

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125522Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|--------------------------------------|---|
| NDA # BLA # 125522/original 1 | NDA Supplement # BLA Supplement # | If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i> |
| Proprietary Name: Repatha Established/Proper Name: evolocumab Dosage Form: solution | | Applicant: Amgen, Inc. Agent for Applicant (if applicable): N/A |
| RPM: Kati Johnson | | Division: Metabolism and Endocrinology Products |
| NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) | | <p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>8/27/2015</u> | | X AP <input type="checkbox"/> TA CR |
| <ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) | | X None |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain | | <input type="checkbox"/> Received |
| ❖ Application Characteristics ³ | | |

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|--|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation ** | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments: **Orphan drug designation for the HoFH indication only

| | |
|---|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i> | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| ❖ Public communications <i>(approvals only)</i> | |
| • Office of Executive Programs (OEP) liaison has been notified of action | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| • Indicate what types (if any) of information were issued | <input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| ❖ Patent Information (NDAs only) | |
| • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | <input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| CONTENTS OF ACTION PACKAGE | |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i> | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |

| Action Letters | |
|--|---|
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | X |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| <ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) | X Included in outgoing communications |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | X Included |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) | <input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None |
| <ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) | <input type="checkbox"/> Included |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | X Included |
| ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> Most-recent draft labeling | <input type="checkbox"/> Included |
| ❖ Proprietary Name | |
| <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) | 9/26/2014 9/23/2014 |
| ❖ Labeling reviews (<i>indicate dates of reviews</i>) | RPM: None 11/24/2014 DMEPA: <input type="checkbox"/> None 4/15/2015, 6/25/2015 DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input type="checkbox"/> None 8/11/2015 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input type="checkbox"/> None 6/26/2015 Other: Patient Labeling 8/13/2015 |
| Administrative / Regulatory Documents | |
| ❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>) | 11/24/2014 |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee | X Not a (b)(2) |
| ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input type="checkbox"/> Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> Applicant is on the AIP | <input type="checkbox"/> Yes X No |

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

| | |
|--|--|
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>6/24/2015</u> If PeRC review not necessary, explain: | |
| ❖ Breakthrough Therapy Designation | X N/A |
| <ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) | Denied under IND 105188 on 2/12/2014 and 8/13/2014 |
| <ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) | X |
| <ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p> | |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) | X |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) | X |
| ❖ Minutes of Meetings | |
| <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | X N/A or no mtg |
| <ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg CMC-1/24/2014 Clinical-4/10/2014 |
| <ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg CMC-11/2/2012 Clinical 7/10/2012 |
| <ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) | <input type="checkbox"/> N/A 2/12/2015 |
| <ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> N/A 5/28/2015 |
| <ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) | N/A |
| ❖ Advisory Committee Meeting(s) | <input type="checkbox"/> No AC meeting |
| <ul style="list-style-type: none"> • Date(s) of Meeting(s) | 6/10/2015 |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input type="checkbox"/> None 8/27/2015 |
| Division Director Summary Review (<i>indicate date for each review</i>) | X None |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None 8/25/2015 |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input type="checkbox"/> None 9/27/2015, #9 |
| Clinical | |

| | | |
|---|--|---|
| ❖ Clinical Reviews | | |
| • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) | | X No separate review |
| • Clinical review(s) (<i>indicate date for each review</i>) | | 10/20/2014, 8/24/2015 |
| • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | | X None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | | Page 50 of 8/24/2015 review |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) | | X None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | | <input type="checkbox"/> N/A 7/15/2015, no schedule |
| ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | | X None |
| ❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>) | | <input type="checkbox"/> None requested 5/5/2015 |
| Clinical Microbiology | | X None |
| ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) | | <input type="checkbox"/> No separate review |
| Clinical Microbiology Review(s) (<i>indicate date for each review</i>) | | <input type="checkbox"/> None |
| Biostatistics | | <input type="checkbox"/> None |
| ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) | | X No separate review |
| Statistical Team Leader Review(s) (<i>indicate date for each review</i>) | | X No separate review |
| Statistical Review(s) (<i>indicate date for each review</i>) | | <input type="checkbox"/> None 10/9/2014, 6/22/2015 (2) |
| Clinical Pharmacology | | <input type="checkbox"/> None |
| ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) | | <input type="checkbox"/> No separate review |
| Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) | | <input type="checkbox"/> No separate review |
| Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | | <input type="checkbox"/> None 10/17/2014, 12/2/2014, 1/15/2015,6/1/2015 |
| ❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>) | | X None requested |

| Nonclinical <input type="checkbox"/> None | |
|--|--|
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (<i>indicate date for each review</i>) | No separate review 8/20/2015 |
| • Supervisory Review(s) (<i>indicate date for each review</i>) | X No separate review |
| • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | <input type="checkbox"/> None 10/9/2014, 5/15/2015 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | X None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input type="checkbox"/> No carc 12/29/2014 |
| ❖ ECAC/CAC report/memo of meeting | <input type="checkbox"/> None Included in P/T review, page 150 |
| ❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>) | X None requested |
| Product Quality <input type="checkbox"/> None | |
| ❖ Product Quality Discipline Reviews | |
| • Tertiary review (<i>indicate date for each review</i>) | X None |
| • Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>) | X None |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>) | <input type="checkbox"/> None 10/22/2014 7/29/2015 |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>) | None 6/2/2015, 6/17/2015, 7/9/2015 |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) | Page 30 of 6/2/2015 review |
| <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) | N/A |
| <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) | N/A |
| ❖ Facilities Review/Inspection | |
| <input type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>) | X Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable |

| Day of Approval Activities | |
|---|--|
| ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>) |
| <ul style="list-style-type: none"> • Finalize 505(b)(2) assessment | <input type="checkbox"/> Done |
| ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager | <input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>) |
| ❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications | <input type="checkbox"/> Done |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | <input checked="" type="checkbox"/> Done |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | <input checked="" type="checkbox"/> Done |
| ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name | <input checked="" type="checkbox"/> Done |
| ❖ Ensure Pediatric Record is accurate | <input checked="" type="checkbox"/> Done |
| ❖ Send approval email within one business day to CDER-APPROVALS | <input checked="" type="checkbox"/> Done |

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

/s/

KATI JOHNSON
09/24/2015

From: Johnson, Kati
To: "Kubasak, Marc"; Rupert, Adam
Cc: Johnson, Kati (Kati.Johnson@fda.hhs.gov)
Subject: RE: Repatha PI to firm 08 27 2015
Date: Thursday, August 27, 2015 1:42:00 PM

We note your agreement to the labeling dated 8/27/2015.

Thanks, Kati

From: Kubasak, Marc [mailto:mkubasak@amgen.com]
Sent: Thursday, August 27, 2015 11:52 AM
To: Johnson, Kati; Rupert, Adam
Subject: RE: Repatha PI to firm 08 27 2015

Hi Kati,

I am confirming that Amgen find the change **acceptable**. We will not resend the UPSI formally or informally😊

Quick question- can I assume the IFUs are acceptable or should I have the team on the ready to review possible changes?

(b) (4)

Anything else you need?

Thanks

Marc

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Thursday, August 27, 2015 7:49 AM
To: Kubasak, Marc; Rupert, Adam
Subject: Repatha PI to firm 08 27 2015
Importance: High

Hi Marc/Adam,

We have a single revision left for which we need your OK.

If this labeling is acceptable, you can just respond to this email and let me know it is acceptable. You do NOT need to send the labeling back to me or submit it officially; I can archive your acceptance email, and attach this version of this labeling (Clean version) to that email.

Kati

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products

15 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS)
immediately following this page

Food and Drug Administration
301-796-1234
Kati.johnson@fda.hhs.gov

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

/s/

KATI JOHNSON
08/31/2015

From: [Kubasak, Marc](#)
To: [Johnson, Kati](#); [Rupert, Adam](#)
Cc: [Hanan, Elisabeth](#)
Subject: RE: Repatha PMR/PMC list, need final clearance
Date: Wednesday, August 26, 2015 12:55:46 PM

Hi Kati,

Confirming receipt.

Marc

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Wednesday, August 26, 2015 9:53 AM
To: Kubasak, Marc; Rupert, Adam
Cc: Hanan, Elisabeth
Subject: Repatha PMR/PMC list, need final clearance

Please get this back to us as soon as possible.

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

**PMR/PMC list for BLA 125522
REPATHA (evolocumab)**

While review of your application continues, we are sending you a draft list of PMRs/PMCs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR and PMC studies/trials to us with milestone dates, which include **Final Protocol Submission**, **Study Completion** and **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.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA.
- For PMCs, include a statement that you agree to conduct these studies/trials.

Postmarketing Requirements

- 1) Conduct an efficacy and safety study evaluating [Repatha \(evolocumab\)](#) in patients with heterozygous familial hypercholesterolemia (HeFH) ages 10 years to less than 18 years. The study will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study (Part A) followed by an 18-month open-label extension in patients 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C \geq 130 mg/dL (Part B).

| | |
|--|----------------|
| Final Protocol (b) (4) -Submission (Part A): | December 2015 |
| Final Protocol (b) (4) -Submission (Part B): | December 2015 |
| Study Completion (Part A): | March 2018 |
| Study Completion (Part B): | September 2019 |
| Final Report Submission (Parts A and B): | April 2020 |

- 2) Conduct a prospective observational study of pregnant women exposed to Repatha (evolocumab) to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to evolocumab and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression. The study should have validated/adjudicated outcomes, a comparator group, be powered to detect the outcomes of interest, and include the justification for the proposed detectable differences in incidence rates.

| | |
|-----------------------------|---|
| Final Protocol Submission: | August 2016 |
| Interim Report Submissions: | October 2017 (b) (4) |
| | <u>October 2018</u> |
| | <u>October 2019</u> |
| | <u>October 2020</u> |
| | <u>October 2021</u> |
| | <u>October 2022</u> |
| | <u>October 2023</u> |
| | <u>October 2024</u> |
| | <u>October 2025</u> |
| | <u>October 2026</u> |
| | <u>October 2027</u> |
| | <u>October 2028</u> |
| | <u>October 2029</u> |
| Study Completion: | October 2030 |
| Final Report Submission: | April 2031 |

- 3) Conduct a large, randomized, controlled, long-term trial in which the incidence and severity of new-onset diabetes mellitus, injection site reactions, hypersensitivity, immunogenicity, and adverse events potentially related to demyelination with Repatha (evolocumab) will be evaluated.

| | |
|----------------------------|----------------|
| Final Protocol Submission: | January 2016 |
| Trial Completion: | September 2017 |
| Final Report Submission: | June 2018 |

- 4) Conduct a randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with Repatha (evolocumab) treatment. The trial must be adequately powered to exclude a clinically meaningful adverse effect.

| | |
|----------------------------|----------------|
| Final Protocol Submission: | November 2015 |
| Trial Completion: | September 2017 |
| Final Report Submission: | June 2018 |

Postmarketing Commitments:

- 5) To establish the evolocumab drug substance (DS) stability acceptance criteria for the 9- and 12-month stability timepoints at the (b) (4) C condition based on available stability data.

Study Completion: November 2016
Final Report Submission: December 2016

- 6) To demonstrate that the identity by ELISA assay performed at Amgen Thousand Oaks (ATO) for evolocumab drug product (DP) lot release testing functions within the parameters identified for the validated assay prior to releasing evolocumab lots tested for identity at ATO.

Study Completion: September 2015
Final Report Submission: December 2015

- 7) To re-evaluate the evolocumab drug substance (b) (4) limits (b) (4). The final report should include the corresponding data, the analysis and statistical plan used to evaluate (b) (4) limits, and any proposed changes to the limits.

Study Completion: March 2017
Final Report Submission: July 2017

- 8) To re-evaluate the evolocumab DP acceptance criteria (b) (4) as specified in PMC 7. The DP lots will include the lots which were used in the analysis of specifications submitted in the BLA and subsequent drug product lots manufactured. The final report should include the corresponding data, the analysis and statistical plan used to evaluate the (b) (4) limits, and any proposed changes to the limits. The analysis should also include linkage to the drug substance (b) (4) limits (b) (4) based on the re-evaluation specified in PMC 7.

Study Completion: March 2017
Final Report Submission: July 2017

- 9) To re-evaluate the evolocumab drug product release and stability acceptance criteria for the prefilled syringe and autoinjector presentations after the manufacture of DP lots from an additional 2 DS manufacturing campaigns. The final report should include the

corresponding data, the analysis and statistical plan used to evaluate the results and acceptance criteria, and any proposed changes to the criteria.

| | |
|--------------------------|------------|
| Study Completion: | March 2017 |
| Final Report Submission: | July 2017 |

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

/s/

KATI JOHNSON
08/27/2015

From: [Kubasak, Marc](#)
To: [Johnson, Kati](#)
Cc: [Smith, James P. \(FDA/CDER\)](#); [Craig, Eileen](#); [Rupert, Adam](#)
Subject: RE: REPATHA USPI and PPI
Date: Wednesday, August 26, 2015 2:35:57 PM

Thanks Kati.

I confirm receipt of this email☺

Marc

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Wednesday, August 26, 2015 11:26 AM
To: Kubasak, Marc
Cc: Smith, James P. (FDA/CDER); Craig, Eileen; Rupert, Adam; Johnson, Kati
Subject: RE: REPATHA USPI and PPI

Marc, For BLA 125522, Repatha (evolocumab), we find the **PPI revisions** contained in the email sent on 8/25/2015 at 10:18 pm to be **ACCEPTABLE**.

Thanks for your assistance with this.

Kati

From: Kubasak, Marc [mailto:mkubasak@amgen.com]
Sent: Tuesday, August 25, 2015 10:18 PM
To: Johnson, Kati
Cc: Smith, James P. (FDA/CDER); Craig, Eileen; Rupert, Adam
Subject: REPATHA USPI and PPI

Dear Kati,

Please find attached the clean and redline USPI and PPI. Please contact me with any questions.

If you could, please confirm receipt of all 4 documents.

Have a great night.

Best,

Marc

Marc Kubasak, Ph.D., RAC
Regulatory Affairs
Amgen
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-1799
805-447-1000
Direct Dial: 805-313-6240
General Fax: 805-449-7232

FDA Fax: 805-480-1330
E-mail: mkubasak@amgen.com

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

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/s/

KATI JOHNSON
08/26/2015

From: Johnson, Kati
To: [Kubasak, Marc \(mkubasak@amgen.com\)](mailto:mkubasak@amgen.com)
Subject: BLA 125522, Repatha (evolocumab) carton/container labeling comments
Date: Monday, April 27, 2015 9:24:00 AM
Attachments: [125522 carton container comments to firm 4 27.pdf](#)

Hi Marc,

Here are our comments. They are asking for revised labeling by 5/5/2015. If that is an issue, please let me know. If the labeling you submit contains a unique identifier and adequately responds to these requests, then we can consider them Final Printed Labeling. Most of the review are still ongoing, so sending you this labeling does not necessarily imply that the drug is going to get approved.

Contact me if you have any questions.

Kati

Kati Johnson
Senior Regulatory Project Manager
Food and Drug Administration
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234

BLA 125522/0
Repatha (evolocumab)
Container Label and Carton Labeling Comments

We have the following comments regarding your proposed container labels and carton labeling submitted on November 24, 2014.

A. Carton Labeling for Prefilled Syringe (PFS)

1.  (b) (4)
1
2. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3. Add the dosage form, Injection, to appear under the proper name, evolocumab, in the identical font size and color as the proper name. Due to lack of space on the small prefilled syringe (PFS) container label, omission of the finished dosage form is acceptable.
4. Increase the prominence of the strength that currently appears below the proper name per 21 CFR 201.15(a)(6) by increasing the font size.
5. Relocate the net quantity statement '(1 mL)' away from the product strength and decrease its prominence as the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.²

¹ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

² See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.
"The net quantity statement should appear on the PDP but should be separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded)."

6. Revise the strength statement in the blue circle from (b) (4) to "140 mg/mL", as per USP 12/1/2014 – 4/30/2015 General Chapters: <1> Injections. The strength per total volume should be the primary and prominent expression on the principal display panel for single-dose injectable products.
7. Change any reference from "single-use" to "Single-Dose" to ensure that the entire dose is delivered and the injectable device is not reused. "Single-Dose" is the appropriate term per United States Pharmacopeia USP 37/NF 32, 12/1/14 – 4/30/15, General Chapters: <659> PACKAGING AND STORAGE REQUIREMENTS.
8. Unbold the Rx only statement as it competes in prominence with other important information on the labels and labeling.³
9. Relocate the route of administration, For Subcutaneous Use Only, to appear under the the statement, 140 mg/mL Prefilled Syringe. Include the package type statement, to be located immediately after the route of administration, to clearly identify how the drug product should be safety used and handled. For example: "For Subcutaneous Use Only. Single-Dose Only."
10. Include complete storage instructions if Repatha is removed from the refrigerator, as mentioned in Section 16 of the Prescribing Information labeling. The complete instructions should provide instructions separate instructions for patients to store at room temperature. Additionally, provide a space for documentation of the date of initial removal from the refrigerator. For example:

Pharmacy

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

Patient/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. Use space below to record the date removed from the refrigerator.

³ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. "Other information on the PDP such as the Rx-only statement...should not compete in size and prominence with the important information listed above."

11. Revise the list the names of the inactive ingredients in alphabetical order in the following format “inactive ingredient (amount)” per United States Pharmacopeia (USP) 37/NF 32 (12/1/2014 - 4/30/2015), General Chapters: <1091> Labeling of Inactive Ingredients. For example:

Each single-dose prefilled syringe contains a 1 mL deliverable volume of 140 mg evolocumab in a sterile, preservative-free solution, containing acetate (1.2 mg), polysorbate 80 (0.1 mg)..., Sodium hydroxide may be used to adjust to pH 5.0.

Note use of the term “single-dose” and deletion of the hyphen (1-mL to 1 mL) and trailing zero (0.10 mg to 0.1 mg).

12. Images should represent the actual dosage form (i.e., prefilled syringe or prefilled autoinjector) and reflect the true size and color; schematic or computer-generated images should not be used. We recommend removing the images of the prefilled syringe and prefilled autoinjector on the carton labeling (and carton tray labeling for the prefilled syringe).⁴ If an actual image of the prefilled syringe or prefilled autoinjector is used, the image should not compete in size or prominence with the proprietary name and/or established name and strength.

B. Carton Labeling for Autoinjector

1. See comments A1 through A12.
2. Delete (b) (4) that appears below the proper name.
3. Add “SureClick” to appear with “Repatha”. For example:

Repatha SureClick
(evolocumab)
Injection
140 mg/mL
Prefilled Autoinjector
For Subcutaneous Use Only.
Single-Dose Only.

⁴ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

“If an image is used on the PDP, the image should appear at the bottom of the label and should not compete in size or prominence with the proprietary and/or nonproprietary name and strength information. Images should...reflect the true size, color, and imprint.”

C. PFS Blister Tray Labeling

1. See comments A1 to A12.
2. Delete the list of ingredients to decrease crowding and readability. The list of ingredients appears on the carton labeling.
3. Relocate the statements, "Sterile Solution – No Preservative", to the right side of the panel.
4. Delete (b) (4) above the barcode and replace with the text that appears on the carton labeling.

D. Autoinjector Container Label

1. See comments A1, A2, A3, A5, A7, A8, B2, and B3.
2. Delete (b) (4) and replace with Single-Dose Only. The latex warning and instructions to consult accompanying documents appear on the carton labeling.

E. PFS Container Label

1. See comments A1, A2, A5, A7, and A8.
2. We consider the PFS Container Label a partial label due to its small size per 21 CFR 610.60(c). Our recommendations below are intended to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability
3. Add the route of administration statement "For Subcutaneous Use Only" below the strength statement.
4. Delete the statement "(b) (4)" to provide space for the route of administration statement.
5. Delete the (b) (4) and replace with Single-Dose Only.

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/s/

KATI JOHNSON
04/27/2015



BLA 125522

MID-CYCLE COMMUNICATION

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

Dear Dr. Kubasak:

Please refer to your Biologic License Application (BLA) submitted August 27, 2014, under section 351(a) of the Public Health Service Act for Repatha (evolocumab) injection.

We also refer to the teleconference between representatives of your firm and the FDA on February 12, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: February 12, 2015, noon – 1 pm EST

Application Number: BLA 125522

Product Name: Repatha (evolocumab) injection

Indication: Hyperlipidemia and Mixed Dyslipidemia
Homozygous Familial Hypercholesterolemia (HoFH)

Applicant Name: Amgen Inc.

Meeting Chair: James P. Smith, MD, MS

Meeting Recorder: Kati Johnson

FDA ATTENDEES

Office of Drug Evaluation and Research II (ODE II)
Curt Rosebraugh, MD, MPH-Director
Mary Parks, MD-Deputy Director
Sara Stradley-Associate Director for Regulatory Affairs

Division of Metabolism and Endocrinology Products
Jean-Marc Guettier, MD-Director
James P. Smith, MD, MD-Deputy Director
Eileen Craig, MD-Clinical Reviewer
Kati Johnson-Senior Regulatory Project Manager

Office of Biostatistics
Mark Rothmann, PhD-Lead Statistical Reviewer
Shuxian Sinks, PhD-Statistical Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology II
Jaya Vaidyanathan, PhD-Clinical Pharmacology Team Leader (Acting)
Sury Sista, PhD-Clinical Pharmacology Reviewer

Office of Clinical Pharmacology/Division of Pharmacometrics
Nitin Mehrotra, PhD-Team Leader
Justin Earp, PhD-Reviewer

Office of Pharmaceutical Quality
Patricia Hughes, PhD-Microbiologist/Quality Assessment Lead
Lakshmi Narasimhan, PhD-Microbiologist

Center for Biologics, Office of Biologic Products
Chana Fuchs, PhD-Product Quality Team Lead, DMA

EASTERN RESEARCH GROUP ATTENDEES
Christopher Sese

APPLICANT ATTENDEES

| Name | Title |
|-----------------------------|--|
| Steven Galson, MD, MPH | Vice President, Global Regulatory Affairs |
| Mark Taisey | Vice President, Global Regulatory Affairs |
| Rob Scott, MD | Vice President, Global Development (Therapeutic Area Head) |
| Scott Wasserman, MD | Vice President, Global Development (Therapeutic Area Head) |
| Kathy Kross | Executive Director, Regulatory Affairs (Inflammation, Metabolism, and Endocrine Therapeutic Area Head) |
| Dominique Bertin-Millet, MD | Executive Medical Director, Global Safety (Therapeutic Area Head) |
| Arline Nakanishi, MS | Executive Director, Biostatistics (Therapeutic Area Head) |
| Ashley Hall, JD, RAC | Director, Regulatory Affairs (Global Regulatory Lead) |
| Lisa Carlson | Director, Regulatory Affairs (CMC Regulatory Lead) |
| Graeme Moffat, PhD | Director, Preclinical, Comparative Biology and Safety Sciences (Nonclinical Lead) |
| Maurice Emery, PhD | Director, Preclinical, Comparative Biology and Safety Sciences |
| Thomas Liu, PhD | Director, Biostatistics (Global Statistical Lead) |
| Michelle Geller, MD | Medical Director, Global Safety (Global Safety Lead) |
| Marc Kubasak, PhD, RAC | Senior Manager, Regulatory Affairs (US Regulatory Lead) |
| Adam Rupert, MS, RAC | Manager, Regulatory Affairs (US Regulatory Lead) |
| Shirin Pillay, RAC | Senior Associate, Regulatory Affairs (US Regulatory Professional) |
| Hemant Mistry | Senior Project Manager |
| Rex Atienza | Project Manager |

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If

you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical

The clinical review is progressing. No new significant issues have been identified that warrant additional discussion. Clinical information requests have been sent as needed during the review cycle, including requests sent to Amgen on 2/9 and 2/11/2015. It is premature to discuss potential labeling.

