we recommend including a task to simulate complete device failure. • The feedback mechanism regarding dose delivery may also be insufficient. Consider color-blind patients who may not be able to distinguish between the blue, green, and red lights. The beeps may not be helpful if the patient is distracted or loses track of the count or has trouble hearing. You may want to consider simplifying this aspect of your device. • Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. We expect you to collect both empirical and qualitative data in a design validation study. • Performance Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without Performance Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. • Subjective Data – We expect you to ask open-ended questions of

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Meeting Date/ Type	Meeting Purpose	Event/Notes
		<p>participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?"</p> <ul style="list-style-type: none"> •Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. •The currently proposed phase 3 lipid-lowering trials do not use the proposed devices (AI and LVI), and we are not confident that the substudies within an open-label extension study will provide sufficient data to demonstrate whether the home use of these devices affects their clinical effectiveness (i.e., LDL-C). We will require you to provide sufficient phase 3 data using these devices in controlled clinical trials that have LDL-C as an outcome.

Labeling:

In Module 1.14, the applicant submitted draft labeling text in SPL format. The proposed Package Insert and Patient Package Insert are submitted in Microsoft word format and include an annotated version. I have reviewed the PI and PPI labeling and have no edits or comments at this point in the review.

Risk Evaluation and Mitigation Strategy (REMS):

A risk management plan, Elements to Assure Safe Use (ETASU) and the Implementation System are not proposed.

Priority or Standard Review:

Amgen requested a CMC 4-month review of this application but this application will be designated a 10-month Standard review due to the inclusion of clinical data.

Pediatric:

Amgen has not included a Module 1.9 Pediatric Administrative Information as this PAS does not include a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration; and therefore, PREA requirements do not apply.

Debarment Certification:

Not included in submission, cross-referenced to original BLA.

Financial Disclosures:

Not included in submission, cross-referenced to original BLA.

Site Inspection: Lakshmi Narasimhan and Patricia Hughes from the Office of Combination Products, OMPT/CDER/OPQ/OPF/DMA/MABIV, recommend the inspection of the following manufacturing sites:

 (b) (4)

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(b) (4)

[Redacted]

Preliminary Review of Device Safety Data From Module 5.3.5.3-Clinical Device Safety Summary

As of 01 July 2014, the total number of complaint issues reported for the AMD device during clinical use and the number of associated product failures is provided in the table below.

Table 3. Total Complaint Issues and Failures Received for the Evolocumab Clinical Program (AMD)

Device	Number of Device Injection Attempts	Number of Complaint Issues	Number of Failures
AMD	828	70	53

AMD = automated mini-doser.

Note: This table includes aggregated data from clinical studies 20110135, 20120138, 20110168, and 20120356. Complaint Issues and Failures Source: Intake Response Product Complaints for complaint issue data; Data cutoff is 01 July 2014. Injection Data from: Table 14-11.1, Table 14-1.1, Table 14-5.5.403, Table 14-5.5.504, Table 14-5.5.406; Data cutoff is 01 July 2014.

The applicant states that 70 AMD complaint issues were reported in clinical trials, during which time 828 injections were administered using the device. Of these 70 complaint issues, 53 were determined to be device failures/device malfunctions (see table below).

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Table 4. AMD Complaint Codes with Failures Reported in the Evolocumab Clinical Program (in descending order of frequency)

Complaint Code	Description	Number of Failures (n = 53)
Device Not Functioning	Delivery device not functioning (e.g. no beep after liner removal, no three beeps upon injection start, no three beeps upon injection completion, no pumping sound during injection, no blue blinking light upon liner removal, no blinking green light during injection or no solid green light after completed injection).	33
Drug Injection Failed	Delivery device stalls and/or fails to complete injection	11
Cartridge other	Any event or condition applicable to this item that is not covered by any other Event/Cause Code.	5
Device Cartridge Door Broken	Delivery device door is broken, not functioning properly or cartridge not able to be loaded during or after handling.	2
Device Application Adhesive Does Not Function as Expected	Delivery device application adhesive did not function as expected, including not adhering to skin or partially adhering to skin.	1

Source: Complaint Issues and Failures Source: Intake Response Product Complaints with data cutoff 01 July 2014.

The applicant states that design changes were made for the AMD device as a response to these failures.

Clinical Effect of Failures reported for the AMD Device

The applicant states, and I agree, that the most likely clinical effect following an instance of the reported failures above for the AMD device would be under-dosing due to a missed or partial dose of evolocumab. A missed dose of evolocumab with each of these devices is described by the applicant with a severity rating of 3 (on scale of 1-9) which is considered a mild severity (one that may result in temporary impairment not necessarily requiring significant professional intervention, inconvenience or temporary discomfort). A missed dose would not constitute an immediate safety or efficacy risk to the patient, provided that this was not a chronic issue.

As of the data cutoff of 01 July 2014, there were no serious device-related adverse events reported during use of the AMD device in the clinical trials. Nearly all device-related adverse events were mild in severity and were associated with the injection site.

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to	X			

File name: Clinical Filing Checklist for BLA 125522/S-001 Repatha®/Evolocumab

CLINICAL FILING CHECKLIST FOR BLA 125522/S-001

	Content Parameter	Yes	No	NA	Comment
	allow substantive review to begin?				
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?			X	
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	BLA 351 (a)			
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Location in submission: Module 5.3.1.2 Bioequivalence Study Report 20110168 (Cross-reference to original BLA): Phase 1 pharmacokinetic equivalence study conducted to bridge the phase 3 data obtained using the AI/pen (3 x 1 mL at 140 mg/mL) to the AMD (3.5 mL at 120 mg/mL).	X			This study was NOT performed with the final device.
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			

File name: Clinical Filing Checklist for BLA 125522/S-001 Repatha®/Evolocumab

CLINICAL FILING CHECKLIST FOR BLA 125522/S-001

	Content Parameter	Yes	No	NA	Comment
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			2 AMD Human Factors Studies Both studies used placebo that mimics the appearance and viscosity of the evolocumab drug product; both were simulated use with injections into skin pads. Changes between the first and second study included

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: Clinical Filing Checklist for BLA 125522/S-001 Repatha®/Evolocumab

CLINICAL FILING CHECKLIST FOR BLA 125522/S-001

	Content Parameter	Yes	No	NA	Comment
					(b) (4)  use illustrations were modified to address the changes described above, as well as enhanced instructions for hand washing, cleaning of injection site, cartridge insertion and door closing
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
37.	Are all datasets to support the critical safety analyses available and complete?			X	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes__

File name: Clinical Filing Checklist for BLA 125522/S-001 Repatha®/Evolocumab

CLINICAL FILING CHECKLIST FOR BLA 125522/S-001

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

Information request sent to applicant 10/15/2015:

1. Please confirm that the following studies did not use the to-be-marketed AMD device:
 - a. 20110168
 - b. 20120135
 - c. 20120356
2. Clarify which studies actually used the to-be-marketed AMD device
3. Provide your rationale on why the clinical studies can be relied on for approval consideration given that they were conducted using a “base device” that then underwent various design changes. Specifically address whether the design changes that have been made since conducting the clinical studies (including the bridge to the autoinjector) could be expected to change or influence the patient’s experience with the AMD device.
4. You have provided a report that summarizes complaints and adverse device effects as reported for 3 completed clinical trials and an ongoing clinical trial with a data cutoff of 01 July 2014. We are requesting the following updated data from the OLE studies. Provide your data cutoff date for this response (such as 01 July 2015):
 - a. Adverse events related to immunogenicity, skin-related adverse events, injection-site reactions, hypersensitivity, and other relevant adverse events for the patients who used the AMD.
 - b. Any information regarding patients switching from the AMD back to the AI and, if they did, why?
 - c. Clarify if the patients in the OLE studies are using the to-be-marketed AMD device.
 - d. Provide information on the number of patients using the AMD device and the duration of use

The firm states they will respond during the week of November 16th.

Amgen also provided AMD sample units and printed IFUs. This reviewer tested the AMD sample unit (using a grapefruit to substitute for a subject) and found the device straight-forward to use and the instructions were easy to follow.

Clinical Issues

1. It will be a review issue whether the design changes that they made since conducting their clinical studies (including the bridge to the autoinjector) preclude us from relying on those studies.
2. From the clinical studies using the base device reported in the original BLA, there were 53 reported device failures/device malfunctions out of 828 device injection attempts. Thus, 6.4% of injection attempts resulted in reported device failures/device malfunctions. The applicant states that design changes were made for the AMD device as a response to these failures. This submission does not contain any clinical data that demonstrates that

File name: Clinical Filing Checklist for BLA 125522/S-001 Repatha®/Evolocumab

CLINICAL FILING CHECKLIST FOR BLA 125522/S-001

these reliability issues of device failure/malfunction have been improved. AN IR was sent mid-October asking for updated clinical data on the to-be-marketed commercial device.

Eileen Craig	11/04/15
Reviewing Medical Officer	Date
<hr/>	
Clinical Team Leader	Date

File name: Clinical Filing Checklist for BLA 125522/S-001 Repatha®/Evolocumab

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EILEEN M CRAIG
11/05/2015

JAMES P SMITH
11/05/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125522Orig1s001

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY MEMORANDUM

BLA	125522, S-0082
Submission Date	September 10, 2015
Brand Name	Repatha
Generic Name	Evolocumab
Reviewer	Suryanarayana Sista, Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Amgen, Inc.
Formulation; Strength	Pre-filled AutoInjector (140 mg) Automated Mini Doser (AMD) (120 mg)
Indication	Indicated as an adjunct to diet and: <ul style="list-style-type: none">• Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C)• Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

The sponsor submitted a Prior Approval Supplement pursuant to 21 CFR 314.70(b) and 601.12(b) seeking approval of a new drug product presentation comprising a 120 mg/mL prefilled cartridge co-packaged with an automated mini-doser (AMD) administration device.

The primary clinical study supporting the new AMD presentation is a comparability study (study 20110168) conducted to bridge data obtained using the currently approved prefilled autoinjector (AI/Pen). The comparability data supporting this new device was previously submitted to the original BLA and cross-referenced within this supplement, and was reviewed in the original BLA (Document ID: 3772601 dated 01 June 2015, in DARRTS).

Study 20110168 evaluated the comparability of a dose of 420 mg evolocumab delivered either via 3.5 mL AMD or 3 AI/Pens in healthy volunteers.

For the reference treatment (prefilled AI/pen), evolocumab was presented as a sterile, preservative-free solution in a single use, disposable, handheld mechanical (spring-based) prefilled AI/pen for fixed dose 140 mg SC/injection. The prefilled AI/pen contained a 1.0 mL deliverable volume of 140 mg/mL evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. Subjects in the reference treatment received a total dose of 420 mg

evolocumab via 3 prefilled AI/pens. The injections were administered into 3 different quadrants in the subject's anterior abdominal wall. The 3 SC injections were administered in a consecutive fashion with each injection separated by no more than 1 minute from the previous injection.

For the test treatment, evolocumab was presented as an AMD for fixed-dose 420 mg SC/injection. The AMD contained a 3.5 mL deliverable volume of 120 mg/mL evolocumab in 220 mM proline, 20 mM acetate, and 0.01% (w/v) polysorbate 80, pH 5.0. Subjects in the test treatment received an evolocumab 420 mg dose as a single SC injection in the anterior abdominal wall via the AMD. The complete dose with the AMD was administered over 9 minutes.

Similar mean unbound evolocumab serum concentration time profiles were observed after a 420 mg SC dose of evolocumab when delivered using the AMD or 3 AI/pens. Median t_{max} was 4.0 days for both AMD (range = 2.0 to 9.9 days) and 3 AI/pens (range = 1.9 to 10 days). The geometric least square mean ratios (90% CI) of the AMD to 3 AI/pens for C_{max} and AUC_{last} were 1.10 (1.03 - 1.18) and 1.06 (0.97 - 1.14), respectively, indicating comparability between the formulations from the two devices.

Mean serum evolocumab concentration profiles for the two treatments are shown in [Figure 1](#). Mean pharmacokinetic (PK) parameters are shown in [Table 1](#), and statistical comparison of evolocumab PK parameters is shown in [Table 2](#).

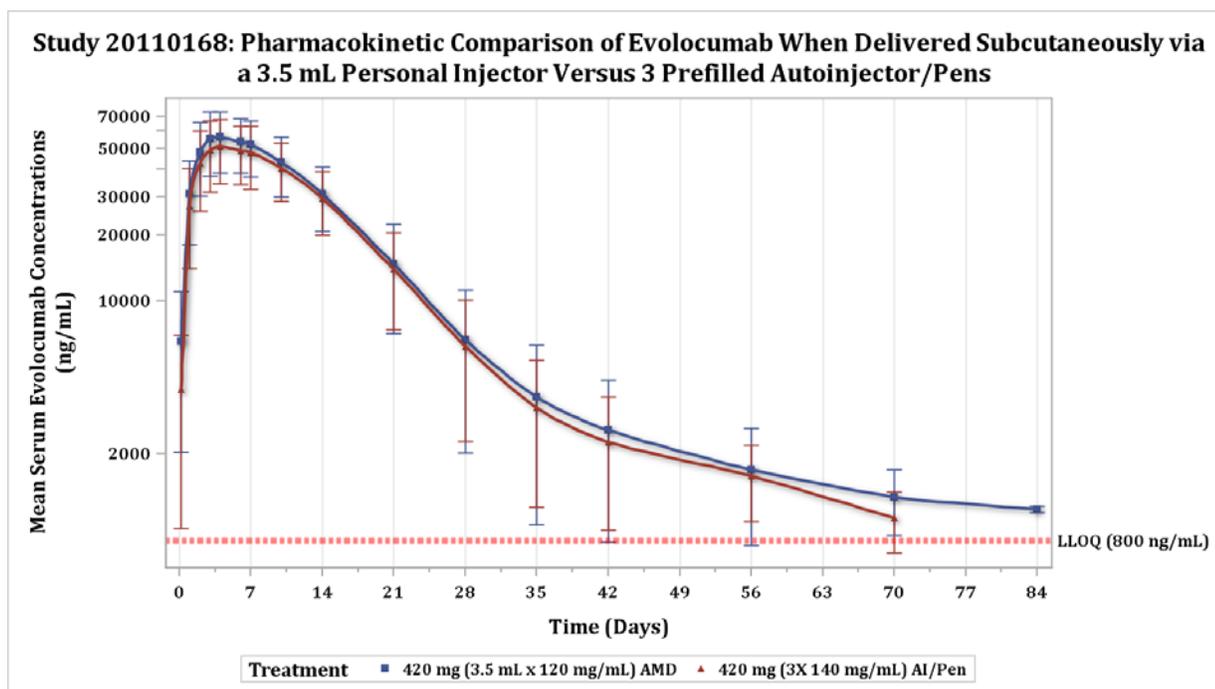


Figure 1 Mean unbound serum evolocumab concentration following subcutaneous administration of a 420 mg dose delivered either via 3.5 mL AMD or 3 AI/Pens

Table 1 Serum Evolocumab Pharmacokinetic Parameter Estimates After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-doser (Test) Versus 3 Autoinjector/Pens (Reference) in Healthy Subjects

Descriptive Statistics	Evolocumab 420 mg AMD (Test)			Evolocumab 420 mg 3 AI/pens (Reference)		
	t _{max} (day)	C _{max} (µg/mL)	AUC _{last} (day·µg/mL)	t _{max} (day)	C _{max} (µg/mL)	AUC _{last} (day·µg/mL)
N	130	130	118	135	135	122
Mean	NR	59.0	924	NR	53.7	870
SD	NR	17.2	346	NR	16.8	309
Min	2.0	8.63	162	1.9	14.8	190
Median	4.0	56.6	841	4.0	51.2	815
Max	9.9	103	2150	10	108	2010
CV%	NR	29.2	37.5	NR	31.3	35.5

AI/Pen = autoinjector/pen; AMD = automated mini-doser; AUC_{last} = AUC from time zero to time of last quantifiable concentration; C_{max} = Maximum observed drug concentration; CV = coefficient of variation; SD = standard deviation; t_{max} = Time to reach C_{max}

(source: report for study 20110168, table 11-1, page 43)

Table 2 Summary of Statistical Evaluation of Pharmacokinetic Parameter Estimates of Evolocumab After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-Doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects

Parameter(unit)	n	AMD (Test) (N = 130)		n	3 AI/pens (Reference) (N = 135)		Ratio of Test/Reference ^a	
		LSMean	90% CI		LSMean	90% CI	LSMean	90% CI
AUC _{last} (day·ug/mL)	118	862.62	(815.31, 912.68)	122	817.55	(773.43, 864.18)	1.06	(0.96, 1.14)
C _{max} (ug/mL)	130	56.19	(53.59, 58.93)	135	51.07	(48.74, 53.51)	1.10	(1.03, 1.18)

CI = Confidence Interval.

LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.

AMD = automated mini-doser

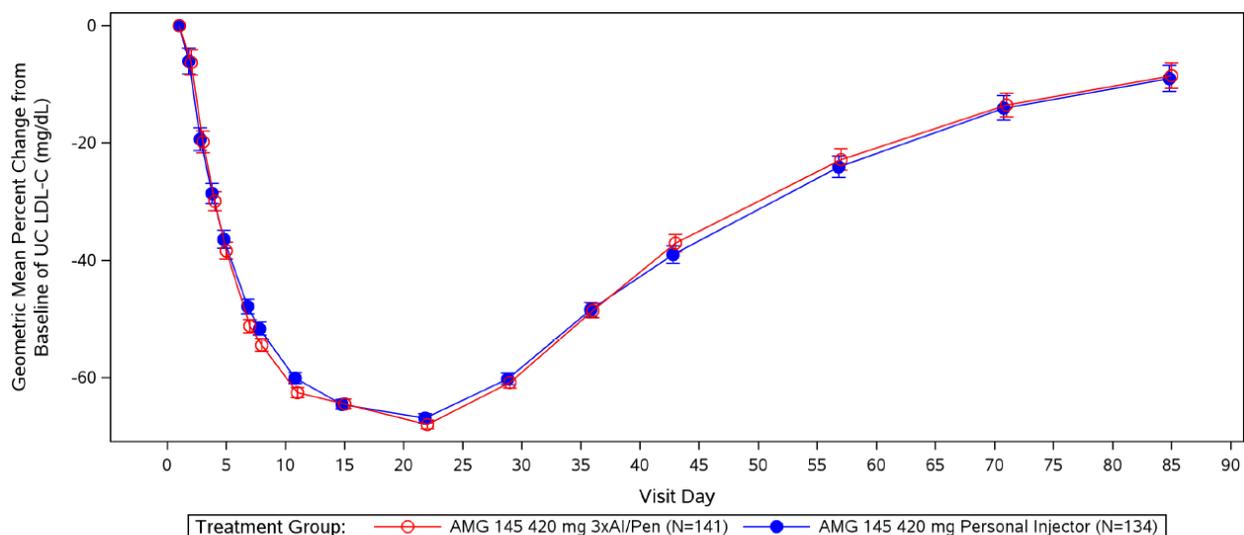
^aRatio and CI are based on natural log scale data converted back to the original scale

(source: report for study 20110168, table 11-1, page 44)

Analysis of the pharmacodynamic (PD) data for LDL-C and PCSK9 indicated that the reductions over time in LDL-C and PCSK9 were nearly identical between groups. The geometric LS mean ratio (90% CIs) of the AMD to 3 AI/pens for LDL-C AUEC_{day1-day85} was 1.00 (0.96 - 1.04), indicating PD comparability.

Between days 1 to 11, unbound PCSK9 serum concentrations reached the LLOQ (15 ng/mL) of the assay (> 94% mean reductions from baseline) in both groups. By day 22, the mean percent reduction from baseline in unbound PCSK9 serum concentrations was approximately 85% for both groups; by end of the study, mean percent reductions from baseline were approximately 15% and 18% for the AMD and AI/pen groups, respectively.

Mean LDL-C profiles are shown in [Figure 2](#), and summary of statistical comparison are shown in [Table 3](#).



Values on the x-axis have been shifted slightly for ease of reading.
 Geometric mean percentage change is generated by (modeled based ratio to baseline - 1)*100

Figure 2 Geometric Mean Percent Change from Baseline (+/- Standard Error) of LDL-C (mg/dL) over Time After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-Doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects

(source: report for study 20110168, Figure 11-2, page 48)

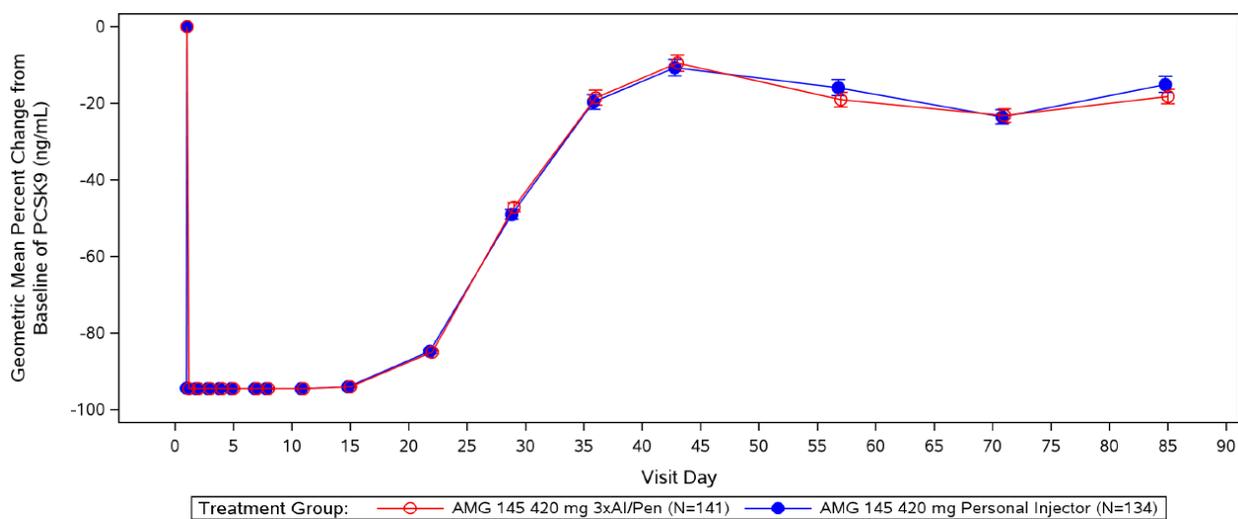
Table 3 Summary of Statistical Evaluation of AUEC_{day1-day85} for Ultracentrifugation LDL-C After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-Doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects

Treatment Parameter(unit)	AMD (N = 134)			3xAI/Pens (N = 141)			Ratio of AMD to 3xAI/Pens ^a	
	n	LSMean	95% CI	n	LSMean	95% CI	LSMean	95% CI
AUEC (day•mg/dL)	123	6073.19	(5908.88, 6242.06)	130	6066.34	(5907.30, 6229.67)	1.00	(0.96, 1.04)
AUEC (day•mmol/L)	123	157.05	(152.80, 161.42)	130	156.88	(152.76, 161.10)		

AI/pen = autoinjector/pen; AMD = automated mini-doser ; AUEC = area under the effect curve ; CI = Confidence Interval.
 LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.
^a Ratio and CI are based on natural log scale data converted back to the original scale.

(source: report for study 20110168, table 11-3, page 46)

Mean PCSK9 profiles are shown in [Figure 3](#), and summary of comparison between the two treatments are shown in [Table 4](#).



Values on the x-axis have been shifted slightly for ease of reading.
 Geometric mean percentage change is generated by (modeled based ratio to baseline - 1)*100
 BQL of PCSK9 is set at low limit level of 15 ng/mL.

