CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761062Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761062

MEETING MINUTES

Amgen Inc.
Attention: Molly Salyers
Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-B
Thousand Oaks, CA 91320

Dear Ms. Salyers:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for romosozumab.

We also refer to the meeting between representatives of your firm and the FDA on October 26, 2017. The purpose of the meeting was to discuss the content of your planned resubmission in response to our July 13, 2017, Complete Response letter.

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 Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
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:	A
Meeting Category:	End of Review
Meeting Date and Time:	October 26, 2017, 11:00 A.M. to 12:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 21, Conference Room: 1539 Silver Spring, Maryland 20903
Application Number:	BLA 761062
Product Name:	romosozumab
Proposed Indication:	Treatment of osteoporosis in postmenopausal women at increased risk of fracture
Sponsor/Applicant Name:	Amgen Inc.
Meeting Chair:	Theresa Kehoe, M.D.
Meeting Recorder:	Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products:
Christine Nguyen, M.D., Acting Director
Linda Jaffe, M.D., Medical Officer
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff

Office of New Drugs, Office of Drug Evaluation III:
Hylton V. Joffe, M.D., M.M.Sc., Acting Deputy Office Director
Julie Beitz, M.D., Office Director

Office of Translational Sciences (OTS), Office of Biostatistics (OB):
Jia Guo, Ph.D., Biometrics Reviewer, Division of Biometrics III (DBIII)
Mahboob Sobhan, Ph.D., Biometrics Team Leader, DBIII
Clara Kim, Ph.D., Statistical Reviewer, Division of Biometrics VII
Thanh Tran, Ph.D., Statistical Reviewer, Division of Biometrics VII

Division of Cardiovascular and Renal Products:
Shari Targum, M.D., Clinical Team Leader
Karen Hicks, M.D., Medical Officer

Office of Surveillance and Epidemiology (OSE), Immediate Office:
Mammah Borbor-Lebbie, M.S., MBA, Project Manager

OSE, Office of Medication Error Prevention and Risk Management:
Leah Hart, Pharm.D., Team Leader, Division of Risk Management (DRISK)
Courtney Cunningham, Pharm.D., Reviewer, DRISK

OSE, Office of Pharmacovigilance and Epidemiology:
Jie (Jenni) Li, Ph.D., MBBS, Team Leader, Division of Epidemiology

SPONSOR ATTENDEES
Andreas Grauer, M.D., Vice President, Global Development
Rachel Wagman, M.D., Executive Medical Director, Global Development
Jeffrey Petersen, M.D., Clinical Research Medical Director
Armando Lira Pineda, M.D., Clinical Research Medical Director
Mark Taisey, Vice President, Global Regulatory Affairs
Paul Nitschmann, M.D., Executive Director, Global Regulatory Affairs
Pamela Danagher, M.Sc., Director, Global Regulatory Affairs
Mary "Molly" Salyers, Manager, Regulatory Affairs
Judy Maddox, DO, Medical Director, Global Safety
Li Chen, Ph.D., Sc.D., Director, Global Biostatistical Science
Hong "Amy" Xia, Ph.D., Executive Director, Global Biostatistical Science
Michelle Geller, M.D., Executive Medical Director, Global Safety

1.0 BACKGROUND

Romosozumab is an IgG2 monoclonal antibody to sclerostin generated by humanizing mouse sclerostin monoclonal antibody m13C7. Amgen submitted an original BLA in July 2016 for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

The FDA issued a complete response letter for BLA 761062 on July 13, 2017, based on the cardiovascular results from Studies 20110142 and 20110174. Amgen would like the discuss the deficiencies and content of the planned resubmission including the proposed principal concepts of the integrated safety and efficacy summaries, the integrated analysis on serious cardiovascular events, and the Safety Update.

FDA sent Preliminary Comments to Amgen on October 24, 2017.

2. DISCUSSION

Question 1: Does the Agency agree with Amgen's inclusion of (b) (4) ***as displayed in Section 2.3?***

FDA Response to Question 1:

As outlined in the "To Address This Deficiency" section of the Complete Response (CR) letter dated July 13, 2017, the focus of the CR submission should be a thorough characterization of the cardiovascular safety of romosozumab. In addition, we will need to perform a comprehensive efficacy and safety review of the new, large head-to-head trial comparing romosozumab to alendronate and incorporate those findings into the overall benefit/risk assessment for postmenopausal osteoporosis.

We anticipate that the new or updated data and analyses provided in the CR submission will be extensive, requiring considerable review time and an advisory committee meeting to arrive at the appropriate regulatory decision. Therefore, in this unusual situation, we expect that we will need up to 10 months to render a regulatory decision, which is more than the usual 6 months allotted to the review of a CR submission.

We do not agree (b) (4)

Discussion at the Meeting:
Amgen asked how they could facilitate the FDA's ability to complete a review within 6 months. The FDA maintained that, given the scope and complexity of the data contained in the CR resubmission and the need to have an Advisory Committee meeting, it is unlikely that the Agency could complete a thorough review and take regulatory action within the 6-month clock. The FDA stated Amgen could facilitate review of the application by responding to FDA requests for information promptly.

(b) (4)

Question 2: Does the Agency agree with the proposed presentation of efficacy data for Studies 20110142, 20070337, and 20110174, as shown in Section 4.1, (b) (4) ***?***

FDA Response to Question 2:

We will not need additional efficacy data analyses from trial 20070337. Of note, you should present all fracture and bone mineral density results using standard deviation (SD), not standard error (SE).

(b) (4)

Discussion at the Meeting:
Amgen will not provide month 36 efficacy analyses from Study 20070337 in the resubmission. Amgen asked if side by side presentation of the efficacy data from Studies 20070337 (original analyses) and 20110142 would be helpful for the FDA's review (see Slides 8 and 9 for examples). The Agency agreed to both the side by side presentation and the presentation of SD and SE as proposed in the slides.