Clinical Statistics

Primary analyses of all major studies have been verified. No statistical issues have been identified as significant issues at this point.

Clinical Pharmacology

It appears that the data available to support the use of 420 mg evolocumab Q2W in non-apheresis patients with homozygous familial hypercholesterolemia (HoFH) is rather limited. First, in those non-apheresis patients that switched (Open-label study 0271) from QM to Q2W, the median decrease in LDL-C after the switch compared with before the switch was approximately six percent, whereas the between-subject variability in response remained the same. This is apparent when evaluating each individual's time course of response. Some individuals showed mild improvement, whereas others exhibited no change in LDL-C after switching. (b) (4)

The following questions were intended to be included in a previously issued request for clinical information, but were inadvertently omitted from that request. The questions will be forwarded to Amgen following the meeting:

1. We note that there is a decrease (up to 50%) in evolocumab exposure in hepatic impaired patients (Study 20120341). Please provide an explanation as to why this decrease is observed.
2. What percentage of evolocumab, if any, is cleared by the apheresis procedure?

Chemistry, Manufacturing and Controls

FDA is in the middle of reviewing the CMC section, having covered characterization, development and comparability assessments as well as (b) (4) drug substance manufacturing (b) (4) Review of drug substance microbiology is also close to completion. Drug Product review is ongoing. At this juncture we have not identified major issues, but a request for additional information related to the sections reviewed was issued on February 10, 2015 with a request for completion by March 2, 2015.

Microbiology

Information request items submitted on January 23, 2014, were reiterated. The current Container Closure Integrity (CCI) test used for the PFS is not sensitive from a microbiological perspective and a sensitive method for CCI testing should be developed. Amgen stated that they have committed to requalify the CCI testing in their response. Additionally, (b) (4) validation studies have to be revalidated because the validation study was conducted using (b) (4)

Dr. Smith noted that the nonclinical review team had not raised significant issues to be communicated at this meeting.

3.0 INFORMATION REQUESTS

Information requests have been sent from the project manager to the regulatory contact person at Amgen as they have been requested by the reviewers throughout the review to date.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

None to communicate at this time. Representatives from the Office of Surveillance and Epidemiology were not in attendance, but Dr. Smith noted that it is premature to comment on the potential need for post-marketing requirements or post-marketing commitments.

5.0 ADVISORY COMMITTEE MEETING

The application is tentatively scheduled for discussion on Wednesday, June 10, 2015.

In response to questions from Dr. Galson, the Division stated that we are not at liberty to discuss applications of other sponsors, including the scheduling of potential advisory committee meetings for such applications.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The late-cycle meeting/telecon is currently scheduled for May 28, 2015, at 12 noon.

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/s/

JEAN-MARC P GUETTIER
04/01/2015

From: [Kubasak, Marc](#)
To: [Johnson, Kati](#)
Subject: RE: BLA 125522, Repatha (evolocumab), Revised PI
Date: Tuesday, March 31, 2015 2:49:59 PM

Hi Kati,

I am confirming receipt. Three weeks puts us at around 21 April 2015. I will let you know if we have any issues meeting a date close to that date.

Thanks so much.

Marc

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Tuesday, March 31, 2015 11:33 AM
To: Kubasak, Marc
Subject: BLA 125522, Repatha (evolocumab), Revised PI

Hi Marc,

Here is the revised labeling that I mentioned.

These are preliminary comments.

It would be helpful if you used Track Changes to accept the changes you are OK with. One less thing to discuss later. Some of these are PLR comments, and some are reformatting of the information to make it clearer ((b) (4) (b) (4)

If there are changes that we made that you don't agree with, we request that you "accept" our changes, and then use Track changes to make your revisions, even if you go back to your initial wording.

Sections 8.1-8.3 need to be redone to meet the new PLLR guidance document

Section 12 ADME information needs to be redone to meet the ClinPharm guidance document. I give you the titles of both documents in the labeling, but if you don't have them and can't find them, let me know.

Do not assume that if we have NOT commented on your labeling that we find it acceptable. Most of the disciplines are still in the throes of their review and are not yet prepared to do the nitty gritty labeling revisions.

Lastly, this labeling does NOT contain the revisions that you made prior to sending me a revised PI on 11/24 (I think). The PLR person who worked on this worked on the labeling that was included in the initial BLA. Sorry about that. It would be great if you could include those revisions when you send it back.

Let me know if you can get this back to us in 3 weeks.

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/s/

KATI JOHNSON
04/01/2015

Executive CAC

Date of Meeting: December 9, 2014

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Linda Fossom, Ph.D., DPP, Alternate Member
Karen Davis-Bruno, Ph.D., DMEP, Pharm Tox Supervisor
C. Lee Elmore, Ph.D., DMEP, Presenting Reviewer

Author of Minutes: C. Lee Elmore, Ph.D., DMEP

The following information reflects a brief summary of the Committee discussion and its recommendations.

BLA #125522

Drug Name: Repatha (Evolocumab, AMG-145)

Sponsor: Amgen, Inc.

Background

Evolocumab is a PCSK9 inhibitor monoclonal antibody being developed by Amgen, Inc. for the chronic treatment of hypercholesterolemia. No genetic toxicology studies have been conducted. The Executive CAC provided concurrence on dose selection for the hamster carcinogenicity study protocol (minutes dated 1 September 2011).

Hamster Carcinogenicity Study

Golden Syrian hamsters (60/sex/group) were administered evolocumab subcutaneously at 0, 10, 30, and 100 mg/kg once every two weeks in 10 mM sodium acetate, 9% (w/v) sucrose, 0.004% (w/v) polysorbate-20 (pH 5.2). Doses were selected based on achievement of a maximal pharmacologic effect in the hamster that is at least comparable to the anticipated systemic clinical exposure.

The applicant terminated the entire female study prematurely at Week 86 with concurrence from CDER's Executive CAC, based on excess mortality in the control group. The male study was terminated as scheduled at Week 105.

There was no significant effect of evolocumab on male or female Golden Syrian hamster mortality or body weight. The pharmacodynamic effect of evolocumab was maintained throughout the study, which indicates exposure was durable for the duration of the study. No drug-related tumors were observed in a lifetime carcinogenicity study with evolocumab at up to 100 mg/kg administered once every two weeks.

Executive CAC Recommendations and Conclusions

Hamster:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Abby Jacobs, Ph.D.

Acting Chair, Executive CAC

cc:\

/Division File, DMEP
/KDavisBruno, DMEP
/CEImore, DMEP
/KJohnson, DMEP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
12/10/2014

ABIGAIL C JACOBS
12/10/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 24, 2014

Application Number: BLA 125522

Product Name: Repatha (evolocumab) injection

Sponsor/Applicant Name: Amgen, Inc.

Subject: Bridging of Formulation used in a pivotal study to the formulation proposed for market

FDA Participants :

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, MD-Division Director

James P. Smith, MD, MS-Deputy Director (Acting) and Clinical Team Leader

Kati Johnson-Regulatory Project Manager

Applicant Participants:

Amgen, Inc.

Ashley Hall, JD, RAC-Director, Regulatory Affairs (Global Regulatory Lead)

Marc Kubasak, PhD, RAC-Sr. Manager, Regulatory Affairs (US Regulatory Lead)

Shirin Pillay, RAC-Senior Associate, Regulatory Affairs (US Regulatory Professional)

Mark Taisey-Vice President, Global Regulatory Affairs

Kathy Kross – Executive Director, Regulatory Affairs (Therapeutic Area Head)

Adam Rupert, Manager, Regulatory Affairs (US Regulatory Lead)

1.0 BACKGROUND:

A BLA for Repatha (evolocumab) was submitted August 27, 2014, proposing to market the product for the treatment of primary hyperlipidemia and mixed dyslipidemia and homozygous familial hypercholesterolemia (HoFH).

The investigational product used in Phase 1 and Phase 2 studies was manufactured using Process 1 and has a different formulation ((b) (4)) than the to-be marketed product used in the Phase 3 studies, which was manufactured using Process 2. The only placebo-controlled long-term (52-week) trial (20110109) was initiated as a Phase 2 trial but was subsequently re-categorized by the applicant to a Phase 3 trial. This particular trial did not use the to-be-marketed product, and this trial is the only placebo-controlled trial in the application that provides safety and efficacy information of longer than 12 weeks duration.

The filing date for the application is October 25, 2014.

2.0 DISCUSSION:

The firm was called and notified of the following:

As you know, during our communications around the time of the pre-BLA meeting when we were discussing the size of your safety database, we became aware that you would be relying

heavily on your phase 2 program, especially for our evaluation of long-term safety. Unfortunately, your phase 2 program did not use the to-be-marketed formulation and method of administration. Furthermore, we noted that your only placebo-controlled long-term safety data comes from the trial that you refer to as DESCARTES, and you did not use the to-be-marketed formulation in this trial either, despite you stating at the EOP2 meeting that the phase 3 trials would be performed with the formulation intended for market.

Only after you provided a breakdown of your phase 2 vs. phase 3 safety database, at our request, did we realize the extent to which you would be relying on a formulation of your drug not intended for market. In our post-BLA-meeting comments, we highlighted this and asked how you planned to bridge your phase 2 and phase 3 programs for the evaluation of safety.

During our filing review, the relevant disciplines have reviewed what you have submitted with regard to a bridge between Process 1 and Process 2. In short, our assessment during the filing review is that your bridge is very, very weak, (b) (4)

 In addition, as we noted around the time of the pre-BLA meeting, you have very little long-term data for your to-be-marketed product; it appears, for example, that only 16 patients treated with evolocumab have completed year 1 – the controlled, albeit open-label, period – of your phase 3 extension study. This will be a substantial review issue, but I bring it up because it underscores the reliance our review will have on a drug substance process that will not be marketed, which is a concern of its own.

We will have more detailed recommendations in our 74-day letter, but we strongly suggest that you begin designing a clinical PK/PD study that could be used to bridge Process 1 and Process 2 if needed. This would need to be performed in an appropriate population, with an appropriate duration, and using a dose expected to be on the steep portion of the dose-response curve with respect to a relevant pharmacodynamic biomarker or biomarkers so that you would have assay sensitivity for formulation-related differences in PK/PD. If, in fact, these data are needed and you are able to submit the data during this review cycle, it is certainly possible that this would be considered a major amendment to the application.

In addition, you should be aware that if we determine that you have not adequately bridged your two formulations with data that have been submitted to the BLA, leaving us uncertain to what extent your phase 2 efficacy and safety data reflects your to-be-marketed product, we would not anticipate taking this application to an advisory committee for discussion. As we have stated throughout your development program, our primary safety concerns with PCSK9 inhibition relate more to long-term use than to short-term use. If the majority of your long-term data derive from a drug formulation that will not be marketed, we must be certain that these data are relevant to the marketed product.

As I hope you can tell, we were extremely close to refusing to file this application, and these issues have been discussed with senior management across relevant offices reviewing your application. Ultimately, we have decided to file the application given that you have at least provided some data to review, which you believe should bridge your phase 2 and phase 3

programs. Our filing of the application, however, should not be reflected as our acceptance that these data are adequate; it simply indicates that we are willing to subject the application to further review.

In response to a question from the firm, the Division encouraged the firm to submit the proposed PK/PD protocol for review prior to conducting it, and committed to an expeditious review of the protocol once submitted.

The firm also asked whether it would be useful to separate out Process 1 from Process 2 data in the ISS to show consistency. The Division responded that this would be useful and that an information request from the clinical reviewer would be forthcoming.

Before ending the call, the Division also informed the firm that, unrelated to the bridging issues, the Division has made the decision that the application would be reviewed under a standard review timeline. The observed treatment effect on LDL-cholesterol among patients with HoFH was simply not compelling enough compared with alternative therapies to warrant a priority review. (b) (4)

The firm stated their understanding.

3.0 ACTION ITEMS:

FDA will provide additional comments in the 74-day letter regarding the design of the PK/PD study to be conducted. The letter will issue on or before November 9, 2014.

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/s/

KATI JOHNSON
11/13/2014



BLA 125522

**FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED**

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

Dear Dr. Kubasak:

Please refer to your Biologics License Application (BLA), dated and received on August 27, 2014, submitted under section 351(a) of the Public Health Service Act for Repatha (evolocumab) injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application was filed on October 25, 2014. The review classification for this application is **Standard**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm> . Therefore, the user fee goal date is August 27, 2015.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 30, 2015. In addition, the planned date for our internal mid-cycle review meeting is January 29, 2015. We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical & Clinical Pharmacology

1. As we communicated to you during a teleconference on October 24, 2014, we identified a major review issue during our filing review of your application. During our discussions

regarding the size of your safety database during the weeks that followed your pre-BLA meeting, we became aware that you would be relying heavily on your phase 2 program for this application, especially for our evaluation of long-term safety. Unfortunately, your phase 2 program used neither the to-be-marketed formulation nor the intended method of administration. This was true even for DESCARTES, the trial that provides your only placebo-controlled 52-week data for safety and efficacy. We highlighted this issue in our post-BLA-meeting comments and asked how you planned to bridge your phase 2 and phase 3 programs for the evaluation of safety. During our filing review, the relevant disciplines reviewed what you have submitted with regard to a bridge between the clinical drug substance (Process 1) and the commercial drug substance (Process 2) and determined that your bridge is very weak, (b) (4)

and therefore it remains uncertain if the safety data from Process 1 material can be extrapolated to those from Process 2 material. During our October 24, 2014 teleconference, we recommended that you begin designing a clinical study that could be used to bridge your phase 2 and phase 3 programs. We also informed you that if we remain uncertain to what extent your phase 2 efficacy and safety data reflects your to-be-marketed product, we would not anticipate taking this application to an advisory committee for discussion during this review cycle.

We received your official submission of a protocol synopsis for a proposed PK/PD bridging study on November 5, 2014 (Study 2011167, “An Open Label Randomized Parallel Study in Healthy Volunteers to Compare the Pharmacokinetics of Evolocumab (AMG 145) Process 2 Material (Test) to Evolocumab Process 1 Material (Reference) When Delivered Subcutaneously by Prefilled Autoinjector/Pen and by Syringe”). To the extent that we can evaluate the proposed study given the brevity of the synopsis provided, we agree that the proposed primary objective to demonstrate the PK equivalence of evolocumab Process 2 material (test) to Process 1 material (reference) is reasonable. In addition to evaluating AUC_{last} and C_{max} , you should also include AUC_{inf} as a primary endpoint. Furthermore, because detail is not provided regarding the administration of the Process 1 formulation, we remind you that both arms should receive the products as administered in their respective phases of development (b) (4)

. We concur with the collection of samples for anti-evolocumab antibodies.

As we indicated during the October 24, 2014 teleconference, we will also be requesting safety data presented in a manner that facilitates comparison between phase 2 and phase 3. You will receive details regarding this request for information under separate cover.

2. As we have stated previously, it will be a review issue whether evolocumab could be approved based on effects on lipid parameters such as LDL-C before CV outcomes data

are available. [REDACTED] (b) (4)

3. As we have stated previously, we believe it would be inappropriate to use evolocumab as first-line monotherapy in the general population before cardiovascular (CV) outcomes data are available. Thus, if approved on the basis of changes in LDL-C, it is unlikely that we would entertain a monotherapy indication without CV outcomes data with the possible exception of providing a mechanism to allow on-label prescribing of PCSK9 inhibitors to patients unable to take statins or unable to tolerate an effective dose of statin.
4. [REDACTED] (b) (4)
5. We note that you have included effects on multiple lipid parameters in your proposed indication statement (LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG, Lp(a), HDL-C, and ApoA1). If evolocumab is approved based on its effects on LDL-C, it remains a review issue what, if any, additional lipid-related claims would be approved.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of potential issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above request for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient information. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient labeling, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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 evolocumab for the treatment of homozygous familial hypercholesterolemia has orphan drug designation, you are exempt from this requirement for this indication.

We reference the following requests for waivers and deferrals of the Pediatric Research Equity Act (PREA) for the following indications:



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 (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JAMES P SMITH
11/07/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 105188
BLA 125522

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Amgen Incorporated
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320-1799

ATTENTION: Marc Kubasak, PhD, RAC
Senior Manager, Regulatory Affairs

Dear Dr. Kubasak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act and Biologics License Application (BLA) dated and received August 27, 2014, submitted under section 351(a) of the Public Health Service Act for Evolocumab, 140 mg/mL.

We also refer to your IND correspondence dated and received May 27, 2014, and BLA correspondence dated and received September 16, 2014, requesting review of your proposed proprietary names, Repatha and Repatha SureClick.

We have completed our review of the proposed proprietary names, Repatha and Repatha SureClick and have concluded that they are acceptable.

If any of the proposed product characteristics as stated in your September 16, 2014, BLA submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. 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}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
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 on behalf of KELLIE A TAYLOR
09/26/2014



BLA 125522

BLA ACKNOWLEDGEMENT

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

Dear Dr. Kubasak:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Evolocumab injection (Tradename TBD)

Date of Application: August 27, 2014

Date of Receipt: August 27, 2014

BLA Number: 125522

Proposed Use:

1. Hyperlipidemia and Mixed Dyslipidemia
2. Homozygous Familial Hypercholesterolemia (HoFH)

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(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).

The BLA Number provided above should be cited 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.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any 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
09/05/2014



IND 105188

MEETING MINUTES

Amgen, Inc.
Attention: Marc Kubasak, PhD
Senior Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-B
Thousand Oaks, CA 91320-1799

Dear Dr. Kubasak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG 145 (evolocumab) injection.

We also refer to the meeting between representatives of your firm and the FDA on April 10, 2014. The purpose of the meeting was to discuss your proposed BLA application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: Thursday, April 10, 2014, 10:00 am
Meeting Location: FDA, White Oak Campus, Building 22, Conference Room 1415

Application Number: IND 105188
Product Name: AMG 145 (evolocumab) injection
Indication: **Hyperlipidemia/Mixed Dyslipidemia**

(b) (4)

Homozygous Familial Hypercholesterolemia (HoFH)

(b) (4)

Sponsor/Applicant Name: Amgen, Inc.

Meeting Chair: Eric Colman, MD
Meeting Recorder: Kati Johnson

FDA ATTENDEES

Office of the Center Director

Richard Moscicki, MD-Deputy Center Director for Science Operations

Office of Drug Evaluation II

Mary H. Parks, MD-Deputy Director

Office of Combination Products

Patricia Love, MD, Deputy Director

Bindi Nikhar, MD, Acting Senior Clinical Advisor

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, MD-Director

Eric Colman, MD-Deputy Director

James P. Smith, MD-Clinical Team Leader

Eileen Craig, MD-Clinical Reviewer

Karen Davis Bruno, PhD-Supervisory Toxicologist

Lee Elmore, PhD-Nonclinical Reviewer

Kati Johnson-Senior Regulatory Project Manager

Office of Biometrics II, Division of Biometrics II

Bradley McEvoy, PhD-Statistician

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Immo Zadezensky, PhD-Clinical Pharmacology Team Leader

Ritesh Jain, PhD-Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology

Naomi Redd, PharmD-Office of Medication Error Prevention and Risk Management

Sarah Vee, PharmD-Division of Medication Error Prevention and Analysis

Office of Scientific Investigations

Cynthia Kleppinger, MD-Medical Officer

Center for Biologics, Office of Biologic Products

Chana Fuchs, Ph.D. Product Quality Team Lead, DMA

Sang Bong Lee, Ph.D. Product Quality Review, DMA

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou

SPONSOR ATTENDEES

Wei Cui, MS-Senior Manager, Biostatistical Programming (Global Programming Lead)

Rekha Garg, MD, MS-Exec. Dir., Regulatory Affairs (Therapeutic Area Head)

Michelle Geller, MD-Medical Director, Global Safety (Global Safety Lead)

John Gibbs, PhD-Scientific Director, Pharmacokinetics and Drug Metabolism

Ashley Hall, JD, RAC-Director, Regulatory Affairs (Global Regulatory Lead)
Marc Kubasak, PhD, RAC-Sr. Manager, Regulatory Affairs (US Regulatory Lead)
Thomas Liu, PhD-Director, Biostatistics (Global Statistical Lead)
Arline Nakanishi, MS-Executive Director, Biostatistics (Therapeutic Area Head)
Shirin Pillay, RAC-Senior Associate, Regulatory Affairs (US Regulatory Professional)
Rob Scott, MD-Vice President, Global Development (Therapeutic Area Head)
Mark Taisey-Vice President, Global Regulatory Affairs
Scott Wasserman, MD-Exec. Medical Dir., Global Development (Global Development Lead)

1.0 BACKGROUND

Evolocumab (also referred to as AMG 145) is a fully human monoclonal immunoglobulin G2 that specifically binds to proprotein convertase subtilisin/kexin type 9 (PCSK9) and inhibits the interaction between PCSK9 and the low-density lipoprotein receptor (LDLR). This leads to increased LDLR cell surface expression and subsequent decreased circulating concentrations of LDL-C.

The proposed indications for the initial BLA are the following:

Hyperlipidemia/Mixed Dyslipidemia

(b) (4)

The controlled, pivotal, 12-week parent studies to be submitted in support for these indications:

- 20110114:** Evolocumab monotherapy dose-ranging compared with placebo and ezetimibe (MENDEL-2)
- 20110115:** Evolocumab in combination with statins (with or without ezetimibe) compared with placebo (LAPLACE-2)
- 20110116:** Evolocumab compared to ezetimibe in statin-intolerant subjects (GAUSS-2)
- 20110117:** Evolocumab in combination with statins (with or without ezetimibe) compared with placebo in heterozygous familial hypercholesterolemia (RUTHERFORD 2)

Controlled, pivotal, long-term studies to be submitted:

- 20110109:** Long-term evolocumab alone and in combination with statins (with or without ezetimibe) compared to placebo (DESCARTES)
- 20120138:** (ongoing) Long-term, controlled, open-label extension (OSLER-2)

Homozygous Familial Hypercholesterolemia (HoFH)

(b) (4)

Pivotal Efficacy and Safety Studies for HoFH (Phase 2/3):

20110233: Two-part evaluation of evolocumab in homozygous familial hypercholesterolemia.