Figure 3 Geometric Mean Percent Change from Baseline (+/- SE) of PCSK9 over Time After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-Doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects

(source: report for study 20110168, Figure 11-3, page 50)

Table 4 Comparison of PCSK9 over time (Safety Analysis Set)

Statistics	AMG 145 420 mg	
	3xAI/Pen (N = 141)	Personal Injector (N = 134)
Baseline		
n	141	134
LS Geometric Mean	268.4	276.8
Day 1 Post Dose 4 Hours		
n	141	134
LS Geometric Mean	15.1	15.3
LS Geometric Mean Ratio to Baseline	0.06	0.06
Percentage Change from Baseline with 95% CI	-94.49 (-94.73, -94.24)	-94.38 (-94.63, -94.11)
Ratio to 3xAI/Pen with 95% CI		1.02 (0.96, 1.09)
p-value		0.53

(source: report for study 20110168, table 14-11.13, page 255)

Labeling Comments (Preliminary)

In the proposed label, information about the AMD was added to the existing approved product label. The following sections of the label were updated:

Section 2.2 (Important Administration Instructions)

Section 3 (DOSAGE FORMS AND STRENGTHS)

Section 11 (DESCRIPTION)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Section 17 (PATIENT COUNSELING INFORMATION)

There were no changes in Section 12 (CLINICAL PHARMACOLOGY).

Conclusion:

PK and PD comparability was demonstrated between the 420 mg dose of evolocumab delivered either via a single 3.5 mL unit AMD (120 mg/mL) or 3 AI/pens (1 mL, 140 mg/mL).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURYANARAYANA M SISTA
05/19/2016

JAYABHARATHI VAIDYANATHAN
05/19/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	125522/S-001 (Seq: 0082)	SDN	107
Applicant	Amgen	Submission Date	10 Sep 2015
Generic Name	Evolocumab	Brand Name	Repatha
Drug Class			
Indication	REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and: <ul style="list-style-type: none"> Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C) Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C 		
Dosage Regimen	<ul style="list-style-type: none"> Primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH: 140 mg every 2 weeks or 420 mg once monthly in abdomen, thigh, or upper arm HoFH: 420 mg once monthly 		
Dosage Form	Liquid	Route of Administration	SC Injection
OCP Division	DCP2	OND Division	DMEP
OCP Review Team Division	Primary Reviewer(s) Suryanarayana Sista, PhD	Secondary Reviewer/ Team Leader Jayabharathi Vaidyanathan, PhD	
Pharmacometrics			
Genomics			
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	11/9/2015	74-Day Letter Date	2/4/2016
Review Due Date	5/15/2016	PDUFA Goal Date	7/10/2016
Application Fileability			
Is the Clinical Pharmacology section of the application fileable? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes list comment(s)			
Is there a need for clinical trial(s) inspection? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes explain:			
Clinical Pharmacology Package			
Tabular Listing of All Human Studies		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Clinical Pharmacology Summary
Bioanalytical and Analytical Methods		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Labeling
			<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Clinical Pharmacology Studies			
Study Type	Count	Comment(s)	

In Vitro Studies			
<input type="checkbox"/>	Metabolism Characterization		
<input type="checkbox"/>	Transporter Characterization		
<input type="checkbox"/>	Distribution		
<input type="checkbox"/>	Drug-Drug Interaction		
In Vivo Studies			
Biopharmaceutics			
<input type="checkbox"/>	Absolute Bioavailability		
<input type="checkbox"/>	Relative Bioavailability		
<input checked="" type="checkbox"/>	Bioequivalence	1	20110168, a Phase 1 pharmacokinetic equivalence study conducted to bridge the phase 3 data obtained using the AI/pen (3 x 1 mL at 140 mg/mL) to the AMD (3.5 mL at 120 mg/mL) ^a .
<input type="checkbox"/>	Food Effect		
<input type="checkbox"/>	Other		
Human Pharmacokinetics			
Healthy Subjects	<input type="checkbox"/>	Single Dose	
	<input type="checkbox"/>	Multiple Dose	
Patients	<input type="checkbox"/>	Single Dose	
	<input type="checkbox"/>	Multiple Dose	
<input type="checkbox"/>	Mass Balance Study		
<input type="checkbox"/>	Other (e.g. dose proportionality)		
Intrinsic Factors			
<input type="checkbox"/>	Race		
<input type="checkbox"/>	Sex		
<input type="checkbox"/>	Geriatrics		
<input type="checkbox"/>	Pediatrics		
<input type="checkbox"/>	Hepatic Impairment		
<input type="checkbox"/>	Renal Impairment		
<input type="checkbox"/>	Genetics		
Extrinsic Factors			
<input type="checkbox"/>	Effects on Primary Drug		
<input type="checkbox"/>	Effects of Primary Drug		
Pharmacodynamics			
<input type="checkbox"/>	Healthy Subjects		
<input type="checkbox"/>	Patients		
Pharmacokinetics/Pharmacodynamics			
<input type="checkbox"/>	Healthy Subjects		
<input type="checkbox"/>	Patients		
<input type="checkbox"/>	QT		
Pharmacometrics			
<input type="checkbox"/>	Population Pharmacokinetics		
<input type="checkbox"/>	Exposure-Efficacy		
<input type="checkbox"/>	Exposure-Safety		
Total Number of Studies		In Vitro	In Vivo
Total Number of Studies to be Reviewed			1 0 ^a

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	Note: This is a 351(a) application.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Note: Information was submitted in the original BLA (Sequence: 0000) ^a
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No',	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	

*Study was already reviewed in the original BLA submission (Sequence 0000; see Clinical Pharmacology review dated 01 Jun 2015 in DARRTS, document ID 3772601)

Since no new data was submitted for the Clinical Pharmacology component for this BLA supplement, and since no labeling changes relevant to Clinical Pharmacology have been made, the Office of Clinical Pharmacology is not planning to have a review of this supplement.

Filing Memo

The sponsor submitted a Prior Approval Efficacy Supplement seeking approval of a new drug product presentation comprising a 120 mg/mL prefilled cartridge co-packaged with an automated mini-doser (AMD) administration device, referred to as the 120 mg/mL AMD, according to the approved dosing schedule and route of administration for which evolocumab is currently approved.

The sponsor submitted clinical information for the 120 mg/mL AMD to BLA 125522 in the original BLA (Sequence No. 0000); however, as the 120 mg/mL AMD was still under development at the time of the original BLA submission, it was not part of the formal approval. The primary clinical study supporting the added 120 mg/mL AMD is a Phase 1 bioequivalence study (study 20110168) conducted to bridge clinical data obtained using the currently approved prefilled autoinjector. The sponsor also conducted a phase 0 study (20120135) to assess the drug delivery performance of the AMD using a placebo buffer, and a phase 3 home-use study (20120356) to assess drug delivery performance using either the AMD or the commercially approved prefilled autoinjector. All three studies are also referenced in this supplement.

The phase 1 bioequivalence study (20110168) was reviewed in the original submission (dated 01 Jun 2015 in DARRTS, document ID 3772601).

The results are briefly summarized below:

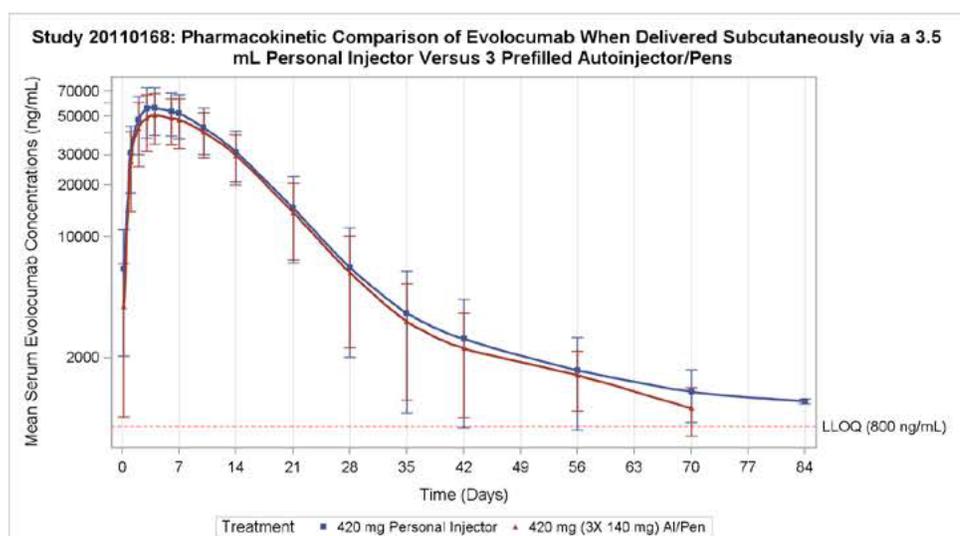


Figure 1 Mean unbound serum evolocumab concentration following subcutaneous administration of a 420 mg dose delivered either via 3.5 mL AMD or 3 AI/Pens

As seen from Figure 1 above, similar mean unbound evolocumab serum concentration time profiles were observed after a 420 mg SC dose of evolocumab when delivered using the AMD or 3 AI/pens. Median t_{max} was 4.0 days for both AMD (range = 2.0 to 9.9 days) and 3 AI/pens (range = 1.9 to 10 days). The geometric least square mean ratios (90% CI) of the AMD to 3 AI/pens for C_{max} and AUC_{last} were 1.10 (1.03 - 1.18) and 1.06 (0.97 - 1.14), respectively, indicating bioequivalence between the formulations from the two devices..

Statistical comparison of pharmacokinetic parameters is shown in Table 1 below:

Table 1: Summary of Statistical Evaluation of Pharmacokinetic Parameter Estimates of Evolocumab After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects

Parameter(unit)	n	AMD (Test) (N = 130)		n	3 AI/pens (Reference) (N = 135)		Ratio of Test/Reference ^a	
		LSMean	90% CI		LSMean	90% CI	LSMean	90% CI
AUClast (day*ug/mL)	118	862.62	(815.31, 912.68)	122	817.55	(773.43, 864.18)	1.06	(0.96, 1.14)
Cmax (ug/mL)	130	56.19	(53.59, 58.93)	135	51.07	(48.74, 53.51)	1.10	(1.03, 1.18)

CI = Confidence Interval.

LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.

AMD = automated mini-doser

^a Ratio and CI are based on natural log scale data converted back to the original scale

(source: report for study 20110168, table 11-1, page 43)

Analysis of LDL-C and PCSK9 data indicated that the reductions over time in LDL-C and PCSK9 were nearly identical between groups. The geometric LS mean ratio (90% CIs) of the AMD to 3 AI/pens for LDL-C AUECday1-day85 was 1.00 (0.96 - 1.04), indicating PD equivalence.

Mean LDL-C and PCSK9 profiles shown in Figure 2 and 3, respectively, show that profiles for LDL-C and PCSK9 were also similar between the two devices.

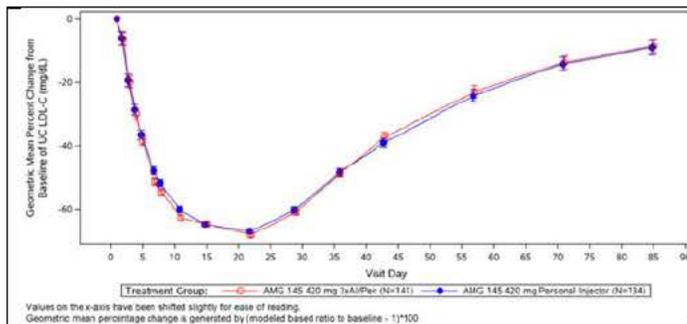


Figure 38 Geometric Mean Percent Change from Baseline (+/- Standard Error) of LDL-C (mg/dL) over Time After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects

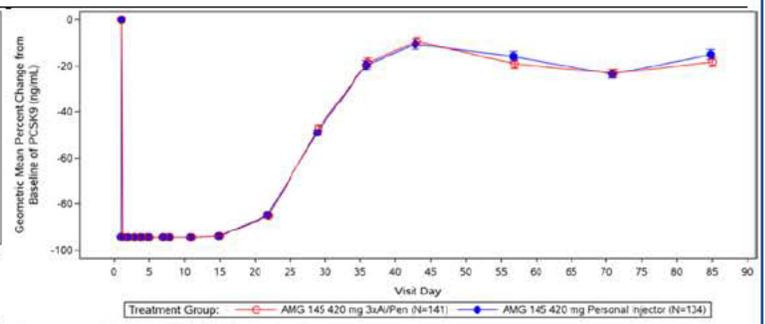


Figure 39 Geometric Mean Percent Change from Baseline (+/- Standard Error) of PCSK9 over Time After Subcutaneous Administration of Evolocumab at 420 mg Using an Automated Mini-doser (Test) versus 3 Autoinjector/Pens (Reference) in Healthy Subjects

Filing Memo

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes No

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to Sponsor:

None

Suryanarayana M. Sista

05 Nov, 2015

Reviewing Clinical Pharmacologist

Date

Jayabharathi Vaidyanathan

05 Nov, 2015

Acting Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURYNARAYANA M SISTA
11/06/2015

JAYABHARATHI VAIDYANATHAN
11/06/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125522Orig1s001

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 17, 2016
Application Type and Number:	BLA 125522/S-001
Product Name and Strength:	Repatha Pushtronex (evolocumab) Injection, 420 mg/3.5 mL (120 mg/mL) [On-Body Infusor]*** ¹
Product Type:	Combination
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amgen
Panorama #:	2016-3067924
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

¹ We note that the device common name is under review by Center for Devices and Radiological Health.

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Repatha Pushtronex, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant submitted an external name study, conducted by (b) (4) for this product.

1.1 REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, Repatha (b) (4) on May 27, 2014. However, the The Office of Prescription Drug Promotion (OPDP) found the name, Repatha (b) (4) unacceptable because (b) (4) in OSE Review #2015-17396², dated September 22, 2014. The root name, Repatha, was found acceptable in OSE Review #2014-26440¹, dated September 22, 2014. BLA 125522 was approved on August 27, 2015 under Repatha. Repatha is currently available as a prefilled syringe and an autoinjector (Repatha SureClick).

The Applicant submitted a prior approval supplement to seek approval for a “new drug product presentation comprising a 120 mg/mL prefilled cartridge co-packaged with an automated mini-doser (AMD) administration device, referred to as the 120 mg/mL AMD, on 10 September 2015.” Thus, the Applicant submitted the name, Repatha Pushtronex, for review on March 18, 2016.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 18, 2016 proprietary name submission.

Intended Pronunciation	ri-PATH-a push-troe'-nex
Active Ingredient	Evolocumab
Indications of Use	Evolocumab is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce elevated LDL-C, total cholesterol, ApoB, non-HDL-C, VLDL-C, triglycerides and Lp(a), and to increase HDL-C and ApoA1: <ul style="list-style-type: none">• As monotherapy, or• In combination with an HMG CoA reductase inhibitor (statin), or• Alone or in combination with a statin or other lipid-lowering therapies in patients who are statin-intolerant or unable to tolerate

² Mistry M. Proprietary Name Review for Repatha, Repatha SureClick, and (b) (4) (BLA 125522). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 SEP 22. 29 p. OSE RCM No.: 2014-17396, 2014-26441.

	<p>an effective dose of a statin.</p> <p>Evolocumab is indicated in patients at least 12 years of age with homozygous familial hypercholesterolemia to reduce elevated LDL</p>
Route of Administration	subcutaneous injection
Dosage Form	solution for injection
Strengths	<ul style="list-style-type: none"> • 140 mg/mL • 420 mg/3.5 mL (120 mg/mL)
Dose and Frequency	<p>The proposed dosing regimens for primary hyperlipidemia and mixed dyslipidemia are:</p> <ul style="list-style-type: none"> • 140 mg subcutaneously every 2 weeks • 420 mg subcutaneously once monthly. <p>The proposed dosing regimens for homozygous familial hypercholesterolemia are:</p> <ul style="list-style-type: none"> • 420 mg subcutaneously once monthly • 420 mg subcutaneously every 2 weeks
How Supplied	<p>Prefilled syringe (PFS):</p> <ul style="list-style-type: none"> • The PFS is a prefilled, single-use, disposable, handheld, injection device that is provided ready to use. <p>Autoinjector(AI)/pen:</p> <ul style="list-style-type: none"> • The AI/pen is a prefilled, single-use, disposable, handheld, mechanical (spring-based) injection device that is provided ready to use, pre-assembled with the prefilled syringe. <p>Automated Mini-Doser (AMD):</p> <ul style="list-style-type: none"> • The AMD is a compact, sterile, single-use, disposable, electro-mechanical (battery powered, micro-processor controlled), on-body injection device that is co-packaged with a prefilled cartridge to administer a single, fixed dose of drug product into the subcutaneous tissue.
Storage	<p>Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. If removed from the refrigerator, evolocumab should be kept at controlled room temperature (up to 25°C [77°F]) in the original carton and must be used within 30 days. Protect evolocumab from direct light and do not expose to temperatures above 25°C (77°F). Do not freeze.</p>
Container and Closure Systems	<p>Prefilled syringe (PFS):</p> <ul style="list-style-type: none"> • The PFS consists of a 1mL (b) (4) glass syringe with a (b) (4) needle covered with an (b) (4) needle shield and a (b) (4)

	<ul style="list-style-type: none"> • The (b) (4) needle shield is made from dried natural rubber, protects the needle cannula, (b) (4). • (b) (4). <p>Autoinjector(AI)/pen:</p> <ul style="list-style-type: none"> • The AI/pen is a modified version of the SureClick autoinjector currently approved for Enbrel (etanercept). • The AI/pen differs from the SureClick autoinjector in color (b) (4). <p>Automated Mini-Doser (AMD):</p> <ul style="list-style-type: none"> • The AMD and the prefilled cartridge are assembled by the user at point of use and has an integrated, biocompatible adhesive which attaches the device to the skin for dose administration. • The combination product with adhesive is removed from the skin following completion of the dose. • Primary packaging for the AMD consists of a blister tray with tray lid that forms a sterile barrier for the AMD. • Instructions for Use are included in each carton.
--	---

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Metabolism and Endocrinology Products (DMEP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 *United States Adopted Names (USAN) Search*

There is no USAN stem present in the proprietary name³.

³USAN stem search conducted on April 7, 2016.

2.2.2 Components of the Proposed Proprietary Name

The proposed proprietary name contains two components: 1) the root name Repatha and 2) the device name Pushtronex. The Applicant indicated in their submission that “Repatha® Pushtronex™ is the delivery device co-packaged with a prefilled cartridge of evolocumab (420 mg dose). The use of the word “Push” refers to the action needed to initiate the injection. “Tronex” is derived from “Electronics,” referring to the electronic device.” An analysis of the root name and appropriateness of the modifier is discussed in Section 2.2.6.

2.2.3 FDA Name Simulation Studies

Eighty-five practitioners participated in DMEPA’s prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, April 8, 2016 e-mail, DMEP did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.5 Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving *Repatha* that would be relevant for this review.

Table 2. FAERS Search Strategy	
Search Date	March 25, 2016
Drug Name	Repatha [product name]
Event (MedDRA Terms)	DMEPA Official Proprietary Name Review Search Terms Event List: Product name confusion (PT) Medication error (PT) Intercepted medication error (PT) Drug dispensing error (PT) Intercepted drug dispensing error (PT) Circumstance or information capable of leading to a medication error (PT)
Date Limits	August 1, 2015 to March 25, 2016

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

No cases were identified.

2.2.6 Analysis of Root Name and the Proposed Modifier Pushtronex

The root name, ‘Repatha’ is approved for the product, evolocumab, and has been on the market since August of 2015. As noted in section 2.2.5, we have not received any medication errors related to name confusion. Repatha is currently available as a prefilled syringe and an autoinjector (Repatha SureClick) in 140 mg/mL strength. Currently approved doses are 140 mg every two weeks or 420 mg every two or four weeks, depending on the indication. Three injections using the either the prefilled syringe or the autoinjector is currently required to administer the 420 mg dose. Thus the Applicant is seeking for approval of the AMD that can deliver the entire 420 mg as a single injection using the Repatha Pushtronex device. We agree with the use of the same root name “Repatha” for the proposed product.

The Applicant proposes to use the modifier ‘Pushtronex’ to differentiate the proposed AMD from the currently marketed prefilled syringe and the autoinjector. It is not uncommon for modifiers to be used to denote a specific formulation or packaging configuration (e.g., Advair Diskus and Advair HFA) as part of a product line extension. The applicant states that the modifier ‘Pushtronex’ *is from the use of the word “Push” refers to the action needed to initiate the injection. “Tronex” is derived from “Electronics,” referring to the electronic device.* The device is not currently marketed.

Additionally, the modifier ‘Pushtronex’ has not been previously marketed and is not available on its own. However, we also note that omission and oversight of a modifier is cited in literature² as a common cause of medication error. Postmarketing experience shows that the introduction of product line extensions result in medication errors if the modifier is omitted and the product characteristics are similar or overlap. We note that in this instance there would be no delay in treatment or missed dose since the patient should be able to receive the intended dose (dose will be noted on a prescription) with the available product presentations since the addition of the proposed device is intended to provide an alternate means of administering the 420 mg dose, which is currently approved.

2.2.7 Communication of DMEPA’s Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Metabolism and Endocrinology Products (DMEP) via e-mail on May 5, 2016. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from DMEP on May 17, 2016, they stated no additional concerns with the proposed proprietary name, Repatha Pushtronex.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

² Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

If you have any questions or need clarifications, please contact Deveonne Hamilton-Stokes, OSE project manager, at 301-796-2253.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Repatha Pushtronex, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your March 18, 2016 submission are altered prior to approval of the prior approval supplement application, the name must be resubmitted for review.