Question 3: Does the Agency agree with the proposed presentation of safety data (b) (4) (b) (4) ***as shown in Section 4.3.3 and Section 4.3.1, respectively?***

FDA Response to Question 3:

We do not need additional safety data from Trial 20070337. Romosozumab or placebo was administered in the first year of the trial, followed by administration of denosumab to all subjects in years 2 and 3. It is unclear whether safety findings from year 3 of the trial are relevant to romosozumab, given the mean effective half-life of romosozumab is 12.8 days.

We request an integrated safety analysis comprised of trials 20070337 and 20110142, in addition to your proposed placebo-controlled osteoporosis population and your osteoporosis population analyses. Do not include data from Trial 20110174 in the proposed placebo-controlled osteoporosis or osteoporosis populations.

(b) (4)

Discussion at the Meeting:
Amgen agreed to not provide month 36 safety analyses from Study 20070337 in the resubmission. Amgen will provide a 12-month integrated safety analysis comprised of Studies 20070337 and 20110142. Amgen will exclude Study 20110174 from the placebo-controlled osteoporosis and osteoporosis populations. The FDA agreed with Amgen's proposed datasets and data cutoff dates to be included for the safety data in the resubmission (slide 12).

Question 4: ***Does the Agency agree with the proposed analysis of cardiovascular events for the Resubmission, as shown in Section 4.3.2?***

FDA Response to Question 4:

The evaluation of cardiovascular safety events should include the Major Adverse Cardiovascular Event (MACE) composite, as well as analyses of each individual component.

Note that Figure 3 on page 25 of the briefing document shows a separation of the event curves by Month 2. Your analyses of romosozumab's cardiovascular safety should include demonstration that romosozumab does not have off-target effects on platelet aggregation (e.g., via an *in vitro* platelet aggregation study), vasoconstriction, and systolic and diastolic blood pressure. You should also provide an analysis of non-serious cardiac ischemic events (i.e., angina).

Discussion at the Meeting:
Amgen presented their proposed resubmission content (Slide 13), which will include:

- A validated human *in vitro* assay for platelet aggregation.
- An integrated cardiovascular safety report with:
  - Systolic and diastolic blood pressure assessments and information to help address the vasoconstriction question
    - Electrocardiograms (phase 1 and phase 2)
    - Comprehensive blood pressure analyses
  - Analysis of serious and non-serious cardiac ischemic events including:
    - An ischemic heart disease Standardised MedDRA Queries (SMQ) based assessment of adverse events
    - Duke Clinical Research Institute (DCRI) adjudicated events (only serious)
    - Thrombolysis In Myocardial Infarction (TIMI) adjudicated events (both serious and non-serious)

The FDA asked Amgen to include an analysis of the difference in methods between DCRI and TIMI.

Post-Meeting Comments:
We have the following additional comments regarding the TIMI Clinical Events Committee (CEC) charter and recommendation for inclusion in the submission:

1. Submit the CEC packets and Case Report Forms for all TIMI-adjudicated cardiovascular (CV) events. By trial and USUBJID, create a dataset that indicates what the Duke CEC adjudication diagnosis was for an event in one column and what the TIMI adjudication diagnosis was for the same event. Include the CEC packets and this dataset in the resubmission.

2. Regarding page 18 of the Briefing Package, also conduct analyses including atrial fibrillation/atrial flutter as a baseline risk factor. The proposed adverse event analyses

discussed on page 33 of the Briefing Package should include atrial fibrillation/atrial flutter as one of the subgroups. For those individuals with atrial fibrillation/atrial flutter, also specify whether they were on a) aspirin; b) warfarin; c) novel oral anticoagulant such as rivaroxaban, apixaban, dabigatran, or a combination of these medications.

3. From the Duke CEC review, include the percentage of CV events, separated by type of event (myocardial infarction, stroke, etc.) that were adjudicated as negative because of missing data. Provide USUBJID numbers and CEC packets/case report forms (CRFs) for all of these subjects by trial and event type.

   Also include a sensitivity analysis where those events adjudicated as negative by Duke (because of missing data) are adjudicated as positive events to determine how this affects overall trial results.

4. For the resubmission, separate study results (and results of TIMI CEC adjudication of serious and non-serious CV events) by trial – 20070337, 20110142, and 20110174 - and by CV event. Also categorize CEC packets/case report forms according to event to facilitate access. For each trial and each CV event, provide a summary regarding the final adjudication diagnosis, the USUBJID number, and n/N (%).

5. If TIMI is unable to adjudicate an event **OR** if an adjudicator checks the box for myocardial infarction (MI) or stroke that states: "suspected diagnosis of MI (or stroke) but insufficient documentation to meet charter definition," the CEC adjudicator should specify what particular documentation was missing (e.g., cardiac biomarkers).

6. For each study, by CV event type, TIMI should compile a list of cases that were adjudicated as negative because of missing data (and include USUBJIDs).

7. TIMI should provide a dataset indicating what the adjudication diagnosis was for CEC Reviewer 1, CEC Reviewer 2, and the tie breaker (CEC Chairman), if needed, in case there is non-agreement between the CEC Reviewers.

8. TIMI should prespecify what standardized MedDRA queries (SMQs) and trigger terms will be used to identify additional events.

Question 5: ***Does the Agency agree with the proposal for the Safety Update for the Resubmission, as described in Section 4.3.5?***

FDA Response to Question 5:

Yes.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 6: ***Assuming the Agency will convene an Advisory Committee meeting, what does the Agency foresee are the key items that will be covered at the meeting?***

FDA Response to Question 6:

If an Advisory Committee is convened, at this time, we anticipate that the focus would be on the cardiovascular risks of romosozumab, and whether the benefits of romosozumab outweigh those risks.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 7: ***Amgen is working with the TIMI Study Group to perform an independent blinded review of the adverse event data in Studies 20070337, 20110142, and 20110174 for potentially undetected major adverse cardiac events. TIMI will also, for consistency, adjudicate all previously adjudicated cardiovascular serious adverse events (see Section 4.3.2.5). Does the Agency agree with this approach?***

FDA Response to Question 7:

The approach appears acceptable.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 7a: ***Does the Agency agree with or have comments on the charter/protocol for the review and adjudication to ensure the results will support the Agency's review of the Resubmission to the Complete Response Letter? See Appendix 2 for the draft TIMI charter.***

FDA Response to Question 7a:

The charter document appears reasonable. In the BLA, you should outline the differences between the original Duke Clinical Research Institute (DCRI) charter and the Thrombolysis in Myocardial Infarction (TIMI) study group charter.