Part A – phase 2, open-label pilot study.

Part B – phase 3, double-blind, randomized, placebo-controlled study (TESLA)

20110271: (ongoing) A long-term evaluation of evolocumab in subjects with severe familial hypercholesterolemia, including HoFH (TAUSSIG)

The HoFH indication was granted Orphan Designation (13-4041) on September 12, 2013.

(b) (4)

A Special Protocol Assessment (SPA) review was requested for the following protocols:

1. Study 114976, entitled *104-Week Subcutaneous Lifetime Pharmacology Study in Hamsters*. The protocol was submitted August 11, 2011, and an agreement letter was issued September 1, 2011.
2. A cardiovascular outcomes trial (CVOT)(Protocol 20110118) entitled *A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Assessing The Impact Of Additional LDL Cholesterol Reduction On Major Cardiovascular Events When AMG 145 is Used In Combination With Statin Therapy In Patients With Clinically Evident Cardiovascular Disease* (FOURIER). The protocol was submitted on October 1, 2012, and an agreement letter was issued January 31, 2013. The protocol was modified in a submission dated October 1, 2012; the revisions were found acceptable and the firm was notified in a letter dated November 21, 2013.

At the End-of-Phase 2 (EOP2) clinical meeting held on July 10, 2012, the Division stated that 25% of endpoint events in the FOURIER study should be accrued prior to submission of a BLA for evolocumab, to ensure a timely completion of the study. In a letter dated February 25, 2014, the Division clarified that the 25% benchmark should consist of adjudicated events.

The firm is proposing to market the following presentations:

1. Prefilled syringe (PFS) (140 mg/mL). For this presentation, the drug product is supplied as a sterile, single-use, preservative-free solution for subcutaneous (SC) injection, and contains a 1.0 mL deliverable volume of 140 mg/mL evolocumab.
2. Prefilled autoinjector/pen (AI/pen) (140 mg/mL). This is a single-use, disposable, handheld mechanical injection device that administers, over a 15 second period, a fixed dose of evolocumab into SC tissue.

Both the PFS and the AI are appropriate for SC administration every 2 weeks (Q2W). (b) (4)

The proposed dosing regimens for the Hyperlipidemia/Mixed Dyslipidemia indications are 140 mg evolocumab administered SC Q2W and 420 mg administered SC once monthly.

The proposed dosing regimen for the HoFH indication is 420 mg SC Q2W and 420 mg SC once monthly.

An EOP2 meeting to discuss chemistry, manufacturing and controls (CMC) topics was held on November 2, 2012.

A Pre-BLA (CMC only) meeting was held on January 24, 2014. This pre-BLA (clinical) was requested January 7, 2014.

The Agency issued a letter to the sponsor on February 10, 2014, requesting an assessment of potential neurocognitive adverse events (AEs) across the development program. In addition, we were interested in the feasibility of incorporating prospective neurocognitive testing in at least a subset of patient enrolled in the CVOT. A teleconference with the firm was held on March 20, 2014, to discuss their proposed protocol to test for neurocognitive events. Meeting minutes of that teleconference issued April 28, 2014. Additional information regarding the potential neurocognitive AEs observed in the sponsor's program to date were submitted and received by the Agency on April 30, 2014.

2. DISCUSSION

Preliminary responses to the firm's questions were conveyed to them on April 7, 2014.

Prior to the meeting, the firm notified us that they did not need any clarification or discussion on agency responses to questions 1, 2, 3, 5, 7b, 8, 9, 10, 11, 12, and 13.

The firm's question is followed by our **bolded** preliminary response. Any references to Sections, Appendices, Tables or Figures refer to the background package submitted March 10, 2014. Any meeting discussion is in *italicized* text, and post-meeting comments are in **underlined bolded** text.

Regulatory Format and Content Questions-Follow-up from the Type C Meeting Written Response Issued on July 15, 2013

Question 1:

FDA comments to Question 1 of the Type C Meeting in the Written Response issued on 15 July 2013 (Appendix 4) stated, “In addition, we note that you do not plan to include any datasets for phase 1 studies. The dataset needs of the clinical pharmacology reviewers would be an appropriate question to ask at the pre-BLA meeting.”

In addition to the SDTM and ADaM datasets for the phase 2 and phase 3 studies as described in the Data Standardization Plan (submitted 30 April 2013 [Serial No. 0191]) Amgen plans to submit [REDACTED] (b) (4) [REDACTED]. These data will be provided in Module 5, Section 5.3.5.3 of the eCTD.

Does the FDA agree with the proposed submission of clinical pharmacology data as described above?

FDA Preliminary Response: No, we do not agree with your proposal. You should plan to submit all available pharmacokinetic data from all the phase 1, phase 2 and phase 3 studies. In addition, we noted that you plan to include data from certain phase 1 and phase 2 studies in your population pharmacokinetic analysis. We encourage you to also use data from available phase 3 studies in your population pharmacokinetic analysis.

We suggest you to refer to the following pharmacometric data and models submission guidelines for your submission.

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>

Meeting Discussion: None

Question 2:

FDA comments on Question 2, of the Type C Meeting in the Written Response issued on 15 July 2013 (Appendix 4) stated, “The Agency prefers that you submit summarized output of standards validation issues with explanation.”

Amgen plans to provide summarized outputs of standards validation issues with explanations in the Case Report Tabulations CRT Reviewer’s guide, as requested, in Module 5, Section 5.3.5.3 of the eCTD.

Does the FDA agree with the location in the eCTD for the requested summarized output of the validation issues with explanation?

FDA Preliminary Response: Yes.

Meeting Discussion: None

Question 3:

FDA comments on Question 7, Part 1 of the Type C Meeting in the Written Response issued on 15 July 2013 (Appendix 4) stated, "For the pre-BLA meeting, it would be helpful to have a summary of electronic case report form (eCRF) data elements that you do not plan to include in tabulation datasets to ensure that items you plan to exclude from tabulation datasets are acceptable to the review team. For example, from our preliminary review, it seems from the blank CRF that "surgical intervention," "device/procedure intervention," and "emergency room visit" would not be captured in the dataset as actions taken in response to an AE, although these would be relevant to include."

Amgen plans to submit all eCRF data to FDA in the tabulation dataset of the BLA, except for responses to some indicator questions (such as "Were there any AEs (Y/N)?"), since such questions were exclusively for operational purposes and, if answered yes, would have detailed information collected elsewhere on the CRF.

Does the FDA agree with this proposal?

FDA Preliminary Response: Yes, this approach seems reasonable. Clinically relevant fields from your eCRFs should be included in analysis datasets as well, as appropriate. Regarding your eCRFs, note that audit trail information should be accessible such that any changes from originally recorded values could be traced by a reviewer if needed, including all data queries and responses from the sites.

Meeting Discussion: None

Question 4:

FDA comments to Question 1 of the Type C Meeting in the Written Response issued on 15 July 2013 (Appendix 4) stated, "The DSP looks acceptable in general, but we do have a statistical concern regarding the different definitions of the primary efficacy endpoint in phase 2 and phase 3 studies (see our response to question 5)." The FDA comments to Question 5 (Appendix 4) stated, "(b) (4)

Please provide your clarification."

To clarify, (b) (4) The Integrated Summary of Safety (ISS)/ISE statistical analysis plans were initially submitted on 25 October 2013 (Serial No. 0256) and the amended ISE statistical analysis plan was submitted on 10 December 2013 (Serial No. 0273). In addition, Amgen has provided examples of column headers of the ISS/ISE planned output to help illustrate the planned analysis for the BLA (Appendix 6). The ISS and ISE will be provided in CTD Module 5, Section 5.3.5.3. Summaries and discussion of the integrated analyses will be provided within CTD Module 2.7.3 (Summary of Clinical

| Table X: Incidence of All Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission | | | | | | | | | |
|---|-----------------------|-----------------------|---------------------------------|------------------------------|------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| System Organ Class | Preferred Term | Pooled Placebo | Pooled Active Comparator | All Pooled Comparator | All Pooled Study Drug Doses | Pooled Study Drug Dose A | Pooled Study Drug Dose B | Pooled Study Drug Dose C | Pooled Study Drug Dose D |
| | | N= n (%) | N= n (%) | N= n (%) | N= n (%) | N= n (%) | N= n (%) | N= n (%) | N= n (%) |
| n = number of patients who experienced a given event Source: (link to dataset) | | | | | | | | | |

- **For Table 16 on page 112 (and any other tables displaying liver enzyme abnormalities), please include a row for potential “Hy’s Law” cases (ALT or AST >3x upper limit of normal AND TBL > 2xULN)**
- **It is also acknowledged that the SAP for the ISE describes a formal multiplicity adjustment strategy for the planned integrated analyses. We note that the conclusion from this testing algorithm will be interpreted as exploratory and not confirmatory due to the supportive role the integrated summary provides.**

Meeting Discussion:

Amgen clarified that they will be using a consistent relative cutoff date for safety for all studies and the ISS: AEs occurring between the first dose of investigational product (IP) and End of Study (EOS). For individual studies Amgen will include an on-treatment sensitivity analysis based on a 4-week cutoff after last actual IP.

The Agency asked how this 4-week cutoff for on-treatment analyses was determined and whether it was based on the PK/half-life data. Amgen stated that 4 weeks was the standard cutoff in many clinical trials and was not based on PK data. The Agency stated that especially since the pharmacodynamic effect of evolocumab is longer than most approved LDL-lowering drugs (e.g., statins), it is plausible that adverse events that occur beyond 4 weeks after the last dose of treatment could be associated with the drug. Amgen noted that 95% of subjects continued IP until trial completion and 98% finished all scheduled assessments; most subjects were also enrolled in open-label extension studies. FDA acknowledged that if this is the case, on-treatment and ITT safety analyses ought to be very similar; therefore, it was agreed that the plan for on-treatment analyses was reasonable for BLA submission and that the review team would let them know if a different data cutoff (based on PK data) would be necessary for any on-treatment sensitivity analyses during the review.

The Agency asked if the on-treatment analyses in the individual studies would be linked to the ISS. Amgen stated that they would only appear in the individual CSRs and not in the ISS.

Additional Regulatory Format and Content Questions

Question 5:

As summarized in Section 4.2 the proposed structure and format of the BLA were a part of the Type C meeting on 15 July 2013 (Meeting Request-Written Responses provided in Appendix 4). The proposed table of contents for the BLA is provided in Appendix 5. The content of CTD Module 3 (Quality) was discussed with the FDA at a Type B pre-BLA CMC/Device-specific teleconference held on 24 January 2014 (meeting minutes provided in Appendix 4). The proposed content of CTD Module 4 (Nonclinical) and Module 5 (Clinical), and related summaries in CTD Module 2, are summarized in Section 7 and Section 6, respectively, of this document.

Does the FDA agree with the proposed format and content of the eCTD table of contents for the BLA?

FDA Preliminary Response: In general, yes. We have some additional comments:

- **Your eCTD table of contents in Appendix 5 lists “Safety Narratives – Withdrawals” for phase 2 trials in Section 5.3.5.1, but does not list narratives for phase 3 trials in the same section. Ensure that you include narratives for deaths, serious adverse events, and adverse events leading to drug discontinuation for every trial. Hyperlinks should be used to allow navigation between eCRFs and corresponding narratives. In addition, provide a table of contents for narratives for each trial, with active hyperlinks, organizing the listing by deaths, SAEs, and AEs leading to drug discontinuation, with subcategorization by treatment group.**

Meeting Discussion: None

Question 6:

As summarized in Section 6.7.5, Amgen intends to provide analyses of adjudicated clinical endpoints from both phase 2 and phase 3 studies. These analyses will be provided in CTD Module 5, Section 5.3.5.3, as part of the Integrated Cardiac Safety Report. Complete adjudication packages will also be provided in the submission as described in Section 4.2.

Does the FDA agree to the content, format and location of this information in the BLA?

FDA Preliminary Response: Yes.

Meeting Discussion: The firm clarified that the adjudicated events will be provided in the CSRs. Rather than incorporating these events to the Integrated Cardiac Safety Report (ICSR), they would like to provide this in the Summary of Clinical Safety. The Agency agreed that as long as an integrated discussion of adjudicated events is included in one document, it does not matter whether that document is the ICSR or the Summary of Clinical Safety.

Clinical Safety Topics

Question 7a:

Does the FDA consider the size of the overall safety database and the duration of exposure at the time of the BLA filing, described in Section 6.2, sufficient to support approval for the proposed indication of primary hyperlipidemia and mixed dyslipidemia?

FDA Preliminary Response: As we have previously discussed, we are most concerned about the potential for long-term adverse effects of either PCSK9 inhibition or very low LDL-C. We note that your current description of your long-term safety database is substantially different than the safety database you described at the EOP2 meeting. Specifically, at that time you estimated that (b) (4) patients would be exposed to evolocumab for at least one year, (b) (4) for ≥ 18 months, and (b) (4) for ≥ 24 months. Your pre-BLA package, however, describes 1045 patients exposed for ≥ 12 months, 630 for ≥ 18 months, and only 160 for ≥ 24 months. Please provide us with an estimate of when you will have accrued the long-term safety experience that you described at EOP2.

Ultimately, whether your safety database and duration of exposure will be sufficient to support approval for each of your proposed indications is a review issue. Anytime that approval is based on a biomarker, there is uncertainty with regard to the magnitude of the treatment effect on actual clinical outcomes. If the relationship between changes in LDL-C and CV risk observed in clinical trials of statin therapy can be extrapolated to very low levels of LDL-C (as well as across drug classes), the absolute risk reduction for a given change in LDL-C would be expected to be smaller for lower-risk populations than higher-risk populations. As a consequence, even if one accepts LDL-C as a surrogate endpoint, the benefit/risk could plausibly be found favorable for higher-risk populations but too uncertain for others. Furthermore, the absence of an event in a given safety database may or may not be reassuring depending on the size of the database compared with the size of the targeted treatment population. We encourage you to include your assessment/estimate of overall clinical benefit, taking these uncertainties into account, for each of your proposed indications as part of the BLA.

Furthermore, as we noted previously (EOP2 meeting), your long-term experience with evolocumab will need to include a heterogeneous population with respect to demographics, CV risk, etc. From what we have received to date, we do not have an adequate sense for whether your safety database for long-term exposure (particularly in controlled trials) has sufficient representation from the types of patients expected to use your drug if approved. Please provide the numbers of patients that have been treated with evolocumab for at least one year in the following categories: age ≥ 65 ; established cardiovascular disease; high-risk for CVD; moderately high risk for CVD; concomitant high-intensity statin; concomitant moderate-intensity statin; diabetes; congestive heart failure or ischemic cardiomyopathy.

Meeting Discussion: In the attached handout (slide 10) provided to the agency prior to the meeting, the firm provided a proposed estimated subject exposure to evolocumab in the ISS. The firm explained that the discrepancy from the exposure projected at the July 2012 end-of-phase 2 (EOP2) meeting was (b) (4).

The Agency stated that we have serious concerns whether this safety database, (b) (4), would constitute a complete application for a first-in-class product intended for chronic administration with a potential for use in a large patient population, if marketed. FDA also indicated that the (b) (4) data cutoff for studies 20110110 and 20120138 seemed unnecessarily distant from the projected date of submission. The Agency voiced concern that approximately half of the safety data would be planned for submission in the 120-day safety update. The spirit of PDUFA V legislation is that a complete application will be submitted, including all information required for a regulatory decision in the initial submission.

The sponsor justified the (b) (4) data cut-off, (b) (4)

The Agency clarified that our concern was not with the cut-off date per se but with the amount of safety data that will be submitted 4 months into the review, as it would be very challenging to integrate all of this volume of new information into the safety review with the PDUFA timeline. The Agency noted that the data cut-off for June/July 2014 provides the safety database that was agreed to at the end-of-phase 2 meeting.

(b) (4) She also noted that this first-in-class therapy would be expected to be discussed at an Advisory Committee meeting, which affects the timelines during the review. She affirmed that the Division has valid concerns leading to these requests regarding the safety database.

The firm countered (b) (4)

Regarding the size of the safety database with long-term exposure, the Agency reiterated that the firm's proposal was not acceptable, but they were free to provide an alternative for consideration.

Question 7b:

In addition to the totality of data in the hyperlipidemia and mixed dyslipidemia patient population, does the FDA consider the size of the overall safety database and the duration of exposure in the HoFH population, a rare disease with FDA Orphan Designation, at the time of

the BLA filing (described in Section 6.2) sufficient to support approval for the proposed indication of HoFH?

FDA Preliminary Response: This will be a review issue

(b) (4)

Meeting Discussion: None

Question 8:

The 120-day safety update will be submitted within 120 days after submission of the BLA or 2 months after the start of the Prescription Drug User Fee Act clock under “The Program”.

Does the FDA agree with the proposed timing and content of the 120-day Safety Update to the BLA, as described in Section 4.5?

FDA Preliminary Response: Yes

Meeting Discussion: None

Question 9:

The FDA Amendments Act of 2007 gave FDA the authority to require a REMS from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. Amgen recognizes that the final determination of the benefit:risk profile of evolocumab will be based on a full review of the data included in the BLA submission and that the benefit:risk profile will be continually re-evaluated as new data becomes available.

Based on Amgen’s assessment of the initial efficacy and safety data, as described in Section 6.5 and Section 6.7, does the FDA agree that a REMS will not be required for the submission of the evolocumab BLA?

FDA Preliminary Response:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion: None

Clinical Development Topics

Question 10:

Does FDA agree that the Division will accept the evolocumab BLA for filing, provided it meets FDA requirements for filing, even if less than 25% of potential events have been accrued and adjudicated in the FOURIER study prior to filing of the BLA (subject to the establishment of the outcomes study as a postmarketing requirement)? (See Section 4.3 for discussion.)

FDA Preliminary Response: We continue to believe that accrual of a minimum of 25% of MACE (with timely adjudication) prior to BLA submission is the appropriate method to encourage timely CVOT completion. If you decide to submit prior to reaching the 25% of endpoints threshold, you should include the number (%) of first secondary endpoint events that have been accrued, the number (%) that have been adjudicated and the results of adjudication (i.e., the number accepted as endpoints vs. rejected), and the number (%) of subjects that have been randomized at the time of BLA submission.

Meeting Discussion: None

Question 11:

Since evolocumab is intended to treat a serious medical condition for which an unmet medical need still exists (see Section 5) and based on the efficacy (Section 6.5 and Section 6.6) and safety (Section 6.7) data that demonstrate that evolocumab may provide a significant improvement in the treatment of subjects with primary hyperlipidemia and mixed dyslipidemia and HoFH, Amgen considers that a priority review designation is appropriate with submission of the BLA (see Section 4.4).

Does the FDA agree that evolocumab may meet the requirements for a request for priority review designation?

FDA Preliminary Response: A determination for priority review designation will be made following submission of the BLA.

Meeting Discussion: None

Complete Application Topics

Question 12:

Does the FDA agree, based on the totality of information provided in this briefing document and specifically the summary in Section 4.2, that the data to be presented in the BLA would constitute a complete application?

FDA Preliminary Response: Please see our response to Question 10. The types of data you have summarized in this document, pending review, constitutes a complete application. We have previously stated that we are unlikely to consider a monotherapy indication or an indication explicitly referencing “statin intolerant” patients without positive data from a CVOT. Furthermore, we expect that the approvability of a PCSK9 inhibitor, in the absence of outcomes data, will be a topic for discussion with an advisory committee.

As part of your BLA, please include a justification for each lipid parameter that you intend to list in your indications. For each, you should justify why you believe that drug-induced changes in the parameter are clinically meaningful.

Meeting Discussion: None

Question 13:

Amgen has assessed the potential environmental impact of the evolocumab combination product presentations and believes that they are excluded under 21 CFR Part 25 - Environmental Impact Considerations, Subpart C - Categorical Exclusions, Sec. 25.31, Human Drugs and Biologics, and Sec. 25.34, Devices and Electronic Products, since the product is filed as a biologic combination product (see Section 4.2).

Does the FDA agree with this assessment?

FDA Preliminary Response: We confirm that the prefilled syringe (PFS) and the PFS in an Autoinjector formats are excluded under the CFR sections referenced above.



Meeting Discussion: None

Additional FDA questions/comments:

- We note that Study 20110110 has a data cutoff date of (b) (4) and Study 20120138 has a data cutoff date of (b) (4). Please provide an explanation for why the data cutoff is so far removed from the submission of the BLA.

Meeting Discussion: See discussion under Question 7a.

- Exposure data should be presented as the mean and median duration of time on study medication for the placebo group and the AMG 145 group (for each dose) for the 12-week studies and the long-term studies. Similar data should be presented for the HoFH studies for the 420 mg Q2W and the 420 QM dose.

Meeting Discussion: None

- **At BLA submission, provide the minutes of all DSMB and steering committee meetings.**

Meeting Discussion: The firm will submit the minutes from the DMC (open and closed) from studies that will form the basis of the initial lipid-lowering indication and will include them in Module 5.3.5.3. There are no Steering Committees for the studies that will form the basis for the initial lipid-lowering indications. The DMC minutes for the ongoing randomized, double-blind, controlled studies (FOURIER, GLAGOV, GAUSS-3, Yukawa-2) will not be submitted.

The Agency found this acceptable. The Agency commented that suspected unexpected serious adverse reactions (SUSARs) will need to be submitted for these ongoing trials as a matter of standard IND safety reported. The Agency commented that, in other therapeutic areas, companies have had an internal firewalled safety team look at safety databases in ongoing trials, and the Division had suggested previously to the firm to consider the logistics of establishing such a team. Since SUSARs should be considered in aggregate and since unblinding these types of events would not be expected to compromise the integrity of an ongoing trial, the sponsor ought to consider whether there would be a way to report these events from their ongoing trials (especially FOURIER) with denominators to support the safety database.