4 REFERENCES

1. *USAN Stems* (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page>)

USAN Stems List contains all the recognized USAN stems.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment:** For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment:** The safety assessment is conducted by DMEPA, and includes the following:
 - a. **Preliminary Assessment:** We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.⁴

Appendix A1: Description of FAERS

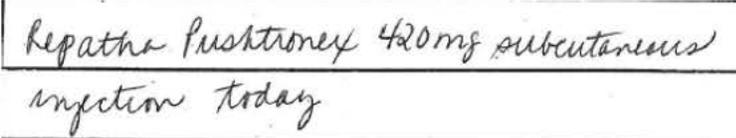
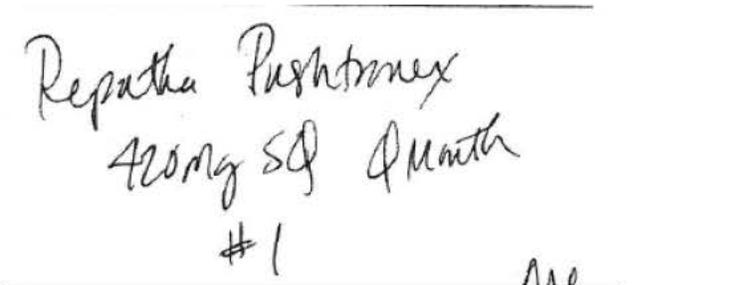
The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes

⁴ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Repatha Pushtronex Study (Conducted on 4/4/2016)

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u></p> 	<p>Repatha Pushtronex</p> <p>Inject 420 mg subcutaneously once a month</p> <p>Disp: #1</p>
<p><u>Outpatient Prescription:</u></p> 	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

286 People Received Study

85 People Responded

Total	32	27	26	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
RAPATHA	0	1	0	1
RAPATHA WISTRONICS	0	1	0	1
REBATA PRESTRONICS	0	1	0	1
REBHATA RESTATIS	0	1	0	1
REPAPPA RESTONICS	0	1	0	1
REPATHA	0	3	0	3
REPATHA HISTRONICS	0	1	0	1
REPATHA PESTRONICS	0	1	0	1
REPATHA PISTRADEX	0	1	0	1
REPATHA PLUSTRANIX	0	1	0	1
REPATHA PLUSTRONICS	0	1	0	1

REPATHA POSTRATIX	0	1	0	1
REPATHA POSTRONICS	0	1	0	1
REPATHA POSTRONICS INJ	0	1	0	1
REPATHA PRISHTRONEX	0	0	2	2
REPATHA PROSTRONICS	0	1	0	1
REPATHA PUGHTMEX	1	0	0	1
REPATHA PUSH TRONICS	0	1	0	1
REPATHA PUSHTMEX	1	0	0	1
REPATHA PUSHTOMEX	2	0	0	2
REPATHA PUSHTONEX	1	0	0	1
REPATHA PUSHTONNEX	1	0	0	1
REPATHA PUSHTRANEX	2	0	0	2
REPATHA PUSHTRENEX	1	0	0	1
REPATHA PUSHTRINEX	2	0	0	2
REPATHA PUSHTRONEX	18	0	23	41
REPATHA PUSHTRONIX	0	0	1	1
REPATHA PUSHTRUEX	1	0	0	1
REPATHA PUSHTRUMEX	1	0	0	1
REPATHA PUSTRATIS	0	1	0	1
REPATHA PUSTRONIX	0	1	0	1
REPATHA QUISTRONICS	0	1	0	1
REPATHA VISTRONIX	0	1	0	1
REPATHA VUSTRONIX	0	1	0	1
REPATHA WITH TRIAX	0	1	0	1
REPATHAPUSTRATICS	0	1	0	1
REPETA PROSTONICS	0	1	0	1
REPUTHA PUSHTRONEX	1	0	0	1
RIPATHA	0	1	0	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH K VEE
05/17/2016

YELENA L MASLOV
05/17/2016

LUBNA A MERCHANT
05/17/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125522Orig1s001

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 1, 2016

To: Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Ankur Kalola, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)

Drug Name (established name): REPATHA (evolocumab)

Dosage Form and Route: Injection, for subcutaneous use

Application Type/Number: BLA 125522

Supplement Number: S-001

Applicant: Amgen, Inc.

1 INTRODUCTION

On September 10, 2015, Amgen submitted, for the Agency's review, a chemistry, manufacturing, and controls (CMC) Prior Approval Supplement (PAS) for REPATHA (evolocumab) injection, for subcutaneous use. The purpose of the submission is to seek approval for a new drug product presentation comprising a 120mg/mL prefilled cartridge co-packaged with an automated mini-doser (AMD) administration device. On September 15, 2015, the FDA reclassified the CMC prior approval supplement to a clinical efficacy supplement. On May 9, 2016, the Agency communicated to the sponsor during a meeting the decision to classify and label the automated mini-doser (AMD) as an infusion pump. On May 19, 2016, the Agency conditionally accepted the Applicant's request for the proposed proprietary name, Pushtronex System (On-Body Infusor and Prefilled Cartridge).

REPATHA is indicated for long-term treatment of patients with primary hyperlipidemia, mixed dyslipidemia, as well as homozygous familial hypercholesterolemia (HoFH).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by DMEP on October 18, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for REPATHA (evolocumab) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate review of the IFU was completed on June 8, 2016.

2 MATERIAL REVIEWED

- Draft REPATHA (evolocumab) injection, for subcutaneous use, PPI received on May 27, 2016, revised by the Review Division throughout the review cycle and received by DMPP on June 1, 2016.
- Draft Pushtronex System (On-Body Infusor and Prefilled Cartridge) for REPATHA (evolocumab) injection, for subcutaneous use, IFU received on September 10, 2016, and received by DMPP on June 1, 2016.
- Draft REPATHA (evolocumab) injection, for subcutaneous use, PPI received on May 27, 2016, revised by the Review Division throughout the review cycle and received by OPDP on June 28, 2016.
- Draft Pushtronex System (On-Body Infusor and Prefilled Cartridge) for REPATHA (evolocumab) injection, for subcutaneous use, IFU received on September 10, 2016, and received by OPDP on June 28, 2016.
- Draft REPATHA (evolocumab) injection, for subcutaneous use, Prescribing Information (PI) received on September 10, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on June 27, 2016.
- Draft REPATHA (evolocumab) injection, for subcutaneous use, Prescribing Information (PI) received on September 10, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on June 27, 2016.

- Division of Medication Error, Prevention, and Analysis (DMEPA) review dated June 8, 2016.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. In our review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

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Date: June 24, 2016

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From: Carolyn Cochenour
CDRH/ODE/DAGRID/GHDB

Subject: CDRH Consult for BLA 125522 S001, ICC1500492, Repatha (evolocumab) subcutaneous infusion using Amgen, Inc's On-Body Infusor for Repatha

CDRH Review Team

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Review Summary

CDRH performed a review of the device constituent of the combination product for BLA 125522/S001 for Amgen's ON-Body Infusor for subcutaneous infusion of Repatha. The device constituent part of the combination product is an on-body infusion pump that delivers the entire contents of a pre-fill cartridge over 9 minutes. The device is controlled through software that directs a motor to slowly infuse the drug. There are colored flashing lights, which provide communication to the user (ie. Start, finish, error). Repatha is currently approved for subcutaneous injection using either a prefilled syringe or pen-injector.

The focus of this review is on the risk assessment and performance testing of the device risk including design verification, design validation, biocompatibility testing and software validation. The device underwent extensive testing to verify the device against specifications. The commercial iteration of the device passed all testing requirements, biocompatibility tests, and software validation. The risk assessment identified the critical aspects of the device and linked to test reports used to reduce the residual risk to an acceptable level.

The Shelf Life testing was completed using accelerated aging technique to simulate (b)(4) shelf life to support a 2 year shelf life. Amgen will need to provide real time aging device design verification data for the shelf life tests, including: Device Function Test, Deliverable Volume Test, Injection Time test, (b)(4) Integrity test, (b)(4) Function test, and Shelf life adhesive function test.

The shelf-life for the 120mg/mL prefilled cartridge co-packaged with the pump is 24 months stored at the recommended storage condition of 5°C. Additionally, to enhance convenience and facilitate dosing compliance, an optional short-term storage at room temperature (controlled, 25°C or less) of not more than 1 month is supported after removal from storage at 5°C. The batch release criteria for the on-body infusor is deliverable volume ≥3.5mL.

CDRH recommends that the device constituent part of the combination product for BLA 125522/S001 is appropriate for the intended use of subcutaneous infusion of Repatha. There are no device concerns that would prevent approval of BLA 125522/S001. Amgen will have to provide real time aging shelf-life testing as it becomes available for review at 12 months and 24 months.

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1. Purpose of Memo and Review Summary

CDER has requested that CDRH provide review for the supplement 001 to BLA 125522. This is supplement to add the use of the automated mini-doser (AMD) which is manufactured by Amgen Inc to deliver Repatha (evolocumab). The AMD is an on-body medication delivery system.

A Chemistry, Manufacturing, and Controls (CMC) Prior Approval Supplement (PAS) is being filed to support the approval of a new evolocumab drug product presentation, the 120 mg/mL prefilled cartridge co-packaged with an automated mini-doser (AMD) administration device, referred to as the 120 mg/mL AMD. According to the application, this is a compact, sterile, disposable, electro-mechanical (battery-powered, micro-processor controlled), on-body injection device. It adheres to the skin for approximately 9 minutes to administer a 420 mg dose from the 3.5 mL prefilled cartridge.

The clinical development of evolocumab included the evaluation of (b) (4) presentations for subcutaneous administration (b) (4) 140 mg/mL prefilled syringe [PFS], 140 mg/mL prefilled autoinjector/pen [AI/pen], and 120 mg/mL automated mini-doser [AMD]). The 140 mg/mL prefilled AI/pen and the PFS were included for approval in the original BLA filing submitted on 27 August 2014 (Sequence No. 0000). Clinical information for the 120 mg/mL AMD was also submitted to BLA 125522 in the original BLA (Sequence No. 0000); however, the 120 mg/mL AMD was still under development at the time of the original BLA submission, and thus was not part of the formal review and approval.

1.1. Summary of Recommendations

CDRH recommends **APPROVAL** of BLA 125522/S001 for Amgen's on-body infusor for delivery of Repatha with the post approval real time aging testing provided at 12 and 24 months intervals.

1.2. Topics not Covered in this Review

- Human factors deferred to CDER/OSE/DMEPA
- In-use stability assessments deferred to CDER/OPQ
- Device manufacturing review deferred to CDRH/OC
- Final combination product benefit / risk assessment

2. Background

The 140 mg/mL prefilled AI/pen and the PFS were included for approval in the original BLA filing submitted on 27 August 2014 (Sequence No. 0000). Clinical information for the 120 mg/mL AMD was also submitted to BLA 125522 in the original BLA (Sequence No. 0000); however, the 120 mg/mL AMD was still under development at the time of the original BLA submission, and thus was not part of the formal review and approval.

3. Review of Device Materials [COMPLETE]

3.1. Product Description

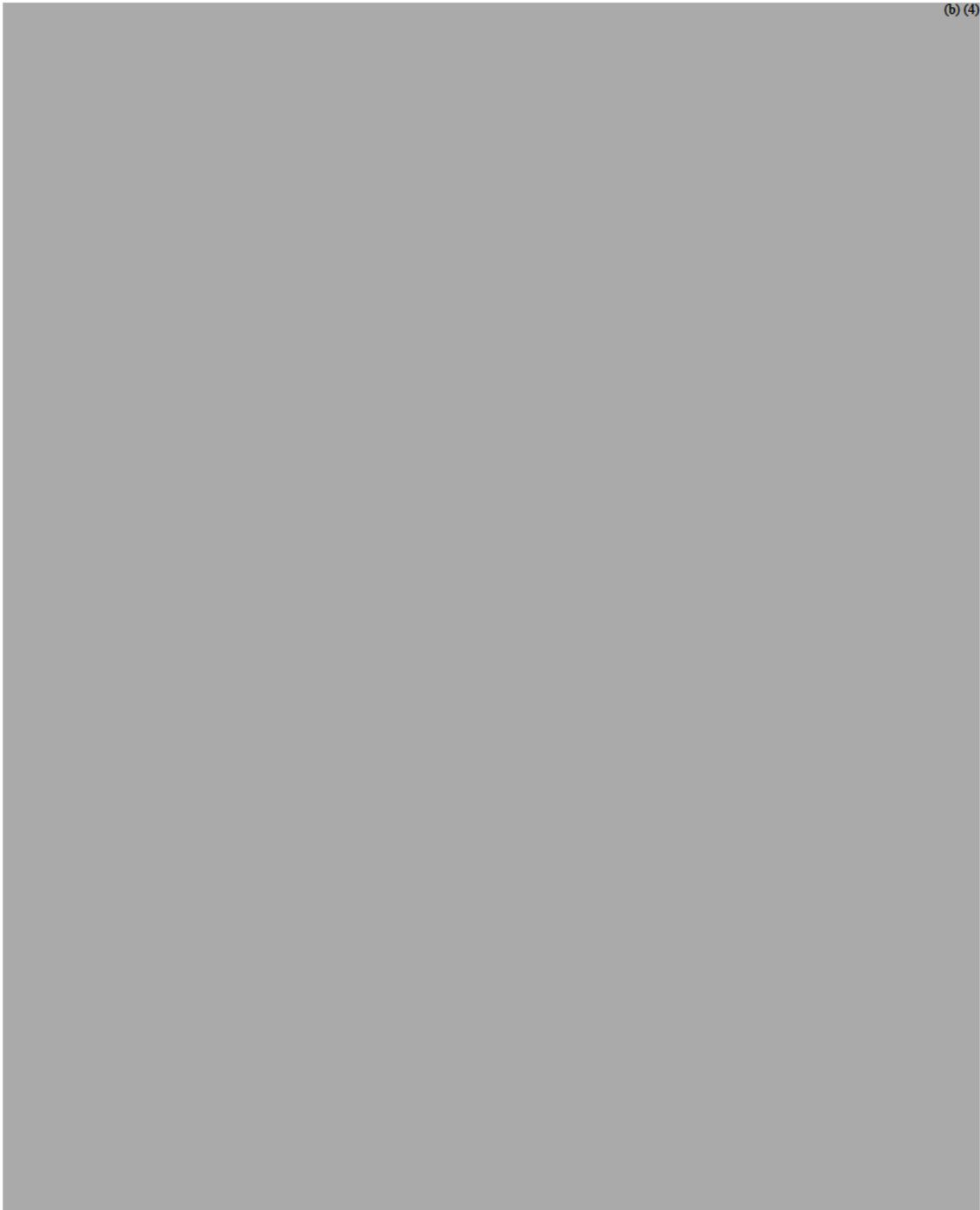
Amgen Inc., holder of Establishment License 1080, seeks licensure to market evolocumab, a fully human IgG2 monoclonal antibody that inhibits the PCSK-9 pathway, for the treatment of primary hyperlipidemia and mixed dyslipidemia. Amgen also seeks licensure to market evolocumab for the treatment of homozygous familial hypercholesterolemia (HoFH).

Amgen is seeking approval of a new drug product presentation comprising a 120 mg/mL prefilled cartridge co-packaged with an automated mini-doser (AMD) administration device, referred to as the 120 mg/mL AMD, according to the approved dosing schedule and route of administration for which evolocumab is currently approved.

3.2. Device Constituent

The AMD (Figure 1) is a compact, sterile, single-use, disposable, electro-mechanical (battery powered, micro-processor controlled), on-body injection device which includes a (b) (4) administration needle (b) (4) and an integrated adhesive backing to adhere the device to the skin for administration of a fixed dose of evolocumab from a prefilled cartridge into subcutaneous (SC) tissue. The prefilled cartridge assembly is co-packaged with the AMD administration device. The device administers a 420-mg dose of evolocumab from the 3.5 mL prefilled cartridge assembly over approximately 9 minutes.

Figure 1. Automated Mini-Doser Loaded With Prefilled Cartridge Assembly



3.2.1. Indications for Use

The AMD administers a single 3.5 mL (420 mg), fixed dose of drug product from a prefilled cartridge assembly into SC tissue of the arm, abdomen, or thigh. It may be self-administered or administered by a caregiver or healthcare provider in a clinical or non-healthcare environment for user populations where the dose is approved.

3.2.2. Conditions of Use

Table 1. Automated Mini-Doser System Conditions of Use

Biologic product for injection	evolocumab only, for subcutaneous injection
Dosage capability	Single dose: 3.5 mL of 120 mg/mL
Method of injection	Electro-mechanical (battery powered, micro-processor controlled)
Packaging configuration	One AMD in a sterilized blister pack with (b) (4) cover, co-packaged with a cartridge assembly, in a single carton.
Environment of use conditions	Clinical or non-healthcare environment
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze.
Handling	Acclimate to room temperature for 45 minutes. Keep in carton to protect from light.

3.2.3. Description of Drug/Biological Product for Injection

The 120 mg/mL prefilled cartridge contains a 3.5 mL deliverable volume of 120 mg/mL evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The viscosity is approximately (b) (4)

3.2.4. Design Features

There is no dose setting for the AMD; the dose is fixed and the AMD is designed to administer the entire dose without user intervention. Both visual and auditory notifications provide feedback on the progress of drug administration. In the event of a drug delivery error, visual and auditory alarms will notify the user. Additionally, a viewing window that allows the user to see the prefilled cartridge allows inspection to confirm dose completion.

(b) (4)

(b) (4)

(b) (4) Pressing the activation button prior to successful adhesion of the AMD to the skin will result in a (b) (4) error state (auditory and visual alarms will be triggered) and (b) (4)

Following the completion of the injection, the user removes the AMD from the skin

(b) (4)

(b) (4)

3.2.5. Notifications and Alarms

The user interface of the AMD consists of 1 activation button, a viewing window to observe the prefilled cartridge assembly, 1 multicolor (b) (4) light, and a (b) (4) speaker for auditory feedback.

The user is provided with both auditory and visual notifications during the injection process.

- A flashing blue light indicates to the user that injection is ready.
- A flashing green light indicates to the user that the injection is in process.
- A solid green light indicates to the user that an injection is complete.

The ready state and complete states as well as transitions between states are additionally accompanied by an auditory pulse. A red light and a series of (b) (4) auditory pulses, both of which are unique to the alarm state, indicate an error.

3.2.6. Software

The software contained in the AMD controls functions for both drug delivery control and man-machine-interface (MMI).

(b) (4)

4. Relevant Clinical Studies [COMPLETE]

4.1. Study Number: 20110168

Title: An Open-label, Randomized, Parallel Study in Healthy Volunteers to Compare the Pharmacokinetics of AMG 145 When Delivered Subcutaneously via a 3.5 mL Personal Injector Versus 3 Prefilled Autoinjector/Pens

Development Phase: 1

Objective(s):

Primary

- to demonstrate pharmacokinetic equivalence of the 3.5 mL personal injector (also referred to as automated mini-doser [AMD] in this report) (test article) to 3 prefilled autoinjector/pens (AI/pens) (reference article)

Secondary

- to evaluate single-dose safety, tolerability, and additional pharmacokinetic parameters of AMG 145 administered by 3.5 mL personal injector and 3 prefilled AI/pens
- to compare low-density lipoprotein cholesterol (LDL-C) responses after administration with a 3.5mL personal injector and 3 AI/pens
- to assess complete delivery of 3.5 mL personal injector and 3 AI/pens

Endpoint(s):

Primary Endpoints:

- area under the drug concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration, AUClast
- maximum observed concentration (Cmax)

Secondary Endpoints:

- treatment emergent adverse events
- changes in vital signs, electrocardiograms (ECGs), and laboratory safety tests
- anti-evolocumab antibodies
- area under the effect curve (AUEC) for LDL-C through Day 85, AUECday1-day85 (area above 0 and below LDL-C values)
- complete delivery of AI/pen defined by entire window on AI/pen turning yellow
- complete delivery of AMD as defined by device light turning solid green, no observed fluid leakage during delivery, and window on device showing complete delivery
- additional serum pharmacokinetic parameters of evolocumab including but not limited to time of maximum concentration (tmax)
- serum levels of PCSK9

Number of Subjects (planned/enrolled): 280 subjects (140 AMD group; 140 AI/pen group)/292 subjects (146 AMD group; 146 AI/pen group)

Conclusions:

The study met its primary endpoint by demonstrating that the AMD and AI/pen devices were pharmacokinetically equivalent based on the pre-defined 90% CI for the ratio (AMD to AI/pen) for both AUClast and Cmax. In addition, changes in LDL-C and PCSK9 indicated a similar pharmacodynamic response for each device.

Treatment emergent adverse events were mainly related to injection site reactions (erythema and induration events) and were transient and mild in severity. Safety analyses were consistent with previous studies of evolocumab and did not identify any new risks.

Device related events for each group were anticipated and consistent with administration differences between the 2 devices (3 separate 1.0 mL injection less than a minute apart for AI/pen vs a single 3.5 mL injection over 9 minutes for AMD). None of these events were serious.

- device related adverse events in the AI/pen group were similar to those reported in a previous evolocumab studies which utilized the AI/pen device
- device related adverse events in the AMD group in this study were similar to those reported in a previous placebo buffer study which utilized the AMD device

Complete delivery of evolocumab was achieved for 430/435 (98.9%) of the AI/pens used and for 134/144 (93.1%) of the AMDs used.

4.2. Study Number: 20120356

Title: A Multi-Center, Randomized Study in Subjects With Primary Hypercholesterolemia or Mixed Dyslipidemia to Assess Subjects' Ability to Administer a full Dose of AMG 145 in Home-use, Using Either a 3.5 mL Personal Injector or a Prefilled Autoinjector/Pen.

Development Phase: 3

Objective(s):

The primary objective of this study was to assess users' ability to administer a full dose (420 mg) of evolocumab in a home-use setting using either an automated mini-doser (AMD; previously referred to as 3.5 mL personal injector) or autoinjector/pens (AI/pen). The secondary objective was to assess the effect of evolocumab on low-density lipoprotein cholesterol (LDL-C) using the specified drug delivery option.

Endpoint(s):

The primary endpoint for this study was the subject-reported outcomes of attempted full-dose administration at each of weeks 4 and 8. Subjects who discontinued IP had their subsequent responses recorded as 'discontinued IP prior to administration time.' Therefore, each primary endpoint had 3 possible values (yes/no/discontinued IP prior to administration time).

The secondary endpoint for this study was the percent change from baseline in LDL-C at the mean of weeks 10 and 12.

Subject incidence of adjudicated cardiovascular endpoint events (death by any cause, cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, hospitalization for heart failure, or transient ischemic attack) was an exploratory endpoint. Noncoronary revascularizations were also collected but were not adjudicated. Other exploratory endpoints are provided in Section 8.8.5.6.

Number of Subjects (planned/enrolled): 140/164-All 164 subjects received at least 1 of the 3 planned doses of SC evolocumab QM; 157 subjects (81 subjects in the AMD group and 76 subjects in the AI/pen group) completed IP.

Conclusions:

This study demonstrated that, after training, subjects were subsequently able to successfully self-administer a full dose of evolocumab (420 mg) in a home-use setting using either the AMD (one 3.5 mL dose administered over 9 minutes) or AI/pen (3 separate 1.0 mL injections administered within 30 minutes). The ability to successfully administer evolocumab in the home-use setting was similar using the AMD or AI/pen.

Clinically equivalent reductions from baseline in LDL-C at week 12 and at the mean of weeks 10 and 12 were observed for evolocumab delivered via AMD or AI/pen in the home-use setting. Also, following evolocumab 420 mg SC, unbound evolocumab and unbound PCSK9 serum concentrations were similar in the AI/pen and AMD groups at both weeks 10 and 12. The pharmacokinetic and pharmacodynamic data indicate that both methods of evolocumab administration (AMD or 3 AI/pens) were clinically equivalent with respect to treatment effect.

Adverse events and DRAEs were similar among subjects who used either the AMD or AI/pen. Based on patient reported successful administrations, both the AMD and AI/pen, with accompanying IFU, appear to be appropriate device systems for their intended use for the self-administration of evolocumab in patients with primary hyperlipidemia and mixed dyslipidemia on a stable dose of statin with or without ezetimibe.

The results of this study found that the AMD and AI/pen were both effective, safe, and well tolerated for their intended use and the conditions of use, including successful self-administration in the home-use setting, by subjects with primary hyperlipidemia and mixed dyslipidemia on a stable dose of statin with or without ezetimibe.

4.3. Study Number: 2012138

Title: A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145 - 2 (Interim Clinical Study Report) - OSLER 2

Development Phase: 3

Objective(s):

The primary objective of this study was to characterize the safety and tolerability of long-term administration of evolocumab.

The secondary objective was to characterize the efficacy of long-term administration of evolocumab as assessed by low-density lipoprotein cholesterol (LDL-C) in subjects with primary hyperlipidemia and mixed dyslipidemia.

The objective of this interim analysis is to summarize the safety and lipid data collected up to a data cutoff date for subjects with at least 12 weeks of potential safety and efficacy follow up in this open-label extension study.

Endpoint(s):

The primary endpoint of this study was the subject incidence of adverse events.