Discussion at the Meeting:
Amgen presented a comparison of the DCRI and TIMI reviews (slide 16). The FDA asked Amgen to separate out events adjudicated as negative based on complete data from those adjudicated negative because of missing data. The FDA also suggested Amgen could

investigate differences in troponin assays and concomitant medications (including, but not limited, to aspirin) for the resubmission.

Amgen is expecting the TIMI review to be completed at the end of May 2018 with a targeted BLA resubmission in July 2018.

Question 8: ***With the current knowledge on the romosozumab efficacy and safety profiles, and the extent of safety data, Amgen considers the benefit-risk profile of romosozumab favorable in the proposed indications and considers that labeling can adequately define the risks and risk minimization measures. Does the FDA agree that a Risk Evaluation and Mitigation Strategy (REMS) proposal would not be considered necessary for the Resubmission to the Complete Response letter?***

FDA Response to Question 8:

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.

Discussion at the Meeting:
There was no further discussion at the meeting.

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 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	November 25, 2017

6.0 ATTACHMENTS AND HANDOUTS

BLA 761062 26Oct2017 Romosozumab Type A Meeting Presentation 25Oct2017

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/s/

THERESA E KEHOE
11/22/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100391

MEETING MINUTES

Amgen Inc.
Attention: Julia Zhu, Pharm.D., R.A.C.
Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-1-C
Thousand Oaks, CA 91320

Dear Dr. Zhu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for romosozumab (AMG 785).

We also refer to the meeting between representatives of your firm and the FDA on May 18, 2016. The purpose of the meeting was to discuss your proposed Biologics License Application (BLA).

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 Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
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:	May 18, 2016, 10:00 A.M. to 11:30 A.M.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 100391
Product Name:	Romosozumab (AMG 785)
Proposed Indication:	Treatment of osteoporosis in postmenopausal women at increased risk of fracture
Sponsor/Applicant Name:	Amgen Inc.
Meeting Chair:	Theresa Kehoe, M.D.
Meeting Recorder:	Samantha Bell

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products:
Hylton V. Joffe, M.D., M.M.Sc., Director
Theresa Kehoe, M.D., Clinical Team Leader
Stephen Voss, M.D., Medical Officer
John Stinson, M.D., Medical Officer
Debuene Chang, M.D., Medical Officer
Gemma Kuijpers, Ph.D., Pharmacology and Toxicology Reviewer
Mukesh Summan, Ph.D., D.A.B.T., Acting Pharmacology and Toxicology Supervisor
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff

Office of New Drugs, Office of Drug Evaluation III:
Julie Beitz, M.D., Director

Office of Pharmaceutical Quality (OPQ):
Chikako Torigoe, Ph.D., Reviewer, Office of Biotechnology Products (OBP)
Joel Welch, Ph.D., Reviewer, OBP
Rashmi Rawat, Ph.D., Acting Team Leader, OBP

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP):
Christine Hon, Ph.D., (Acting) Clinical Pharmacology Team Leader
Lin Zhou, Ph.D., Clinical Pharmacology Reviewer
Fang Li, Ph.D., Pharmacometrics Reviewer, Division of Pharmacometrics (DPM)

OTS, Office of Biostatistics (OB), Division of Biometrics III:
Mahboob Sobhan, Ph.D., Biometrics Team Leader
Jia Guo, Ph.D., Biometrics Reviewer

Office of Combination Products:
Bindi Nikhar, M.D., Associate Clinical Director

OSE, Office of Medication Error Prevention and Risk Management:
CAPT Walter Fava, R.Ph., M.S.Ed., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Danielle Harris, Pharm.D., BCPS, Team Leader, DMEPA
Kimberly Lehrfeld, Pharm.D., BCPS, Team Leader, Division of Risk Management (DRISK)
Leah Hart, Pharm.D., Reviewer, DRISK

Center for Devices and Radiological Health (CDRH), Office of Device Evaluation, General Hospital, Respiratory, Infection Control, and Dental Devices (DAGRID), General Hospital Devices Branch:
Sapana Patel, Pharm.D., Pharmacist

Office of Scientific Investigations (OSI)
Roy Blay, Ph.D., Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Peggah Khorrami

SPONSOR ATTENDEES
Andreas Grauer, M.D., Executive Medical Director, Global Development
Mark Taisey, Vice President, Regulatory Affairs
Pamela Danagher, Director, Regulatory Affairs
Julia Zhu, Pharm.D., Manager, Regulatory Affairs
Judy Maddox, D.O., Medical Director, Global Safety

Via Teleconference:
Deborah Wenkert, M.D., Clinical Research Medical Director, Global Development
Rogely Boyce, DVM, Ph.D., Executive Director, Comparative Biology and Safety Sciences (CBSS)
Michelle Geller, M.D., Executive Director, Global Safety
Li Chen, PhD, Sc.D., Director, Global Biostatistical Science
Matt Hsu, Ph.D., Principal Scientist, Clinical Pharmacology Modeling and Simulation
Allegra Kaufman, M.D., Medical Sciences Medical Director, Early Development
Mike Abernathy, Director, Regulatory Affairs CMC

Chelsea O'Connell, M.S., Manager, Regulatory Affairs Device
Amy Compton, Senior Manager, Global Regulatory Writing
Stephen Wertheimer, Regulatory Affairs Associate, U.S. Regulatory Affairs
Amy Xia, Executive Director, Global Biostatistical Science
Cassie Milmont, Manager, Global Biostatistical Science
Grace Gachanja, Manager, Global Safety
Pegah Mehdizadeh, Senior Medical Scientist, Global Safety
Mary Gavin, Medical Director, Global Safety

1.0 BACKGROUND

Romosozumab is a high affinity, full length IgG2 monoclonal antibody to sclerostin generated by humanizing mouse sclerostin monoclonal antibody m13C7. Amgen is planning to submit a Biologics License Application (BLA) for romosozumab in July 2016. The Agency previously met with Amgen on July 28, 2015, to discuss the proposed structure and format of the electronic data package to be submitted to support the initial BLA.