The firm did not respond directly to that comment but did state (b) (4)

The Agency responded that (b) (4)

- **Perform SMQs on the ISS adverse event data that may further inform the safety profile for your investigational agent, and include the results in the ISS report.**

Meeting Discussion: None

- **Provide time to event analysis that includes time to onset and resolution and overall duration for selected events (common AEs/SAEs/AEs that led to study drug discontinuation) that are relevant for your investigational agent. An example table is provided below.**

| Preferred Term or selected AE (such as liver test abnormalities, liver-related abnormalities, CK abnormalities, muscle-related abnormalities, injection site reactions, memory impairment etc) | Placebo (N=) n (%) | Total NB (N=) n (%) |
|---|-----------------------------------|------------------------------------|
| Name of selected AE | | |
| Median time to onset (days or weeks) | | |
| Median duration (days or weeks) | | |
| Subjects with event resulting in discontinuation from study medication | | |
| Subjects with event that resolved on or prior to discontinuation from study medication | | |
| Subjects with event that resolved after discontinuation from study medication | | |

| | | |
|--|--|--|
| Subjects with event that persisted after discontinuation from study medication | | |
| Study Disposition subsequent to discontinuation from study medication | | |
| Completed | | |
| Withdrew | | |
| Adverse event | | |
| Lost to follow up | | |
| Other | | |
| Withdrawal of consent | | |

Meeting Discussion: None

- **Include a chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.**

Meeting Discussion: None

- **For patients listed as discontinued due to “investigator decision,” “sponsor request,” “withdrew consent,” “other,” or similar reasons, the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.**

Meeting Discussion: None

- **We note that your briefing document mentions that long-term studies demonstrated that lowering LDL-C with evolocumab “did not lead to changes in normalized vitamin E levels...” Although you do not specify how you normalized the levels, (b) (4) [redacted] In your submission, you should also include results for total vitamin E (b) (4) [redacted], including appropriate reference ranges.**

Meeting Discussion: None

- **In our preliminary responses to your EOP2 meeting questions, we noted, “Please specify your definitions for nonfamilial hyperlipidemia and mixed dyslipidemia. You will need to ensure that a reasonable number of subjects with each of these definitions are enrolled in trials intended to support each claim.” Ensure that you submit data specifically supporting the use of your drug in each of these populations, including descriptive data for the populations themselves (i.e., demographics, baseline characteristics, etc.).**

Meeting Discussion: None

- As part of your Safety Evaluation Plan (Section 6.7.2.1), you mention that you will perform key safety analyses by eGFR tertiles. Although it is difficult to make a specific request at this time given that we do not know the distribution of eGFR in your trials, consider using eGFR cutpoints that are commonly used in clinical practice (e.g., <30, 30-60 [or 30-45 and 45-60], ≥60 mL/min/1.73m²).

Meeting Discussion: None

- The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:
 - a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
 - b) Exposure-Response Relationships – important exposure-response assessments.
 - c) Less common adverse events (between 0.1% and 1%).
 - d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
 - e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
 - f) Marked outliers and dropouts for laboratory abnormalities.
 - g) Analysis of vital signs focused on measures of central tendencies.
 - h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
 - i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
 - j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
 - k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
 - l) Standard analyses and explorations of ECG data.
 - m) Overdose experience.
 - n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
 - o) Explorations for:
 - i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.

- ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
 - iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
 - iv) Drug-demographic interactions
 - v) Drug-disease interactions
- p) Drug-drug interactions
- i) Dosing considerations for important drug-drug interactions.
 - ii) Special dosing considerations for patients with renal insufficiency and patients with hepatic insufficiency.

Meeting Discussion: None

- **Laboratory values from narratives should be included in your submitted datasets. If a reviewer wanted to independently tabulate peak ALT or creatinine values, for example, this should be possible from using the laboratory dataset alone (e.g., LB.xpt) as opposed to some values only appearing in a narrative describing results obtained during a hospitalization.**

Meeting Discussion: None

- **We would like you to submit additional data in your Adjudication Listing and the related datasets. We recognize that these data are exploratory for your lipid-lowering phase 2/3 trials, but our comments should be applied to your ongoing cardiovascular outcome trial as well. Your CEC charter states that two CEC adjudicators will independently review each complete endpoint event. If the adjudicators agree, then the adjudication of the potential endpoint event is considered complete. If they disagree, the adjudicators will discuss the potential endpoint event at a moderated CEC meeting until they come to consensus or agree that they are unable to reach final consensus; in the latter case, the CEC Chairman will determine the final adjudication result. Thus, you should submit the following information in addition to the event description as reported by the investigator:**
 - **Date of adjudication by adjudicator #1 along with the event description that the adjudicator reports (which may or may not be the same as what the investigator reported, especially if the adjudicator assigns a subcategory to an event, such as cause of death)**
 - **Same information as above for adjudicator #2**
 - **Final event categorization along with date of final adjudication**
 - **Listing of who made the final adjudication decision (i.e., consensus or CEC chairman)**
 - **How the potential endpoint event was identified and referred for adjudication (i.e., Investigator, CEC, Amgen)**

Meeting Discussion: None

-  (b) (4)
- **Please tell us how many total potential clinical endpoints were forwarded for adjudication in phase 2/3 so that we can discuss potential options for addressing this concern.**
- **In addition, we strongly suggest that you immediately revise your adjudication procedures for all ongoing trials such that: (1) all data that could potentially unblind an adjudicator are redacted from adjudication packages, and (2) add a checkbox to your adjudication CEC case report form for an adjudicator to mark whether they felt that there was anything in the adjudication package that may have unblinded them to treatment assignment. Ideally, the first adjudicator would complete their adjudication of a given event before the package is sent to a second adjudicator; if the first reports the existence of data that potentially unblinded them, the package would be redacted appropriately and sent to two new adjudicators.**
- **Any packages that have already been forwarded for adjudication in your cardiovascular outcomes trial should be examined for data that could have**
- **potentially led to unblinding. Please inform us whether you identify packages that require additional redaction and how you plan to address this concern.**

Meeting Discussion:

 (b) (4)

. They are
conducting a thorough assessment to ensure adjudicators were appropriately blinded to study treatment and to ensure blinding in the ongoing studies.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. With regard to the safety information, all of the data needed to make a regulatory decision should be included in the initial submission.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that there is currently insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

We acknowledge receipt of your PSP on March 13, 2014, which is currently under review.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|-----------|--------------|--|---|---|
| 1. | | | | |
| 2. | | | | |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|-----------|--------------|--------------------------------|----------------------|---------------|
| 1. | | | | |
| 2. | | | | |

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/contract research organization (CRO) inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Items I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in

the submission in the format described, the Applicant can identify the location(s) and/or provide link(s) to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (*Technical Instructions: Submitting Bioresearch Monitoring [BIMO] Clinical Data in eCTD Format*).

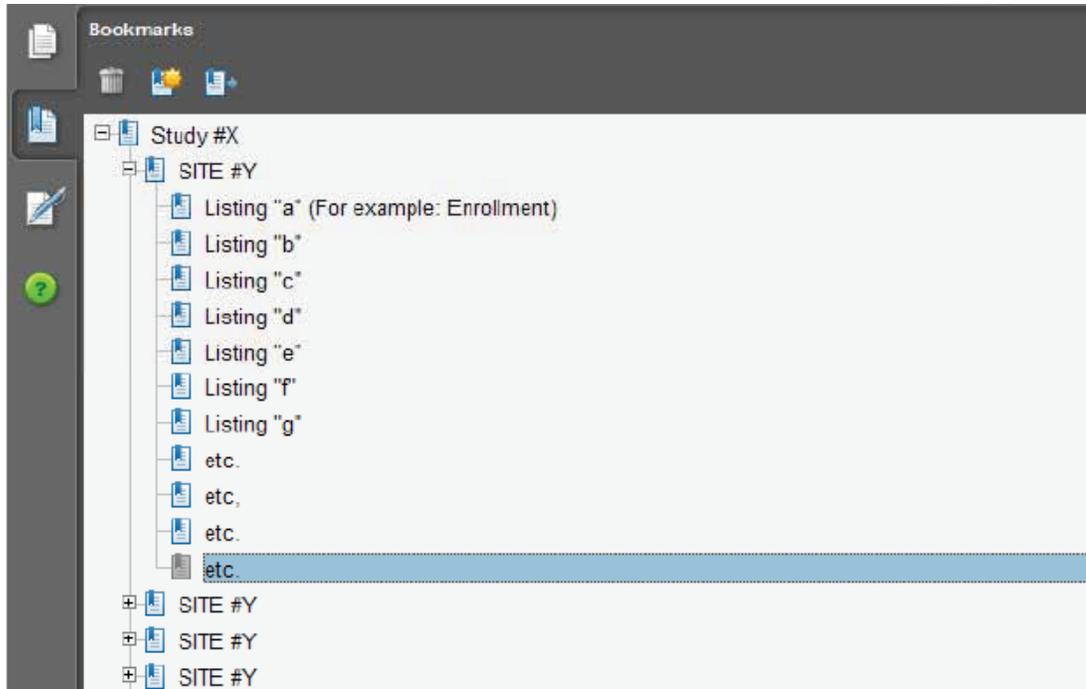
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in the submission, describe the location or provide a link to the requested information).

1. Please include the following information in a tabular format in the original NDA/BLA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal Investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA/BLA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued at each site
3. Please include the following information in a tabular format in the NDA/BLA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571) you may identify the location(s) and/or provide link(s) to information previously provided.

- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated case report form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial, provide the original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per-protocol subjects/ non per-protocol subjects and reason not per-protocol
 - e. By subject, listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject, listing of AEs, SAEs, deaths and dates
 - g. By subject, listing of protocol violations and/or deviations reported in the NDA/BLA, including a description of the deviation/violation
 - h. By subject, listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject, listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject, listing of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Meeting Discussion: The firm proposed providing the information listed under I and III, but proposed providing the information requested under II for those clinical sites selected by the agency to inspect. The firm was notified that they should provide the information under II for all clinical sites, and the firm agreed to do so.

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

| OSI Pre-NDA Request Item ¹ | STF File Tag | Used For | Allowable File Formats |
|---------------------------------------|------------------------------|---|------------------------|
| I | data-listing-dataset | Data listings, by study | .pdf |
| I | annotated-crf | Sample annotated case report form, by study | .pdf |
| II | data-listing-dataset | Data listings, by study (Line listings, by site) | .pdf |
| III | data-listing-dataset | Site-level datasets, across studies | .xpt |
| III | data-listing-data-definition | Define file | .pdf |

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The firm will provide a revised data cut-off date for inclusion in the initial BLA, to more closely resemble the estimate provided at the July 2012 end-of-phase 2 meeting.

5.0 ACTION ITEMS

| Action Item/Description | Owner | Due Date |
|--|---------|--|
| Revised amount of safety data to be included in the initial BLA submission | Sponsor | As soon as possible (It was provided via e-mail on April 15, 2014 and is provided as an attachment to the minutes) |

6.0 ATTACHMENTS AND HANDOUTS

Attachment 1-Firm's handout for the meeting [Evolocumab Pre-BLA Clinical Meeting with FDA]

Attachment 2-Firm's counterproposal for the amount of safety data that will be included in the initial BLA submission (Question 7a above)

Post-Meeting Activity

On April 16, 2014, the sponsor sent a revised proposal for their safety database via e-mail. Using a data cutoff of April 1, 2014, they state that approximately (b)(4) evolocumab-treated subjects with 1-year (365.25 days) exposure would be included in the ISS ((b)(4) with ≥ 18 months and (b)(4) with ≥ 24 months). On April 18, 2014, the Agency requested additional information:

Agency Request #1. For each phase 2 and phase 3 trial, please provide the number of patients who continued into an open-label, controlled extension trial and the proportion of available (i.e., not prematurely discontinued) patients who will have completed the 52-week controlled period as of your proposed data cutoff of April 1, 2014.

Agency Request #2. Please provide the estimated last-patient last-visit dates for the controlled phase of your extension trial(s), stratified by parent trial.

Agency Request #3. The baseline characteristic data published in your NEJM report of the DESCARTES trial seem inconsistent with the “high-risk” population that you have indicated are most appropriate for evolocumab therapy. Specifically, more than half of the trial’s population fall into the “diet alone” or “diet plus atorvastatin 10 mg” groups, which do not seem consistent with high-risk populations. Overall, it appears that only 271 patients were treated for a year with high-dose atorvastatin (with or without ezetimibe) combined with evolocumab. Considering the entire trial population, the majority (65%) of subjects were categorized as either low or moderate risk by the ATP-III classification. Furthermore, the mean baseline LDL-C among all patients was 104 mg/dL, which is quite well controlled and does not appear consistent with the population that you describe as having an unmet medical need (i.e., “high” LDL-C despite statin therapy).

Especially since you believe that this trial represents the highest-quality safety data for your program, we continue to have concerns regarding long-term safety among the target population likely most appropriate for evolocumab before outcomes data are available. Thus, we anticipate having to rely substantially on data from your open-label controlled extensions that studied higher-risk populations. As we previously requested in the pre-BLA meeting preliminary comments, any information you can provide with regard to the numbers of patients that have been treated with evolocumab for at least one year in relevant categories of demographic or baseline characteristics would be helpful to guide our decisions regarding agreements with your safety database. Please let us know if, and when, you would be able to provide additional information.

Agency Request #4. We note in your 16 April 2014 proposal that you would only plan to update

(b) (4)

Regardless of the data cutoff date ultimately agreed upon, this proposal is unacceptable. We consider the full study reports for required long-term safety data to be components of a complete application; therefore, any data that composes your original submission should be appropriately integrated into all impacted CSRs and integrated summaries.

On April 30, 2014, the firm provided a response to these queries via e-mail. At the time of these post-meeting comments, the response has not been officially submitted to the IND.

Post-Meeting Comments:

It is our understanding that a data cutoff on April 1, 2014 would provide (b) (4) patients with ≥361 days exposure to evolocumab. We also note that (b) (4) (%) of these subjects would come from your phase 3 program ((b) (4) of them from your DESCARTES trial) and (b) (4) (%) would come from your phase 2 program.

We still question whether the summary of baseline characteristics that you have provided are consistent with the “high-risk” population that you have indicated as most appropriate for evolocumab therapy. This is an issue of concern that will be discussed during the review of your application.

As we mentioned previously, we anticipate having to rely substantially on data from your open-label controlled extensions that studied higher-risk populations. Therefore, the controlled data from the 120-day safety update should be incorporated into updated analyses of the controlled phases of these trials and should not be submitted solely as a separate data presentation.

Provided that the 120-day safety update is submitted as described above, we do not anticipate that an April 1, 2014 data cutoff for Studies 20110110, 20120138, and 20120271 would preclude filing of a BLA for the proposed indications of primary hyperlipidemia and mixed dyslipidemia and HoFH. Whether the safety database will be sufficient for approval of the proposed indications will be a subject of review.

Additional Request: As noted above, you anticipate that $\frac{(b)(4)}{(4)}\%$ ($(b)(4)$) of the subjects with ≥ 361 days of evolocumab exposure will come from your phase 2 program and its open-label extension studies. We note that you administered evolocumab differently in phase 2 (total volume per administration drawn from six sterile vials) with a formulation (70 mg/mL) that you do not intend to market and that you did not use in phase 3. Please explain how you plan to bridge your phase 2 and phase 3 programs for the evaluation of clinical safety.

ATTACHMENT 1

15 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

KATI JOHNSON
05/07/2014



IND 105188

MEETING MINUTES

Amgen Inc.
Attention: Lisa Carlson
Director, Regulatory Affairs (CMC)
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Ms. Carlson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG 145 (evolocumab).

We also refer to the telecon between representatives of your firm and the FDA on January 24, 2014. The purpose of the meeting was to discuss the proposed Chemistry, Manufacturing, and Control (CMC) and device plans to support the initial BLA submission and registration of AMG 145 for use in combination with (b)(4) proposed delivery devices (prefilled syringe, autoinjector/pen (b)(4)).

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lyndsay Hennessey, Regulatory Project Manager at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Chana Fuchs, Ph.D.
Team Lead
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: CMC Pre-BLA
Meeting Date and Time: January 24, 2014
Meeting Location: Teleconference
Application Number: IND 105188
Product Name: AMG 145
Indication: Hypercholesterolemia
Sponsor/Applicant Name: Amgen Inc.

Meeting Chair: Chana Fuchs, Ph.D.
Meeting Recorder: Lyndsay Hennessey

FDA ATTENDEES

| | |
|------------------------|-------------------------------------|
| Chana Fuchs, Ph.D. | Product Quality Team Lead, DMA |
| Sang Bong Lee, Ph.D. | Product Quality Review, DMA |
| Patricia Hughes, Ph.D. | Microbiology Team Lead, BMAB |
| Jaqueline Ryan, M.D. | Medical Officer, CDRH/ODE |
| Sajjad, Syed | Electrical Engineer, CDRH/ODE |
| Patricia Love, M.D. | Deputy Director, OCP |
| Bindi Nikhar, M.D. | Acting Senior Clinical Advisor, OCP |
| Sarah Vee, Pharm.D. | Safety Evaluator, DMEPA |
| Lyndsay Hennessey | Regulatory Project Manager, OBP |

SPONSOR ATTENDEES

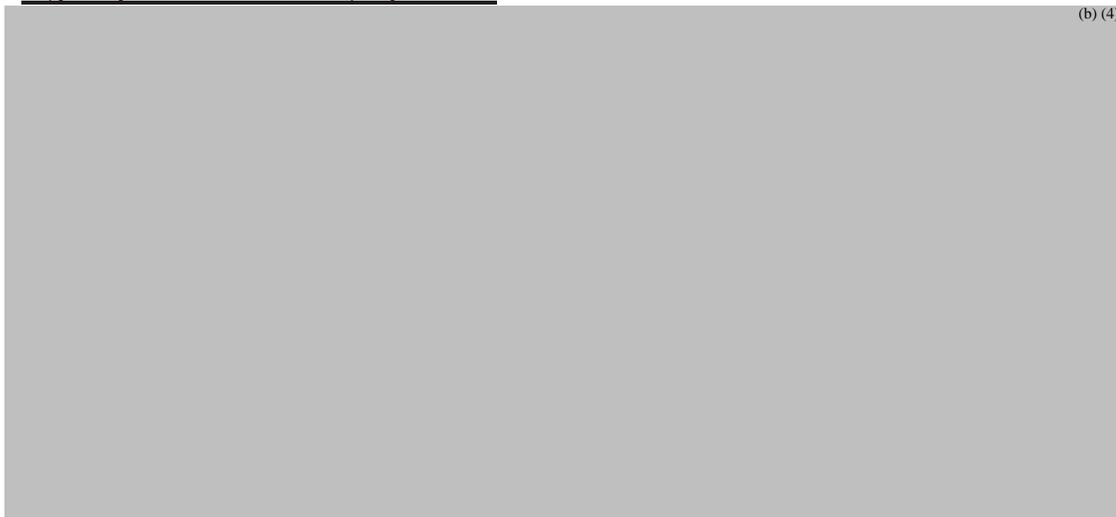
| | |
|----------------------|---|
| Lorena Barron, Ph.D. | Principal Scientist, Process Development (Drug Product Lead) |
| Don Busby | Principal Engineer, Device Engineering |
| Lisa Carlson | Director, Global Regulatory Affairs (CMC) |
| Ashley Hall | Director, Regulatory Affairs (Global Regulatory Leader) |
| Kristi Kistner | Executive Director, Regulatory Affairs (Devices) |
| George Klein | Director, Product Quality |
| Marc Kubasak | Senior Manager, Regulatory Affairs (US Regulatory Lead) |
| Lori de los Reyes | Senior Manager, Global Regulatory Affairs (Devices) |
| Rick Lit | Vice President, Regulatory Affairs (CMC, Devices and Biosimilars) |
| Frank Maggio, Ph.D. | Sr. Scientist, Analytical Sciences |
| Rex Atienza | Manager, Regulatory Affairs (Project Management) |

1.0 BACKGROUND

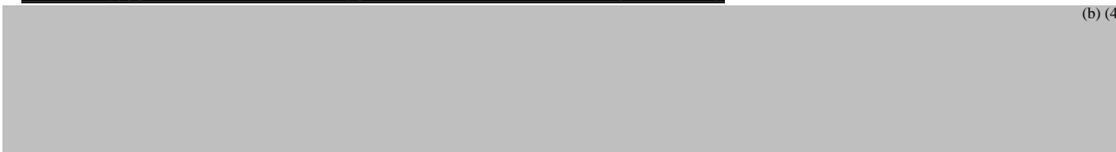
- (i) **Purpose of meeting:** To discuss the proposed Chemistry, Manufacturing, and Control (CMC) and device plans to support the initial BLA submission and registration of AMG 145 for use in combination with ^{(b) (4)} proposed delivery devices (prefilled syringe, autoinjector/pen ^{(b) (4)}
- (ii) **Names of drug:** AMG 145 (evolocumab)
- (iii) **Brief history:** Evolocumab (also referred to as AMG 145) is a human monoclonal immunoglobulin G2 that specifically binds to proprotein convertase subtilisin/kexin type 9 (PCSK9) and inhibits the interaction between PCSK9 and the low-density lipoprotein receptor (LDLR). This leads to increased LDLR cell surface expression and subsequent decreased circulating concentrations of LDL-C.

The proposed indications for the initial BLA are the following:

Hyperlipidemia/Mixed Dyslipidemia



Homozygous Familial Hypercholesterolemia (HoFH)



The firm is proposing to market the following presentations in the initial BLA:

1. Prefilled syringe (PFS)(140 mg/mL). For this presentation, the drug product is supplied as a sterile, single-use, preservative-free solution for subcutaneous (SC) injection, and contains a 1.0 mL deliverable volume of 140 mg/mL evolocumab.

2. Prefilled autoinjector/pen (AI/pen) (140 mg/mL). This is a single-use, disposable, handheld mechanical injection device containing a PFS that administers, over a 15 second period, a fixed dose of evolocumab into SC tissue.



Both the PFS and the AI are appropriate for SC administration every 2 weeks (Q2W).



The proposed dosing regimens for the Hyperlipidemia/Mixed Dyslipidemia indications are 140 mg evolocumab administered SC Q2W and 420 mg administered SC once monthly.

The proposed dosing regimen for the HoFH indication is 420 mg SC Q2W and 420 mg SC once monthly.

There was a Clinical End-of-Phase 2 (EOP2) held on July 10, 2012, with a CMC EOP2 meeting following on November 2, 2012.

The hyperlipidemia/mixed dyslipidemia phase 3 studies used the PFS. At the Clinical EOP2 meeting, Amgen proposed the following clinical bridging program to support commercialization of the AI (b) (4)

- Clinical home use studies to evaluate the ability of subjects to use the devices as intended (with associated instructions and labeling) in non-healthcare settings.
- PK/PD comparability studies between the PFS and AI (b) (4)

Preliminary comments regarding the proposal were provided by CDER (Division of Medical Error Prevention and Analysis [DMEPA]) and Center for Devices and Radiological Health (CDRH). There was also clinical comment stating that sufficient phase 3 data using the to-be-marketed devices would be required, and one option provided to obtain sufficient data was to extend the currently proposed trials to involve a second dosing period during which subjects are randomized to the various administration methods. During the meeting discussion, Amgen presented a revised strategy for testing

the delivery devices in phase 3. They proposed using the AI in the pivotal LDL-lowering trials. Subjects assigned to Q2W dosing regimen would use one AI every 2 weeks; subjects assigned to QM (Q4W) regimens would use three AIs every 4 weeks. (b) (4)

According to the August 2, 2012 meeting minutes, this proposal was found acceptable by the Agency.