The secondary endpoints for this interim analysis were:

- percent change from parent study baseline in LDL-C at each visit with planned lipid measurements
- change from parent study baseline in LDL-C at each visit with planned lipid measurements
- percent change from parent study end of study in LDL-C at each visit with planned lipid measurements
- change from parent study end of study in LDL-C at each visit with planned lipid measurements

Exploratory endpoints for this interim analysis included:

- subject incidence of adjudicated cardiovascular events
 - death (all cause, cardiovascular)
 - cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, coronary revascularization)
 - hospitalization for heart failure
 - cerebrovascular events (transient ischemic attack, stroke)
- subject incidence of non-coronary revascularization
- change and percent change from parent study baseline and from parent study end of study at each scheduled visit in each of the following lipid and other lab parameters
 - non-high-density lipoprotein cholesterol (non-HDL-C)
 - apolipoprotein B (ApoB)
 - total cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio
 - total cholesterol
 - ApoB/apolipoprotein A1 (ApoA1) ratio
 - lipoprotein(a) (Lp[a])
 - triglycerides
 - HDL-C
 - very low-density lipoprotein cholesterol (VLDL-C)
 - ApoA1
 - high sensitivity C-reactive protein (hsCRP)

Other safety endpoints for this interim analysis included:

- changes from parent study baseline in safety laboratory values (including glycosylated hemoglobin [HbA1c]) and vital signs at each scheduled visit
- development of anti-evolocumab antibodies

Number of Subjects (planned/enrolled): 3,500/3,121

Conclusions:

A total of 3121 subjects from 7 parent studies were included in the interim analysis of this long-term, open-label extension study. Of these, 2928 subjects had at least 12 weeks of potential follow up in this study and were included in the ICOAS evaluated in this report; 1951 subjects were randomized to receive evolocumab plus standard of care (evolocumab group) and 977 were randomized to receive standard of care alone (control group). This interim analysis provides data for 1951 subjects with a total of 1066.5 patient-years of exposure to evolocumab.

Data from this interim analysis support the following conclusions on long-term treatment with evolocumab:

- Reductions of $\geq 50\%$ in LDL-C were observed and maintained in subjects receiving chronic administration of evolocumab during this extension study regardless of parent study treatment assignment (ie, evolocumab or control).
- Reductions in LDL-C and other lipid parameters at week 12 and week 24 are consistent with those at the end of the parent study for subjects who received evolocumab in the parent study, demonstrating a stable effect of evolocumab on lipid parameters with long-term use.
- Reductions in LDL-C and other lipid parameters are reversible upon cessation of treatment, with no evidence of rebound.
- At the beginning of the open-label extension study, approximately 30% subjects switched dosing regimens (Q2W and QM). Thereafter, few subjects switched between dosing regimens.
- Long-term treatment with evolocumab is well tolerated. The overall incidence of adverse events, grade 3 to 4 adverse events, and serious adverse events was generally similar between the evolocumab and control groups. The overall safety assessment of evolocumab was not changed after the review of the broad search strategy for events of interest.
- No trends indicative of clinically important treatment related laboratory abnormalities were observed. Anti-evolocumab binding antibody formation was rare; no neutralizing antibodies were detected.
- The overall incidences of cardiovascular endpoint events and non-coronary revascularizations were similar between the evolocumab and control groups.
- Administration of evolocumab with the AI/pen by self-administration in the home-use setting is safe and effective for its intended use and the conditions of use.

Based on the interim results of this study, chronic treatment with evolocumab Q2W or QM has a favorable benefit:risk profile and maintains reductions in LDL-C and improvements in other lipid parameters in subjects with primary hyperlipidemia or mixed dyslipidemia.

5. Clinical Development & Device Design Changes [COMPLETE]

Studies 20110168, 20120135, and 20120356 did not use the to-be-marketed AMD device. The device used in these studies is referred to as the “base device”. The to-be marketed AMD device was only used on a commercial configuration summative Human Factors Study. A transitional device between the base and commercial device was used in the clinical study 20120138.

Final data from 3 completed studies (20120135 [placebo only], 20110168 and 20120356) in the evolocumab clinical development program that used the automated mini-doser (AMD) were included in the supplemental biologics license application (sBLA) submitted to the FDA on 10 September 2015 (125522/Original 1/S-001, SN 0082). The AMD was also introduced into the ongoing, phase 3, long-term, open-label extension Study 20120138 in April 2014. Updated data provided herein include all available data from Study 20120138 with a data cut-off date of 02 April 2015. As of the data cutoff date, a total of 255 unique subjects have used the AMD in Study 20120138 to administer evolocumab; 95 subjects used the AMD during year 1 and 196 subjects during year 2+. It should be noted that some subjects may have used the AMD in both year 1 and year 2+, and therefore, the total number of subjects is not additive. Median (min, max) exposure to evolocumab using the AMD was 5.5 months (2.1, 9.0) in year 1 and 5.6 months (0.3, 11.8) in year 2+ of Study 20120138.

The device changes are further described in the Device Design Development Documentation in Module 3. The design changes were undertaken during development as a result of observations made during human factors studies, clinical trials and design verification testing. These **APPEARS THIS WAY ON ORIGINAL**

The consulting reviewer believes the device subsystem changes described by the sponsor in Table 1. Chronological Summary of Device Design Subsystem Changes (shown below) could affect the safety of the device as well as the drug delivery. The differences between the three generations of the device are shown in the table below:

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8. Device Design Validation Review [COMPLETE]

8.1. Intended User Population

The intended user of the AMD may be a patient, patient caregiver, or health care provider (HCP). The instructions for use (IFU) states patients and patient caregivers should receive training from their HCP prior to self-injecting. HCPs are provided with training tools to help instruct their patients and patient caregivers on how to use the device in a safe and effective manner.

Patient-Evolocumab patients fall into one indication category: individuals diagnosed with hypercholesterolemia. Patients in this indication category do not differ significantly from the general population in terms of experience with medical devices or physical, cognitive, or perceptual capabilities, nor do they exhibit particular physical, cognitive, or perceptual impairments.

Patient Caregiver-Caregivers are individuals who care for patients with special medical needs and are often parents, spouses, adult children, or professionals from a healthcare organization. Caregivers for patients with this indication do not differ significantly from the general population in terms of experience with medical devices or physical, cognitive, or perceptual capabilities, nor do they exhibit particular physical, cognitive, or perceptual impairments.

Healthcare Provider (HCP)-HCPs include doctors, nurses, device technicians, and medical assistants. Although demographic statistics are not available, HCPs are typically required to have a certain level of physical, cognitive, and perceptual attributes, such as adequate eyesight, dexterity, hearing and memory to perform their job functions. They have varying degrees of formal medical education and experience with medical devices. HCPs who prescribe evolocumab should be familiar with the drug attributes as well as the safety procedures for administration using injection devices. However, it is possible that some HCPs do not receive training on the proper drug safety and usage, including the AMD used to deliver the drug.

Known Use Problems

The known use problems for this type of device can be summarized as (1) failure to fully insert the cartridge and (2) shut the cartridge door completely.

8.2. Formative Human Factors/Usability Engineering Studies

Amgen performed seven human factors formative usability studies, a summative study and a supplemental summative study. Studies were performed with participants who are representative of the intended user population. Participants were observed to assess if performance and safety critical tasks using the AMD and device-interface could be completed safely and effectively. The table below shows a summary of the different human factors/usability studies.

Table 1. List of Human Factors/Usability Engineering Studies for AMD

Type of Study	Number of Participants	User Training	Key Learnings
Human factors engineering formative study #1	19	N/A	Some auditory and visual display feedback options were identified as more appropriate than others.
Human factors engineering formative study #2	19	N/A	Showed that, when directed, people were able to use the device appropriately. Identified one of the configurations as more comfortable than the others.
Human factors engineering formative study #3	26	Trained ^a and Self-Trained	Identified opportunities to simplify and clarify the device interface and the IFU.
Human factors engineering formative study #4	34	Self-Trained	IFU was optimized based the observations during this iterative study.
Human factors engineering formative study #5	28	Trained ^a and Self-Trained	The device is appropriate for clinical trials.
Human factors engineering formative study #6	29	Trained ^b and Self-Trained	Study results showed that there was no significant difference between the English IFU and its Spanish translation.
Human factors engineering formative study #7	10	Trained ^b and Self-Trained	All but one of the users were able to complete the simulated injection in an induced error situation.
Human factors engineering summative study	93	Trained ^c and Untrained	Product is safe and effective from a usability perspective.
Human factors engineering supplemental summative study	45	Self-Trained	Demonstrated that changes made post summative study did not negatively impact safe and effective use and improved the usability.

Self-Trained consisted of participants training themselves by reading the IFU before performing the tasks

Untrained consisted of participants receiving no moderator training.

^a Training consisted of review of IFU and demonstration of injection technique using a training unit

^b Training consisted of a demonstration of injection technique using a training unit

^c Training was performed by a Registered Nurse, based on the IFU

8.3. Summative Human Factors Usability Engineering Study

The purpose of the HFE/UE summative study was to validate the usability of the AMD by participants who are representative of the intended user population to safely and effectively use the device, along with the IFU (b)(4), to simulate the evolocumab administration procedure. The materials used for the study were representative of the intended

commercial configuration (b) (4) The use-related tasks that were in the scope of this study are included in Table 2.

Table 2. Task Priority for Summative Human Factors Usability Engineering Study

Step	Classification
Retrieve carton from storage.	Essential
Open carton.	Essential
Remove white paper cover (b) (4)	Essential
Remove plastic cover.	Essential
Wash hands.	Safety-Critical
Clean injection site with alcohol wipe	Safety-Critical
Remove device from clear tray.	Essential
Open cartridge door.	Essential
Remove cartridge from clear tray.	Essential
Inspect drug appearance.	Safety-Critical
Inspect cartridge for damage.	Safety-Critical
Check expiration date.	Safety-Critical
Clean cartridge bottom with alcohol wipe.	Safety-Critical
Insert cartridge in device.	Essential
Close cartridge door.	Essential
Peel off adhesive tabs (device activates)	Essential
Properly place device onto the (valid) injection site.	Essential
Press the start button.	Essential
Wait until injection has completed.	Essential
Remove device.	Essential
Discard device properly avoiding needle stick.	Safety-Critical

Essential steps are required in order to successfully complete an injection. Safety Critical steps are those which are associated with a safety risk with a severity rating of 5 or higher.

The summative study included 3 user groups consisting of adults diagnosed or working with those diagnosed with hypercholesterolemia. A 93-individual sample included patients (N = 31), caregivers (N = 31) and Healthcare Providers (N = 31) which represented the intended user population. Users were divided evenly into trained and untrained groups. For the trained group, a registered nurse trainer followed the IFU and highlighted the steps for device preparation, placement, monitoring, and removal. During training, the nurse held a device in hand and pointed to the device and sections of the IFU as appropriate, but did not demonstrate device functionality. Untrained users were provided with a kit as they would receive by the physician or pharmacy. All materials were available to them (eg, IFU, (b) (4) etc) and they could choose to use whatever materials they wanted to help them with the injection. However, these participants were not required to read the instructions prior to performing the injection as they may or may not read the instructions in the real world. Both trained and untrained users had all of the materials available throughout the injection task.

8.4. Supplemental Summative Human Factors/Usability Engineering Study

The purpose of the supplemental summative HFE/UE study was to validate that the changes made to the user interface post summative study do not negatively impact the safe and effective use and improve the usability of the device.

The following changes were made post summative study:

(b) (4)

(b) (4)

(b) (4) (b) (4)

- Instructions for Use (b) (4) illustrations were modified to address the changes described above, as well as enhanced instructions for hand washing, cleaning of injection site, cartridge insertion and door closing

These changes were evaluated for their impact on essential steps, safety critical step(s) and user needs. Participants were asked to perform task of removing the device from packing, inserting the cartridge, closing the door and detecting alarm and alert condition to evaluate the impacted essential steps and user needs. No safety critical step was impacted due to post summative changes. The study sample consisted of 45 participants from 3 user groups: Patients (N = 15), Caregivers (N = 15), and HCPs (N = 15). All participants self-trained by reading the IFU prior to the performance portion of the study.

Reviewer Comments

Design validation for the AMD consisted of HFE/UE studies that have been completed according to the validation master plan. The product has been validated from a use perspective by showing that all of the use-related safety risks have been successfully mitigated with acceptable residual risk as discussed in Device Risk Management Summary [AMD]. The AMD is considered safe and effective for use by the intended population to administer evolocumab.

(b) (4)

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13. Post Approval Studies [COMPLETE]

The Shelf Life testing was completed using accelerated aging technique to simulate (b) (4) shelf life for support of a 2 year shelf life. Amgen will need to provide real time aging device design verification data for the shelf life tests at intervals of 12 months and 24 months, including:

Device Function Test, Deliverable Volume Test, Injection Time test, (b) (4) Integrity test, (b) (4) Function test, and Shelf life adhesive function test.

These tests should be conducted using the same protocols used in the device verification test protocols.

14. CDRH General Comments to the Sponsor [COMPLETE]

Communicated in the February 25, 2016 IR Letter:

General Comment:

CDRH considers on-body medication delivery devices, like the automated mini-doser (AMD) used to deliver Repatha (evolocumab), to be a type of infusion pump. CDRH has issued a guidance document, "*FDA Guidance for Industry and Staff: Infusion Pumps Total Product Life Cycle*," outlining the types of information expected in a submission for an

infusion pump. Since the guidance issued on December 2, 2014, the Agency is expecting submissions for infusion pumps to contain an assurance case. However, we are not going to request that your device documentation be organized into an assurance case for this submission because of the many discussions between Amgen and FDA regarding the submission content for the Repatha AMD product, which preceded the issuing of the FDA infusion pump guidance document. Note that the evidence supporting safety and effectiveness of the device constituent parts must still be present within the submission such that Agency is able to adequately to make a risk/benefit determination. Future submissions for this product or other infusion pump devices of this type will need to address the recommendations contained in the referenced guidance document.

15. Review Summary and Recommendation for BLA 125522/S001 [COMPLETE]

CDRH performed a review of the device constituent of the combination product for BLA 125522/S001 for Amgen’s Automated Mini-Doser for on-body subcutaneous infusion of Repatha. The device consistent part of the combination product is an on-body infusion pump that delivers the entire contents of a pre-fill cartridge over 9 minutes. The device is controlled through software that directs a motor to slowly infuse the drug. There are colored flashing lights, which provide communication to the user (ie. Start, finish, error). Repatha is currently approved for subcutaneous injection using either a prefilled syringe or pen-injector.

The focus of this review is on the risk assessment and performance testing of the device risk including design verification, design validation, biocompatibility testing and software validation. The device underwent extensive testing to verify the device against specifications. The commercial iteration of the device passed all testing requirements, biocompatibility tests, and software validation. The risk assessment identified the critical aspects of the device and linked to test reports used to reduce the residual risk to an acceptable level.

The Shelf Life testing was completed using accelerated aging technique to simulate (b) (4) shelf life. Amgen will need to provide real time aging device design verification data for the shelf life tests, including:

Device Function Test, Deliverable Volume Test, Injection Time test, (b) (4) Integrity test, (b) (4) Function test, and Shelf life adhesive function test.

The shelf-life for the 120mg/mL prefilled cartridge co-packaged with the pump is 24 months stored at the recommended storage condition of 5°C. Additionally, to enhance convenience and facilitate dosing compliance, an optional short-term storage at room temperature (controlled, 25°C or less) of not more than 1 month is supported after removal from storage at 5°C.

Section	Status	Deficiencies	Status
Review of Device Materials	Complete & Acceptable	none	-
Relevant Clinical Studies	Complete & Acceptable	none	-
Clinical Development & Device Design Changes	Complete & Acceptable	D5.1.	Resolved
		D5.2.	Resolved
		D5.3.	Resolved
Device Risk Management	Complete & Acceptable	D6.1.	Resolved
Device Design Verification**	Complete & Acceptable	D7.1.	Resolved
		D7.2.	Resolved
		D7.3.	Resolved
Device Design Validation	Complete & Acceptable	none	-

Biocompatibility Review	Complete & Acceptable	D9.1.	Resolved
		D9.2.	Resolved
Software Review	Complete & Acceptable	D10.1.	Resolved

CDRH recommends that the device constituent part of the combination product for BLA 125522/S001 is appropriate for the intended use of subcutaneous infusion of Repatha. There are no device concerns that would prevent approval of BLA 125522/S001. Amgen will have to provide real time aging shelf-life testing as it becomes available for review. The accelerated aging tests simulated (b) (4) under refrigerated conditions as well as storage for a limited time (1 month) at room temperature. The labeled expiry date for the device constituent of the combination product is 24 months.

The batch lot release for the on-body infusor for Repatha is below:

Table 2. 120 mg/mL Automated Mini-Doser Drug Product Specification

Parameter	Test Method	Method Type	Acceptance Criteria
General - device functionality	Deliverable volume	Gravimetric	Pass (≥ 3.5 mL)

16. Proposed Deficiencies/Comments for the BLA 125522/S001 Sponsor [NONE]
 None

17. Concurrence Table

Digital Concurrence	
CDRH Lead Reviewer	
Branch Chief	

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/s/

KATI JOHNSON
06/30/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 27, 2016

To: Kati Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

BLA 125522 / S-001 REPATHA (evolocumab) injection, for subcutaneous use

On September 21, 2015, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU) for Repatha. OPDP's review of the proposed draft PI was based on the version sent via email by Kati Johnson on June 27, 2016, and is provided below. We have no comments on it at this time.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the PPI and IFU under separate cover.

If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov. Thank you for the opportunity to comment on these materials.

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/s/

ANKUR S KALOLA
06/27/2016

HUMAN FACTORS, LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: June 8, 2016
Requesting Office or Division: Division of Metabolic and Endocrine Products
Application Type and Number: BLA 125522 S-001
Product Name and Strength: Repatha
Product Type: Combination Product
Rx or OTC: Rx
Applicant/Sponsor Name: Amgen
Submission Date: September 10, 2015
OSE RCM #: 2015-2109 and 2016-584
DMEPA Primary Reviewer: Hina Mehta, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD
**DMEPA Acting Associate
Director for Human Factors:** QuynhNhu Nguyen, MS
DMEPA Deputy Director: Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

The Division of Metabolism and Endocrinology requested DMEPA to evaluate the results of the Human Factors Study (HFS), container label, carton labeling, Prescribing Information, Instructions for Use, and (b) (4) for Repatha (evolocumab) prefilled cartridge and automated mini-doser, BLA 125522 S-001, submitted on September 18, 2015.

1.1 REGULATORY HISTORY

BLA 125522 for Repatha (evolocumab) injection pre-filled syringe and Repatha SureClick (evolocumab) injection pre-filled autoinjector was approved on August 27, 2015. Repatha is administered at a dose of 140 mg once every two weeks or 420 mg once a month. The Applicant is proposing a new pre-filled cartridge co-packaged with an automated mini-doser administration device for their product line so the 420 mg dose can be delivered without the need for multiple injections.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTORS STUDIES

The Applicant conducted two human factors studies for the Repatha pre-filled cartridge and automated mini-doser: validation human factors study and supplemental human factors study. During validation human factors study, multiple failures occurred with various tasks (See Section 3.2 and Appendix C). As a result, the Applicant modified the device and instruction

materials and tested the modified device and instructional materials in the human factors supplemental study to ensure the revisions were effective in addressing use errors observed in the previous study and did not introduce any new errors. The results of both studies are summarized below.

In the validation and supplemental human factors studies, the Applicant categorized the tasks as follows:

- Essential: tasks necessary for the successful use of the device for its intended purpose. Our evaluation indicates that failures of these tasks (e.g. insert cartridge into device, closing cartridge door) may result in underdoses and missed doses. Therefore, our review focused only on the errors occurred with these tasks.
- Safety critical: tasks associated with potential use errors that could lead to a significantly clinical impact. Our evaluation indicates that failure of these tasks does not necessarily affect safe administration of a dose of Repatha using the automated mini-doser (e.g., washing hands, cleaning injection site with alcohol wipe, inspecting drug appearance, inspecting cartridge for damage, checking expiration date, cleaning cartridge bottom with alcohol wipe, discarding device properly avoiding needle stick). Although we agree with the Applicant that these tasks may be safety-critical, we note that these tasks are not unique for this particular product and apply to other injectable product that are already in the market and require these steps. After considering the interface, including labeled instructions, between the proposed product and similar products and known use errors for these tasks, we determined that the residual risk is acceptable and we do not recommend any further risk mitigation strategies for these steps. Therefore, our review focuses on tasks that are unique to the proposed product.
- Non-essential/non-safety critical: tasks that are not crucial for successful use of the device (e.g., wait 45 min to reach room temperature, gather supplies, check the medicine window, check that green light turned off, examine injection site). We agree with the Applicant's definition of these tasks as they are not crucial in terms of being able to administer a correct dose and will not result in significant clinical harm.

3.2 Human Factors Validation Study

Repatha Automated Mini-Doser (AMD)

The study was conducted with 93 representative users (31 patients, 31 caregivers, and 31 healthcare providers) with about half trained and half un-trained (please refer to Appendix C for the study details). We noted in the study prior to administering the first testing scenario, the moderator advised the participants on the injection site and a skin pad was secured to the

assigned location. In the actual use environment, we expect that this patient population will typically receive training and therefore be advised on the injection site from their health care providers prior to use since there are currently no marketed electro-mechanical on-body injectable therapies for this indication (primary hyperlipidemia, mixed dyslipidemia, homozygous familial hypercholesterolemia).

Table 2 below lists the essential tasks where failures occurred and the number of participants that failed the tasks. A total of 30 use errors were associated with the essential tasks. They are described in additional details below.

<u>Table 2: List of all essential tasks where failures occurred and number of participants that failed the task</u>	
<u>Task</u>	<u>Number of participants committing error</u>
Opening the cartridge door*	4
Inserting cartridge in device*	3
Closing cartridge door*	12
Peeling off adhesive tabs	2
Properly place device onto the (valid) injection site	2
Press the start button	4
Wait until injection has completed	3

* Tasks retested in the supplemental study (discussed in section 3.2)

Error in opening the cartridge door (3 errors by 2 untrained participants and 2 errors by 2 trained participants)

- The four participants (one participant committed this error twice) inadvertently closed the cartridge door while performing other tasks. (b) (4)

[Redacted text block containing seven lines of greyed-out information]

We note that this task was retested in the supplemental study.

Failed to Insert cartridge into the device (1 error by 1 untrained participant (same participant that committed two errors in the open cartridge door task) and 2 errors by 2 trained participants)

- One untrained caregiver inadvertently closed the door during the process of inserting the cartridge (discussed above).
- One trained healthcare professional did not push the cartridge in all the way and forced the door close during two attempts of the first scenario. This was done because the individual did not recall the explanation during the training and did not remember reading about it in the IFU. Without properly inserting the cartridge in device the correctly users would not be able to proceed as the door would not be able to be closed.
- One trained healthcare professional removed the cartridge top when inserting the cartridge into the device. The individual did not use the IFU and thought the top was like a cap like those in syringes at work.
- Our evaluation of the root cause analysis indicates the errors were not related to the product user interface. If the user fails to insert the cartridge into the device, they cannot proceed with further steps. The user will need to figure out how to properly insert the cartridge by referring to the IFU, this type of error may result in delayed therapy. Our review of the IFU indicates that it should be modified to call out the users' attention to properly perform this task. We recommend that the Applicant move the statement "Do not remove or rotate the cartridge (b) (4) top or bottom" to the first bullet in step 2C of the IFU. Of note, the Applicant changed the IFU by replacing (b) (4) with "press down firmly" in step 2D to mitigate this error. We also recommend

(b) (4)

We note that this task was retested in the supplemental study.

Did not completely close cartridge door (8 errors by 7 participants (1 participant was the same one that made errors in the two tasks listed above) and 5 errors by 5 trained participants)

- In all but one of the instances the participants did not completely close the cartridge door and believed it was closed. In some instances the plunger came down to fill the medicine window and in others it did not.