Amgen would like to discuss the romosozumab development program and to follow up on the previous July 2015 meeting regarding the structure, format, and content of the BLA for the proposed indication.

FDA sent Preliminary Comments to Amgen on May 13, 2016.

2. DISCUSSION

2.1. Clinical

Question 1: *Amgen concludes that the results of Study 20070337 meet the criteria specified by the Agency (10 November 2014 Type C Clinical Written Response) and the study will serve as a single pivotal study to support the BLA filing. Does the Agency agree that the proposed content of the overall data package as outlined in Section 8 constitutes a complete BLA?*

FDA Response to Question 1:
The phase 3 fracture study with adequate supportive studies appears acceptable for BLA filing and review. We note, however, that only 2.5% of the study population was enrolled from North America and that the primary endpoint is not evaluable in this population due to the low fracture rate. Also, the nonvertebral fracture findings are of concern when North America is compared with other geographic locations. In your BLA, you should provide in-depth justification as to why the data from trial 20070337 are applicable to the intended United States (U.S.) population and U.S. medical practice.

Discussion at the Meeting:
Amgen intends to address the applicability of the global 20070337 trial data to the intended

United States (U.S.) population and U.S. medical practice in the BLA submission. Amgen noted the challenges of recruiting for a placebo controlled trial in the U.S. Amgen summarized the study design and results for study 20070337, including region specific data (see Slides 7-14 in the attached). Amgen recognizes the limited contribution of the North American study population to the global trial for study 20070337, and the associated low number of vertebral fracture events, therefore statistically conclusive results of the North American subgroup of the study population alone cannot be expected. Amgen explained, overall, with regard to the primary endpoint, that a consistent treatment effect was seen across all pre-defined subgroups. This included age, race, other baseline risk factors, and geographic regions. This is corroborated by bone mineral density (BMD) measurements, which also show comparable increases at both the spine and hip across geographic regions. Amgen also noted that there was an inclusion criterion for Vitamin D in study 20070337 that applied to all regions. Amgen believes that the trial population remains applicable to the intended U.S. population and U.S. medical practice data. The Agency explained that a justification, including BMD data, will be important to include in the BLA submission.

Regarding the secondary endpoint of nonvertebral fractures, Amgen acknowledged that the small sample size in the North American population yielded a low number of events. Amgen stated that the secondary endpoint of nonvertebral fractures missed statistical significance ($p= 0.096$) in the overall trial population in the context of lower than expected fracture rates. The Agency confirmed that statistical significance for nonvertebral fractures is not a requirement for approval.

Amgen explained the statistical testing sequence used for study 20070337 (see slide 16) and the importance of clinical fracture along with the study results (presented on slides 17-18).

Amgen's intended approach to support the relevance of the study 20070337 data to the U.S. population is to address the recommendations noted in International Conference on Harmonisation (ICH) E5 Guideline Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH, 1998) in the BLA submission. This will include discussion of intrinsic factors and extrinsic factors, such as consistency of medical practice and disease definition across the globe, the relevance of study population including pretreatment status, calcium and vitamin D supplementation, and underlying illnesses/concomitant therapies. The Agency recommended that the discussion also address baseline nutrition (e.g., there is calcium and vitamin D supplementation in some foods in the U.S., but not in other countries).

2.2. Labeling

Question 2: *In light of discussions at the 4 November 2015 Food and Drug Administration (FDA) Public Workshop on topics related to Osteoporosis drug development, Amgen proposes an alternative indication statement for romosozumab. Does the Agency agree with the following proposed indication (for inclusion in the romosozumab United States (US) Prescribing Information, Indications and Usage)?* (b) (4)

treatment of osteoporosis in postmenopausal women at increased risk of fracture. (b) (4)

(b) (4)

FDA Response to Question 2:
It is premature to discuss an alternative indication statement. You should note that the fracture groups generally included in the treatment of postmenopausal osteoporosis indication statement are vertebral, nonvertebral, and hip fracture, where relevant.

Discussion at the Meeting:
Amgen asked if "premature" was in relation to the anticipated revisions to the Osteoporosis Drug Development Guidance, or in relation to the review of the full BLA. The Agency stated that we are still discussing the indication statement for osteoporosis therapies and have not reached a conclusion. The Agency also noted that romozosumab has a unique treatment regimen (treatment for 1 year with romosozumab followed by denosumab) that would likely impact its indication. Amgen plans to focus the indication on romosozumab. The Agency stated that the limitation to 1 year of therapy would need to be addressed in the labeling.

The Agency is undecided about (b) (4) the indication statement as it is vague and may not be informative to providers. Amgen believes (b) (4) (b) (4) and hopes the Agency will consider (b) (4) the statement. Amgen also explained they considered the indication statement for zoledronic acid when proposing the indication statement for romozosumab.

Amgen will include its proposals for the indication statement with rationale in the BLA and further discussions will take place during the BLA review cycle if the application can be approved.

2.3. Follow up to 28 July 2015 Type C Structure Format Meeting

Question 3: FDA feedback included the following: "Agreement on the clinical data package for the marketing application will occur at the Pre-Submission meeting. Your application should be complete upon submission."

Does the Agency agree with the proposed content of the clinical data package for the marketing application, as summarized in Section 8.1 including the plan for ongoing studies?