In response to our request, Amgen submitted AI samples January 28, 2013; (b) (4)

(iv) Expected outcome for the meeting:

- Provide the Agency with an overview of clinical and manufacturing history for evolocumab drug substance and drug product.
- Achieve resolution of topics previously raised at the Type B (EOP2, CMC/Device) meeting.
- Reach agreement with Agency on the presented CMC and device strategies and structure and format of the BLA.

2.0 DISCUSSION

2.1. [REDACTED] (b) (4)

Question 1a: Does the Agency agree the information contained within the cross-referenced drug master files (DMFs) is adequate to enable a complete review for commercial registration of the [REDACTED] (b) (4)?

FDA Response to Question 1a:

We were not able to access the DMFs for review of full content prior to this meeting as two centers and multiple reviewers would need to access these non-electronic DMFs. Please note that it would be helpful if the Master Files submitted to support the BLA would be in electronic form, including your Master File identified in question 5a, below. Additionally, since the different reviewers would need to access the Master Files for specific information relevant to their area of review, for any information in cross-referenced Master Files, the specific location of each referenced information e.g. [REDACTED] (b) (4) [REDACTED] should be clearly identified in the Letter of Authorization (LOA) to the DMF.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

Question 1b: Does the Agency agree that the data package supporting the use of the [REDACTED] (b) (4) [REDACTED] is adequate to enable a complete review for commercial registration?

FDA Response to Question 1b:

[REDACTED] (b) (4)

(b) (4)

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

2.2. Data Package Supporting Registration of the Autoinjector/Pen (1.5)

Question 2: Do CDER and CDRH agree with the proposed plan for inclusion of clinical data on the AI/pen (1.0) and design verification/validation data on the AI/pen (1.5) in Module 3.2.R. of the BLA to support commercial approval of the AI/pen (1.5)?

FDA Response to Question 2:

No, we disagree with location of the human factors data and design verification/validation data in Module 3.2.R. These data should be provided in Module 3 using the principles described further in the additional comments section. The Home Use studies should be submitted in the clinical module. Also, we reference previous Agency comments of February 26 and December 5, 2013.

However, your proposal to use HFE/UE studies and to perform them in accordance to established standards and guidance appears reasonable. When you submit the HFE/UE studies protocol and report, please ensure that you include a use-related risk analysis. This analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies. We need this information to ensure that all potential risks involved in using your device have been considered and adequately mitigated and the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the device).

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. There is a more recent draft guidance document that includes the current thinking on human factors at CDRH and recommended approaches to human factors evaluation and testing: *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*.

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

Discussion: *The sponsor requested clarification of the Agency's preliminary comment (please see attached slide presentation). The Agency clarified that the decision on whether the data are or are not sufficient for approval will be made during the review. This decision will take into consideration all clinical, PK, and clinical use data in addition to human factors study for the safe and correct use of the product.*

FDA also clarified an inconsistency in preliminary responses to this question and question 7. Specifically the Agency stated that the approval of the AI/Pen (1.5) will be based on a review of all supportive data submitted with the application, including but not limited to that obtained from HF studies, and a comprehensive benefit-risk assessment. The related sentence in the response to #5 is deleted.

2.3. Stability Strategy for Drug Substance and Drug Product

Question 3a: Does the Agency agree that the proposed stability strategy for drug substance and the drug product combination products is appropriate to enable a complete review to support commercial registration?

FDA Response to Question 3a:

- A. A ^(b)₍₄₎-month shelf life for the DS at the recommended storage condition of ^(b)₍₄₎°C based on 18 months of stability data from DS lots manufactured by the to-be-marketed process at time of BLA submission would be appropriate to support commercial registration if the data support DS stability.
- B. Testing specifications identified for stability of DS from the validation lots are significantly reduced; the meeting package identifies that these lots will be tested by assays for potency, SE-HPLC and appearance. We cannot at this time comment on the acceptability of paradigm but please note that during BLA review relevant data that are not available could impact on the ability to assess the stability of the AMG-145 DS and assign a shelf life that is not supported by information that is lacking. We would also like to remind you of our response and discussion for question 3 regarding the specification strategy during the November 2, 2012 EOP2 CMC meeting. Although the question was specific for lot release, some of the discussion points are also relevant for specifications used for stability. Assessment of the data, assay capabilities and final decision on acceptability of the proposed stability testing paradigm will be part of the BLA review.
- C. The ability to assign a DP expiration dating of 24 months based primarily on 18 months stability data from 3 primary stability lots manufactured at the clinical manufacturing site, with data from up to 3 months from validation lots manufactured at the commercial

manufacturing site(s) and 24 months stability data from 1 lot manufactured at the clinical site will depend on an assessment, during review of the BLA, of whether manufacturing of the primary lots at the clinical manufacturing site is fully representative of and simulating the commercial manufacturing processes at AML and at any other DP fill site that will be included in the BLA (identified as TBD in table 40). This was also specified in our response to question 4 during the November 2, 2012 EOP2 CMC meeting. The BLA should include detailed information about the ATO manufacturing process to enable this assessment.

- D. The meeting package identifies that selection of test methods for the various validation programs were done based on available data on the relevance of certain methods for addressing product stability. With the data available in the meeting package we cannot comment on the acceptability of the test methods selected. The BLA should include sufficient data that would support removal of specific methods from the stability studies.
- E. We also note in table 40 that DP primary stability lots were made from DS that was manufactured (b) (4) of DP manufacturing. The ability to assign any relevant expiration dating to DP would depend on the stability data of the DS when stored at - (b) (4) °C. If DS stored at (b) (4) °C exhibits changes in stability through the proposed expiration dating it may be difficult to address the impact of manufacturing DP from lots of DS that have been stored for an extended time
- F. Sponsor should ensure that data available from accelerated stability are from conditions that would enable a comparison of degradation rates for this product in its various manufacturing paradigms. This is especially critical to support any expiration dating for the multiple manufacturing processes, presentations and sites which were identified in the meeting package; especially as expiration dating for DP is to be dependent on material manufactured by the clinical manufacturing process.
- G. Data identified as intended to support DP storage at room temperature (controlled, 25°C or less) for (b) (4) month would not be sufficient for the intended purpose. As was noted for previous drug products, controlled room temperature is usually not available for the end-user. Data supporting storage of DP for 1 month outside of refrigeration should include conditions that would represent common conditions, such as summer temperatures in various US regions which are usually much higher than 25°C or even 30°C (86°F). Additionally, if the end-user would be allowed to maintain the DP outside of refrigeration, it is likely that temperature excursions at much higher temperatures would occur. We do note that as part of the general accelerated stability studies Amgen plans to collect data from DP stored at 40°C for 1 month. Data from this study or a similar study would be more supportive of the conditions that the drug may encounter should the end-user be allowed to store the drug product out of refrigeration for an extended timeline.

Discussion: *The sponsor provided additional information in response to the Agency's preliminary comment 3a(B) (please see attached slide presentation), and identified that the DS manufacturing site, scale and process are unchanged between primary and validation lots so that stability data from validation lots are supplemental to the primary stability data. The Agency replied that general primary data may support the shelf life of DS and that reduced testing of the validation lots may be acceptable for purposes of expiration dating if the manufacturing and stability data are as identified. However, the full data package will have to be assessed during the BLA review for a final concurrence on acceptability. The Agency agreed that protocols for post-approval stability can be discussed during the review process.*

Question 3b: Does the Agency agree that additional stability data may be submitted within the first 3 months of the initial file and that such submission, provided the data remains supportive of the initial proposal and does not reflect an unexpected trend, will not result in an extension of the PDUFA review clock?

FDA Response to Question 3b:

Under PDUFA V, data should not be submitted more than 30 days after the submission of the original application unless it is requested by the Agency.

During the review period, the Agency may request submission of a "simple stability update". "Simple stability updates" are defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. Furthermore, the "simple stability update" will use the same tabular presentation as in the original submission, as well as the same mathematical or statistical analysis methods (if any), and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA.

Discussion: *The sponsor provided additional information in response to the Agency's preliminary comment (please see attached slide presentation). The Agency agreed that a simple stability update as outlined in the preliminary comments in regard to expiration dating can be submitted within the first 30 days of initial submission. Although the Agency did not commit to ask for additional stability data during the review cycle, the sponsor stated a schedule will be provided to identify when additional data will be available.*

Question 3c: For the drug substance, where the primary stability lots were manufactured by the commercial site, scale, and process and stability data is collected in accordance with an approved protocol; does the Agency agree that shelf-life extensions based on real time data may be notified through an annual report?

FDA Response to Question 3c:

A stability protocol that would be approved with the BLA would allow extension of shelf life, per protocol, and notification through an AR. Any deviation from this paradigm due to reasons identified during the BLA review will be relayed to the sponsor at that time. The BLA section containing the protocols should identify the proposed post approval notification plan. Please note our comments to question 3a regarding testing specifications for stability.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

Question 3d: For the drug product presentations, where stability data is collected in accordance with an approved protocol, does the Agency agree that shelf-life extensions based on real time data from primary stability lots may be notified by an annual report?

FDA Response to Question 3d:

A stability protocol that would be approved with the BLA would allow extension of shelf life, per protocol, and notification through an AR. Note that the protocol for extension of shelf life should address stability of the full DP combination device. Deviation from this paradigm due to reasons identified during the BLA review will be relayed to sponsor at that time. The BLA section containing the protocols should identify the proposed post approval notification plan. Please note our comments to question 3a regarding testing specifications for stability.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

2.4. Addition of Alternate Drug Product Manufacturing Facility(s)

Question 4a: Does the Agency agree that remaining minor components of the comparability data including 3 months of stability data may be submitted within the first 3 months of the initial file to enable approval of the additional site(s) with the initial BLA without resulting in an extension of the PDUFA review clock?

FDA Response to Question 4a:

No, under PDUFA V, data should not be submitted more than 30 days after the submission of the original application unless it is requested by the Agency.

Discussion: *The sponsor provided additional information in response to the Agency's preliminary comment (please see attached slide presentation) and identified their intent to submit a stability update from the 3 months time point within the first 30 days of initial submission. As discussed for Question 3, the Agency stated that only simple stability data updates to support expiration dating should be submitted within 30 days of the initial submission.*

Question 4b: Does the Agency agree that inclusion of (b) (4) in the establishment information for the initial BLA is appropriate and sufficient to trigger and complete the inspection, if deemed necessary, to support approval of (b) (4) either in the initial BLA or as a post-approval supplement?

FDA Response to Question 4b:

No. (b) (4) or any other facility, should only be included in the establishment information if the DP manufactured at that site is intended to be approved in the first cycle BLA approval. Note that the full CMC package to support DP manufacturing at (b) (4) would need to be submitted in the BLA, and the drug product validation and (b) (4) process validation of the new line is complete and available at the time of BLA submission. Otherwise, a PAS should be submitted. Please also see our reply to question 4a.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

Question 4c: Does the Agency agree inclusion of an acceptable comparability protocol and either a successful GMP inspection for evolocumab or a GMP inspection waiver based on a successful inspection from a comparable Amgen commercial product, is sufficient to result in a reduced reporting category from a PAS to a CBE-30 for the addition of a new drug product manufacturing site?

FDA Response to Question 4c:

The addition of a new line will require an inspection and we cannot provide at this time a determination on the proposed inspection and reporting strategies. A specific inspection for evolocumab cannot be conducted during the BLA timeline based on a comparability protocol in the BLA, and would have to be conducted during the time of the subsequent submission if no relevant and successful GMP inspection were to occur prior to that submission. During the review of the comparability protocol, the inspection history of the new line, the GMP status of the new line, the process similarities between the evolocumab and the comparable Amgen commercial product with same container closure system will have to be available in order to consider whether the subsequent reporting category can be downgraded.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

Question 4d: Does the Agency have any additional advice on approaches that may be used to bring additional facilities on-line as quickly as possible while minimizing burden to the Agency?

FDA Response to Question 4d:

Sponsor may consider submission of an expanded change protocol that would cover multiple DP manufacturing sites.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

2.5. Structure and Format of Module 3

Question 5a: Does the Agency agree the proposed Module 3 structure and format of data, including use of MAFs for technical device documentation, will facilitate a joint review by both CDER and CDRH?

FDA Response to Question 5a:

We agree that the DP section will be split for each DP presentation as described. Where relevant, the sections for each presentation should be further divided into subsections (e.g. 3.2.P.3, manufacture should have duplicate sub-sections for each manufacturing site for a presentation) (b) (4) validation, (b) (4) process validation, and container closure integrity for pre-filled syringe, autoinjector pen (b) (4) should be included in the BLA application.

Regarding the use of Master Files, these should only be for confidential proprietary information that is not otherwise known to the BLA holder. Also, if a master file is used only one file should be submitted for the information. Duplicate files should not be submitted in a DMF and MAF. To facilitate the intercenter reviews please provide master files in electronic format.

As a combination product, the various configurations (PFS, AI/Pen (b) (4)) are subject to 21 CFR Part 4. Based on the briefing document it appears that that the drug CGMPs will serve as the primary operating system for this combination product. The manufacturing sections of the submission should include details on the required sections of 21 CFR 820. For example for Design Control, Purchasing Control, and Corrective and Preventive Action include the procedures that were used during the development of the finished combination product. Within this section, also provide a production flow of the finished combination product, which includes a description of the facility or facilities where the finished combination product will be subject to final inspection and release. The production flow should also include information about the packaging used for the finished combination product.

For additional information on manufacturing information and its location in the eCTD see other responses below in Section 3.0 Manufacturing Facilities and Additional Comments: eCTD format related to the device constituent part.

Discussion: *The sponsor provided additional information in response to the Agency's preliminary comment (please see attached slide presentation). The Agency clarified that the information in the preliminary comment to Question 5a as well as in the additional comments section is for the combination product, not a stand-alone device. The*

information was provided to assist in the overall review process by clarifying the type of information the reviewers would expect to see in the submission.

The Agency stated they would provide post-meeting comments on the level of detail that is needed regarding the Quality Systems procedures for a combination product. (See Post meeting comment section.)

These responses are for this IND combination product and any broad combination policy comments should be directed to the Office of Combination Products.

Question 5b: Does the Agency agree with the proposed plan for inclusion of complaint reporting related to device malfunctions in the initial BLA?

FDA Response to Question 5b:

We disagree with the location of reports of device related complaints, adverse events or other safety data. All safety information should be included in the clinical module safety sections. The location of the information should be identified in Module 1.2 Reviewers Information.

Discussion: *The sponsor provided additional information in response to the Agency's preliminary comment (please see attached slide presentation). The Agency stated that further clarification on the definition of device compliant data will need to be provided as well as the sponsor's intent in submitting the device issues data. The sponsor stated they would provide this information to the Agency.*

Question 5c: Does the Agency agree that the executed batch records planned for inclusion in the BLA submission are sufficient to enable BLA review?

FDA Response to Question 5c:

The BLA should include an executed batch record for every manufacturing process identified for DS and the various presentations and manufacturing sites of DP that are to be marketed. Batch records should also be included for assembly processes into the AI/pen (b) (4) as these are part of the final DP manufacturing process. Note that the batch records to be submitted in the original BLA should only be included for those manufacturing processes, sites, and presentations intended to be licensed in the original BLA.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

Question 5d: Does the Agency agree the proposed content of the CMC/device information is considered a complete application as underscored by PDUFA V?

FDA Response to Question 5d:

Please note our responses to the other questions in this document regarding location and content of required information.

Evolocumab drug product contains excipients (e.g., polysorbate) that could result in low endotoxin recovery (LER) (see K.L. Williams, "Endotoxin Test Concerns of Biologics," American Pharmaceutical Review, October 28, 2013). To determine if endotoxin recovery is affected by the polysorbate-containing evolocumab drug product formulation, undiluted drug product should be spiked with endotoxin, and satisfactory endotoxin recovery demonstrated over time. The studies should be conducted in the same type of containers (e.g., (b)(4) syringes, cartridges) in which the product and samples are held prior to endotoxin testing.

For biological products, 21 CFR 610.13(b) requires a rabbit pyrogen test. The requirement in 21 CFR 610.13(b) may be waived if a method equivalent to the rabbit pyrogen test is demonstrated in accordance with 21 CFR 610.9. The protocol and data from the rabbit pyrogen testing of 3 lots of drug products should be provided in the BLA.

Please refer to minutes from the end of phase II Type B meeting held November 2, 2012 for additional information that should be included in the BLA application with respect to (b)(4) validation, (b)(4) process validation, (b)(4), container closure integrity for pre-filled syringe, autoinjector pen (b)(4) and shipping validation. For the (b)(4) processes, please ensure that the initial validation and the requalification program with the most recent requalification data are included in the BLA.

We disagree with the location of the device information in module 3.2.R (as summarized in the briefing document appendix 1). For the eCTD location of information, see Agency comments below under Additional Comments: eCTD format related to the device constituent part.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

2.6. Specification Strategy for Drug Substance and Drug Product

Question 6a: Does the Agency agree with the proposed specification strategy for volume for the three drug product presentations?

FDA Response to Question 6a:

Yes.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

Question 6b: Does the Agency agree that the proposed data package after collection of additional stability data is sufficient to enable the assessment for removal of the (b) (4) and use of the receptor-ligand binding assay as the sole potency assay for evolocumab drug substance and drug product specifications?

FDA Response to Question 6b:

The proposed studies described in the meeting package appear appropriate to enable the assessment for removal of the (b) (4) and use of the receptor-ligand binding assay as the sole potency assay for DS and DP release and stability specifications. The full datasets and not only a summary report should be submitted to the BLA for assessment.

Discussion: *The sponsor accepted FDA's response, no discussion occurred.*

2.7. Estimated Clinical Usage of AI/Pen (b) (4)

Question 7: Does the Agency agree that the estimated device usage for each presentation (PFS, AI/pen (b) (4)) is sufficient to enable approval?

FDA Response to Question 7: No, it is premature to determine if the estimated usage information is sufficient for approval; the specific assessment will be made during the submission review. However, for the AI/pen the briefing package notes that several modifications occurred. In the submission please provide a subset analysis based on the iterative design modifications. (b) (4)

(b) (4)

Discussion: *The Agency inquired if any version between the 1.0 and 1.5 API was used in clinical trials. The sponsor confirmed only versions 1.0 and 1.5 API were used. The Agency confirmed that based on this information a subset analysis did not appear feasible.*

ADDITIONAL COMMENTS:

Combination Products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>

The following recommendations apply to the location of device manufacturing information in the marketing application.

1. All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations should be located in Section 3.2.P.3.
2. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.
3. Suggestions on the types of documents to submit for review related to 21 CFR Part 820 can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

eCTD Format Related to the Device Constituent Parts

The following provides recommendations apply to combination drug and device product such as PFS, pens and other injectors in an eCTD application. Please do not use module 3.2.R for this information.

1. For eCTD format and use of the system, please adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say "Container Closure System."
2. Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.
3. We recommend the following when including and referencing device information:
 - a. You may reference files under 3.2.P.7 which are not currently listed as numerical items in ICH and FDA specifications and guidance.

- b. In 3.2.P.7 you could include a leaf titled something similar to the following, “Table of Contents for Drug-Device Autoinjector. This leaf/document could provide reference links to the other files in module 3.2.P.7. Obtaining concurrence from the Review Division on the proposed outline is recommended.
 - c. The leaf titles should be clear, concise and indicative of the document's content.
4. Module 1.4.4 cross reference to other applications is a location where you can provide references to other applications and you can include copies of an application’s table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 Letter of Authorization, 1.4.2 Statement of Right of Reference, 1.4.3 List of Authorized Persons to Incorporate by Reference). If there are standards you will reference in the Performance Specifications which also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.

Although it’s not required, providing a "Information to Reviewers” or “Reviewers Guide” document in Module 1.2 Cover letters can be helpful. This document would be separate from the cover letter and referenced after the cover letter. It would provide a high level overview (with reference links) of the submission’s content and list where the information is located in the eCTD. For example, it would identify where drug, device and combination product information including manufacturing and human factors information is located.

Discussion: *The sponsor inquired whether the establishments for raw material testing sites need to be included on the 356h form. The Agency responded that raw material testing sites are not required; however, cell bank manufacturing and testing sites are required.*

The sponsor also inquired whether the Agency wanted to discuss their acceptance and confirmations on the Agency’s preliminary comments. The Agency did not see the need and stated that the preliminary comments stood as the Agency’s response.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed. All applications are expected to include a comprehensive and readily located list of all manufacturing facilities included or referenced in the application.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a multidiscipline pre-submission meeting is scheduled for April 10, 2014. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

4.0 POST-MEETING AGENCY COMMENTS

In reference to 21 CFR Part 4, the submission should provide the procedures necessary to demonstrate that it has satisfied the requirements of 21 CFR 820.30 (Design Control), 820.50 (Purchasing Controls) and 820.100 (Corrective and Preventive Action). These procedures should be provided to demonstrate compliance for these specific areas of the Quality System Regulation for the combination product as a whole, not just the device constituent parts. The procedural information to provide and level of detail necessary to be provided should be consistent with what is recommended in the Agency guidance referenced above under Additional Comments item 3. If Amgen has specific questions please submit them to the IND.

The device constituents are part of the combination product as a whole. The facilities on the 356h form or attachment to the form should include manufactures of the device constituent part(s) and the location from which the finished combination product is distributed.

The new 356h form to be used for BLA submissions can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf> Instructions can be found at www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf

5.0 ACTION ITEMS

| Action Item/Description | Owner |
|--|---------|
| Provide the level of detail needed regarding the Quality Systems procedures for a combination product | FDA |
| Provide definition of device compliant data as well as the intent in submitting the device issues data | Sponsor |

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's slide presentation attached.

25 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

CHANA FUCHS
02/20/2014



IND 105188

MEETING MINUTES

Amgen Inc.
Attention: Lisa Carlson
Regulatory Affairs Senior Manager
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Ms. Carlson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG 145.