- There were three participants (all untrained caregivers) that did not detect the alarm and thought the injection was completed, two of which were [REDACTED] (b) (4) [REDACTED]. One of these caregivers made this error on two attempts however they did detect the alarm on the second attempt. All of the other participants that made this error did detect the alarm.
- One untrained caregiver intentionally closed the door before inserting the cartridge on the second attempt then forced the cartridge door open while the device was already attached to the skin pad and pumping in order to insert the cartridge. This participant committed this error as they were [REDACTED] (b) (4) [REDACTED].

We noted that in all the cases, failure to close the cartridge door generated the alarm/alert. We note that only one participant referred to the full IFU. Therefore these errors could be attributed to participants only [REDACTED] (b) (4) [REDACTED] while performing the tasks. Our review also indicates that use performance with the untrained group was worse than the trained group. As a result of these errors, the Applicant changed the IFU to list the closing of the cartridge door as its own step and added “squeeze tight” at the depiction of this step in the IFU. These changes were tested in the supplemental human factor study which is discussed in Section 3.2 below. Our review of the IFU indicates that adding an additional statement such as “Apply enough pressure when closing the door and make sure a snap is heard before proceeding” to step 2E can further clarify this task. We also recommend [REDACTED] (b) (4) [REDACTED]

Failure to completely peel off adhesive tab (device activates) (2 errors by 2 untrained participants)

- The patient participant removed the entire adhesive by ripping it off. The participant was not using the IFU [REDACTED] (b) (4) [REDACTED] during the simulation and assumed this is the way it was supposed to be done.
- The healthcare professional participant did not completely peel off the small adhesive tab as the participant encountered resistance and believed something was wrong with the device as a result stated they would not use the device. The participant was using the IFU.

We can attribute these errors to pre-existing notions of the participants that when tabs are seen the thought is to pull them off sometimes too abruptly. Our review of the IFU indicates that adding the statement such as “Do not pull the skin adhesive backing off the

(b) (4)" as the first bullet in step 3A to increase clarity on how to perform this task.

Failure to place device onto (valid) injection site in a correct orientation (2 errors by 2 untrained participants, one of which was the same participant that made an error in the peel off adhesive tab task)

- The patient participant was orienting the device with the start button pressing against the skin pad and their finger on the needle door during placement. The moderator intervened to avoid a potential needle stick. The participant corrected the orientation (b) (4).
- The healthcare professional participant placed the device on the skin pad with the light facing down and then peeled it off and repositioned it with the light facing up. The participant was confused because they thought (b) (4) was not clear.

The root cause analysis indicates that these errors were resulted from the participant's unfamiliarity with the device. We recommend that training should be provided to all users before their first use.

Press the start button prior to placing the device on the injection site and prior to inserting the cartridge (3 errors by 3 untrained participants (one of which was the same participant that made errors in close the door, insert cartridge, and open the door tasks) and 1 error by 1 untrained participant which was the same participant that made an error in close the cartridge door task)

- The untrained patient pressed the start button prior to placement of the device on the skin pad after removing the adhesive tabs. The participant was exploring the device as they were reading the IFU and did not realize you can only press the button once.
- One untrained participant pressed the start button prior to placement of the device on the skin pad after removing the adhesive tabs. The participant was not using the IFU (b) (4) and believed that is what was supposed to be done to use the device.
- One untrained caregiver pressed the start button after placing the device on the skin pad but without inserting the cartridge. This was in the second attempt at the simulated injection scenario. This participant committed this error as they were using (b) (4).
- One trained caregiver during session 1 pressed the start button prior to placement on the skin pad due to a cognitive failure. The participant placed the device on the skin pad and was unaware of what caused the error alarm/alert after detecting it.

The root cause analysis indicates that these errors were resulted from participant's unfamiliarity with the device, incorrectly using the reference materials, and lack of re-call.

Did not wait until injection has completed (1 error by 1 untrained participant and 2 errors in 2 trained participants)

- One untrained caregiver did not wait for the injection to complete because they did not know it took 9 minutes. The participant removed the device quickly after the injection began because of pre-conceived notion that it was like a traditional shot. The participant also saw the flashing green light so they were thinking it was complete, as they [REDACTED] (b) (4).
- One trained healthcare professional did not wait for the injection to complete removing the device 2 minutes into the injection. The participant did not see the plunger advancing in the window and thought the device was malfunctioning. This error occurred during the second session as the participant thought that during the first scenario they saw the plunger after about a minute. The participant also thought there may be a problem because she saw a red light flash during the startup cycle (after tab removal). The error alarm/alert was detected.
- One trained healthcare professional did not wait for the injection to complete and removed the device toward the end of the 9 minute injection. The participant thought the medicine window was completely filled by the plunger so the dose was completely delivered.

The root cause analysis indicates that the participants misinterpret the device feedback (for example, the flashing green light, the plunger rod advancing in the dose window). Our review of the IFU indicates that it does not sufficiently describe the device feedback that the users should be aware. As a result, we recommend adding “Plunger completely fills medicine window” as a bullet in Step 3E and bolding “solid green” to ensure users do not miss this important information.

3.2 SUPPLEMENTAL HUMAN FACTORS STUDY

Due to the errors that occurred in the validation human factors study, the Applicant made changes to the user interface and IFU [REDACTED] (b) (4). The changes were as follows: [REDACTED] (b) (4)

[REDACTED] and modified IFU [REDACTED] (b) (4)

[REDACTED] to address errors that occurred in the summative study. We note that this supplemental study only focused on evaluating those changes initiated by the Applicant and only evaluated a subset of the user tasks which include the following: retrieve carton from storage, open carton, remove white paper cover, remove plastic cover, remove device from clear tray, open cartridge door, remove cartridge from clear tray, insert cartridge in device, and close cartridge door.

Discussed below are the two tasks evaluated in which an error occurred.

Inadvertent closure of the cartridge door (one error by caregiver)

The caregiver closed the door while attempting to open it but realized the mistake and stated they would call the support line for help. The caregiver was given a second device to perform the simulation and exhibited successful performance with the second device. The participant reported being nervous and indicated that they interpreted the IFU as instructing to press on the right side of the cartridge door (as opposed to swinging the door to the right). The participant thought the door would act like a medicine cabinet (by pushing the door in to release the lock and then open). This same error was seen in the validation study, and therefore, our recommendation remains unchanged that the Applicant should add this statement [REDACTED] (b) (4)

Close the cartridge door (one error by patient)

The error of closing the cartridge door was done by a patient as they did not apply enough pressure for it to lock shut and then went on to the next step. The participant did not think any mistakes were made. The patient was told the door was not closed properly at which point the participant stated they “didn’t finish” and knew that it clicks when shut. The participant then demonstrated the ability to perform this step successfully by snapping the door closed. Additional information provided by the Applicant on the cartridge door design concludes that a [REDACTED] (b) (4)

[REDACTED] causing the alarm when the door is not fully closed. [REDACTED] (b) (4)

[REDACTED] The device has a viewing window allowing the user to see the pre-filled cartridge and to confirm [REDACTED] (b) (4) position after the device is removed from the body as instructed in the IFU. This same error was seen in the validation study, and therefore, our recommendation remains unchanged that the Applicant should add this statement “Apply enough pressure when closing the door and make sure a snap is heard before proceeding” to step 2E of the IFU to ensure the door is closed all the way prior to proceeding.

3.3 LABELS AND LABELING

In addition to the human factors study evaluation, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We noted that the container labels, carton labeling, Prescribing Information, and Instructions for Use for Repatha pre-filled cartridge and automated mini-doser can be improved to increase the readability and prominence of important information, to promote the safe and effective use of the product, to mitigate any confusion, and to clarify

information. We defer to Pharmaceutical Quality/CMC for appropriateness of the term “single use” on the labels and labeling. We provide recommendations in Section 4.1 for the Prescribing Information and 4.2 for the Instructions for Use, container label, and carton labeling to address the concerns.

In summary, DMEPA expects that patients, caregivers, and health care professionals will be able to use Repatha pre-filled cartridge and automated mini-doser safely and effectively when training is provided and training materials (i.e., Instructions for Use) are available for review.

4 CONCLUSION & RECOMMENDATIONS

The results of the human factors validation study and the supplemental validation study indicate that there are several areas of improvements necessary with respect to the IFU. The improvements suggested are to enhance key information already in the IFU or add additional information for further clarity. In addition, the proposed container labels and carton labeling can be improved to increase the readability and prominence of important information. Finally, we recommend (b) (4)

[Redacted text block]

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this supplement.

1. Highlights of Prescribing Information, Dosage and Administration
 1. The ability to administer the 420 mg dose via the automated mini-doser needs to be added to the bullet on administering this dose. For example:
 - “To administer the 420 mg dose, give 1 Repatha injection using the automated mini-doser with the pre-filled cartridge. Alternatively give 3 Repatha injections using the autoinjector or pre-filled syringe consecutively within 30 minutes.”

2. (b) (4)

[Redacted text block]

4.2 RECOMMENDATIONS FOR AMGEN

We recommend the following be implemented prior to approval of this supplement:

Instructions for Use:

1. In Section 2A of "Step 2: Get Ready" we recommend adding [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
2. In Section 2C of "Step 2: Get Ready" we recommend moving to the first bullet the statement "Do not remove or rotate the cartridge [REDACTED] (b) (4) top or bottom" in order to mitigate this error seen in the Human Factors study.
3. In Section 2E of "Step 2: Get Ready" we recommend adding "Apply enough pressure when closing the door and make sure a snap is heard before proceeding."
4. In Section 3A of "Step 3: Inject" we recommend moving to the first bullet the statement "Do not pull the skin adhesive backing off the [REDACTED] (b) (4)" in order to mitigate this error seen in the Human Factors study.
5. In Section 3E of "Step 3: Inject" we recommend adding "Plunger completely fills medicine window" as a bullet and bolding "solid green" in the sentence "The status light turns solid green, and the device beep...". This is recommended in order to mitigate the error seen in the Human Factors study where participants did not wait for the injection to completely finish.
6. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Container Label and Carton Labeling:

- A. Carton Labeling (Dispensing Carton and Replacement Carton)
 1. Replace the Proprietary name for the prefilled cartridge co-packaged with an automated mini-doser administration device with the conditionally accepted name throughout all carton labeling.
 2. Please consider changing the color scheme on carton labeling [REDACTED] (b) (4)
[REDACTED]
[REDACTED].

3. Increase the font size of the strength as currently displayed it is not prominent and may be overlooked.
4. Place the strength under the icon of the device on the Principal Display Panel and all side panels to increase readability of this important information.
5. Revise the storage information statement to “Store refrigerated at....” on the Principal Display Panel. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked and to be consistent with the side panel.
6. On the side panel for the patient/caregiver storage instructions add “Discard after 30 days”. We recommend “Discard after” since it is an affirmative statement, and has been shown to result in the desired action.

(b) (4) add “ __/__/__ ” to allow users to fill in the actual date. Also, revise the statement (b) (4) (b) (4) to read “Write the date removed from the refrigerator”.

B. Container Label

1. (b) (4) Label
 - i. Replace the name on the (b) (4) label with the conditionally acceptable name of the device. For example:

On-body Infusor for
 Repatha
 (evolocumab)
 420 mg/3.5 mL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Repatha automated mini-doser that Amgen submitted on September 10, 2015.

Table 2. Relevant Product Information for Repatha pre-filled cartridge and automated mini-doser and Repatha PFS/Repatha SureClick		
Product Name	Repatha	Repatha PFS/Repatha SureClick
Initial Approval Date	Pending	August 27, 2015
Active Ingredient	evolocumab	
Indication	Adjunct to diet and: <ul style="list-style-type: none"> • Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of low density lipoprotein cholesterol (LDL-C) • Other low density lipoprotein lowering therapies (e.g. statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL-C 	
Route of Administration	Subcutaneous injection	
Dosage Form	Solution for injection	
Strength	420 mg/3.5 mL	140 mg/mL
Dose and Frequency	Primary hyperlipidemia with established clinical atherosclerotic CVD or heterozygous familial hypercholesterolemia: <ul style="list-style-type: none"> • Administer 140 mg every 2 weeks, or • 420 mg once monthly in the upper arm, thigh, or the abdomen Homozygous familial hypercholesterolemia:	

	Administer 420 mg either once monthly.	
How Supplied	Repatha 420 mg/3.5 mL pre-filled cartridge and automated mini-dose: supplied as a 1-pack, 120 mg/mL single-use automated mini-doser with prefilled cartridge	Repatha 140 mg/mL single-use prefilled syringe: supplied as a 1-pack, 1 ml of a 140 mg/mL solution of evolocumab Repatha SureClick 140 mg/mL single-use prefilled autoinjector: supplied as a 1-pack, 2-pack, and 3-pack, 1 ml of a 140 mg/mL solution of evolocumab
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. For patients/caregivers: If removed from the refrigerator, Repatha should be kept at controlled room temperature (up to 25°C [77°F]) in the original carton and must be used within 30 days. Protect Repatha™ from direct light and do not expose to temperatures above 25°C (77°F). Do not freeze. Do not shake.	

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 13, 2016, we searched the L:drive and AIMS using the terms, Repatha to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews relevant to this review.

APPENDIX C. HUMAN FACTORS STUDIES

C.1 Study Design

The Human Factors Study Results and IFU for Repatha Automated Mini-Doser submitted on September 10, 2015 were evaluated. Below is a brief overview of the study objectives, description of the study participants, study design, data collection, and data analysis. The study evaluated all the tasks necessary for the injection process (e.g. activating the device and administering a dose).

Study Objectives

- To validate essential and safety-critical steps to demonstrate that the device can be safely and effectively operated by the intended user population
- To validate that users can read, comprehend and properly use the packaging, package and device labeling, Instructions for Use (IFU) (b) (4) to safely and effectively operate the device and its constituent components
- Evaluate the impact of learning decay for the trained participants
- To validate satisfaction of use needs identified for the Human Factors validation study
- To ensure that use error identified during the risk management process and during formative human factor studies are eliminated or their frequency reduced to an acceptable level

Study Participants

Table 1 provides information on the study participants and demographics

Table 1. Distinct End User Groups			
User Groups	Trained (Return session)	Untrained (Single session)	Total
Patients Age ranged from 31 to 79 years old 2 patients had color blindness	3 injection experienced	4 injection experienced*	7
	13 injection naïve	11 injection naïve	24
Total	16	15	31
Caregivers Age ranged from 24 to 78 years old 4 caregivers had color blindness	9 injection experienced	9 injection experienced	18
	7 injection naïve	6 injection naïve	13

Total	16	15	31
HCPs Age ranged from 25 to 69 years old 1 health care professional had color blindness	16 injection experienced	15 injection experienced	31
	0 injection naïve	0 injection naïve	0
Total	16	15	31
Total	48	45	93

**1 untrained caregiver and 1 untrained health care professional were withdrawn (caregiver was unwilling to perform scenario without assistance and was assessed not to be representative of device’s intended user population and health care professional was deceptive regarding credentials and occupation)

Training and Testing Sessions

Half of the participants (n=48) received training from a registered nurse based on the IFU (b) (4). The nurse trainer followed the IFU and highlighted the steps for device preparation, monitoring, and removal. The nurse held the device in hand and pointed to the device and sections of the IFU as appropriate but did not demonstrate device functionality. After the training walk-through the nurse trainer left the testing room for the remainder of the simulated injection scenario. The trained participants returned a minimum of 5 days later for a second study session lasting up to 1 hour to assess learning decay. Half the participants (n=45) did not receive training and went directly into the simulated injection scenario.

All participants were asked to perform a simulated injection. They were told to imagine the doctor advised them on the injection site to use, and a skin pad was secured to the assigned location of injection. Half the patients performed the simulated injection into a skin pad attached to their abdomen and the other half performed in into a skin pad attached to their thigh. For caregivers and HCP’s site location was the abdomen, thigh, or arm of a mannequin. The device was validated against the essential, safety-critical, and non-essential/non-safety critical steps:

- Essential steps: tasks/steps necessary for successful use of the device for its intended purpose (i.e. successfully administer a full dose)
- Safety critical steps: tasks/steps associated with potential use errors that could lead to a significantly clinical impact (a severity rating of 5 or higher)
- Non-essential/non-safety critical steps were evaluated as part of the overall workflow and did not have an impact on the overall success

Data Collection and Analysis

Performance success and failure in completing the injection were scored as either:

- Success: participant was able to deliver a complete dose and perform the injection without harm to themselves or others
- Fail: participant was unable to deliver a complete dose or perform the injection without harm to themselves or to other

Each individual step in the process (essential, safety-critical or otherwise) of performing an injection was evaluated as success or failure and further qualified into these categories:

- Use Error: A case in which a user committed an action (or omitted an action) that could potentially lead to harm and/or not receiving the prescribed therapy
- Close Call: A case in which a user almost committed a use error, but “caught” him or herself in time to avoid making the use error
- Operational Difficulty: A case in which a user appeared to struggle to perform a task

Study Limitations (per Applicant)

During data collection 3 devices appeared to malfunction:

- 1 trained patient appeared to operate the device as intended, but the device generated an error/alarm at the end of the 9-minute injection (Note: the plunger DID NOT come down and fill the medicine window during the 9-minute injection)
- 1 trained patient appeared to operate the device as intended, but the device generated an error/alarm at the end of the 9-minute injection (Note: the plunger DID NOT come down and fill the medicine window during the 9-minute injection)
- 1 trained caregiver appeared to operate the device as intended, but the device generated an error/alarm after the small adhesive tab was removed

C.2 Results

Overview:

- 14 out of 45 (31%) untrained participants committed at least (5 patients, 6 caregivers, 3 HCP’s) one use error on an essential step
- 5 out of 48 trained (10%) participants (1 patient, 2 caregivers, 2 HCP’s) committed a use error during session 1
- 6 out of 48 trained (12%) participants (2 patients, 2 caregivers, 2 HCP’s) committed a use error during session 2 (none of these participants committed a use error on an essential step during session 1)

Table . Success Rate on Essential Steps (Session 1 and 2) = 30 participants made errors			
Essential Step	Untrained (session 1)	Trained (session 1)	Trained (session 2)
Retrieve carton from storage	45/45 (100%)	48/48 (100%)	48/48 (100%)
Open carton	45/45 (100%)	48/48 (100%)	48/48 (100%)
Remove white paper cover (b) (4)	45/45 (100%)	48/48 (100%)	48/48 (100%)
Remove plastic cover	45/45 (100%)	48/48 (100%)	48/48 (100%)
Remove device from clear tray	45/45 (100%)	48/48 (100%)	48/48 (100%)
Open cartridge door	43/45 (96%)	48/48 (100%)	46/48 (96%)
Remove cartridge from clear tray	45/45 (100%)	48/48 (100%)	48/48 (100%)
Insert cartridge in device	44/45 (98%)	46/48 (96%)	48/48 (100%)
Close cartridge door	38/45 (84%)	45/48 (94%)	46/48 (96%)
Peel off adhesive tabs (device activates)	43/45 (96%)	48/48 (100%)	48/48 (100%)
Properly place device onto the (valid) injection site	43/45 (96%)	48/48 (100%)	48/48 (100%)
Press the start button	42/45 (93%)	47/48 (98%)	48/48 (100%)
Wait until injection has completed	44/45 (98%)	48/48 (100%)	46/48 (96%)
Remove device	45/45 (100%)	48/48 (100%)	48/48 (100%)

Table . Failures Observed on Essential and Safety Critical Steps During First and Second Visits								
Task E-essential; SC=safety critical; N=non-essential & non-safety essential	Session #	Trained (Attended 2 sessions)			Untrained (Attended 1 session)			Total Errors
		Patients	Caregivers	HCPs	Patients	Caregivers	HCPs	
Retrieve carton from storage (E)	Session 1	0	0	0	0	0	0	0
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	0	0	0	0

Wait 45 minutes to reach room temperature (N)	Session 1	3	3	6	5	4	1	22
	Session 2	1	0	1	N/A	N/A	N/A	2
Total Errors – Sessions 1 & 2		4	3	7	5	4	1	24
Open carton (E)	Session 1	0	0	0	0	0	0	0
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	0	0	0	0
Remove white paper cover- (b) (4) (E)	Session 1	0	0	0	0	0	0	0
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	0	0	0	0
Remove plastic cover (E)	Session 1	0	0	0	0	0	0	0
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	0	0	0	0
Gather supplies (N)	Session 1	0	0	0	0	0	0	0
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	0	0	0	0
Wash hands (SC)	Session 1	4	1	1	6	3	1	16
	Session 2	1	0	0	N/A	N/A	N/A	1
Total Errors – Sessions 1 & 2		5	1	1	6	3	1	17
Clean injection site with alcohol wipe (SC)	Session 1	1	2	1	11	6	5	26
	Session 2	0	1	0	N/A	N/A	N/A	1
Total Errors – Sessions 1 & 2		1	3	1	11	6	5	27
Remove device from clear tray (E)	Session 1	0	0	0	0	0	0	0
	Session 2	0	0	0	N/A	N/A	N/A	0

Total Errors – Sessions 1 & 2		0	0	0	0	0	0	0
Open cartridge door (E)	Session 1	0	0	0	1	1	0	2
	Session 2	1	1	0	N/A	N/A	N/A	2
Total Errors – Sessions 1 & 2		1	1	0	1	1	0	4
Remove cartridge from clear tray (E)	Session 1	0	0	0	0	0	0	0
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	0	0	0	0
Inspect drug appearance (SC)	Session 1	1	1	0	9	11	3	25
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		1	1	0	9	11	3	25
Inspect cartridge for damage (SC)	Session 1	1	1	0	11	12	6	31
	Session 2	0	1	0	N/A	N/A	N/A	1
Total Errors – Sessions 1 & 2		1	2	0	11	12	6	32
Check expiration date (SC)	Session 1	2	3	4	14	13	9	45
	Session 2	0	1	3	N/A	N/A	N/A	4
Total Errors – Sessions 1 & 2		2	4	7	14	13	9	49
Clean cartridge bottom with alcohol wipe (SC)	Session 1	1	2	1	1	2	1	8
	Session 2	3	2	2	N/A	N/A	N/A	7
Total Errors – Sessions 1 & 2		4	4	3	1	2	1	15
Insert cartridge in device (E)	Session 1	0	0	2	0	1	0	3
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	2	0	1	0	3
Close cartridge door (E)	Session 1	1	2	0	2	4	1	10
	Session 2	1	1	0	N/A	N/A	N/A	2

Total Errors – Sessions 1 & 2		2	3	0	2	4	1	12
Peel off adhesive tabs-device activated (E)	Session 1	0	0	0	1	0	1	2
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	1	0	1	2
Properly place device onto the (valid) injection site (E)	Session 1	0	0	0	1	0	1	2
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	1	0	1	2
Press the start button (E)	Session 1	0	1	0	1	2	0	4
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	1	0	1	2	0	4
Wait until injection has completed (E)	Session 1	0	0	0	0	1	0	1
	Session 2	0	0	2	N/A	N/A	N/A	2
Total Errors – Sessions 1 & 2		0	0	2	0	1	0	3
Remove device (E)	Session 1	0	0	0	0	0	0	0
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	0	0	0	0
Check medicine window (N)	Session 1	4	2	2	5	2	4	19
	Session 2	4	0	1	N/A	N/A	N/A	5
Total Errors – Sessions 1 & 2		8	2	3	5	2	4	24
Check green light turned off (N)	Session 1	6	4	5	6	6	10	37
	Session 2	6	6	4	N/A	N/A	N/A	16
Total Errors – Sessions 1 & 2		12	10	9	6	6	10	53

Examine the injection site (N)	Session 1	0	0	1	3	3	2	9
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	1	3	3	2	9
Discard device properly avoiding needle stick (SC)	Session 1	0	1	0	4	4	1	10
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	1	0	4	4	1	10
Total Errors – All Tasks		41	36	36	81	75	46	315

Essential steps = 30 participants made errors in simulated injection scenario (additional 5 errors in essential steps occurred in simulated error/alarm scenario)

Safety Critical steps = 175 participants made errors

Non-essential and non-safety critical steps = 110 participants made errors

Error Alarm/Alert Detection Scenario

After the simulated injection scenario all participants were asked to perform a simulated device error scenario. For this scenario, the study moderator placed an AMD on the skin pad secured to the assigned injection site and started the injection. Participants were asked to monitor the injection until the injection is completed, and evaluated for their ability to detect the end of a successful injection via the solid green light and hazard alarm via the flashing red light. To effectively test the hazard alarm, devices used for this particular scenario were modified to trigger the alarm, which would occur at some point within the 9 minute injection.