FDA Response to Question 3:
The proposed content of the clinical data package for the marketing application, to be provided in Module 5 of the Common Technical Document, appears generally acceptable.

In general, an Applicant should submit a complete marketing application to maximize the efficiency of the review process. However, because the area under the curve (AUC) from Day 57 to Day 85 after single dose subcutaneous administration of romosozumab contributes only about 1% to the overall AUC, pharmacokinetic (PK) data after Day 57 are not expected to significantly shift the estimates of AUC_{last} and AUC_{inf}. In addition, PK data after Day 57 do not affect the calculation of maximum plasma concentration (C_{max}) or the time taken to reach the maximum concentration (T_{max}). For these reasons, in this instance and under this

condition, we agree that you can submit the primary analysis for Study 20150197 based on data collected for 57 days after dosing with the initial BLA, followed by the final analysis with the complete dataset up to 85 days after dosing as part of the 120-day safety update. Additionally, the 120-day update should include a comparative analysis of the Day 57 data extrapolated to infinity and the Day 85 data extrapolated to infinity.

Our evaluation of the PK comparability between the two products from different manufacturing sites will be based on the final analysis.

Discussion at the Meeting:
Amgen confirmed that they now do intend to include the final analysis of data for Study 20150197 in the BLA submission, including the complete study report, final tables, listings, figures and datasets. Comparative analysis of the Day 57 data extrapolated to infinity and the Day 85 data extrapolated to infinity will be part of this final analysis.

Question 4: FDA feedback included the following: "Submit study specific datasets for the 16 studies that contain PK and/or PD data." Information on the study-specific datasets for 4 additional studies (20090153, 20120274, 20090418, 20150197) are provided in an updated version of the DSP (Sections 5.1 and 5.2 of the DSP, submitted 08 April 2016, SN 0422).

Does the Agency agree with Amgen's plan for the study-specific data format of the above-mentioned studies?

FDA Response to Question 4:
For these 4 additional studies, the provision of ADaM datasets in XPT file format and Define files, version 2.1, is acceptable.

In your BLA submission, use the format of Table 5 in Section 8.3 to create a table that summarizes the formulation information for each clinical study characterizing the PK and pharmacodynamics (PD) of romosozumab. The formulation information should include the drug substance manufacturing process and site, the drug product fill site, and the concentration and presentation of the drug product.

Discussion at the Meeting:
There was no additional discussion at the meeting.

Question 5: FDA comments shared at the 28 July Type C Meeting provided the below feedback. Does the Agency have any further guidance on the proposals outlined below (in Questions 5 a-d) or the plan for presentation of data in the BLA as outlined in Section 8.1?

Question 5a: *During the discussion at the meeting, Amgen proposed to include data from the 3 supportive studies, including side-by-side presentation of efficacy data from Studies 20060326, 20101291, and 20120156. The Agency asked Amgen to integrate the 3 supportive studies referenced above.* Amgen has responded to the Agency's feedback by adding a

column of integrated efficacy data to the originally proposed side-by-side presentation of data from Studies 20060326, 20101291, and 20120156 (the 12-month placebo-controlled efficacy analysis set). Does the Agency accept the approach for data presentation of this analysis set in the Integrated Summary of Efficacy (ISE), as shown in Table 12?

FDA Response to Question 5a:
Our comments in the July meeting regarding the studies listed focused on data standardization, not presentation of efficacy data. We note your proposal on page 67, Table 12 and agree that your approach to integrating efficacy data is acceptable.

Question 5b: *"the ISE should focus on dose response, when treatment ends, and retreatment"* Amgen plans to include a section on off-treatment and retreatment from Study 20060326 in the ISE, with additional details in the reports for this study. Data on off-treatment and retreatment from Study 20060326 are presented in Section 8.4.8.

FDA Response to Question 5b:
Your proposal is acceptable. We note, however, that the population in Study 20060326 is not an osteoporosis treatment population, but a low bone mass population. You should include a discussion of the potential differences in effect in these two populations.

Question 5c: *"the ISE (should) include an in-depth discussion of how the Phase 3 dose was chosen."* Amgen has responded to the Agency's request by adding a second data pool to the ISE – The Dose-Ranging Efficacy Analysis Set. Data showing this new efficacy analysis set are presented in Section 8.4.5, Table 13. This information will be complemented by population PK/PD analyses presented in the Summary of Clinical Pharmacology which will provide in-depth analyses regarding the dose rationale for the phase 3 studies.

FDA Response to Question 5c:
We acknowledge the addition of the second data pool, The Dose-Ranging Efficacy Analysis Set. We also acknowledge that you will complement the dose-finding analysis with population PK/PD analyses. In your submission, you should specify in detail how population PK/PD analyses support the dose rationale and provide supportive evidence for efficacy and safety. Submit all datasets and modeling codes used for PK/PD modeling and simulations. Specifically, include the following:

- NONMEM control streams for the population PK or PK/PD analysis
- The output tables for final model runs for population PK and PK/PD models
- A model development decision tree and/or tables which give an overview of modeling steps
- Datasets and codes (NONMEM, SAS, or R) for dose/exposure-response analysis for efficacy and safety

In addition, include a USUBJID (unique subject ID) column in all the population PK and PK/PD datasets so that we can relate these datasets to other clinical analysis datasets.

Question 5d: *In reference to Amgen's proposal to include an additional postmenopausal osteoporosis (PMO) safety analysis for all phase 2 and phase 3 studies included in the BLA, the Agency stated "Doses should be presented separately in the ISS."* Amgen has added separate doses (70 mg QM, 140 mg QM, and 210 mg QM) to the PMO Population for the Integrated Summary of Safety (ISS) in order to evaluate the dose response of the safety data (see Table 17 for example). Does the Agency have any further guidance on the proposals outlined above (in Questions 5 a-d) or the plan for presentation of data in the BLA as outlined in Section 8.1?

FDA Response to Question 5d:
See our responses under the safety sections for Questions 8 and 9.