We also refer to the meeting between representatives of your firm and the FDA on November 2, 2012. The purpose of that meeting was an End-of-Phase II CMC meeting.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Joel Welch, Regulatory Project Manager at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Chana Fuchs, Ph.D.
Team Leader
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

| | |
|-------------------------------|---|
| Meeting Type: | Type B |
| Meeting Category: | End of Phase II (CMC Only) |
| Meeting Date and Time: | November 2, 2012; 1:00 p.m. |
| Meeting Location: | NIH Campus, Bld 29B, Conf Room A/B |
| IND Number: | 105188 |
| Product Name: | AMG 145 |
| Indication: | Indicated as an adjunct to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol, apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), lipoprotein(a) (Lp[a]), very-low-density lipoprotein cholesterol (VLDL-C), and triglyceride (TG) levels, and to increase HDL-C levels |
| Sponsor Name: | Amgen, Inc. |
| Meeting Requestor: | Lisa Carlson |
| Meeting Chair: | Chana Fuchs |
| Meeting Recorder: | Joel Welch |

FDA Participants:

Office of Pharmaceutical Science
Office of Biotechnology Products
Division of Monoclonal Antibodies

| | |
|----------------------|-----------------------------------|
| Sang Bong Lee, Ph.D. | Product Quality Reviewer |
| Chana Fuchs, Ph.D. | Team Leader |
| Patrick Swann, Ph.D. | Deputy Division Director |
| Joel Welch, Ph.D. | Regulatory Health Project Manager |

Office of Compliance

Office of Manufacturing and Product Quality

Biotechnology Manufacturing Assessment Branch

| | |
|--------------------------------|-----------------------|
| Colleen Thomas, Ph.D. | Microbiology Reviewer |
| Candace Broughton-Gomez, Ph.D. | Microbiology Reviewer |

Office of New Drugs

Office of Drug Evaluation II

Division of Metabolism and Endocrinology Products

| | |
|----------------|-----------------------------------|
| Raymond Chiang | Regulatory Health Project Manager |
|----------------|-----------------------------------|

Office of New Drugs

Office of Safety and Epidemiology

Division of Medication and Error Prevention Analysis

| | |
|-------------------------|-----------------------------------|
| Margarita Tossa, M.S. | Safety Regulatory Project manager |
| Sarah Vee, Pharm.D. | Reviewer |
| Yelena Maslov, Pharm.D. | Team Leader |

Center for Devices and Radiological Health
Office of Device Evaluation
Division of Anesthesiology, General Hospital, infection Control, and Dental Devices
Jacqueline Ryan, M.D. Team Leader
CDR Quynh Nhu Nguyen, Pharm.D. Human Factors Specialist

Center for Devices and Radiological Health
Office of Compliance
Layota Oliver-Powell Consumer Safety Officer

Amgen, Inc.
Lisa Carlson Senior Manager, Global Regulatory Affairs (CMC)
Jill Crouse-Zeineddini, PhD Principal Scientist, Functional Biocharacterization
Maurice Emery, PhD Scientific Director, Pharmacokinetics & Drug Metabolism
(b) (4) Principal Consultant, (Device Engineering)
Kristi Kistner Director, Global Regulatory Affairs (Devices)
George Klein Director, Product Quality

| | |
|-----------------|--|
| Eli Kraus, PhD | Scientific Director, Process and Product Engineering (Commercial Site Drug Substance Manufacturing Lead) |
| Mark Lee, PhD | Executive Director, Engineering (Drug Delivery) |
| Richard Lit, MS | Vice President, Regulatory Affairs (CMC, Devices and Biosimilars) |

(b) (4) (b) (4)

| | |
|-----------------------|---|
| William Sietsema, PhD | Director, Regulatory Affairs (Global Regulatory Leader) |
| Scott Wasserman, MD | Executive Medical Director, Global Development (Global Development Leader) |
| Jette Wypych, MS | Scientific Director, Process and Product Development (Drug Substance Lead) |
| Xin Zhang, PhD | Senior Scientist, Process and Product Development (Development Analytical Lead) |

1.0 BACKGROUND

AMG 145 is a human monoclonal immunoglobulin (Ig) G2 that specifically binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9) and prevents the interaction of PCSK9

with the low-density lipoprotein receptor (LDLR). On July 30, 2012 Amgen, Inc. requested a Type B CMC only meeting. The Agency granted that meeting request on August 15, 2012.

2.0 DISCUSSION

Sponsor Question 1:

Does the Agency agree that material manufactured from Process 2 is sufficiently similar to the previously used material manufactured from Process 1 to permit introduction of Process 2 material into clinical studies, including initiation of phase 3 studies?

FDA Response:

No. For Drug Substance (DS) comparability, there was no information in the meeting package for process 2 lots manufactured at clinical scale at the (b) (4) site to enable assessment and response to this question. The meeting package contains preliminary analytical comparability data between the clinical Process 1 lots manufactured at ATO and nonclinical lots manufactured at ATO using a (b) (4) version of process 2. Our understanding is that the clinical Process 2 drug substance lots will be manufactured at (b) (4) using a (b) (4) L scale. For drug product (DP), we note that comparability will be executed in a couple of stages, (b) (4). Please clarify the timeline of these studies as they relate to your proposed implementation in the various clinical studies planned. We also note (b) (4).

The section on characterization testing describes using an (b) (4) the IND amendment should identify the methodology used for this assessment and include the data used in this assessment.

It appears that (b) (4) acceptance criterion (b) (4) please also report the (b) (4) levels separately (b) (4).

Comparability studies between DS and DP lots manufactured by process 1 and process 2 should be submitted to the IND for review and receipt of concurrence on the comparability of the material manufactured. The overall strategy for the proposed comparability study appears to be acceptable for this stage of development based on the information provided. Detailed results submitted in to the IND should including individual sample results and the analyses for assessing comparability using the Equivalence test for those methods that were recently revised. In addition to comparability data, prior to use of process 2 material in clinical trials Amgen should submit to the IND manufacturing information for process 2, and (b) (4) validation data for process 2 or data supporting that process 2 (b) (4) is within the currently validated ranges for the AMG145 process. Include in this amendment information on any differences seen between process 1 and process 2 materials such as cause and potential clinical impact. For example, (b) (4).

We note the inclusion of nonclinical comparability data between process 1 material and material manufactured by the (b) (4) process 2 at ATO. As these data are reviewed by the non-clinical group which are not participants of this CMC only meeting, the relevant non-clinical comparability data should also be included in the amendment which will contain the final CMC comparability, manufacturing, and (b) (4) safety data.

Additional Discussion During Meeting:

The Sponsor clarified that the clinical drug substance will be manufactured at (b) (4) at the (b) (4) L scale. Additionally, the Sponsor committed to submitting results of the comparability studies between DS and DP lots manufactured using process 1 and process 2 clinical scale at (b) (4). The Sponsor clarified that drug product comparability studies for each presentation will be completed and submitted to the IND prior to use in clinical studies. (b) (4)

The Sponsor then asked for clarification what is meant by “review and receipt of concurrence”. Specifically, what is the concurrence and how will it be communicated to the Sponsor? The Agency stated that the RPM from the clinical division (Office of New Drugs) will be the conduit for the information.

The Sponsor inquired if the data presented thus far would allow a preliminary assessment that would allow them to proceed. The Agency did not agree because changes to be made in scale and site are considered significant manufacturing changes which on their own would require a comparability assessment prior to the material being used in clinical trials.

The Sponsor inquired to the timeline for review of the comparability package due to tight timelines associated with their schedule. The Agency noted that safety reviews are typically conducted within 30 days of submission, though the comparability data package includes considerably more information in addition to the typical safety review that would be required. A proposal was discussed for the Sponsor to submit detailed manufacturing information, including (b) (4) safety testing data in an in an early amendment in order to facilitate a quicker turnaround time on the review of the comparability package amendment.

Sponsor Question 2:

2a: Does the Agency agree that the new receptor-ligand binding assay and the (b) (4) (b) (4) both using (b) (4), are appropriate to replace the current (b) (4) using (b) (4))?

FDA Response:

Yes, the proposed two new potency assays appear to be appropriate to replace the current (b) (4) assay at this time.

Additional Discussion During Meeting:

There was no additional discussion.

2b: Does the Agency agree that the proposed potency assay implementation strategy for drug substance and drug product testing will support phase 3 clinical studies?

FDA Response:

No. We do not agree (b) (4)

Additional Discussion During Meeting:

[REDACTED] (b) (4)

However, the Agency stated that it was willing to address this question again once sufficient data was available, and that a robust data package would be needed to consider the issue during the review of the BLA. It was noted that this specification can initially have broader acceptance criteria, and be tightened based on accumulated data throughout the course of development. The Sponsor agreed.

2c: Does the Agency agree that the proposed potency assay implementation strategy for drug substance and drug product testing will support commercial registration?

FDA Response:

No. We do not agree [REDACTED] (b) (4)

Additional Discussion During Meeting:

Discussion is included as a part of Question 2b.

Sponsor Question 3:

3a: Does the Agency agree the proposed specification strategy is adequate with respect to identification of all proposed release test methods and method types for initiation of phase 3 clinical studies?

FDA Response:

No. The proposed strategy with respect to method and method types is not adequate. [REDACTED] (b) (4)

[REDACTED] (b) (4)

These should be monitored in process 2 lots.

[REDACTED] (b) (4)

Additional Discussion During Meeting:

The Sponsor agreed to monitor [REDACTED] (b) (4)

[REDACTED] Additionally the Sponsor noted they are collecting data on breakloose and extrusion and will add this test to the specification upon the collection of adequate data. The Agency stated it would prefer this specification be added now with either a broad specification limit, or a “report results” value, and agreed that numerical limits can be set once sufficient data, [REDACTED] (b) (4)

[REDACTED] are available, and prior to the BLA. [REDACTED] (b) (4)

3b: Does the Agency agree the proposed specification strategy is adequate with respect to identification of all proposed release test methods and method types for collection of data to establish specifications for commercial registration?

FDA Response:

No, the proposed strategy with respect to method and method types is not adequate. [REDACTED] (b) (4)

[REDACTED] *Breakloose and Extrusion are not proposed as measurements in the DP release testing, but should be included. Please note our reply to question no 2c with regard to potency assays. We also note, as in our response to 3a,* [REDACTED] (b) (4)

[REDACTED] *A decision on whether these would require a specification post approval would be based on the accumulated data from characterization testing and from lots used in the phase 3 clinical trial. In general, the other proposed release test methods and method types appear appropriate at this time, however we do not have data on material manufactured by process 2, to be used in your registration supporting studies, in order to definitively state that the proposed specification strategy will be sufficient for registration; a final assessment and agreement on the adequacy of the test methods and method types for commercial registration can only be done after the full product characterization and release data package has been assessed.*

Additional Discussion During Meeting:

[REDACTED] (b) (4)

Sponsor Question 5:

5a: Does the Agency agree that the design verification requirements and identified applicable standards and guidance in Table 31 are adequate for approval of the AI for healthcare provider administration or self-administration in non-healthcare or clinic environment at the time of the initial BLA submission?

FDA Response:

No, we do not agree that the design verification requirements and applicable standards are adequate for approval of the autoinjector for healthcare provider administration or self-administration in non-healthcare or clinic environment at the time of the initial BLA submission. While your testing plan appears comprehensive, approval will depend on review of the results of your performance testing. FDA would like further clarification regarding how you will conduct drug compatibility testing of the autoinjector. We suggest that you test the fully assembled combination product at or near the end of shelf life and that you confirm the delivered dose for the fully assembled combination product at or near the end of shelf life

Additional Discussion During Meeting:

The Sponsor clarified it will test the assembled combination product at the end of shelf life, including drug product compatibility. The drug product release specification will be met after delivery of the drug product through the autoinjector. Finally, they stated that deliverable volume will also be included in the testing. The Agency agreed.

5b: Does the Agency agree (b) (4)
[Redacted]
at the time of the initial BLA submission?

FDA Response:

No, we do not agree (b) (4)
[Redacted]

Additional Discussion During Meeting:

There was no additional discussion.

5c: Does the Agency agree with the classification assignments of Moderate Level of Concern and Class B?

FDA Response:

Yes, we agree with the classification assignments of Moderate Level of Concern and Class B with regards to software validation and verification.

Additional Discussion During Meeting:

There was no additional discussion.

5d: Does the Agency agree that evaluation of the AI primary container (PFS) in accordance with compendial testing requirements is sufficient for approval of the AI in the initial BLA submission?

FDA Response:

The compendial testing requirements should include relevant items in USP <1>; the others identified appear appropriate.

Additional Discussion During Meeting:

There was no additional discussion.

5e: [REDACTED] (b) (4)

Additional Discussion During Meeting:

[REDACTED] (b) (4)

5f: [REDACTED] (b) (4)

FDA Response:

[REDACTED] (b) (4)

Additional Discussion During Meeting:

There was no additional discussion.

5g: Does the Agency agree with Amgen's definition of special training and the proposed study design?

Please note that to respond fully to this question requires feedback from multiple groups in CDER and CDRH. FDA typically requires at least 90 days to review human factor protocols, and therefore the replies to the questions below are not complete.

Additional Discussion During Meeting:

The Sponsor asked for an estimate when feedback would be received and how it would be communicated. The Agency indicated the document is typically submitted to the IND, and then written comments are typically provided within 90 days. An agreement was reached that the clinical RPM would be the conduit for providing written feedback and that the Agency would target the end of December to give the advice to the Sponsor. However, the Agency stated that it is more realistic that we will provide the advice regarding Human Factors Usability studies in January. The Sponsor indicated they would discuss with the clinical RPM offline if the Human Factors Usability study documents should be resubmitted separately to the IND.

5h: Does the Agency agree with the scope, tone, and triggers for the scripted questions in Appendix H of the Usability Plans?

Please note that to respond fully to this question requires feedback from multiple groups in CDER and CDRH. FDA typically requires at least 90 days to review human factor protocols, and therefore the replies to the questions below are not complete.

Additional Discussion During Meeting:

See item 5.g.

5i: Does FDA agree that the intent of Section V in the Usability Plans will provide the breadth of information FDA will want to review in the final report?

Please note that to respond fully to this question requires feedback from multiple groups in CDER and CDRH. FDA typically requires at least 90 days to review human factor protocols, and therefore the replies to the questions below are not complete.

Additional Discussion During Meeting:

See item 5.g.

ADDITIONAL FDA COMMENTS

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

The CMC Drug Substance section of your BLA (Section 3.2.S) should include the following *product quality microbiology information*:

- *Monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).*
- *Three successful product (b) (4) hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowable hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5). Studies should be performed to determine whether endotoxin recovery is inhibited in material held for the maximum allowable times.*

- [REDACTED] ^{(b) (4)} sanitization and storage validation data and information (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications. The bioburden limit should be [REDACTED] ^{(b) (4)} mL for bulk materials allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).
- Qualification data for bioburden and endotoxin test methods performed for [REDACTED] ^{(b) (4)} and the drug substance (3.2.S.4).

The CMC Drug Product section of your BLA (Section 3.2.P) should include validation data summaries supporting the [REDACTED] ^{(b) (4)} and sterility assurance. For guidance on the types of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”.

- The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:
 - Bacterial retention study for [REDACTED] ^{(b) (4)}
 - Sterilization and depyrogenation of equipment and components that contact the sterile drug product. The equipment requalification program should be described.
 - [REDACTED] ^{(b) (4)}
 - In-process microbial controls and hold times. Hold times should be validated at manufacturing scale. Studies should be performed to determine whether endotoxin recovery is inhibited in material held for the maximum allowable times.
 - [REDACTED] ^{(b) (4)}, if applicable.
 - Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
 - Shipping validation studies for the pre-filled syringe, the assembled AI, [REDACTED] ^{(b) (4)}
- The following method validation information should be provided:
 - Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated for the complete manufacturing process including shipping. For AI systems, system integrity should be demonstrated for the full manufacturing process including AI assembly and AI shipping. [REDACTED] ^{(b) (4)}

- *Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that container closure integrity testing be performed in lieu of sterility testing for stability samples at initial time point and every 12 months (annually) until expiry (3.2.P.8.2).*
- *Qualification data for bioburden, sterility and endotoxin test methods performed for (b) (4) (if applicable) and the drug product, as appropriate (3.2.P.5).*

Additional Discussion During Meeting:

The Sponsor noted these suggestions were helpful, but that they relate to a more traditional validation approach, while Amgen would like to have future discussions on an approach based on (b) (4). The Agency agreed and noted these were general template comments.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

Sponsor will communicate with the OND RPM regarding the human factor studies review.

5.0 ATTACHMENTS AND HANDOUTS

The Sponsor used a slide presentation to guide the discussion. Those slides are presented as an attachment.

6 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

CHANA FUCHS
11/30/2012



IND 105188

MEETING MINUTES

Amgen, Inc.
Attention: Marc Kubasak, Ph.D., RAC
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Kubasak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG 145 (for injection).

We also refer to the meeting between representatives of your firm and the FDA on July 10, 2012. The purpose of the meeting was to discuss the proposed AMG 145 clinical development program and device clinical study strategy for the indications (1) hyperlipidemia and mixed dyslipidemia, to be filed in an original BLA and [REDACTED] (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, MPT, MS, MS
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes for End-of-Phase 2 meeting held on July 10, 2012



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: July 10, 2012; 11:00 AM - 12:30 PM EST
Meeting Location: White Oak Building 22, Room 1417

Application Number: IND 105188
Product Name: AMG 145 (for injection)
Proposed Indication: Hyperlipidemia and mixed dyslipidemia
Sponsor/Applicant Name: Amgen, Incorporated

Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Raymond Chiang

FDA ATTENDEES

Office of Drug Evaluation II

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|-----------------------------|---|
| Eric Colman, M.D. | Deputy Director, Division of Metabolism and Endocrinology Products (DMEP) |
| James Smith, M.D., M.S. | Clinical Reviewer, DMEP |
| Karen Davis- Bruno, Ph.D. | Pharmacology/Toxicology Team Leader, DMEP |
| Raymond Chiang, MPT, MS, MS | Regulatory Project Manager, DMEP |
| Mehreen Hai, Ph.D. | Acting Chief, Project Management Staff, DMEP |

Office of Clinical Pharmacology

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| Manoj Khurana, Ph.D. | Clinical Pharmacology Reviewer |
| Immo Zadezensky, Ph.D. | Acting Clinical Pharmacology Team Leader |

Office of Biotechnology Products

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| Sang Bong Lee, Ph.D. | Quality Reviewer |
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Office of Biometrics

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| Dongmei Liu, Ph.D. | Biostatistics Reviewer |
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Center for Devices and Radiological Health

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| Quynh Nhu Nguyen | CDRH reviewer |
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Office of Surveillance and Epidemiology

Yelena Maslov, Pharm.D. Acting OSE team leader (DMEPA)

SPONSOR ATTENDEES (Amgen Representatives)

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| Steven Galson, MD, MPH Rekha Garg, MD, MS | Vice President, Global Regulatory Affairs Executive Director, Regulatory Affairs (Global Regulatory Leader and Therapeutic Area Head) |
| John Gibbs, PhD | Scientific Director, Pharmacokinetics and Drug Metabolism |
| Kristi Kistner Elias Kouchakji, MD | Director, Regulatory Affairs (Devices) Executive Director, Global Safety (Therapeutic Area Head) |
| Marc Kubasak, PhD, RAC | Senior Manager, Regulatory Affairs (US Regulatory Leader) |
| Thomas Liu, PhD Graeme Moffat, PhD Arline Nakanishi, MS | Director, Biostatistics (Global Statistical Leader) Director, Preclinical Executive Director, Biostatistics (Therapeutic Area Head) |
| Rob Scott, MD | Vice President, Global Development (Therapeutic Area Head) |
| Karen Smirnakis, MD, PhD, MPH | Medical Director, Global Safety (Global Safety Officer) |
| Scott Wasserman, MD | Executive Medical Director, Global Development (Global Development Leader) |

1.0 BACKGROUND

AMG 145 is a monoclonal antibody that binds to proprotein convertase subtilisin/kexin type 9 (PCSK9). The proposed mechanism of action is that AMG 145 prevents PCSK9 from binding with the hepatic low-density lipoprotein receptor (LDLR), leading to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C. The sponsor states that AMG 145 is supplied as a sterile, single-use, preservative free solution for subcutaneous (SC) injection either once every 2 weeks (Q2W) or once every 4 weeks (Q4W). The purpose of the meeting is to discuss the proposed AMG 145 clinical development program and device bridging strategy to support Amgen's two proposed indications.

2.0 DISCUSSION

The sponsor's questions are repeated below, followed by FDA's preliminary responses in **bold** print and the meeting discussion in *italics*. FDA's post-meeting questions and responses appear in *underlined italics*. The sponsor's post-meeting comments appear in ***bold italics***.

CLINICAL

1. To evaluate the potential of AMG 145 for the treatment of hyperlipidemia and mixed dyslipidemia, Amgen proposes 4 phase 3 studies to evaluate the safety and efficacy of AMG 145 as a monotherapy (20110114), in combination with statins (20110115), in subjects who are statin intolerant (20110116), and in subjects with heterozygous familial hypercholesterolemia (20110117). The planned enrollment in these 4 studies combined is 2900 subjects. To provide long term safety, tolerability, and efficacy data of AMG 145 for the treatment of hyperlipidemia and mixed dyslipidemia, the clinical development plan includes data from 2 phase 2 long term studies that are anticipated to enroll approximately 2500 subjects; a 1 year, randomized, controlled, double blind effect durability study (20110109) and a 5 year OLE study (20110110). These 4 phase 3 studies are supported by 4 dose ranging phase 2 studies with similar designs that enrolled 1360 subjects. The phase 3 study designs are summarized in Section 3.5 and detailed in the protocols in Appendix 1 through Appendix 4.
 - a. Does the Agency agree that the 4 proposed lipid lowering phase 3 studies and the long term effect durability Study 20110109 are adequate to support the proposed indication, hyperlipidemia and mixed dyslipidemia?

FDA PRELIMINARY RESPONSE: There are several issues with the proposed development program that will be addressed in the subsequent responses. However, there are a few general considerations to address.

i) We believe that it would inappropriate to use AMG 145 as monotherapy in the general population before cardiovascular (CV) outcomes data are available. Thus, with the possible exception of an indication for a "statin-intolerant" population (see response to Question 2), it is unlikely that we would entertain a monotherapy indication without CV outcomes data.

ii) We note that the population for each of the lipid-lowering claims (except homozygous familial hypercholesterolemia) includes patients with “primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.” Please specify your definitions for nonfamilial hyperlipidemia and mixed dyslipidemia. You will need to ensure that a reasonable number of subjects with each of these definitions are enrolled in trials intended to support each claim.

iii) With respect to your study populations, you are proposing to enroll subjects (b) (4)

[Redacted]

but we disagree. In contrast to some of the current designs, we would expect that placebo-controlled studies would enroll patients who are not at goal despite taking the maximal tolerated dose of statin, with or without other lipid-modulating agents.

iv) Based on the currently proposed designs, you intend to make superiority claims to ezetimibe ((b) (4)

[Redacted]

We would not include superiority claims to

(b) (4) before cardiovascular outcomes data for AMG 145 are available.

v) For trials that involve treatment decisions based on ATP III goals (e.g., protocol 20110109), we suggest considering chronic kidney disease (eGFR \leq 60 mL/min/1.73m² and/or the presence of micro-/macroalbuminuria) a CHD risk equivalent to be consistent with recommendations from the American Heart Association and the National Kidney Foundation.

vi) A 900-subject (600 AMG 145), one-year, randomized, placebo-controlled trial to assess the long-term tolerability and durability of effect is reasonable, provided that you ensure the enrollment of a heterogeneous population with respect to demographics, CV risk, etc. Please specify what device(s) you plan to use to administer study drug in this trial.