Deviations

- Total of 3 participants did not complete the simulated device error scenario on the first day of data collection due to failed simulations and a limited supply of extra devices at that time. The failed simulations were determined to be the result of a manufacturing inconsistency of the skin pads used by these particular participants (the outer rubber layer was substantially thicker than the other of the same model), and these specific skins pads were set aside and not used for the remainder of the study.
- The participants were provided with cold cartons directly from the refrigerator for the simulated device error scenario (as recommended by Amgen staff) to increase the likelihood of simulating the device failure to test alarm/alert detection.
- 10 participants were not asked to perform the simulated device error scenario because they were exposed to the error/alarm while performing the simulated injection. 9 out of 10 were the result of a use error on an essential step by the participant and one was the result of an apparent device malfunction.

Results

- 6 out of 45 untrained participants did not detect the error/alarm (4 participants thought red alarm light meant injection was complete)
- 39 out of 45 (87%) untrained participants were successful
- 2 out of 45 trained participants did not detect the error/alarm
- 43 out of 45 (96%) trained participants were successful

6 out of 45 untrained participants did not detect the error/alarm (2 patients and 4 caregivers)

- One patient perceived the red flashing light error but did not comprehend its meaning. This participant did not read past step (b) (4) in the IFU. The participant did realize the injection was not being administered but thought the device was reusable and repeatedly attempted to open the cartridge door in order to replace the cartridge.

- Two caregivers thought the red flashing light meant injection was complete. They only referred to the (b) (4).
- One caregiver thought the red flashing light meant injection was complete. The participant looked at the IFU and stated the injection took 9 minutes and filled the injection window.
- One caregiver thought the red flashing light meant injection complete. The participant acknowledged the injection did not last 9 minutes and indicated that information on the red light was not in the IFU. During root cause analysis the participant was showed the troubleshooting section in the IFU and demonstrated comprehension of the meaning and purpose of the light.
- One caregiver perceived the red flashing light but did not realize it meant an error occurred. The participant was using the (b) (4) during the simulation and mentioned being nervous.

2 out of 45 trained participants did not detect the error/alarm (2 caregivers)

- One caregiver did not notice the flashing red light or beeping. The participant went on to dispose the device and then stated they did not check the medicine window. During root cause analysis the participant was shown the device and saw that the plunger did not fill the medicine window at which point they stated they would call the phone number in the IFU for help.
- One caregiver did not detect the error alarm/alert. The participant was shown the device during the root cause analysis and then noticed the red light and indicated they would call the number in the IFU for help. The participant reported being nervous and stated they would go slower at home.

We can attribute these errors to only using the (b) (4) and unfamiliarity with the device.

Supplemental Summative Study

A supplemental human factors study was conducted to validate relevant changes to the user interface (UI) since the summative study was conducted. The changes are as follows:

- (b) (4)
- Instructions for Use (b) (4) updated (modified illustrations to address the above, as well enhanced instructions for cartridge insertion, door closing, hand washing, and cleaning of injection site)

Participants were self-trained as they were asked to read the IFU prior to the performance of the study.

Study Objectives

- Validate the essential steps impacted by changes to the UI since the summative study, demonstrating that the device can be effectively operated by the intended user population to deliver a complete dose without patterns of use errors, close calls or foreseeable misuse that would result in unacceptable harm to a patient or other user from either the device or its constituent components. Note, no safety-critical steps will be evaluated during this supplemental study, as none have been determined to be impacted by design changes
- Validate satisfaction of use needs impacted by changes to the UI since the summative study

Study Participants

- 45 participants with 15 participants in each of the three user groups (patients, caregivers, and healthcare professionals)
- Participants will self-train by being asked to read the IFU prior to the performance portion of the study
- Participants will have the IFU (b) (4) available before and during the performance portion of the study
- Age range 34 to 71 years
- 1 patient was colorblind
- 11 patients and 7 caregivers were injection naïve, 4 patients and 8 caregivers had injection experience

Tasks and Scenarios studied

Only the tasks impacted by changes to the UI and IFU since the summative study were evaluated.

Impacted essential steps to be validated:

- Retrieve carton from storage
- Open carton
- Remove white paper cover (b) (4)
- Remove plastic cover
- Remove device from clear tray
- Open cartridge door
- Remove cartridge from clear tray
- Insert cartridge in device
- Close cartridge door

During the simulated injection scenario the participants were asked to identify the appropriate injection sites. In order to evaluate the steps required for validation in the supplemental summative study, this scenario was considered complete once the participant had inserted the cartridge and closed the cartridge door, at which point the moderator intervened and asked the participant to continue on to the next study scenario.

The participants then were presented with scenarios to evaluate the detection of a successful injection and hazard alarm via the indicator light. In this scenario the study moderator placed the automated mini-doser on the skin pad secured to the assigned injection site and started the injection. Participants were asked to monitor the injection until the injection was complete. Participants were evaluated for their ability to detect the end of a successful injection via the solid green light and hazard alarm via the flashing red light. To effectively test the hazard alarm, devices used for this scenario were modified to trigger the alarm, which occurred at some point within the 9 minute injection.

Results of Supplemental Summative Study

Table . Failures Observed on Essential Steps (Self-trained)				
Task	Patients	Caregivers	HCPs	Total Errors
E-essential				
Retrieve carton from storage (E)	0	0	0	0
Open Carton (E)	0	0	0	0
Remove white paper cover (E)	0	0	0	0
Remove Plastic Cover (E)	0	0	0	0
Remove device from clear tray (E)	0	0	0	0
Open cartridge door (E)	0	1	0	1
Remove cartridge from clear tray (E)	0	0	0	0
Insert cartridge in device (E)	0	0	0	0

Close cartridge door (E)	1	0	0	1
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Error Detection Scenario

All participants (45 out of 45) successfully were able to detect the error/alarm alert. Of note, 1 participant self-reported being half color blind. The successful injection complete was correctly identified by this participant. During the hazard alarm scenario the participant initially identified the light as green but quickly followed up stating it was “reddish-green”. During the root cause the participant stated the lights are clearly distinguishable

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On May 20, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care and Community
Search Strategy and Terms	Match Exact Word or Phrase: Repatha

D.2 Results

The search did not retrieve any articles.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Repatha pre-filled cartridge and automated mini-doser labels and labeling submitted by Amgen on September 10, 2015.

- Container label
- Carton labeling
- Replacement Sample Carton Labeling
- (b) (4) Label
- Instructions for Use

G.2 Label and Labeling Images

Carton Labeling

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS)
immediately following this page

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

HINA S MEHTA
06/08/2016

YELENA L MASLOV
06/08/2016

QUYNHNHU T NGUYEN
06/08/2016

LUBNA A MERCHANT
06/08/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, and Ophthalmic Device Branch

DATE: October 27, 2015

TO: Lakshmi Narasimhan, OMPT/CDER/OPQ/OPF/DMA/MABIV

Lakshmi.Narasimhan@fda.hhs.gov

Pat Hughes, OMPT/CDER/OPQ/OPF/DMA/MABIV

Office of combination products at combination@fda.gov

RPM: Kati Johnson

Through: For Francisco Vicenty, Branch Chief, REGO, DMQ, OC, CDRH,
OMPT. WO-66, Room 3425

From: Bleta Vuniqi, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3429

Applicant: Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
FEI# 1000110364

Application # BLA125522/S-001

Consult # ICC1500493

Product Name: Repatha (Evolocumab)

Consult The Office of Compliance at CDRH received a consult for Repatha (Evolocumab) to assess the suitability of the Automated Mini-Doser (AMD) 120 mg/mL and the need for inspection of the manufacturing sites.

Instructions:

Inspection Needed: Yes

Site: (b) (4)

[Redacted] (b) (4)

Site: [Redacted] (b) (4)

Documentation Review: No additional information required

Final Recommendation: Approval Pending Inspection

PRODUCT DESCRIPTION

Firm noted the purpose of this supplement is to request approval of a new drug product presentation supplied as a 120 mg/mL formulation in a sterile, single use, preservative-free solution for administration by subcutaneous (SC) injection in a prefilled cartridge assembly which is co-packaged with an administration device referred to as an automated mini-doser (AMD). The AMD is a compact, sterile, single-use, disposable, electro-mechanical (battery powered, micro-processor controlled), on-body injection device. The 120 mg/mL AMD presentation was developed to reduce the number of injections required for the once monthly dose to a single injection.

The 120 mg/mL prefilled cartridge assembly consists of a (b) (4) cartridge with a (b) (4) [Redacted] The prefilled cartridge assembly is co-packaged with the AMD. The prefilled cartridge assembly is loaded into the AMD immediately prior to use.

Figure 6. Prefilled Cartridge Assembly and AMD



(b) (4)



(b) (4)

The firm provided a comparison of key characteristics between the currently approved presentations and the proposed 120 mg/mL AMD.

Table 1. Comparison of the Currently Approved 140 mg/mL PFS and AI/Pen Presentations and the Proposed 120 mg/mL AMD Presentation

Presentation	140 mg/mL PFS	140 mg/mL AI/Pen	120 mg/mL AMD
Approval status	Approved	Approved	Proposed
Formulation	140 mg/mL evolocumab 220 mM proline 20 mM acetate 0.01%(w/v) polysorbate 80 pH 5.0	140 mg/mL evolocumab 220 mM proline 20 mM acetate 0.01%(w/v) polysorbate 80 pH 5.0	120 mg/mL evolocumab 220 mM proline 20 mM acetate 0.01%(w/v) polysorbate 80 pH 5.0
Container closure	(b) (4)		
Quantity delivered per container	1.0 mL	1.0 mL	3.5 mL
Number of injections for monthly dosing	3	3	1
Dose per container	140 mg	140 mg	420 mg
Delivery device	Single-use, disposable, handheld syringe	Single-use, disposable, handheld, mechanical (spring-based) injection device	Single-use, disposable, electro-mechanical (battery powered, micro-processor controlled), on-body injection device
Route of administration	SC injection	SC injection	SC injection
Administration method	Health care professional Caregiver Patient	Health care professional Caregiver Patient	Health care professional Caregiver Patient
Drug product manufacturing	AML, USA	AML, USA	(b) (4)
Assembly, packaging, and labeling	AML, USA	AML, USA	(b) (4)
Device manufacturer location	(b) (4)		

AML = Amgen Manufacturing Limited

REGULATORY HISTORY

The following firms were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

Assembly of the prefilled cartridge with a (b) (4) device component, co-packaging of the cartridge with the pre-sterilized AMD, and labeling

occurs at [REDACTED] (b) (4)
The sterilized AMD administration device is manufactured by [REDACTED] (b) (4)

1. Amgen Manufacturing Ltd (AML)
Road 31, Kilometer 24.6
Juncos, Puerto Rico 00777
FEI: 1000110364

The firm is responsible for AMD with cartridge lot release and stability testing. An analysis of the firm's inspection history over the past 2 years revealed a device inspection was conducted from 01/12/2015 to 01/23/2015, and objectionable conditions were identified. However, a 483 was not issued and the inspection was classified VAI. Since there was a recent medical device inspection which was classified as VAI, a pre-approval inspection is not required for this firm.

2. Amgen Inc. (referred to as Amgen Louisville Distribution Center or LDC)
12000 Plantside Drive
Louisville, KY 40299 USA

The firm is responsible for distribution, only. An analysis of the firm's inspection history revealed an initial inspection was conducted of a drug storage and distribution warehouse. A drug inspection was conducted from 01/05/2006 to 01/06/2006, no deficiencies were found and the inspection was classified NAI. No apparent issues related to 21 CFR part 820 were found. The firm's LDC site does not perform activities for the manufacture and assembly of the prefilled autoinjector and pen. Therefore, an inspection is not required for this firm.

3. [REDACTED] (b) (4)

The firm is responsible for [REDACTED] (b) (4), co-packaging and labeling. An analysis of the firm's inspection history revealed an inspection was conducted on [REDACTED] (b) (4) of this contract re-packer of human and veterinary pharmaceuticals and of the [REDACTED] (b) (4) inspection [REDACTED] (b) (4) At the conclusion of this [REDACTED] (b) (4) inspection [REDACTED] (b) (4)

[REDACTED] Inspection was classified VAI. Since there was a recent medical

device inspection which was classified as VAI, a pre-approval inspection is not required for this firm.

4. [REDACTED] (b) (4)

The firm is responsible for AMD manufacturing and assembly, AMD [REDACTED] (b) (4) inspection and release, AMD packaging and labeling, AMD non-sterile functional testing. An analysis of the firm's inspection history revealed that the firm has not been inspected by FDA in the past. Since a medical device inspection has not been conducted, a pre-approval inspection is required for this firm.

5. [REDACTED] (b) (4)

An analysis of the firm's inspection history over the past 2 years revealed a device inspection was conducted from [REDACTED] (b) (4), and no deficiencies were found and the inspection was classified NAI. The firm is responsible for AMD sterilization. Since there was a recent medical device inspection which was classified as NAI, a pre-approval inspection is not required for this firm.

6. [REDACTED] (b) (4)

The firm is responsible for AMD manufacturing and assembly, AMD [REDACTED] (b) (4) inspection and release, AMD packaging and labeling, AMD non-sterile functional testing, AMD post-sterilization release testing and release, [REDACTED] (b) (4) manufacturing and release, and AMD release to [REDACTED] (b) (4). An analysis of the firm's inspection history revealed that the firm has not been inspected by FDA in the past. Since a medical device inspection has not been conducted, a pre-approval inspection is required for this firm.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

The firm explained and provided this information during the BLA125522 application which was approved August, 2015. The firm explained how all firms involved in the manufacturing of the combination product will be controlled to ensure it is designed and produced in accordance with the applicable Quality Systems requirements. Amgen also describes how the quality policy will be implemented and maintained at all levels of the organization. There was no need for the firm to provide this information again.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm provided document detailing the design description and design features of AMD. Document identifies the device description, indication for use, description of conditions of use, principles of operation, operating sequence, design features, materials used in injection construction and manufacturer, and software.

In addition, the firm provided a detailed Design Validation and Design Verification document. The firm's documents provide a summary for design validation and verification activities for devices that are designed and manufactured by Amgen, a partner, or contract-manufacturer, and are a part of an Amgen Combination Product.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

The firm's purchasing controls were provided during the BLA125522 application which was approved on August, 2015. At that time the reviewer noted purchasing controls are provided in the document entitled [REDACTED] (b) (4)

[REDACTED]. Amgen details its controls through requirements for identifying, communicating and managing raw materials and component related non-conformances (NC) and the investigations at Amgen manufacturing locations. This SOP covers NC initiation, management, supplier response evaluation, CAPA, supplier recalls and notification of quality concerns, Amgen contract manufacturing activities, sample collection, site determination of local scope of impact, network triage and supplier response evaluation and raw material lot number information. There was no need for the firm to provide this information again.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The firm's CAPA controls were provided during the BLA125522 application which was approved on August, 2015. Amgen details its CAPA procedure in the operating standard for corrective and preventive action. This document is the firm's operating standard and is used to describe the process requirements for CAPA. The firm states this operating standard is applicable to all Amgen sites or functions performing GMP production, testing storage, and distribution of drug substances, drug products and combination products. There was no need for the firm to provide this information again.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

MANUFACTURING

Production and Process Controls

The firm previously provided procedure entitled [REDACTED] (b) (4) [REDACTED].

In addition the firm noted on section 9, of the firm's [REDACTED] (b) (4) [REDACTED] identifies and provides a detailed assembly description for the major subsystems also noted on the figure below. In addition, section 11, summaries the software contained in the AMD. The software contained in the AMD controls functions for both drug delivery control and man-machine-interface (MMI). Drug delivery control includes the initiation of drug delivery and continuous monitoring of delivery process. The MMI includes visual and auditory notifications to the user, as well as detection of when the user has placed the device against the skin and detection of when the user has mechanically activated the device to insert the needle.

Figure 4. Automated Mini-Doser, Exploded View



Acceptance Activities

The firm provided information regarding acceptance activities of the device. The testing details the acceptance activities of the device as they are processed for the manufacturing of the final combination product.



Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality System requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The Office of Compliance (OC) at CDRH has completed the evaluation of application BLA125522/S001. Application Repatha (Evolocumab) approvability under the Medical Device Regulations should be delayed until an inspection is conducted at the firm's contract manufacturer [REDACTED] (b) (4) [REDACTED] has been conducted and deemed acceptable.

Bleta Vuniqi

Prepared: BVuniqi: 10/27/2015

Reviewed: VVerna: 10/27/2015

CTS No.: ICC1500493

BLA125522/S-001

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/s/

KATI JOHNSON
11/01/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125522Orig1s001

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

From: Johnson, Kati
To: [Rupert, Adam \(arupert@amgen.com\)](mailto:arupert@amgen.com)
Cc: [Craig, Eileen](#); [Johnson, Kati](#)
Subject: BLA 125522/S-001, Repatha, Info Request
Date: Wednesday, July 06, 2016 3:05:00 PM
Attachments: [Information Request for BLA 125522_6 July 2016.doc](#)

Hi Adam,
Please let me know if you can respond by COB Friday or not.
Feel free to call me if you need to chat, but will be leaving shortly.
So sorry.
Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

- From Amgen's RTQ 2015-10-15 AMD document, Table 2 on page 9 of this document (see below) summarizes that there were 4 Grade 3 AEs in Year 1 and 6 Grade 3 AEs in Year 2+. Provide some detail on the nature of these AEs to include preferred terms and a brief description of these AEs. Please do the same for the 3 SAEs in Year 1 and 6 SAEs in Year 2+.

Table 2. Summary of Subject Incidence of Adverse Events Reported While Using the AMD in Year 1 or Year 2+ of Study 20120138 (Interim SoC-Controlled Period and Interim All-IP Period Analysis Set)

	EvoMab	
	Year 1 (SoC-controlled period)	Year 2+ (All-IP period)
	(N = 95) n (%)	(N = 196) n (%)
All adverse events	40 (42.1)	74 (37.8)
Grade ≥ 2	35 (36.8)	51 (26.0)
Grade ≥ 3	4 (4.2)	6 (3.1)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious adverse events	3 (3.2)	6 (3.1)
Leading to discontinuation of investigational product	0 (0.0)	1 (0.5)
Serious	0 (0.0)	0 (0.0)
Non-serious	0 (0.0)	1 (0.5)
Fatal adverse events	0 (0.0)	0 (0.0)
Device related adverse events	2 (2.1)	3 (1.5)
Grade ≥ 2	1 (1.1)	1 (0.5)
Grade ≥ 3	0 (0.0)	0 (0.0)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious	0 (0.0)	0 (0.0)

Page 1 of 1

Data cutoff date of 02APR2015.

AMD = automated mini-doser or 3.5 mL Personal Injector; EvoMab = Evolocumab (AMG 145);
IP = investigational product; SoC = standard of care.

Source: Modified Table *tfd151015q4-06-001-001-ae-inc-all-period2-icoasevo.rtf* and
Table *tfd151015q4-06-001-003-ae-inc-all-period3-iaas.rtf*

- Amgen's Table 2 from 4/4/2016 IR response: 5.3.5.3 – Clinical Device Safety Summary (see below) provides a description of the complaint codes and the corresponding number of AMD device failures. Provide the larger pool of device complaints that were not failures for the modified device used in Study 20120138 from April 2014 through 17 January 2016 as well as for the base device as of 01 July 2014.

From: [Rupert, Adam](#)
To: [Craig, Eileen](#); [Johnson, Kati](#)
Subject: RE: BLA 125522/S-001, Repatha, Info Request
Date: Wednesday, July 06, 2016 10:25:39 PM
Attachments: [RTQ 2016-07-06 Device Adverse Events & Failures-Complaints.pdf](#)

Hi Kati and Eileen,

Amgen's response to the FDA's information request is attached.

Thanks,
Adam

From: Craig, Eileen [<mailto:Eileen.Craig@fda.hhs.gov>]
Sent: Wednesday, July 06, 2016 4:22 PM
To: Rupert, Adam; Johnson, Kati
Subject: RE: BLA 125522/S-001, Repatha, Info Request

Thank you! Greatly appreciated and sorry for the last minute request!
Eileen

From: Rupert, Adam [<mailto:arupert@amgen.com>]
Sent: Wednesday, July 06, 2016 4:53 PM
To: Johnson, Kati
Cc: Craig, Eileen
Subject: RE: BLA 125522/S-001, Repatha, Info Request

We are putting together a response now and will send it ASAP (aiming for tonight).

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]
Sent: Wednesday, July 06, 2016 12:05 PM
To: Rupert, Adam
Cc: Craig, Eileen; Johnson, Kati
Subject: BLA 125522/S-001, Repatha, Info Request

Hi Adam,
Please let me know if you can respond by COB Friday or not.
Feel free to call me if you need to chat, but will be leaving shortly.
So sorry.
Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

- From Amgen's RTQ 2015-10-15 AMD document, Table 2 on page 9 of this document (see below) summarizes that there were 4 Grade 3 AEs in Year 1 and 6 Grade 3 AEs in Year 2+. Provide some detail on the nature of these AEs to include preferred terms and a brief description of these AEs. Please do the same for the 3 SAEs in Year 1 and 6 SAEs in Year 2+.

Table 2. Summary of Subject Incidence of Adverse Events Reported While Using the AMD in Year 1 or Year 2+ of Study 20120138 (Interim SoC-Controlled Period and Interim All-IP Period Analysis Set)

	EvoMab	
	Year 1 (SoC-controlled period)	Year 2+ (All-IP period)
	(N = 95) n (%)	(N = 196) n (%)
All adverse events	40 (42.1)	74 (37.8)
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Grade ≥ 4	0 (0.0)	0 (0.0)
Serious adverse events	3 (3.2)	6 (3.1)
Leading to discontinuation of investigational product	0 (0.0)	1 (0.5)
Serious	0 (0.0)	0 (0.0)
Non-serious	0 (0.0)	1 (0.5)
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Device related adverse events	2 (2.1)	3 (1.5)
Grade ≥ 2	1 (1.1)	1 (0.5)
Grade ≥ 3	0 (0.0)	0 (0.0)
Grade ≥ 4	0 (0.0)	0 (0.0)
Serious	0 (0.0)	0 (0.0)

Page 1 of 1

Data cutoff date of 02APR2015.

AMD = automated mini-doser or 3.5 mL Personal Injector; EvoMab = Evolocumab (AMG 145);
IP = investigational product; SoC = standard of care.