Discussion at the Meeting:
There was no additional discussion for Questions 5a, 5b, or 5c at the meeting. For Question 5d, see Discussion under Questions 8 and 9.

2.4. Biostatistics

Question 6: *Does FDA agree with the proposed subgroup analyses for the ISE and ISS as presented in Section 8.4.3 and Section 8.5.1.3, respectively?*

FDA Response to Question 6:
Yes. Any subgroups of interest should be pre-specified in the statistical analysis plan (SAP) and subgroup analysis should be conducted according to the SAP.

As part of the FDA Safety and Innovation Act of 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on www.fda.gov/drugtrialssnapshot. The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- "MORE INFORMATION" sections that provide more technical, data-heavy information
- Information that focuses on subgroup data and analyses
- Links to the approved labeling for the product and to the FDA reviews at Drugs@FDA

We are requesting summary of baseline demographics, analysis of primary and secondary efficacy endpoints (intended for labeling), summary of any treatment emergent adverse events (TEAEs) and adverse events (AEs) of special interest by age, sex and, race subgroups for the pivotal individual trial, ISE, and ISS databases. Sample table templates are provided for reference.

Table 1. Summary of Baseline Demographics (database used)

Demographic Parameters	Treatment Group(s)			Total (N=XX) n (%)
	Treatment X (N=XX) n (%)*	Treatment X (N=XX) n (%)*	Placebo (N=XX) n (%)*	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, Max (years)				
Age Group				
<XX years				
≥XX years				
Race				
Group 1				
Group 2				
……				
Group X				

Source:

*Percentages are calculated based on the total number of subjects in the respective treatment arm.

Table 2 Subgroup Analysis of *Efficacy Endpoint* (database used)

Subgroup	Treatment X (N=xx)	Treatment X (N=xx)
Endpoint		
Sex		
Male	xx (xx, xx)	xx (xx, xx)
Female	xx (xx, xx)	xx (xx, xx)
Age Group		
<XX years	xx (xx, xx)	xx (xx, xx)
≥XX years	xx (xx, xx)	xx (xx, xx)
Race		
Group 1	xx (xx, xx)	xx (xx, xx)
Group 2	xx (xx, xx)	xx (xx, xx)
……	xx (xx, xx)	xx (xx, xx)
Group X	xx (xx, xx)	xx (xx, xx)

Source:

xx (xx, xx) is the treatment effect vs. placebo and the 95% CI.

Table 3 Subgroup Analysis of Adverse Events (Database used)

Subgroup	Treatment X (N=xxx)		Treatment X (N=xxx)		Placebo (N=xxx)	
	x (%)**	Total, n	x (%)**	Total, n	x (%)**	Total, n
Any TEAEs						
Sex						
Male						
Female						
Age Group						
<XX years						
≥XX years						
Race						
Group 1						
Group 2						
……						
Group X						

Source

** Percentages are calculated based on the number of subjects in the subgroup per arm.

Provide a table in the same format as Table 3 above for each AE of special of interest.

Discussion at the Meeting:
There was no additional discussion at the meeting.

2.5. Nonclinical

Question 7: *An overview of the nonclinical program for romosozumab is presented in Section 7 and the additional 6-week rat toxicology data is presented in Section 7.2. Does the Agency agree that the additional 6-week rat toxicology study conducted with romosozumab confirms the established nonclinical safety profile for romosozumab?*

FDA Response to Question 7:
The additional data from the 6-week rat toxicology data appear to confirm that romosozumab can increase bone formation in flat bones, including the rat skull. The data do not appear to change the nonclinical safety profile for romosozumab.

Additional nonclinical comments and questions:

- The following histopathology findings were described in the 'Results' section of the additional 6-week rat study (Study 121854):

  "*This microscopic change at the calvarium and nasal cavity was characterized by thicker/wider cortical bone comprised of lamellar bone lined by single layered low cuboidal osteoblasts and, in some animals, with subperiosteal intramembranous bone (frontal bone), with overlying periosteum composed of a single layer of low cuboidal osteoblasts."*

  Provide further characterization of subperiosteal "intramembranous" bone. In what type of membranous matrix, if any, was this bone formed?

- Submit the statistical datasets for the carcinogenicity studies (Studies 107895 and 115707) submitted on August 28, 2015, (SD472) per the following data specifications: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf. Submit the data as tumor.xpt files.

Discussion at the Meeting:
Amgen provided additional information about the finding of subperiosteal "intramembranous" bone, including light micrographs, to the Agency prior to the meeting. This information will also be included in the BLA. There was no further discussion at the meeting.

2.6. Safety

Question 8: *Amgen proposes to submit the subject safety narratives for life-threatening serious adverse events, serious adverse events of interest, adverse events leading to the discontinuation of investigational product, and deaths. To identify and assess adverse events of interests for romosozumab, prespecified standard Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ) will be used. Where SMQs do not exist for an event of interest, Amgen will use a pre-identified Amgen MedDRA search strategy.*

Does the Agency agree with this proposal?

FDA Response to Question 8:
We recommend that you include safety narratives from ALL serious adverse events (SAEs) and also from AEs leading to discontinuation of investigational product, in addition to the planned SAEs and AEs of interest. Clarify which case report forms (CRFs) you will include in your application and whether you will make these CRFs searchable. Also, submit your search strategy for events of interest for which SMQs don't exist.

Discussion at the Meeting:
Amgen acknowledged the Agency's comments and plans to include the following types of safety narratives in the BLA: all serious adverse events, adverse events leading to the discontinuation of investigational product, and deaths. Amgen plans to provide electronic Case Report Forms (eCRFs) for subjects in Phase 1, 2, and 3 trials who died, discontinued from investigational product due to an adverse event, or reported a serious adverse event. Amgen confirmed CRFs will be searchable and agreed to submit the search strategy for events of interest for which SMQs don't exist. The Agency agreed with Amgen's plan.