Please see our response to Question 5 with regard to the timing of the initial BLA submission.

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POST-MEETING COMMENT FROM FDA: We do not object to you moving forward with the current study design for protocol 20110115. If AMG 145 is approved, however, which data from this study are ultimately included in labeling will be a review issue. The availability of cardiovascular outcomes data may inform this decision.

- b. Does the Agency agree that results from the phase 2 interim analysis as well as pharmacokinetic/pharmacodynamic (PK/PD) analyses support the proposed phase 3 dosing regimens, 140 mg Q2W and 420 mg Q4W? The dose rationale is provided in Section 3.4. Detailed PK/PD methodology and results are provided in Appendix 10.

FDA PRELIMINARY RESPONSE: Although your rationale for choosing 140 mg from among the Q2W dosing regimens and 420 mg from among the Q4W dosing regimens is reasonable, the rationale for bringing the combination of these two doses into phase 3 is less clear. These dosing regimens seem to have approximately the same pharmacodynamic (PD) effect with regard to LDL-C (b) (4)

(b) (4)

Regarding safety, please provide overall summary tables of adverse events (AEs) for studies 20101154 and 20101155 that show frequencies by dose without combining all doses within the Q2W and Q4W regimens (i.e., similar to how you constructed the tables for studies 20090158 and 20090159).

Please provide additional rationale for this combination of doses to be brought into phase 3 trials, stating why you believe it is not necessary to bring forward a lower dose.

MEETING DISCUSSION: Amgen presented slides (see attachment) summarizing safety data from the interim analysis of the phase 2 program, including the requested breakdown of AE incidence by dose for studies 20101154 and 20101155, suggesting that these data do not indicate the need for lower doses to be brought into phase 3. Amgen suggested that both selected doses were more effective than other tested doses, were associated with more stable LDL levels, and were not associated with any higher incidence of adverse events or laboratory abnormalities. Furthermore, they noted that AMG 145 140 mg Q2W provides a lower drug exposure, based on AUC, than the 420 mg Q4W dose; therefore, these dosages ought to be sufficient to identify dose-related adverse effects. (b) (4)

(b) (4)

- c. Does the agency agree with the primary endpoint proposed in the 4 phase 3 studies of percent change from baseline in LDL C at week 12?

FDA PRELIMINARY RESPONSE: The relative change in LDL-C from baseline is acceptable as a primary endpoint, although we agree with retaining the absolute change in LDL-C as a secondary endpoint.

Regarding the duration of the studies, we would prefer 24 weeks. Because we would also like to ensure that your proposed devices are adequately tested in phase 3 trials (see Question 9), one possibility to consider would be to maintain week 12 as the primary endpoint but to randomize subjects at week 12 to either home administration using the proposed devices or continued use of the pre-filled syringes in the clinic setting for an additional 12 weeks.

MEETING DISCUSSION: See discussion following Additional Clinical Comment (#18).

- d. Interim analysis data from the 4 phase 2 parent studies demonstrated that

(b) (4)

(refer to Section 3.3.2.3). In phase 3, Amgen intends to assess calculated LDL C in all subjects at all time points and use automatic reflexive testing with UC LDL

C for subjects whose calculated LDL C is < 40 mg/dL or whose triglycerides are > 400 mg/dL. Does the Agency agree?

FDA PRELIMINARY RESPONSE: This approach seems reasonable based on the interim data provided.

MEETING DISCUSSION: The sponsor accepted FDA's response, no discussion occurred.

2. Statin intolerant indication: In the phase 3 Study 20110116, statin intolerant is defined as having tried at least 1 statin (b) (4)

Does the Agency agree with the proposed definition for statin intolerant subjects?

FDA PRELIMINARY RESPONSE: No, we are not convinced that this definition would identify a population that is truly "statin intolerant." Both the definition and the study design would require modification as described below.

Regarding a definition for muscle-related statin-intolerance, we would favor: the inability to tolerate at least two previous statins at the lowest approved daily dose as a result of muscle-related symptoms that began or increased during statin therapy and stopped with the discontinuation of statin therapy. Symptoms could include aches, pain, cramping, and/or weakness but should exclude those thought to be the result of strain, exertion, or trauma. Historical information regarding previous statins, doses, and muscle-related events that led to the diagnosis of "statin intolerance" should be recorded.

We also encourage you to consider statin-associated neurocognitive symptoms as another potential cause for "statin intolerance."

Regarding study design, for any trials involving subjects with putative statin intolerance, we would require a design that would incorporate statin re-challenge in a manner to provide convincing evidence that you have successfully identified a distinct patient population. We recognize that subjects with a history of certain serious adverse effects (e.g., documented myositis or rhabdomyolysis on statin therapy) could not be enrolled in such a trial, but these patients are the minority of those who claim to be statin-intolerant.

MEETING DISCUSSION: Amgen presented data from the phase 2 study 20090159 to support a significant unmet medical need for lipid-lowering therapy in the "statin-intolerant" population. The primary differences between the Agency's proposed definition of statin intolerance and Amgen's definition are the number of statins that a subject had attempted (FDA favors ≥ 2 , Amgen favors ≥ 1) and the requirement for re-challenge (FDA favors protocol-mandated re-challenge, Amgen favors a (b) (4) " in subjects

that failed ≥ 2 statins). Amgen suggested [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

The Agency responded that the primary concern is to avoid false-positives, i.e., enrolling a population that is not truly intolerant of statins. The division would be willing to entertain intolerance to ≥ 2 statins at moderate doses, instead of requiring intolerance at the lowest approved daily dose. Amgen countered that requiring intolerance to ≥ 2 statins is reasonable, [REDACTED] (b) (4)

The Agency responded that re-challenge is done by clinicians all the time, and therefore should not pose an ethical dilemma; when patients develop symptoms on one statin, they are often switched to an alternative statin. This is done in an open-label fashion, however, which could bias the response to the second statin; therefore, putative statin intolerance requires more rigorous evaluation in clinical trials. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

The Agency acknowledges that although there exist patients who are truly intolerant of statins and that many of these patients would be expected to benefit from lipid-modulating therapy, the “statin intolerant” population has the potential to become diluted by those who are not truly intolerant. This could lead to patients moving to a novel agent such as AMG 145 before outcomes data are available, perhaps inappropriately. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

The Agency concluded the discussion by agreeing to their proposed definition of statin intolerance (see slide 19) as long as the protocol included blinded statin re-challenge to

support the identification of a unique population. Amgen stated that they would discuss this internally.

- 3. Homozygous familial hypercholesterolemia population:** Study 20110233 is an ongoing 2-part, phase 2/3 study to evaluate the safety, tolerability, and efficacy of AMG 145 in subjects at least 12 years of age with homozygous familial hypercholesterolemia (HoFH). Part A is a single arm, pilot study that will provide an estimate of LDL C reduction in HoFH patients. Part B is a double blind, randomized study that will evaluate whether AMG 145 is well tolerated and will result in greater LDL C reduction compared to placebo. Long term safety and efficacy in patients with HoFH will be assessed in the open label Study 20110271.

Does the Agency agree that Studies 20110233 and 20110271, supported by data from the clinical program in heterozygous familial and non familial (ie, monotherapy, combination therapy, statin intolerant) subjects, are adequate in design to support the proposed indication for hyperlipidemia caused by HoFH?

FDA PRELIMINARY RESPONSE: We agree that the proposed studies could be used to demonstrate efficacy and safety in the HoFH population, supported by other data from the proposed clinical program. We do note that subjects receiving LDL apheresis or other extracorporeal therapies (e.g., plasmapheresis) are ineligible for study 20110233. We would expect plasmapheresis to affect the pharmacokinetics/ pharmacodynamics (PK/PD) of AMG 145, and we are uncertain regarding the effect of LDL apheresis on AMG 145 clearance. Therefore, additional data regarding the effect of these extracorporeal modalities on AMG 145 PK/PD may be required in order to provide adequate dosage and administration instructions for the HoFH population.

MEETING DISCUSSION: The sponsor accepted FDA's response, no discussion occurred.

- 4.** AMG 145 is a fully human monoclonal antibody that binds specifically to PCSK9 and there are no known mechanisms or previous pharmacokinetic or pharmacodynamic experience whereby AMG 145 may precipitate pharmacokinetic drug-drug interactions. Nonclinical and limited clinical data also do not indicate a pharmacokinetic interaction of AMG 145 on statin and AMG 145 has been safely co administered with statins in phase 1 and phase 2 studies. In Phase 3, Amgen plans to evaluate AMG 145 in combination with 5mg and 40 mg of rosuvastatin, (b) (4) 40 mg of simvastatin, or 10 mg and 80 mg atorvastatin (Study 20110115), in subjects unable to tolerate an effective dose of a statin and receiving no statin or a low dose of a statin (Study 20110116), and in subjects with heterozygous familial hypercholesterolemia on statins with optional ezetimibe (Study 20110117). These data will be used to confirm the previous findings demonstrating the lack of a meaningful difference in AMG 145 pharmacokinetics. Therefore, Amgen does not feel that dedicated studies examining the effect of AMG 145 on the pharmacokinetics of drug treatments or the effect of other drug treatments on AMG 145 pharmacokinetics are warranted. A detailed rationale in support of this position can be found in Section 3.6.

Does the Agency agree that additional studies to investigate drug-drug interactions when using AMG 145 with statins are not warranted?

FDA PRELIMINARY RESPONSE: We agree that dedicated studies to investigate drug-drug interactions (DDIs) when using AMG 145 with statins are not required. However, you should collect systemic exposure data for AMG 145 (preferably around Cmax and trough) in the key Phase 3 trials. [REDACTED] ^{(b) (4)}
[REDACTED] ^{(b) (4)} **these data will address the DDI aspect for AMG 145 with concomitant statin use. Additionally, these data will allow for adequate exposure-response (for both efficacy and safety) assessment for AMG-145.**

MEETING DISCUSSION: The sponsor accepted FDA's response, no discussion occurred.

5.

[REDACTED] ^{(b) (4)}
[REDACTED] ^{(b) (4)} Amgen
[REDACTED] ^{(b) (4)} proposes to conduct a large phase 3 cardiovascular outcomes study [REDACTED] ^{(b) (4)} (Study 20110118). This study will be initiated concurrently with the phase 3 lipid lowering studies and enroll approximately 22,500 subjects who will be treated with AMG 145 [REDACTED] ^{(b) (4)} Q2W or [REDACTED] ^{(b) (4)} mg Q4W) or matching placebo (Q2W or Q4W). The expected study duration is approximately 58 months, which includes an 18 month enrollment period. This study will be ongoing at the time of the initial BLA submission, [REDACTED] ^{(b) (4)}
[REDACTED] ^{(b) (4)}

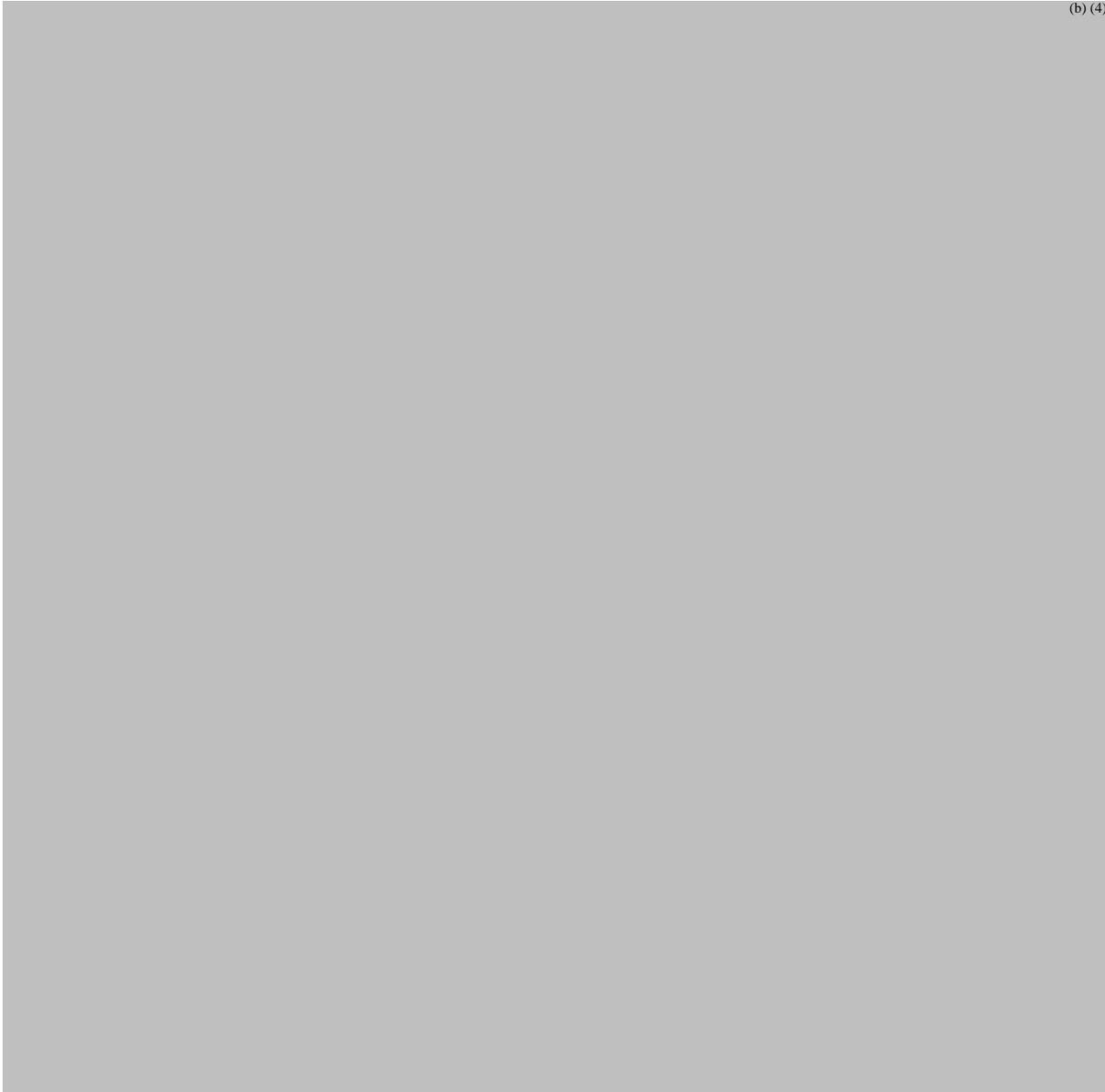
[REDACTED] ^{(b) (4)}
[REDACTED] ^{(b) (4)} The primary endpoint is the composite of time to cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina. The first secondary endpoint is the composite of time to cardiovascular death, myocardial infarction, or stroke. [REDACTED] ^{(b) (4)}
[REDACTED] ^{(b) (4)}

The protocol is provided in Appendix 5.

a.

[REDACTED] ^{(b) (4)}
[REDACTED] ^{(b) (4)}

[REDACTED] ^{(b) (4)}
[REDACTED] ^{(b) (4)}



6. At the time of the initial BLA filing for hyperlipidemia and mixed dyslipidemia, Amgen estimates that exposure to AMG 145 will be equivalent to (b) (4) subject-years and will consist of the following:

| Exposure to AMG 145 | Expected number of subjects ^a |
|---------------------|--|
| ≥ 3 months | (b) (4) |
| ≥ 9 months | (b) (4) |
| ≥ 12 months | (b) (4) |
| ≥ 18 months | (b) (4) |
| ≥ 24 months | (b) (4) |

^a Includes completed, ongoing and planned AMG 145 Studies 20090158, 20090159, 20101154, 20101155, 20110109, 20110110, 20110114, 20110115, 20110116, 20110117, 20110231, 20110233, and 20110271 (refer to Table 1 for study details). For Study 20110110 (OLE study), the calculation is based on (b) (4) of the enrolled subjects from Studies 20101154, 20101155, 20090158, 20090159, and 20110109 roll over to this study, and (2) (b) (4). The database snapshot date for the BLA is approximated as June 2014.

Does the Agency consider the size of the overall safety database and the duration of exposure at the time of initial BLA filing sufficient to support approval for the proposed indication of hyperlipidemia and mixed dyslipidemia?

FDA PRELIMINARY RESPONSE: The anticipated safety database should be sufficient to support approval.

MEETING DISCUSSION: The sponsor accepted FDA's response, no discussion occurred.

7. Monoclonal antibodies are large proteins (molecular weight >140,000 daltons) with a high specificity for their target antigens. It is recognized that monoclonal antibodies, such as AMG 145 (molecular weight of (b) (4) daltons), are unlikely to directly inhibit the function of human ether à go go related gene (hERG) or other ion channels responsible for cardiac repolarization based on their physical size and high specificity. Despite this, QT/QTc assessments were performed from electrocardiogram (ECG) data collected in phase 1 and phase 2 studies and are summarized in Section 3.3.3.12 and detailed in Appendix 7. These analyses do not reveal an effect of AMG 145 on QT/QTc interval. Amgen believes that, because no biologically plausible mechanism exists for AMG 145 to induce QT/QTc prolongation, QT/QTc assessments performed to date are sufficient to demonstrate a lack of QTc liability. Amgen proposes to perform routine ECG monitoring in the proposed phase 3 LDL C lowering studies and does not plan on conducting a thorough QT study.

Does the Agency agree with this proposal?

FDA PRELIMINARY RESPONSE: Although a thorough QT (TQT) study is not required for monoclonal antibodies, we expect in phase 3 studies that safety ECGs will be collected at baseline and at steady state.

ECG and safety data should be submitted to the BLA in an Integrated Cardiac Safety Report format. At the time of BLA submission, you should perform a categorical analysis including number and percentage of individuals with:

- **Absolute QT/QTc values > 450 ms, >480 ms, and >500 ms; as well as the number and percentage of individuals with change from baseline >30 ms and >60 ms.**
- **PR changes from baseline \geq 50% if absolute baseline value was < 200 ms and \geq 25% if absolute baseline value was >200 ms.**

- **QRS changes from baseline $\geq 50\%$ if absolute baseline value was < 100 ms and $\geq 25\%$ if absolute baseline value was > 100 ms.**
- **Number and percentage of individuals with abnormal ECG findings.**
- **Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death.**

MEETING DISCUSSION: The sponsor accepted FDA's response, no discussion occurred.

NON-CLINICAL

8. Does the Agency agree that the nonclinical data package is sufficient to support approval for the proposed indications?

FDA PRELIMINARY RESPONSE: Yes, we agree.

MEETING DISCUSSION: The sponsor accepted FDA's response, no discussion occurred.

MEDICAL DEVICE

9. Amgen intends to seek BLA approval for (b) (4) presentations (pre-filled syringe [PFS], an autoinjector [(b) (4)]). To support the approval of these presentations, design verification and validation will be performed and will include simulated use Human Factors Engineering (HFE) and Usability Engineering (UE) testing. The nonclinical aspects of the device development plan will be the subject of a separate EOP2 meeting.

Amgen plans to use the PFS in the phase 3 lipid-lowering studies for healthcare provider administration in the clinical environment. Amgen proposes to perform the following clinical bridging studies to support commercialization of the AI (b) (4) for administration in non-healthcare settings by patients or their caregiver:

- Clinical home use studies to evaluate the ability of subjects to use the devices as intended (with associated instructions and labeling) in non-healthcare settings.
- PK/PD comparability studies between the PFS and AI, (b) (4)

Additional information on the devices and bridging strategy is presented in Section 5.

Does the Agency agree that the proposed bridging strategy is adequate for approval of the PFS, AI (b) (4) for self-administration in non-healthcare settings at the time of the initial BLA submission?

FDA PRELIMINARY RESPONSE: In order to demonstrate that the (b) (4) proposed device presentations can be used safely and effectively by intended users, we agree

that a simulated use Human Factors/usability validation study be conducted prior to approval. We request that you submit a draft study protocol for our comments and feedback prior to implementation.

Comments from Division of Medical Error Prevention and Analysis (DMEPA):

- 1. 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.**
- 2. 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) [REDACTED] (b) (4) [REDACTED]. You may also consider conducting validation Human Factors usability study for the prefilled syringe, since this is a new user population.**
- 3. Consider the following for your user groups and study methodology:**
 - 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:**
 - 30 representative patients with injection experience (i.e.,15 participants trained and 15 participants untrained).**
 - 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.
 - 30 health care practitioners that will be using the device: nurses and physicians (i.e. 15 participants trained and 15 participants untrained).**
 - If training will not be required as part of the labeling, then study should only have the untrained arm as described above.**
- 4. In your Human Factors study, we recommend including a task to simulate complete device failure.**

- 5. Include a selection task for choosing the right injection device (i.e. between your AI (b) (4) compared to insulin pens and pumps). The patient population that your product is designed for may be on other therapies that are available in pen-devices and/or pumps that are similar to your devices.**

Additional DMEPA comments related to device design and labeling:

Instructions for Use (IFU)

- 6. Ensure that there is a plan in place to remind patients when to give themselves their next dose since the dose is given every 2 or 4 weeks.**

Devices:

There are several features of the devices that do not appear user-friendly.

Autoinjector Pen:

- 7. You propose that your autoinjector should be held firmly against the skin for 15 seconds while counting to deliver a dose of the drug. Currently, there are no subcutaneous injection devices on the market that deliver medications for longer than 10 seconds. Even with devices that deliver medications in 10 seconds, underdose errors occur because patients do not hold the device against the skin for such a long time. Thus, we recommend modifying the device to decrease the amount of time users need to hold the device in the skin.**
- 8. The device feedback for completed dose delivery can be improved. If the patient has a large hand, the viewing window may be blocked. Additionally, in your IFU (3d) it states, "You may hear a second click". Both aspects of the feedback mechanism may not be sufficient to ensure that the patient receives feedback regarding dose delivery. Thus, consider re-evaluating the feedback mechanism for dose delivery for the autoinjector device.**

(b) (4)

Comments from Center for Devices and Radiological Health (CDRH):

Please consider the following comments when you develop the draft protocol for the Human Factors Study:

10. Devices and Labeling Used and Training

We are concerned with the adequacy of the design of your device user interface including the user interface of the device itself and all accessories used with it, instructions for use and training. Your design validation should use final forms of all aspects of the user interface including devices, instructions and training. In addition, to establish the scope and facilitate understanding of the testing you perform, please provide a graphical depiction of the user interface of your device and its accessories, for your device in your test report. Please also explain the overall interaction between users and the device and refer to it as necessary when discussing task priority, specific test results or residual risk.