Source: Modified Table *tfd151015q4-06-001-001-ae-inc-all-period2-icoasevo.rtf* and
Table *tfd151015q4-06-001-003-ae-inc-all-period3-iaas.rtf*

- Amgen's Table 2 from 4/4/2016 IR response: 5.3.5.3 – Clinical Device Safety Summary (see below) provides a description of the complaint codes and the corresponding number of AMD device failures. Provide the larger pool of device complaints that were not failures for the modified device used in Study 20120138 from April 2014 through 17 January 2016 as well as for the base device as of 01 July 2014.

Table 2. AMD Complaint Codes With Failures Reported in the Evolocumab Clinical Program (in Descending Order of Frequency)

Complaint Code	Description	Device Failures as of 01Jul2014¹ (n=53)	Device Failures as of 17Jan2016² (n=76)
Device Not Functioning / Activation Failed	Delivery device not functioning (e.g. no beep after liner removal, no ^{(b)(4)} beeps upon injection start, no ^{(b)(4)} beeps upon injection completion, no pumping sound during injection, no blue blinking light upon liner removal, no blinking green light during injection or no solid green light after completed injection).	33	46
Drug Injection Failed / Leakage	Delivery device stalls and/or fails to complete injection	11	14
Cartridge other	Any event or condition applicable to this item that is not covered by any other Event/Cause Code.	5	7
Device Cartridge Door Broken	Delivery device door is broken, not functioning properly or cartridge not able to be loaded during or after handling.	3	3
Needle Other	Any event or condition applicable to this item that is not covered by any other Event/Cause Code.	0	2
Drug Particles Fibers / Cartridge Foreign Object External	Fibrous particles in the drug or foreign object, including dirt, attached to external surface of the cartridge.	0	2

Complaint Code	Description	Device Failures as of 01Jul2014 ¹ (n=53)	Device Failures as of 17Jan2016 ² (n=76)
Device Application Adhesive Does Not Function as Expected	Delivery device application adhesive did not function as expected, including not adhering to skin or partially adhering to skin.	1	1
Needle Bent During Use	Needle appears deviated from a straight line; appears bowed, or crooked. Needle shows deflection starting anywhere from the base, in the needle cannula or anywhere from the base of the device needle.	0	1

Source: Complaint Issues and Failures Source: Intake Response Product Complaints with data cutoff 17January 2016.

¹Complaint failures originated from clinical studies 20120135, 20110168, and 20120356

²Additional complaint failures occurring after 01Jul2014 originated from clinical study 20120138

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/s/

KATI JOHNSON
07/11/2016

From: [Johnson, Kati](#)
To: [Rupert, Adam](#)
Cc: [Johnson, Kati](#)
Subject: RE: BLA 125522 S001 revised PPI and IFU
Date: Thursday, July 07, 2016 9:40:02 AM
Attachments: [S-Repatha-IFU-v1.1-on-body infusor-C-2016-0701.docx](#)

We have no objections to the revisions made to the IFU.
Therefore, attached to this email is the labeling you submitted on 7/1.
This labeling will be attached to the AP letter.
You can add the revisions date following approval.
Thanks for your assistance.
Kati

From: Rupert, Adam [<mailto:arupert@amgen.com>]
Sent: Friday, July 01, 2016 7:53 PM
To: Johnson, Kati
Subject: RE: BLA 125522 S001 revised PPI and IFU

Hi Kati,

Please find attached the following:

- PPI in clean (C) Word; we accepted all FDA changes
- IFU in clean (C) and tracked changes (AR)

Please confirm receipt.

Have a great Fourth of July!

Thanks,
Adam

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]
Sent: Friday, July 01, 2016 10:51 AM
To: Rupert, Adam
Cc: Johnson, Kati
Subject: BLA 125522 S001 revised PPI and IFU

Adam,

Sorry, the track changes sorta got lost with all the different folks involved. So these are the clean versions.

If you could use TRACK changes when you send them back, that would be great. Or even better, just accept the revisions☺

I am going to be online today until we get another document cleared, which will probably mean I am available until 3:30 or so EST. I will be checking emails over the weekend.

Get these back to me whenever. We are doing great on time.

Hope your weekend isn't totally shot.

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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/s/

KATI JOHNSON
07/07/2016

From: [Johnson, Kati](#)
To: [Rupert, Adam](#)
Cc: [Johnson, Kati](#)
Subject: RE: BLA 125522 S001 revised PPI and IFU
Date: Thursday, July 07, 2016 9:01:27 AM
Attachments: [S-Repatha-US-PPI-v1.1-on-body_infusor-C.2016-0701.doc](#)

We note your acceptance of the attached PPI
It is identical to what you submitted on 7/1/2016
This is what will be attached to the AP letter. You can add the revision date when you submit the SPL

Thanks for your assistance.

Kati

From: Rupert, Adam [<mailto:arupert@amgen.com>]
Sent: Friday, July 01, 2016 7:53 PM
To: Johnson, Kati
Subject: RE: BLA 125522 S001 revised PPI and IFU

Hi Kati,

Please find attached the following:

- PPI in clean (C) Word; we accepted all FDA changes
- IFU in clean (C) and tracked changes (AR)

Please confirm receipt.

Have a great Fourth of July!

Thanks,
Adam

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]
Sent: Friday, July 01, 2016 10:51 AM
To: Rupert, Adam
Cc: Johnson, Kati
Subject: BLA 125522 S001 revised PPI and IFU

Adam,

Sorry, the track changes sorta got lost with all the different folks involved. So these are the clean versions.

If you could use TRACK changes when you send them back, that would be great. Or even better, just accept the revisions☺

I am going to be online today until we get another document cleared, which will probably mean I am available until 3:30 or so EST. I will be checking emails over the weekend.

Get these back to me whenever. We are doing great on time.

Hope your weekend isn't totally shot.

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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/s/

KATI JOHNSON
07/07/2016

From: [Johnson, Kati](#)
To: [Mancini, Audrey](#)
Cc: [Rupert, Adam](#); [Johnson, Kati](#)
Subject: RE: Repatha S-001 Status
Date: Thursday, July 07, 2016 6:48:45 AM
Attachments: [Amgen device labeling.pdf](#)

We find the attached DEVICE PAD Labeling acceptable.
Thanks for your assistance.
Kati

From: Mancini, Audrey [mailto:amancini@amgen.com]
Sent: Tuesday, June 21, 2016 2:03 AM
To: Johnson, Kati
Cc: Rupert, Adam
Subject: RE: Repatha S-001 Status

Dear Kati-

I am filling in for Adam Rupert, who is on vacation this week. Thank you for sending the FDA's feedback on the draft carton and container labeling for the Repatha Automated Mini-Doser Supplement-001 on 15 June 2016. Enclosed are 5 PDF files that contain images of the revised draft labeling which incorporates the FDA's feedback:

- Automated Mini-Doser – (b) (4) labe (b) (4)
- Automated Mini-Doser – Dispensing Carton
- Automated Mini-Doser – Primary Label for Cartridge
- Automated Mini-Doser – Replacement Carton
- Automated Mini-Doser – Pad-Printed Labeling

Also enclosed is a response document with Amgen's clarifications to specified FDA comments/revisions to the carton and container labeling. This document also includes Amgen's rationale for not incorporating certain labeling revisions proposed by the Agency. A formal submission of these documents via the electronic submissions gateway will follow within the next few days.

Please don't hesitate to contact me during Adam's absence if you have any questions on this labeling or if you have any update on when we might expect the FDA's feedback on the draft US Prescribing Information.

Kind Regards-

Audrey Mancini
Regulatory Affairs Senior Manager
Amgen Inc.: 805-447-6514
805-358-5159 (cell)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS)
immediately following this page

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/s/

KATI JOHNSON
07/07/2016

From: [Johnson, Kati](#)
To: [Rupert, Adam](#)
Cc: [Johnson, Kati](#)
Subject: RE: BLA 125522/S-001, revised carton/container labeling
Date: Thursday, July 07, 2016 6:28:11 AM
Attachments: [MCK4105 ART LBL Device 420 mg 145 AMD \(2\).pdf](#)
[MCK4103 ART \(b\) \(4\) Device 420 mg 145 AMD.pdf](#)
[MCK4104 ART CRTN DP Device 420 mg 145 AMD.pdf](#)
[MCK4106 ART CRTN DP Device 420 mg 145 Repl Dose AMD.pdf](#)

We find the attached labeling acceptable:

- Prefilled cartridge label
- (b) (4) Lid labeling
- Carton labeling (trade)
- Carton labeling (replacement)

This labeling is identical to the labeling you submitted via email on 7/5/2016.

Thanks for your assistance.

Kati

From: Rupert, Adam [<mailto:arupert@amgen.com>]
Sent: Tuesday, July 05, 2016 12:04 PM
To: Johnson, Kati
Subject: RE: BLA 125522/S-001, revised carton/container labeling

Hi Kati,

Please find attached the updated carton and container labeling. We accepted all of the FDA's requested updates. If you're able to let me know if the FDA will be requiring any further revisions to these components or if they can be considered 'final,' that would be great.

Thanks,
Adam

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]
Sent: Friday, July 01, 2016 6:45 AM
To: Rupert, Adam
Subject: RE: BLA 125522/S-001, revised carton/container labeling

Thanks for confirming

From: Rupert, Adam [<mailto:arupert@amgen.com>]
Sent: Friday, July 01, 2016 9:40 AM
To: Johnson, Kati
Subject: Re: BLA 125522/S-001, revised carton/container labeling

Confirming receipt.

Sent from my iPhone

On Jul 1, 2016, at 6:38 AM, Johnson, Kati <Kati.Johnson@fda.hhs.gov> wrote:

Hi Adam,

Please confirm receipt.

Here are our requested revisions to the labeling you sent to us via email and official submission on 6/21/2016.

Note that we are not requiring that you bold "on-body infusor" on the device pad, however, we will be sending you a "supplement request" letter following approval asking that you increase the prominence of this information compared to the drug name.

Please send back revised labeling via email and state whether you accept the revisions or have some counterproposals.

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

<BLA 125522.1 Container Carton Comments_07012016.docx>

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/s/

KATI JOHNSON
07/07/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Subject: RE: BLA 125522/S-001, Repatha, updated PMCs
Date: Wednesday, July 06, 2016 6:17:39 PM

Great- thanks for confirming. Looks like the IR is the last piece to complete. We're working on it.

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]
Sent: Wednesday, July 06, 2016 3:12 PM
To: Rupert, Adam
Cc: Johnson, Kati
Subject: RE: BLA 125522/S-001, Repatha, updated PMCs

We find these revisions acceptable.
This text will be included in the approval letter.
Thanks very much,
Kati

From: Rupert, Adam [<mailto:arupert@amgen.com>]
Sent: Wednesday, July 06, 2016 1:09 PM
To: Johnson, Kati
Subject: RE: BLA 125522/S-001, Repatha, updated PMCs

Hi Kati,

Amgen's response to the PMC is attached. We accepted the tracked changes prior to making our additional revisions in order to be clear on what we were updating.

Thanks,
Adam

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]
Sent: Tuesday, July 05, 2016 10:06 AM
To: Rupert, Adam
Subject: RE: BLA 125522/S-001, Repatha, updated PMCs

Thanks Adam.

From: Rupert, Adam [<mailto:arupert@amgen.com>]
Sent: Tuesday, July 05, 2016 11:49 AM
To: Johnson, Kati
Subject: RE: BLA 125522/S-001, Repatha, updated PMCs

Confirming receipt.

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]
Sent: Tuesday, July 05, 2016 8:16 AM
To: Rupert, Adam
Cc: Johnson, Kati
Subject: BLA 125522/S-001, Repatha, updated PMCs

Importance: High

Hi Adam,

Please see the attached document and get it back to us when you can.

Kati

Kati Johnson

Senior Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Food and Drug Administration

301-796-1234

Kati.johnson@fda.hhs.gov

**PMC list for BLA 125522/S-001
REPATHA (evolocumab)**

While review of your application continues, we are sending you a draft list of PMCs based on the data and internal analyses available to date. These brief study summaries are intended to describe the main objective and study characteristics of interest.

Please submit by email a copy of the PMC studies to us with milestone dates, which include **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- **For PMCs, include a statement that you agree to conduct these studies/trials.**

Amgen Response:

Amgen agrees to conduct the postmarketing commitment studies described in the section below.

The data generated will include results for the following shelf life tests for 1-year, 2-year and 31-day, 3-year and 31-daytime points: Device Function Test, Deliverable Volume Test, Injection Time test, Sterile (b)(4) Integrity Test, (b)(4) Function test, and Adhesive Function Test.

The postmarketing committed submission dates account for the time needed to age samples for one year at room temperature (warehouse storage), followed by up to two years at 2°C to 8°C (cold storage), and finally 31 days at room temperature (label allowance), culminating in a study duration of approximately three years. Time point “1-year” corresponds to the time at warehouse temperature (15°C to 30°C). Time points “2-year” and “3-year” correspond to 12 and 24 months cold storage periods (5°C ± 3°C). The “31-day” time point corresponds to the 31 day (label allowance) time following cold storage at room temperature (23°C ± 5°C). An interim report will be generated for the 1-year and 2-year and 31-day time point results. The report will later be updated to include final data for the 3-year and 31-day time points.

Postmarketing Commitments:

- 1) Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the interim 1-year timepoint. These studies should use the methods equivalent to those used to evaluate device performance in the accelerated aging studies. The interim report must include results from the following shelf life tests: Device Function Test, Deliverable Volume Test, Injection Time Test, Sterile (b)(4) Integrity Test, (b)(4) (b)(4) Function Test, and Adhesive Function Test.

Interim Report (1-year timepoint) Submission: 07/2017

- 2) Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the interim 2-year and 31-day timepoint. These studies should use methods equivalent to those used to evaluate device performance in the accelerated aging studies. The final report must include results from the following shelf life tests: Device Function Test, Deliverable Volume Test, Injection Time Test, Sterile (b) (4) Integrity Test, (b) (4) (b) (4) Function Test, and Adhesive Function Test.

Interim Report (2-year and 31-day timepoint) Submission: 07/2018

- 3) Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the final 3-year and 31-day timepoint. These studies should use methods equivalent to those used to evaluate device performance in the accelerated aging studies. The final report must include results from the following shelf life tests: Device Function Test, Deliverable Volume Test, Injection Time Test, Sterile (b) (4) Integrity Test, (b) (4) (b) (4) Function Test, and Adhesive Function Test.

Final Report (3-year and 31-day timepoint) Submission: 07/2019

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/s/

KATI JOHNSON
07/06/2016

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

2. Describe the particular review issue and the goal of the study.

The goal is to evaluate device performance following real time aging studies to ensure there is no decline in essential performance attributes of the device.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Accelerated aging studies were completed using an accelerated aging technique to support 2 years shelf life. Amgen will need to use the identical protocols used to evaluate device performance in the accelerated aging studies as for the real time aging evaluation of the device performance. These studies will need to include the following tests:

Device Function Test, Deliverable Volume Test, Injection Time test, (b) (4) Integrity test, (b) (4) Function test, and Shelf life adhesive function test

Data should be collected at a minimum of 12 month intervals for up to 24 months. Reports should be submitted once the 12 months data has been collected and after the 24 months data has been collected to the Agency for review.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

JENNIFER R PIPPINS
07/06/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Subject: RE: BLA 125522 S001 revised PPI and IFU
Date: Friday, July 01, 2016 3:05:51 PM

Got it – thanks!

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Friday, July 01, 2016 12:00 PM
To: Rupert, Adam
Subject: BLA 125522 S001 revised PPI and IFU

Maybe this will be helpful. Please confirm receipt.
Eileen found some extra spaces in the IFU, so I assume you can find them also. They were corrected in the clean version previously sent you.

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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/s/

KATI JOHNSON
07/04/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Subject: Re: BLA 125522/S-001, revised carton/container labeling
Date: Friday, July 01, 2016 9:40:21 AM

Confirming receipt.

Sent from my iPhone

On Jul 1, 2016, at 6:38 AM, Johnson, Kati <Kati.Johnson@fda.hhs.gov> wrote:

Hi Adam,

Please confirm receipt.

Here are our requested revisions to the labeling you sent to us via email and official submission on 6/21/2016.

Note that we are not requiring that you bold “on-body infusor” on the device pad, however, we will be sending you a “supplement request” letter following approval asking that you increase the prominence of this information compared to the drug name.

Please send back revised labeling via email and state whether you accept the revisions or have some counterproposals.

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

<BLA 125522.1 Container Carton Comments_07012016.docx>

BLA 125522/1
Repatha (evolocumab)
Container Labels and Carton Labeling Comments

We have the following comments regarding your proposed container labels and carton labeling submitted on June 21, 2016.

A. Carton Labeling

1. Revise the manufacturer information from [REDACTED] (b) (4) to "Manufactured by" similar to the presentation on the carton labeling for Repatha prefilled syringe and autoinjector.
2. Move the graphic away from the proprietary name on the carton labeling, as currently displayed it seems like it is part of the proprietary name.

B. [REDACTED] (b) (4) Lid Labeling

1. Currently "Repatha" is the most prominent information on the label. Revise the presentation of the device and drug names such that the device name is more prominent than the drug name by adjusting the font size, bolding, or color.
2. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
3. Relocate the position of the non-proprietary name "evolocumab" to appear below the proprietary name (similar to the carton labeling). This is the appropriate display of the product names for CDER specified biologics. To make room on the labeling for this revision, consider the following:
 - a. Decrease the size of "AMGEN" on the upper left-side of the label.
 - b. Revise the manufacturer information to "Mfd for Amgen Inc"

For example:

On-Body Infusor for
Repatha
(evolocumab)
420 mg/3.5 mL
For Subcutaneous Use Only
Mfd by Amgen Inc.

C. Prefilled Cartridge Label

1. Add the dosage form "Injection" to appear below the non-proprietary name "(evolocumab)" similar to the presentation on the carton labeling for Repatha prefilled syringe and autoinjector. To make room for this revision, consider the following:

- a. Delete [REDACTED] (b) (4)
[REDACTED].

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KATI JOHNSON
07/01/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Subject: RE: BLA 125522/S-001. post marketing commitment document
Date: Thursday, June 30, 2016 10:57:54 AM

Confirming receipt.

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Thursday, June 30, 2016 6:45 AM
To: Rupert, Adam
Cc: Johnson, Kati
Subject: BLA 125522/S-001. post marketing commitment document
Importance: High

Hi Adam,
Confirm receipt of this email.
Please see the attached document.
Please make any edits to the document via tracked changes, to include your commitment to conduct the studies and their proposed Final Report Submission dates.
Let me know if you can return it by COB tomorrow.
Contact me if you have any questions.

Thanks, Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

**PMC list for BLA 125522/S-001
REPATHA (evolocumab)**

While review of your application continues, we are sending you a draft list of PMCs based on the data and internal analyses available to date. These brief study summaries are intended to describe the main objective and study characteristics of interest.

Please submit by email a copy of the PMC studies to us with milestone dates, which include **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- **For PMCs, include a statement that you agree to conduct these studies/trials.**

Postmarketing Commitments:

- 1) Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the 1-year timepoint. These studies should use the identical protocols that were used to evaluate device performance in the accelerated aging studies. The final report must include results from the following tests: Device Function Test, Deliverable Volume Test, Injection Time test, (b) (4) Integrity test, (b) (4) Function test, and Shelf life adhesive function test.

Final Report Submission:

- 2) Conduct Real Time Aging/Shelf-Life Studies for Device Performance for the 2-year timepoint. These studies should use the identical protocols that were used to evaluate device performance in the accelerated aging studies. The final report must include results from the following tests: Device Function Test, Deliverable Volume Test, Injection Time test, (b) (4) Integrity test, (b) (4) Function test, and Shelf life adhesive function test.

Final Report Submission:

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/s/

KATI JOHNSON
06/30/2016

From: Johnson, Kati
To: [Kubasak, Marc \(mkubasak@amgen.com\)](mailto:mkubasak@amgen.com); [Rupert, Adam \(arupert@amgen.com\)](mailto:arupert@amgen.com); [Mancini, Audrey \(amancini@amgen.com\)](mailto:amancini@amgen.com)
Cc: [Johnson, Kati \(Kati.Johnson@fda.hhs.gov\)](mailto:Kati.Johnson@fda.hhs.gov)
Subject: BLA 125522/S-001, proposed PI in response to 5/27 firm submission
Date: Tuesday, June 21, 2016 1:59:00 PM
Attachments: [125522_S001_revised_PI_to_firm_6_21.doc](#)

OK guys, here you go, with the usual caveats:

PLEASE CONFIRM RECEIPT

-this is the first go around. We reserve the right to make further revisions. Can't imagine anything major given the few revisions to begin with, but you never know.

-we haven't touched the highlights section yet. If you are OK with these revisions and want to revise it before sending it back to us, feel free.

-Please accept our revisions, then make your revisions using track changes. I am hoping that we did that with your 5/27/16 submission, but you may want to verify, given the number of folks involved with this.

-just send back the labeling via email (no need for official submission)

-I will archive this labeling being sent to you instead of a letter.

As usual, contact me if you have any questions.

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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KATI JOHNSON
06/22/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Subject: RE: BLA 125522/S-001. Repatha, micro IR
Date: Wednesday, June 15, 2016 3:47:31 PM

Confirming receipt.

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Wednesday, June 15, 2016 12:43 PM
To: Rupert, Adam
Cc: Johnson, Kati
Subject: BLA 125522/S-001. Repatha, micro IR

Please confirm receipt and respond by 6/20, if possible.

FDA's comments on responses in amendment dated June 14, 2016 in sequence # 0139:

You have stated that (b) (4) method is used for real time release testing (RTRT) and (b) (4) is used for routine QC laboratory testing. MET-001000, "Determination of Bacterial Endotoxin Content of Solutions Using Kinetic Limulus Amebocyte Lysate (LAL) Methods", which was added to 3.2.P.5.2 (Overview [120 mg/mL AMD]) includes (b) (4) methodologies for bacterial endotoxin testing at (b) (4) and AML. The scope of the document states that this method is intended for the analysis of bacterial endotoxins for all sample types. It does not specifically state which of these two methods is used for release or (b) (4).

1. Please clarify what you mean by routine QC laboratory testing.
2. Please indicate that (b) (4) method using (b) (4) will be used for release testing of DP in section P.5.

Thanks, Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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KATI JOHNSON
06/15/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Cc: [Abdus-Samad, Jibril](#)
Subject: RE: BLA 125522/S-001, Repatha (evolocumab), Revised carton/container labeling
Date: Wednesday, June 15, 2016 3:41:50 PM

Confirming receipt.

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Wednesday, June 15, 2016 12:31 PM
To: Rupert, Adam
Cc: Johnson, Kati; Abdus-Samad, Jibril
Subject: BLA 125522/S-001, Repatha (evolocumab), Revised carton/container labeling

Hi Adam,

Please confirm receipt.

These comments are based on the review of the labeling included in the initial 9/10/2015 supplement submission. You obviously will need to revise the name, as previously discussed in our telecon. It would be great if you could respond by COB 6/23/2016.

I will archive this email in lieu of sending you a letter. Hopefully, I can get you the PI tomorrow.

A. Carton Labeling

1. Replace the Proprietary name for the prefilled cartridge co-packaged with an on-body-infusor device with the conditionally accepted name throughout all carton labeling.
2. Revise the device common name to On-Body Infusor.
3. Please consider changing the color scheme on carton labeling [REDACTED] (b) (4)
4. Increase the font size of the strength as currently displayed it is not prominent and may be overlooked.
5. Place the strength under the icon of the device on the Principal Display Panel (PDP) and all side panels to increase readability of this important information.
6. Revise the storage information statement to "Store refrigerated at..." on the PDP. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked and to be consistent with the side panel.
7. On the side panel for the patient/caregiver storage instructions add "Discard after 30 days". We recommend "Discard after" since it is an affirmative statement, and has been shown to result in the desired action. [REDACTED] (b) (4) add " ___/___/___ " to allow users to fill in the actual date. Also, revise the statement [REDACTED] (b) (4) to read "Write the date removed from the refrigerator."