Question 9: *Does the Agency agree with the plan for the presentation of safety data in Study 20070337 (ie, cumulative safety data from month 0 to 12 alongside cumulative safety data from months 0 to 24), as shown in Table 18?*

FDA Response to Question 9:
Your proposed summary of cumulative subject incidence of adverse events for presentation of safety data in Study 20070337 is acceptable. It should be clear from the application that the integrated summary of safety (ISS) and other safety reports include all adverse events that were seen during development, not only those judged by investigators or the Applicant to have been potentially drug-related.

We had the following additional recommendations for your submission:

1) For your proposed key safety endpoint summaries, report AEs with ≥ 2% differences (not ≥ (b) (4) as proposed) between 210 mg romosozumab and pooled placebo groups.

2) For laboratory assessments:

   - Report Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 (not ≥ (b) (4) as proposed).

   - Additionally, report clinically significant laboratory value abnormalities separately. Also provide shift tables, marked laboratory value abnormality tables for clinically significant findings which are not SAEs, and AE or laboratory value changes which resulted in dropout, dose change, or addition of concomitant therapy.

   - Highlight ≥2 grade shifts from baseline as proposed.

   - For potential Hy's Law cases, report complete analysis of liver tests, CRFs and include information on potential confounding disease processes such as hepatitis, preexisting or acute liver disease, or other concurrent drug(s) capable of liver injury. Provide additional information on patient follow-up to resolution and/ or re-challenge to drug and resolution.

   - Provide an analysis of serum transaminase elevations in your ISS that shows the number and percentage of patients with serum alanine aminotransferase (ALT) >3x upper limit of normal (ULN), >5x ULN, >10x ULN and >20x ULN in the romosozumab groups and in the placebo group. Conduct similar analyses for serum aspartate aminotransferase (AST).

   - Assessment of mineral metabolism should also include magnesium and phosphorus assessments.

3) QT study: If a thorough QT/ QTc study has not been conducted, your submission should include an in depth discussion of why one is not needed.

Discussion at the Meeting:
There was a discussion regarding the Agency's comment to "report clinically significant laboratory value abnormalities separately. Also provide shift tables, marked laboratory value

abnormality tables for clinically significant findings which are not SAEs, and AE or laboratory value changes which resulted in dropout, dose change, or addition of concomitant therapy."

Amgen presented further explanation for the reporting:

- As part of data collection in the phase 2 and phase 3 studies, per protocol, the investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values.
- In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events.
- In general, except for Study 20060326, clinical sequelae (not the laboratory abnormality) should be recorded as the adverse event. Adverse events that were reported as any laboratory abnormality will be reported separately.

As dose change was not an option for the phase 2 and 3 studies in the romosozumab program, Amgen proposed:

- To report subject incidence of discontinuation of investigational product with ≥ 2 grade shifts from baseline for calcium, phosphorous, parathyroid hormone (PTH), magnesium, white blood cell count, liver tests, and creatinine within 30 days prior to discontinuation in all subjects by treatment group (US FDA Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review [US FDA, 2005]).
- Among these subjects, Amgen will provide a summary of those subjects with addition of concomitant therapy within 30 days prior to discontinuation.

Lastly, Amgen confirmed that the CTCAE analyses will include analyses based only the objective laboratory data (will not be limited to laboratory abnormalities reported by investigators as adverse events).

The Agency agreed the proposed approach is reasonable.

Question 10: *Does the Agency agree with the proposed content, analysis, and proposed data cut-off date for the 120-day safety update as described in Section 8.7?*

FDA Response to Question 10:
The proposed content, analysis, and proposed data cut-off date for the 120-day safety update is acceptable.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 11: *As part of preparation of the BLA, Amgen is conducting a detailed assessment of Study 20070337 efficacy and safety data as well as the integrated safety data, and will consider potential need for risk minimization activities as part of that assessment. Based on the available data presented in this document, does the FDA agree that a Risk Evaluation and Mitigation Strategy (REMS) would not be considered necessary to support initial submission of the romosozumab BLA?*

FDA Response to Question 11:
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 fora REMS during the review of your application.

Discussion at the Meeting:
There was no further discussion at the meeting.

Question 12: *Based on the data presented, does the FDA intend to convene an Advisory Committee Meeting?*

FDA Response to Question 12:
It is premature to discuss the need for an Advisory Committee meeting. You should note that first-in-class new molecular entities are often presented to an Advisory Committee.

Discussion at the Meeting:
There was no further discussion at the meeting.

2.7. CMC - Drug Product Stability

Question 13: *The drug product stability program includes primary, commercial (production) and supporting stability data as outlined in Section 6.*
At the time of BLA filing, the following data are intended to be available:

- *36 months of primary stability data for the 1.17 mL (b) (4) prefilled syringe (PFS) (b) (4) presentation*
- *36 months of supporting stability data for the 1.17 mL (b) (4) PFS (b) (4) presentation*
- *3 months of commercial (production) stability data for 1.17 mL (b) (4) PFS (b) (4) presentation*

Based on stability data for the (b) (4) PFS, Amgen is requesting a (b) (4) month expiry in the BLA. At the time of the original BLA filing, Amgen will have 3 months of stability data for the commercial (b) (4) PFS lots. The 6-month time point stability data for the commercial (b) (4) PFS lots will be available within 30 days of the BLA filing.

Does the Agency agree the 6-month stability data can be submitted within 30 days of the

original BLA filing without extension of the review clock per PDUFA V guidelines?

FDA Response to Question 13:
Yes. We have following comment regarding the use of primary drug product stability data to set expiry of the commercial (b) (4) prefilled syringe ((b) (4) PFS) lots.

- Sufficient data to demonstrate that the primary lots are fully representative of material generated using the commercial manufacturing process should be provided in the BLA.

Discussion at the Meeting:
There was no further discussion at the meeting.