Please perform an analysis of the use population and how your device is likely to be used. Part of this analysis will be to determine the extent and type of training that users will receive. This analysis and conclusions based on it should be summarized in your HF/Usability test report. Following this analysis, you should include users that are representative of anticipated users in your HF/Usability validation study. The necessity of training for safe and effective use should be clearly communicated in the labeling for your device. Following this determination, you should train the user participants for your human factors/usability validation testing in the same manner that actual users will be trained and provide at a least a short break between training and testing. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

During the study, participants should use user instructions as they would normally use them if they were to begin using the device; they should be neither told to read them or to not read them. To determine if essential knowledge contained in the instructions is successfully communicated to users, they can be asked questions directly. After study participants use the device, you should ask specifically about any errors, problems or difficulties that were observed. The participants should also be asked about the adequacy of the instructions including any aspect that was confusing, misleading or incomplete. In a similar way, users should be asked about the training they received (as per the results of the training analysis previously discussed).

11. User Tasks and Use-Related Risks Analysis

The tasks selected for testing should be derived from the results of a comprehensive assessment of risks of use error. The selection of tasks should be prioritized according to the severity of the potential impact of inadvertent use errors. You should provide a clear description in your test report of how you determined which user tasks would be included in the testing and how many trials each participant will perform.

Please provide an analysis of use-related risks and use the results of this analysis to determine the tasks you will include in your testing. Note that tasks may involve performance with the device as well as “knowledge based” tasks which represent the extent to which essential knowledge is derived by users from instructions and training under realistic conditions of use. You should include all critical and essential performance and knowledge-based tasks necessary for safe and effective use of your device in your testing.

12. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates the environments in which you anticipate your device would be used to include potentially challenging use conditions such as use with gloves or wet fingers, dim lighting, noisy situations, etc. Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

13. Study Participants

We expect a minimum of 15 participants in your HF/Usability validation study, but additional participants are acceptable as long as the test conditions are representative of actual use as discussed previously in this review. If users fall into distinct groups that are expected to interact differently with the device (different user tasks) or carry different risk profiles (e.g., level of disabilities/impairments) then the testing should include representative samples from each of these groups.

For devices sold in the United States, FDA has consistently requested that the participants in a validation test be representative of the U.S. population and reside in the U.S. Note that study participants should not be your own employees, or those that have been exposed to your new device prior to the testing.

14. Realism of simulated use

The testing environment and realism of the simulated use was not described in sufficient detail to determine if it is reasonable for a validation study of device use, however a “focus group” approach does not represent realistic use or realistic use conditions and therefore should not be used for HF/usability validation testing.

15. Data Collection and Analysis

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 facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

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?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

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. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

16. Report

Please note that we expect your study report to begin with a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions. A summary of relevant portions of preliminary analyses, evaluations, the validation testing should be used as support of this conclusion. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to identified risks and whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Your data analysis should be prioritized based on identified risk and task priority (from highest to lowest) to determine the magnitude and significance of the use errors, failures and difficulties that occurred during the testing. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the UI should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

We strongly recommend that you submit your draft protocol in advance for us to review in order to ensure that your methods and the resulting data will be acceptable. Guidance on human factors procedures to follow can be found in

Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

Additional Clinical Pharmacology comment:

17. Your proposed approach of conducting PK/PD comparability studies between the PFS and AI (b) (4) PK/PD as part of the overall clinical bridging is reasonable.

Additional Clinical comment:

18. (b) (4) 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. As stated in Question 1(c), one option would be to extend the currently proposed trials to involve a second dosing period during which subjects are randomized to the various administration methods.

MEETING DISCUSSION: Amgen presented a revised strategy for testing AMG 145 delivery devices in phase 3. In the phase 3 pivotal LDL-lowering trials, Amgen proposed to use the autoinjector (AI) in both the clinic and non-clinic setting. Subjects assigned to Q2W regimens would use one AI every two weeks; subject assigned to Q4W regimens would use three AIs every 4 weeks. The studies would remain 12 weeks in duration.

(b) (4)

(b) (4)

FDA agreed with the revised approach to using devices in the phase 3 program with LDL-C as an efficacy outcome.

PEDIATRICS

10. Amgen will request the following regarding the provision of pediatric data for the intended population of the adult program, hyperlipidemia and mixed dyslipidemia:

(b) (4)

Clinical studies are being conducted in subjects at least 12 years of age with HoFH who are on pre-existing lipid-lowering therapy (Studies 20110233 and 20110271). At the time of the initial BLA submission, (b) (4)

Additional details are provided in Section 3.7.

Does the Agency agree with the proposed pediatric plan?

FDA PRELIMINARY RESPONSE: It is premature to comment on the proposed pediatric plan at this time. 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. Please provide your request and rationale for any waiver or deferral at the time of the BLA submission. If you plan to ask for a deferral of the pediatric trial for a certain age group, please provide a brief description of the proposed trial at the time of BLA submission, focusing on the collection of adequate information on dose, safety and efficacy, as well as the protocol submission date, the study completion date, and the final report submission date.

Additional Clinical Pharmacology Comments on Development Plan:

- **Please clarify how you plan to address the specific populations (e.g., hepatic impairment, renal impairment, etc.) in your development plan for AMG 145.**

MEETING DISCUSSION: The sponsor accepted FDA's response, no discussion occurred.

Additional Topics discussed at the meeting: Amgen informed FDA that they intend to reclassify the phase 2 study 20110109 as a phase 3 study. Amgen confirmed that the phase 3 trials will be performed with the formulation of AMG 145 intended for the market.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion

4.0 ACTION ITEMS

| Action Item/Description | Owner |
|--|-------|
| Provide additional data regarding secondary lipid parameters to compare the two regimens (i.e. 140 mg Q2W and 420 mg Q4W). | Amgen |
| Internally discuss use of their proposed definition of statin intolerance with blinded statin re-challenge in phase 3 Study 20110116 | Amgen |

5.0 ATTACHMENTS AND HANDOUTS

Amgen's slides presented at meeting

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/s/

RAYMOND S CHIANG
08/02/2012

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 125522

LATE-CYCLE MEETING MINUTES

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

Dear Dr. Kubasak:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Repatha (evolocumab) injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on May 28, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Enclosure:
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: May 28, 2015, 12 noon
Meeting Location: Teleconference
(b) (4), Conference ID (b) (4)

Application Number: BLA 125522
Product Name: Repatha (evolocumab) injection
Applicant Name: Amgen, Inc.

Meeting Chair: James P. Smith, MD, MS
Meeting Recorder: Kati Johnson

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, MD-Director
James P. Smith, MD, MS-Deputy Director
Eileen Craig, MD-Clinical Reviewer
Stephanie Leuenroth Quinn, PhD-Supervisory Pharmacologist (Acting)
Lee Elmore, PhD-Nonclinical Reviewer

Division of Biometrics II (OBII)

Gregory Levin, PhD-Lead Statistician (Acting)
Susie Sinks, PhD-Statistician

Office of Clinical Pharmacology (OCP), Div. of Clinical Pharmacology II (DCPII)

Jaya Vaidyanathan, PhD-Clinical Pharmacology Team Leader (Acting)
Sury Sista, PhD-Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality/Division of Microbiology Assessment

Patricia Hughes, PhD-Microbiologist/Quality Assessment Lead
Lakshmi Narasimhan, PhD-Microbiologist

Office of Pharmaceutical Quality/ Office of Biologic Products

Chana Fuchs, PhD-Product Quality Team Lead
Sang Bong Lee, PhD-Reviewer
Bazarragchaa Damdinsuren, MD, PhD-Reviewer

Center for Device and Radiologic Health (CDRH)

Lana Shiu, MD-Reviewer

Division of Advisory Committee and Consultant Management
Phil Bautista, PharmD-Designated Federal Officer

Division of Information Disclosure Policy (DIDP)
Howard Phillips
Nicole Zelenak

EASTERN RESEARCH GROUP ATTENDEES
Christopher Sese

APPLICANT ATTENDEES

| Name | Title |
|-----------------------------|--|
| Mark Taisey | Vice President, Global Regulatory Affairs |
| Rob Scott, MD | Vice President, Global Development (Therapeutic Area Head) |
| Scott Wasserman, MD | Vice President, Global Development (Therapeutic Area Head) |
| Kathy Kross | Executive Director, Regulatory Affairs (Inflammation, Metabolism, and Endocrine Therapeutic Area Head) |
| Dominique Bertin-Millet, MD | Executive Medical Director, Global Safety (Therapeutic Area Head) |
| Arline Nakanishi, MS | Executive Director, Biostatistics (Therapeutic Area Head) |
| Ashley Hall, JD, RAC | Director, Regulatory Affairs (Global Regulatory Lead) |
| Lisa Carlson | Director, Regulatory Affairs (CMC Regulatory Lead) |
| Thomas Liu, PhD | Director, Biostatistics (Global Statistical Lead) |
| Michelle Geller, MD | Medical Director, Global Safety (Global Safety Lead) |
| Marc Kubasak, PhD, RAC | Senior Manager, Regulatory Affairs (US Regulatory Lead) |
| Adam Rupert, MS, RAC | Manager, Regulatory Affairs (US Regulatory Lead) |
| Shirin Pillay, RAC | Manager, Regulatory Affairs (US Regulatory Lead) |
| Hemant Mistry | Senior Project Manager |
| Rex Atienza | Project Manager |
| Narimon Honarpour, MD | Clinical Research Medical Director |
| Ransi Somaratne, MD | Global Development Executive Medical Director |
| Suzanne Kiani | Regulatory Affairs Director |
| Keri Monda | Observational Research Director |
| Dawn Meyer | Global Safety Senior Manager |
| Martin VanTrieste | Senior Vice President Quality |

| | |
|--------------|---------------------------------------|
| Emily Razaqi | Executive Director, Global Operations |
| Rick Lit | Vice President, Regulatory Affairs |

1.0 BACKGROUND

BLA 125522 was submitted on August 27, 2014 for Repatha (evolocumab) injection.

Proposed indications:

Primary Hyperlipidemia and Mixed Dyslipidemia

Repatha™ is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), nonhigh-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides (TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1:

- in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
- alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.

Homozygous Familial Hypercholesterolemia

Repatha™ is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).

PDUFA goal date: August 27, 2015

FDA issued a Background Package in preparation for this meeting on May 20, 2015.

2.0 DISCUSSION

Introductory Comments

Following introductions on both sides, the Agency stated that the primary reviews are in the process of being finalized; however, secondary and tertiary reviews remain to be completed. Therefore, the comments below are still preliminary.

Discussion of Substantive Review Issues

Clinical

The issues listed in the Agency's late-cycle meeting (LCM) background package are included for transparency only, as they have been discussed with the sponsor over the development of this product. In particular, whether LDL-C will remain a valid surrogate for cardiovascular (CV) benefit has been discussed numerous times.

There are no safety issues identified to date that would preclude approval from a clinical perspective.

The firm requested feedback from the Agency regarding the question of autoinjector breakage during the injection process. According to the firm, the event rate is very low, and there were no adverse events reported. (b) (4)

The Agency cited the firm's April 27, 2015, response to an information request letter, which mentioned instances of the needle breaking off and remaining in the injection site. The firm said that these 5 events did not occur during any trials contained in the BLA and committed to providing a narrative of each event, including photos.

The firm noted that their review of the Agency's background package for the advisory committee meeting revealed an apparent discrepancy in the number of neurocognitive events between the sponsor and the clinical reviewer, and they were hoping that the FDA's analysis could be clarified. The firm surmised that the clinical reviewer may have combined selected preferred terms instead of using the pre-specified groupings of high-level group terms that FDA had recommended. The Division stated that the discrepancy would be investigated, but as a general matter, reviewers are charged with reviewing safety – including individual cases as appropriate – and do not need to feel confined by any particular analyses to accomplish that task.

Amgen voiced their concern regarding the use of information from the 120-day safety update in the Agency's background package, given that they were told that their briefing package should only contain information from the initial application. They specifically mentioned the adverse events of death, pancreatitis, diabetes, proteinuria, anaphylaxis, and, in the HoFH population, the adverse events and the number of patients who uptitrated to the 420 mg Q2W dose. Dr. Smith said that it was not our intention to put the firm in a position that makes it appear they are not being transparent. Dr. Craig said that the focus of her presentation at the AC meeting will be on the information contained in the initial BLA submission, although agreed that there are a few instances where information in the safety update is referenced. The firm said that they did not plan to include information from the safety update in their core AC presentation; however, they will have back-up slides should any questions arise. The Agency did not have concerns with their plan.

The Agency requested that the firm explain their concern that the public release (via the clinical review in the FDA background document) of some of the information from safety reports from the ongoing cardiovascular outcomes trial will affect study integrity. (b) (4)

The Agency highlighted that the **Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies, December 2012** states:

“The blind should ordinarily be broken for IND safety reports submitted to FDA and all participating investigators. Knowledge of the treatment received is necessary for interpreting the event, may be essential for the medical management of the subject, and may provide critical safety information about a drug that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). The Agency does not believe that unblinding single or small numbers of serious and unexpected adverse event cases will compromise the integrity of the study, in part because such unblinding should

be infrequent. For example, because the requirement under § 312.32(c)(5) specifically describes different reporting requirements for study endpoints, in a trial evaluating death, myocardial infarctions, and strokes as endpoints, a case of liver injury, if unblinded, would have no effect on overall study integrity.”

(b) (4)



The Agency stated that the firm’s concerns would be taken into consideration and discussed further internally.

Chemistry, Manufacturing, and Controls/Microbiology

The reviewers acknowledged receipt of the firm’s May 26, 2015 email response (official response received June 1, 2015) to our May 19, 2015 request for information, and it is currently under review. The Agency is currently reviewing the specifications, stability, commitments and protocols proposed for post-marketing studies. The Agency acknowledged that the applicant did remove the (b) (4) facility from the BLA as there was no information supporting activities at that site. There will be another information request communication that will issue shortly.

In response to a question from the Agency, Amgen confirmed that the initial (b) (4) validation included in the BLA would cover the (b) (4) proposed batch size (b) (4) kg in the comparability protocol.

The Agency confirmed that all facilities had been inspected; however, final assessments for all facilities have not been completed.

3.0 Upcoming Advisory Committee (AC) Meeting

The AC meeting is scheduled for June 10, 2015. The firm will have 90 minutes for their presentation followed by 15 minutes for any follow-up questions. Dr. Craig will be the sole presenter for the Agency. That presentation will also be followed by a 15 minute timeslot for any questions, followed by 1 hour each for lunch and the open public hearing. Other disciplines will be present to field any questions, should they arise.

The draft questions are still being vetted through the Agency. The firm did not raise any concerns with the draft questions.

4.0 Post marketing Commitments/Requirements (PMC/PMR)

The Agency is in the preliminary stages of internal discussion, and we will have further discussions following the AC meeting. The Agency has no plans to discuss PMC/PMRs at the AC meeting.

5.0 Labeling

In response to a comment from the firm, the Agency responded that considerations with regard to consistency in labeling across PCSK9 products would be considered to the extent possible, as appropriate, but each application is independent.

The Agency did not have any specific comments regarding the package insert at this time. Once the package insert is closer to being finalized, then we will address the patient labeling.

6.0 Wrap-up and Action Items

Amgen will provide the following information:

- Table of topics for which they plan to include data from the 120-day safety update
- photos/narratives pertaining to the needle breakage issue
- response to pending clinical/stats information requests

The Agency will provide or address the following:

- the chemistry information request as soon as it is available
- clarification regarding the neurocognitive analysis in the FDA background document for the AC meeting
- consider the firm's request for redaction of safety information from the ongoing cardiovascular outcomes trial

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/s/

JAMES P SMITH
06/26/2015



BLA 125522

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

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

Dear Dr. Kubasak:

Please refer to your Biologic License Application (BLA) submitted August 27, 2014, under the Public Health Service Act for Repatha (evolocumab) injection, 140 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for May 28, 2015. Attached is our background package, including our agenda, for this meeting.

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, M.D., M.S.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING (TELECONFERENCE) BACKGROUND PACKAGE

Meeting Date and Time: May 28, 2015, 12 noon
Meeting Location: Teleconference-Firm to provide a call in number

Application Number: BLA 125522
Product Name: Repatha (evolocumab) injection
Indication: (Proposed)
Primary Hyperlipidemia and Mixed Dyslipidemia

Repatha™ is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides (TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1:

- in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
- alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.

Homozygous Familial Hypercholesterolemia

Repatha™ is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).

Sponsor/Applicant Name: Amgen, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical

Following review of the data contained within the original BLA submission as well as the information submitted in response to the Division's information requests throughout the review cycle, the clinical review team may take into consideration the following when developing our benefit/risk assessment of evolocumab. Please note this is not a comprehensive listing of what may ultimately be considered in the benefit/risk evaluation and is subject to change following discussion with our advisors at the June 10th EMDAC meeting. Furthermore, we are providing this list simply to be transparent with regard to efficacy/safety issues that we have discussed during the review; we do not believe that it would be helpful for you to provide additional data at this time.

- **LDL-C as a surrogate:** As we have stated previously, it will be a review issue whether evolocumab could be approved based on effects on lipid parameters such as LDL-C before cardiovascular (CV) outcomes data are available and, if so, for what population(s). Uncertainty is greater with regard to net clinical benefit when the benefit of a drug is assessed solely by its effects on a biomarker, regardless of whether or not the biomarker is considered a valid surrogate endpoint for a given patient population.
- **The generalizability of the patient population studied in clinical trials compared to the target population for whom benefit/risk might be deemed favorable based on changes in LDL-C alone (see above).**
- **The overall safety and efficacy database for the 420 mg Q2W dose is quite limited.**
- **Glycemic control:** In some analyses in patients with baseline impaired fasting glucose, a higher proportion of evolocumab-treated patients experienced an unfavorable shift in

glycemic control defined by adverse events and laboratory data compared to placebo or ezetimibe-treated patients.

- Hypersensitivity: Serious and non-serious hypersensitivity reactions (to include rash, urticaria, pruritus) have occurred with evolocumab treatment and, in some cases, required discontinuation of treatment.
- Elevations in liver enzymes: While the incidence of hepatic-related adverse events and liver-related tests was low and similar for the evolocumab and control groups, there were cases, some serious, of hepatotoxicity/hepatic function abnormality where there was a reasonable possibility that the event was related to evolocumab, along with other concomitant medications.
- Pancreatitis: An imbalance was observed in cases of pancreatitis. Other risk factors for pancreatitis in these cases included concurrent alcohol use, diabetes, gallstones and concomitant medications associated with pancreatitis; however, we cannot rule out evolocumab as a possible contributing factor in these cases.
- Renal Disease/Proteinuria: An imbalance was observed in cases of serious renal disorders in the parent trials and the Year 1 SoC-controlled period. In the year 1 SoC-controlled period, there was a small but greater incidence of proteinuria in statin-intolerant and diabetic subjects who had no baseline proteinuria in the evolocumab plus SoC group, compared with the SoC alone group. It is not known if evolocumab was a contributing factor in these renal disorder and proteinuria cases.
- Neurocognitive concerns: For the year 1 SoC-controlled period, there was an increase in neurocognitive events in evolocumab-treated patients. Exploratory analyses of the neurocognitive adverse events were performed for LDL-C subgroups defined by post-randomization values. For the year 1 SoC-controlled period, in the LDL-C < 40 mg/dL evolocumab subgroup, the numbers were low but there were numerically more events as compared to the as LDL > 40 mg/dL EvoMab group: [8 (0.6%) vs 1/1427 (0.1%)].
- Safety of very low LDL-C values: The safety database does not permit a robust evaluation of adverse events which may be contingent on longer exposure to low LDL-C levels.
- Autoinjector Device Issue: We note there were several cases of the auto-injector (AI) glass syringe breaking and that the AI needles detached due to the syringe breakage and became embedded into the patient's injection site. Although rare, these types of device-related adverse events may need to be discussed in labeling, if evolocumab is approved.

We recommend you consider how you might further investigate these concerns in ongoing or new clinical trials. In addition, we advise you to consider how you might inform patients and mitigate these potential risks through labeling.

Chemistry (CMC)/Microbiology

CMC: IR issued May 19, 2015 :

Most IR items need to be addressed to enable the reviewers to complete their review.

Note that the IR item 23 requests that Amgen remove (b) (4) from the BLA. (b) (4) cannot be licensed within this BLA because no data, such as assay transfer qualification reports, were included in the BLA to support activities identified for this site on the 356h form and in section 3.2.P.3.1 - manufacturers.

Microbiology:

Data for the microbial ingress CCI test method qualification study and correlation between the microbial and dye ingress methods. We are expecting a response to our IR letter on May 22, 2015.

Drug Master File review is ongoing.

3. Information Requests (IRs):

CMC IR was sent out on May 19, 2015, as noted above. FDA anticipates sending another CMC IR prior to the end of May.

We await revised container and carton labeling, which is due by May 26, 2015.

New CMC IR (in addition to the forthcoming CMC IR referenced above):

- In the Comparability Protocol submitted for the addition of Amgen Manufacturing Limited building (b) (4) (AML (b) (4) located in Juncos, Puerto Rico, as an alternative evolocumab PFS manufacturing facility, you have stated that the proposed batch size is (b) (4) kg. The validated batch scale at AML (b) (4) is (b) (4) kg. Please clarify if the (b) (4) validation studies will be repeated and if the current (b) (4) validation studies support the new batch size, provide justification.

Clinical Statistical:

There will be a forthcoming statistical IR to conduct additional analyses to estimate treatment effects using different assumptions about missing data.

ADVISORY COMMITTEE MEETING

Date of AC meeting: June 10, 2015

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: May 20, 2015

Potential questions and discussion topics for AC Meeting are as follows:

We anticipate that AC members will be asked to discuss and vote on the overall risk-benefit of evolocumab for the proposed indication, as framed by the following considerations:

- Evolocumab-induced lowering of LDL-C as a surrogate for an effect on clinical outcomes in various patient populations

- Proposed dosing regimens
- Considerations related to the HoFH population
- Safety assessment
- Overall benefit/risk assessment

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues
Each issue will be introduced by FDA and followed by a discussion.
3. Information Requests
Outstanding and pending CMC requests.
4. Discussion of Upcoming Advisory Committee Meeting
5. Postmarketing Requirements/Postmarketing Commitments
Potential CMC PMCs are currently under discussion. The possibility of additional PMRs or PMCs remain under internal discussion as well. Some may be informed by the discussion at the AC meeting.
6. Major labeling issues
It is premature to discuss labeling at this time. At a minimum, we anticipate substantive revisions to Indications and Usage, Warnings and Precautions, Adverse Reactions, and Clinical Studies.
7. Review Plans
 - Review of responses to outstanding information requests
 - Obtain feedback from Advisory Committee panel
 - Completion of consults and tertiary reviews
 - Completion of facilities inspections
 - Labeling discussions (as needed)

CMC –We are currently assessing specifications, stability, commitments, protocols proposed (e.g. addition of AML^{(b)(4)}, protocols for post-marketing validation studies, etc.). Items identified in the IR from May 19, 2015 are also still pending completion of review.

8. Wrap-up and Action Items

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/s/

JAMES P SMITH
05/20/2015