8. Revise the statement of ingredients to read:

Each single-use Pushtronex system (on-body infusor with prefilled cartridge) delivers a 3.5 mL sterile, preservative free solution containing 420 mg evolocumab, acetate (4.2 mg), polysorbate 80 (0.35 mg), proline (89 mg) in Water for Injection, USP. Sodium hydroxide may be used to adjust to a pH of 5.0.

9. Consider relocating “No U.S. standard of potency” from the PDP to the rear panel to appear after the statement of ingredients.

10. Consider relocating the license number from the PDP to the side-panel to appear with the manufacturer information.

B. (b) (4) Lid Labeling

1. Replace the name on the (b) (4) label with the conditionally acceptable name of the device. Note the name of the device is more prominent than the drug name. For example.

On-body Infusor for
Repatha
(evolocumab)
420 mg/3.5 mL

C. On-body Infusor Labeling

1. Revise the labeling of the name and strength to appear as:

On-body Infusor for
Repatha
(evolocumab)
420 mg/3.5 mL

Note the name of the device is more prominent than the drug name.

D. Prefilled Cartridge Label

1. Revise (b) (4) to “Single-Use Only”.

Thanks, Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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/s/

KATI JOHNSON
06/15/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Subject: RE: BLA 125522/S-001, Repatha, micro info request
Date: Friday, June 10, 2016 11:32:00 AM

Confirming receipt.

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Friday, June 10, 2016 8:00 AM
To: Rupert, Adam
Cc: Johnson, Kati
Subject: BLA 125522/S-001, Repatha, micro info request

Hi Adam,
Another micro IR. Please respond by 6/14, if possible.

Both (b) (4) and (b) (4) are qualified for endotoxin release testing of the DP at (b) (4) and AML. To avoid confusion as to which method is the definitive test for the drug product release, the submission should specify only one endotoxin release test method. Please indicate which test method will be used for releasing evolocumab drug product and amend section P.5 accordingly.

As always, OK to respond via email and follow up with official submission.
Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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/s/

KATI JOHNSON
06/10/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Cc: [Fuchs, Chana](#)
Subject: RE: BLA 125522/S-001, CMC IR letter
Date: Tuesday, June 07, 2016 4:22:21 PM

Confirming receipt.

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Tuesday, June 07, 2016 1:14 PM
To: Rupert, Adam
Cc: Johnson, Kati; Fuchs, Chana
Subject: BLA 125522/S-001, CMC IR letter

CMC IR

Response requested by noon (EST) June 10, 2016, including the updated sections identified below:

1. The DP manufacturing process as defined by the studies and SOPs described in the 3.2.P.2.3 and 3.2.P.3.5 sections and the batch records are not sufficiently reflected in the process description in section 3.2.P.3.3 and in section 3.2.P.3.4 control of critical steps and intermediates. For example; no information is identified in these sections for the (b) (4).
(b) (4). Similarly, other important parameters that define the process and its controls, including inspection criteria for cartridge and device defects for the AMD were not sufficiently specified in these sections. Update the section 3.2.P.3.3 and 3.2.P.3.4 with a more comprehensive description of your validated process including limits and acceptance criteria of the process as defined by your validation studies. We noted that according to the sponsor response to FDA IRs (SN 0107 on 01/14/2016) (b) (4).
2. The action limits for osmolality as (b) (4) do not aligned with the release acceptance criterion of (b) (4). The historical osmolality release range for the cartridge and AMD lots including the (b) (4) validation lots were (b) (4) based on the 3.2.P.2.3 and 3.2.P.3.5. The (b) (4) action limits should be adjusted, as appropriate, or data supporting these limits and the ability to meet the release acceptance criterion should be provided.
3. Submit the drug product sampling plans used for lot release testing.
4. For the shipping validation, real time transport data from (b) (4), using commercial prefilled cartridges and AMDs, are not identified in the submission. Provide the relevant real time transport data. We note that the submitted report RPT-054636 - Transport Performance Qualification for 120 mg/mL Cartridge and 120 mg/mL AMD showed data using lots manufactured at AML (prefilled cartridge Lot 0010192249 and AMD Lot 0010194151) using what appears to be site specific shippers rather than specific data relevant to, and for , shipping from (b) (4).

5. Based on the Table 4 in Section 3.2.P.3.1, the prefilled cartridge release and stability testing is performed at (b) (4) AML and (b) (4). Information on the qualification, validation and/or method transfer of analytical procedures including compendial methods is not sufficient to assess the suitability of the analytical procedures under actual conditions of use at (b) (4). Submit information to demonstrate that the tests including appearance (MET-002398), color (MET-002403), clarity (MET-001176), protein concentration (MET-000610), pH (MET-001215), osmolality (MET-000170), volume in containers (MET-000578), subvisible particles (MET-002637), and breakloose and extrusion (MET-002940) are suitable for the prefilled cartridge at (b) (4) and would have equivalent results to the same methods run at (b) (4) and AML.

6. Information on the qualification, validation or method transfer of critical analytical procedures, including compendial methods, used for the (b) (4) is not sufficient to allow assessment of the suitability of the analytical procedures under conditions of use. Submit information to demonstrate that the tests including polysorbate 80 (MET-003221), deliverable volume, protein concentration, pH, and osmolality, are suitable (b) (4).

7. Update the stability data for the (b) (4) validation lots with any additional timepoints available.

They wanted me to emphasize the following:

Please make sure they understand that the emailed responses should include the pdf of updated sections. They can update the electronic submission within a few days after if they prefer. But we need final versions of the updated sections.

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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/s/

KATI JOHNSON
06/07/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125522 S-001

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Amgen Inc.
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320-1799

ATTENTION: Adam J. Rupert, MS, RAC
Senior Manager, Regulatory Affairs

Dear Mr. Rupert:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received September 10, 2015, submitted under section 351(a) of the Public Health Service Act for Evolocumab, 420 mg/3.5 mL (120 mg/mL).

We also refer to your correspondence, dated and received March 18, 2016, requesting review of your proposed proprietary name, Repatha Pushtronex.

We have completed our review of the proposed proprietary name, Repatha Pushtronex and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 18, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Kati Johnson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
05/19/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Subject: RE: BLA 125522/S-001, CDRH deficiencies remain with 2/25/2016 IR response
Date: Friday, May 06, 2016 10:10:57 AM

Confirming receipt. I will notify the team and will update you with a timeline for responding.

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Friday, May 06, 2016 5:52 AM
To: Rupert, Adam
Cc: Johnson, Kati
Subject: BLA 125522/S-001, CDRH deficiencies remain with 2/25/2016 IR response

Adam,

Please confirm receipt and provide a response timeline when you can.
I will archive this in lieu of a letter.

Comment 1a-c, 7 Deficiency

CDRH finds the validation and reliability testing completed adequate to confirm that the changes implemented meet the intended specifications and essential performance requirements for the device for the majority of the changes made prior to the global clinical study. However, for the (b) (4) Assembly and the (b) (4) Assembly, the device reliability testing is not sufficient. The changes made to the (b) (4) assembly and the (b) (4) could influence the electromagnetic compatibility, electrostatic discharge and the radiated radio Frequency testing completed on the original configuration. Since these tests were not repeated after these two changes were implemented, it is unknown how the device will perform given the test conditions for these tests. Additionally it is unclear if these changes introduce any new risks or performance issues. Please repeat the following tests using the commercial configuration of the device:

- Electromagnetic compatibility testing
- Electrostatic discharge Testing
- Radiated Radio Frequency Testing

Comment 10 Response Deficiency

The device will be administering the drug to the subcutaneous tissue where it is intended to be delivered systemically and therefore, extractables and leachables will be able to contact the blood. The Agency recommends that indirect (extract) hemolysis testing is performed on the fluid path components of the final finished device.

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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/s/

KATI JOHNSON
05/12/2016



BLA125522/S-001

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Amgen Inc.
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320-1799

ATTENTION: Adam J. Rupert, MS, RAC
Senior Manager, Regulatory Affairs

Dear Mr. Rupert:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received September 10, 2015, submitted under section 351(a) of the Public Health Service Act for Evolocumab, 120 mg/mL and 140 mg/mL.

We acknowledge receipt of your correspondence, dated and received March 18, 2016, requesting a review of your proposed proprietary name, Repatha Pushtronex.

The user fee goal date is June 16, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact, Deveonne Hamilton-Stokes Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Kati Johnson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Deveonne Hamilton-Stokes, RN, BSN
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEVEONNE G HAMILTON-STOKES
04/15/2016

From: [Rupert, Adam](#)
To: [Johnson, Kati](#)
Subject: RE: BLA 125522/S-001, Repatha (evolocumab), Device request
Date: Thursday, February 25, 2016 3:14:35 PM

Hi Kati,

Confirming receipt. I will follow up with you regarding the timeline(s) for responding.

Thanks,
Adam

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Thursday, February 25, 2016 11:48 AM
To: Rupert, Adam
Cc: Johnson, Kati
Subject: BLA 125522/S-001, Repatha (evolocumab), Device request
Importance: High

Hi Adam,

Please confirm receipt as I will archive the email in lieu of drafting a letter.

Please provide a timeline for responding. You may respond in a single submission or multiple submissions. If you choose the latter, please respond, in total, for each section heading below. Contact me if you have any questions.

Clinical Development and Device Design Changes

General Comment:

CDRH considers on-body medication delivery devices, like the automated mini-doser (AMD) used to deliver Repatha (evolocumab), to be a type of infusion pump. CDRH has issued a guidance document, “*FDA Guidance for Industry and Staff: Infusion Pumps Total Product Life Cycle*,” outlining the types of information expected in a submission for an infusion pump. Since the guidance issued on December 2, 2014, the Agency is expecting submissions for infusion pumps to contain an assurance case. However, we are not going to request that your device documentation be organized into an assurance case for this submission because of the many discussions between Amgen and FDA regarding the submission content for the Repatha AMD product, which preceded the issuing of the FDA infusion pump guidance document. Note that the evidence supporting safety and effectiveness of the device constituent parts must still be present within the submission such that Agency is able to adequately make a risk/benefit determination. Future submissions for this product or other infusion pump devices of this type will need to address the recommendations contained in the referenced guidance document.

1. You provide a table in the October 15, 2015 letter describing the device changes between the device used in the original clinical studies (20120356, 20110168 and 20120135), the device used in the global clinical study (20120138) and the commercial to-be marketed device. However, it is unclear based on the description provided to determine the nature of the changes between device iterations. Please provide the following:
 - a. A detailed description of each change made, including any engineering drawings;
 - b. A complete list or table of which performance tests and which human factors studies were completed on which device iterations;
 - c. A risk assessment or bridging discussion for applying the clinical data from the studies using the original base device to the version of the device planned for

commercial release.

2. Device related adverse events for the AMD used in the global clinical study (20120138) could not be found in the submission. Please point to the information within the submission or provide a detailed report including specific event descriptions of all device related adverse events and/or failures captured in the Study 20120138. This information is needed to evaluate the clinical and use safety of the device.

Device Risk Management Summary

3. The risks and hazards associated with the following scenarios could not be found in the submission. Please point to the information in the submission or provide this information for the described scenarios:
 - a. using the device specifically right after removing from the refrigerator
 - b. needle breakage
 - i. during delivery of the drug or
 - ii. during potential “dumping” of all the drug contents due to software failure or
 - iii. other foreseeable instances where the needle has potential to break off
4. In the user risk assessment report, each of the risks were considered. You state the risk for low ambient pressure leading to injector leakage or low ambient pressure leads to plunger movement, CCI breach allows contamination caused by exposure of injector to high altitude >3500m/low pressure has no existing safeguards/controls. The Agency believes there should be a safeguard in place to mitigate carrying or using the device at high altitude (ie airplanes). Please provide language and appropriate documentation to prevent hazards/failures of the combination product at high altitudes/low pressure environments.

Device Design Verification

5. For the following tests, it appears that only one device was tested:
 - EMC Test (IEC 60601-1-2)
 - Alarm Notification Test (IEC 60601-1-8)
 - Delivery Confirmation Notification Test (IEC 60601-1-8)
 - Environment System Noise Test (IEC 60601-1-8)
 - Delivery Cancellation Onset Time Test

Please provide justification for the low sample size or provide testing using a statistically significant sample size.

6. In each of the following tests there was at least one device failure:
 - Deliverable volume test
 - Injection time test
 - System storage temperature and humidity test

The root cause analysis resulted in a design change to the (b) (4). However, it does not appear that once the change was implemented the devices were retested. Please

provide more details on the root cause analysis and results for the new devices with the (b) (4) change or justify why testing is not needed.

7. The following design changes were described in the Device Design Development documentation:

- (b) (4)

The verification for these changes is listed to be in the Device Design Verification document. The information for how the design change was implemented and how the test results were affected by this change could not be found in the submission. Please point to the location of this information in the submission or provide this information for each of the mentioned design changes to confirm the device still meets the functional and performance specifications.

Biocompatibility

8. The chemical characterization of the drug contacting components of the AMD (SmartDose (b) (4)) within the Summary Report and Biological Risk Assessment identifies the surface area of the test article as (b) (4) (using 37 devices); however, you did not provide an extraction ratio. This information is important, as the extraction ratio will directly impact the detection of extracted compounds. Please provide the extraction ratio as well as the justification for the ratio chosen for the chemical characterization.
9. The test article, AMD (SmartDose (b) (4) LM351010S and LM352010): Fluid path containing (b) (4) following (b) (4) sterilization. Please clarify if this represents the sterilization protocol for normal conditions of use.
10. You have identified your device as (b) (4); however, the Agency considers this device as externally communicating with blood path-indirect contact and therefore, the device should be evaluated for hemocompatibility. Please provide hemolysis testing for the fluid contacting components of the subject device.
11. Please provide the CAS number or the MSDS if available for the (b) (4) material used in the (b) (4) component of the (b) (4).

Software

12. Level of Concern

In Section 6.3.4 you concluded that the Level Of Concern was (b) (4). The Agency considers this device should be considered a MODERATE Level of Concern. Please correct the Level of Concern to MODERATE and provide the appropriate software

documentation recommended in the FDA guidance document, Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.

13. **Software Description**

You did not provide a comprehensive software description. Please provide a comprehensive overview of the device features that are controlled by software, and a description of the intended operational environment. This should include information on the programming language, the hardware platform, the operating system (if applicable) and the use of Off-The-Shelf software (if applicable).

14. **Device (including software) Hazard Analysis**

In the document entitled dFMEA you provided an incomplete risk analysis. However, the dFMEA referenced a document entitled Hazard Analysis RTP-046578, which the software reviewer was unable to locate. Please provide the Hazard Analysis RTP-046578 document. After providing this document, please review the Device Hazard Analysis Section to assure that you have provided a description of the hazards (including clinical hazards) presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

Note: This is typically done in an enumerated columnar form, wherein the first column identifies the hazard to the patient, the second column identifies from where in the system that hazard could be caused, the third column presents, for software caused hazards, where in the software the hazard could be caused, and the fourth column provides the specific details of the mitigation including identifying the enumerated tests.

15. **Required Software Documentation**

Once the requested Hazard Analysis Section is completed please provide updated Software Requirements Specifications, Software Design Specification, Traceability Analysis, and Verification/Validation documentation based on the updated Hazard Analysis.

16. **Run-Time Error Detection**

What tools, (such as static analysis tools), if any, do you use to detect run-time errors. For any such tool used, please identify what error types the tool detects, your method and process of applying the tool(s), and a summary report and/or conclusion about the results.

Note: some common run-time errors are:

1. Un-initialized variables
2. Type mismatches
3. Memory leaks
4. Buffer over/under flow
5. Dead and unreachable code
6. Memory/heap corruption
7. Unexpected termination
8. Non-terminating loops

9. Dangerous Functions Cast
10. Illegal manipulation of pointers
11. Division by zero
12. Race conditions

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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/s/

KATI JOHNSON
03/03/2016



BLA 125522/S-001

**ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT**

Amgen, Inc.
Attention: Adam Rupert
Senior Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-B
Thousand Oaks, CA 01320-1799

Dear Mr. Rupert:

We have received your Supplemental Biologics License Application (sBLA) submitted August 27, 2014, under section 351(a) of the Public Health Service Act for the following:

BLA NUMBER: 125522
SUPPLEMENT NUMBER: S-001
PRODUCT NAME: Repatha (evolocumab) injection, 140 mg/mL
DATE OF SUBMISSION: September 10, 2015
DATE OF RECEIPT: September 10, 2015

This supplemental application proposes to market a new device consisting of a 120 mg/mL prefilled cartridge copackaged with an automated mini-doser (AMD), and associated labeling revisions. The application contains clinical data.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **November 9, 2015**, in accordance with 21 CFR 601.2(a).

If the application is filed, the user fee goal date will be **July 10, 2016**.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

- In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at:
 - <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.
 -
 - When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to BLA 125522/S-001 submitted on September 10, 2015, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or

courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
09/21/2015

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-OPDP-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Metabolism and Endocrinology Products PM=Kati Johnson, 6-1234
---------------------------------	---

REQUEST DATE: 9/21/2015	IND NO.	NDA/BLA NO. BLA 125522/S-001	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) CMC supplement with clinical data
----------------------------	---------	------------------------------------	--

NAME OF DRUG: Repatha (evolocumab) inj.	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 6/15/2016
--	-------------------------	------------------------	---

NAME OF FIRM: Amgen, Inc.	PDUFA Date: 7/10/2016
----------------------------------	------------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) X PACKAGE INSERT (PI) X PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE X INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS
---	---	---

EDR link to submission: <\\CDSESUB1\evsprod\BLA125522\0082>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: Repatha was approved 8/27/2015 for the treatment of dyslipidemia. It was approved as a prefilled syringe (PFS) and autoinjector (AI). The firm is now proposing to market a device (automated mini-doser, AMD) which adheres to the skin and delivers (once monthly) a 3.5 ml dose over approx. 9 minutes.

Here is a link to the submission:
The clinical reviewer is Eileen Craig.
A team meeting will be scheduled once I have a more complete list of the assigned reviewers.
A consult has also been sent to patient labeling and OSE.
Thanks for your assistance.

SIGNATURE OF REQUESTER Kati Johnson, PM, DMEP	
--	--

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)
-----------------------	--------------------------------

eMAIL

HAND

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/s/

KATI JOHNSON
09/21/2015

REQUEST FOR CONSULTATION

TO (Division/Office):
Mail: OSE

FROM: Kati Johnson, PM, 6-1234
Division of Metabolism and Endocrinology Products

DATE 9/18/2015	IND NO.	NDA NO. BLA 125522/S-001	TYPE OF DOCUMENT CMC supp with clinical data	DATE OF DOCUMENT 9/18/2015
NAME OF DRUG Repatha (evolocumab) inj		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 6/15/2016

NAME OF FIRM: **Amgen, Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE--NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|---|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Repatha (evolocumab) was approved 8/27/2015 for the treatment of dyslipidemia. It was approved as a prefilled syringe (PFS) and an autoinjector (AI). The firm is now proposing to market an automated mini-doser (AMD) which attaches to the skin and administers a 420 mg dose (once monthly) over an approximately 9 minute timeframe. **The assigned reviewer for the initial BLA was Mishale Mistry.**

This application includes information on the device, results from conducted human factors studies, and proposed labeling. The clinical reviewer on this application is Eileen Craig.

Please provide me the name of the assigned reviewer and the RCM#.

Here is the link to the submission: <\\CDSESUB1\evsprod\BLA125522\0082>

Thanks for your assistance.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

KATI JOHNSON
09/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION	
TO: CDER-DMPP-PatientLabelingTeam		FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Metabolism and Endocrinology Products, Kati Johnson, PM, 6-1234	
REQUEST DATE: 10/18/2015	NDA/BLA NO.: BLA 125522/S-001	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)	
NAME OF DRUG: Repatha (evolocumab) inj.	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) 6/15/2016
SPONSOR: Amgen, Inc.		PDUFA Date: 7/10/2016	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
EDR link to submission: \\CDSESUB1\evsprod\BLA125522\0082			
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.			
COMMENTS/SPECIAL INSTRUCTIONS: Repatha was approved 8/27/2015 with a prefilled syringe (PFS) and an autoinjector (AI). They have now submitted a supplement to market an automated mini-doser (AMD), which is attached to the abdomen, arm or thigh and infuses 3.5 ml over approx. 9 minutes to provide a 420 mg dose once monthly. <u>The assigned reviewer for the initial BLA was Sharon Williams.</u> The clinical reviewer on this application is Eileen Craig. The firm has provided WORD and PDF versions of both the patient information and the IFU. Thanks for your help with this. Filing/Planning Meeting: TBD Mid-Cycle Meeting: TBD			
SIGNATURE OF REQUESTER			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one)	

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/s/

KATI JOHNSON
09/18/2015

MANDATORY: Send a copy of the consult request form to the

Office of Combination Products as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH Office of Compliance

Division:

Mail Code: HFZ-341

Consulting Reviewer Name: Francisco Vicenty

Building/Room #: WO66, Room 2642

Phone #: 6-5577

Fax #:

Email Address: francisco.vicenty@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: Metabolism & Endocrinology Prod

Mail Code: HF D-510

Requesting Reviewer Name: Kati Johnson, PM

Building/Room #: WO22, 3366

Phone#: 6-1234

Fax #:

Email Address: kati.johnson@fda.hhs.gov

RPM/CSO Name and Mail Code:

Requesting Reviewer's Concurring

Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 9/17/2015

Requested Completion Date: 5/15/2016

Submission/Application Number: 125522/S-001
(Not Barcode Number)

Submission Type: sBLA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: 9/10/2015

Official Submission Due Date: 7/10/2016

Name of Product: Repatha (evolocumab)

Name of Firm: Amgen, Inc.

Intended Use: no new indications being sought. Proposing to market a new device.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Here is the link to the submission: \\CDSESUB1\evsprod\BLA125522\0082

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

This BLA was approved 8/27/2015 as a prefilled syringe (PFS) and an autoinjector (AI), both 140 mg/mL. The CDRH reviewer for these applications was Lana Shiu. This current supplement is for an Automated Mini-Doser (AMD) 120 mg/mL. According to the application, this is a compact, sterile, disposable, electro-mechanical (battery-powered, micro-processor controlled), on-body injection device. It adheres to the skin for approximately 9 minutes to administer a 420 mg dose from the 3.5 mL prefilled cartridge.

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/s/

KATI JOHNSON
09/17/2015

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Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH

Division: GHD

Mail Code: HF

Consulting Reviewer Name: Keith Marin

Building/Room #: Bldg. 66/Room 2567

Phone #: 301-796-2462

Fax #:

Email Address: Keith.marin@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: DMEP

Mail Code: HF 510

Requesting Reviewer Name: Kati Johnson, PM

Building/Room #: Bldg 22, Room 3366

Phone#: 6-1234

Fax #:

Email Address: Kati.johnson@fda.hhs.gov

RPM/CSO Name and Mail Code:

Requesting Reviewer's Concurring

Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 9/17/2015

Requested Completion Date: 5/15/2016

Submission/Application Number: BLA 125522/S-001
(Not Barcode Number)

Submission Type: sBLA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: 9/10/2015

Official Submission Due Date: 7/10/2016

Name of Product: Repatha (evolocumab) injection

Name of Firm: Amgen, Inc.

Intended Use: no change to the original BLA indications. Firm is proposing to add a new device.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Here is the link to the submission: \\CDSESUB1\evsprod\BLA125522\0082

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

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