2.8. Device Content

Question 14: *The current presentation for romosozumab in the BLA will be as a combination product in a PFS as outlined in Section 6.2. A comprehensive Device Reviewer's Guide will be provided in Module 1 Section 1.2 that outlines the location of device and combination product information throughout the BLA submission.*

Does the Agency agree that the proposed content, structure, and format of the PFS combination product information, as presented in the Romosozumab Device Reviewer's Guide in Appendix 2, will facilitate the effective review of the BLA?

FDA Response to Question 14:

1) The reviewer guide appears to cover the necessary information needed for review of the device constituent of the combination product. We recommend including hyperlinks to the respective eCTD sections from the reviewer guide. The following are comments on the content within Module 3:

    a. In addition to the device description and specifications provided in the application, include the comprehensive design control documentation for the prefilled syringe, including the design inputs, design outputs, and design verification/validation data.

    b. You have included in your reviewer guide prefilled syringe (PFS) description and specifications and functional testing. We expect that all essential device specifications, dimensional, functional, reliability and safety requirements will be characterized and verified in your submission after manufacturing and at date of expiry. Accelerated aging studies may be acceptable to assess stability of some of the device performance and safety elements. The data should be sufficient to assure the performance of the prefilled syringe throughout the proposed storage and in use conditions.

2) You stated you will provide performance, biocompatibility, and functional testing on

your prefilled syringe. Your application should provide the full test reports for each test performed on the device constituent or provide a letter of authorization for review of master files that support your application.

3) You state you will provide a risk management summary of your device. Your risk analysis information should characterize and evaluate the risks to the user and /or patient during normal use, foreseeable mis-use, and potential failures. The analysis should clearly describe hazards, mitigations implemented to reduce the risk of the hazards, effectiveness of the mitigation, and conclusions of the acceptability of device risks in the final finished device.

4) During review of the application, we will be evaluating lot release criteria to ensure the criteria are adequate to assure the essential performance specifications of your device are verified and validated on released products. Add the appropriate link to eCTD section 3.2.P.5.1 in the device reviewer guide.

Discussion at the Meeting:
Regarding the Agency's comment 1a:
Amgen proposed to include design control documentation in the form of design verification reports, design validation reports, and the use risk assessment.

- Within each design verification report, the design input(s) that were in scope of the test will be provided and the design outputs in the form of design specifications will be listed.
- Within the design validation report, the user needs and essential steps will be identified.

The Agency agreed with the proposal.

ADDITIONAL COMMENTS*:*

Other Clinical Safety Comments:

We remind you that vascular events and progression of osteoarthritis need to be closely evaluated, and that bone quality is a major concern. Your BLA submission should provide a detailed listing of potential cardiovascular and vascular events to be adjudicated and evaluated. In addition, your BLA submission should have detailed explanations regarding the conduct of the osteoarthritis, bone biopsy, audiology, and serum parathyroid hormone / urinary calcium substudies.

Discussion at the Meeting:
There was no further discussion at the meeting.

Manufacturing Information: Combination Product:

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. This provision allows for single-entity and co-packaged combination products to demonstrate compliance with CGMP requirements in one of two ways. Under the first option, manufacturers demonstrate compliance with all CGMP regulations applicable to each of the constituent parts included in the combination product. Under the second option, manufacturers implement a streamlined approach, demonstrating compliance with either the drug CGMPs (21 CFR part 211) or the quality system (QS) regulation (21 CFR part 820) rather than demonstrating full compliance with both, when the combination product contains both a drug and a device, under certain conditions. To assist in the review of applications that rely on a streamlined approach based on a drug CGMP operating system, we request the following quality systems information in the marketing application:

NDA Form 356h: Provide detailed list of all manufacturing facilities; what activities occur at the site (e.g., assembly, filling, sterilization, other); and what constituents are at the site (e.g., drug only, device only, both drug and device). For the facilities that have both the drug and device, identify which combination product operating system is used at the site.

- Management Control (21 CFR 820.20)

Specify which manufacturing firm has ultimate responsibility to assure that the combination product is manufactured in compliance with applicable 21 CFR Part 4 requirements at all levels of the organization. Also, provide a description and responsibility of each facility involved at the different levels of the organizational structure.

- Design Control, General (21 CFR 820.30)

Provide a description of your design control system, which should include requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. Provide a copy or a summary of the plan used to design the combination product. Explain how you implemented the design control system to develop the combination product under review.

- Purchasing Controls (21 CFR 820.50)

Provide a summary of the procedure(s) for purchasing controls. The summary should:

a. Describe your supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.
b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not

affect the final combination product. Provide a description of how you applied the purchasing controls to the suppliers/contractors involved in the manufacturing of the combination product or provide evidence of the application (i.e. supplier's agreement).

- Corrective and Preventive Action (21 CFR 820.100)

Summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require analysis of:

a. Sources of quality data to identify existing and potential causes of nonconforming practices and products;
b. Investigation of the cause of nonconformities;
c. Identification of actions needed to correct and prevent recurrence of non-conformances;
d. Verification or validation of the actions.

Discussion at the Meeting:
There was no further discussion at the meeting.

Human Factors (HF) Comments:

We reference your January 25, 2016 response to our December 11, 2015, advice letter. In this response, you propose to address our concern regarding the risk of wrong dose errors by leveraging other relevant Human Factors validation data. Provided that nothing has changed about your marketing proposal for this product (submitted August 12, 2015) for use by healthcare providers, we find this proposal acceptable and request that the information be included with the BLA submission.

Discussion at the Meeting:
There was no further discussion at the meeting.

Product Quality Microbiology:

We are providing additional product quality microbiology comments for you to consider for the preparation of your BLA submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Include a complete list of the manufacturing and testing sites with their corresponding establishment registration number (FEI) number.

The Chemistry/Manufacturing/Controls (CMC) Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The

provided information should include, but not be limited to, the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful consecutive (b) (4) hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Information and summary results data demonstrating microbial control (b) (4) (b) (4) (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of at least three conformance lots (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance (DS) bioburden and endotoxin release specifications (3.2.S.4). Note that the DS specification for bioburden is (b) (4) (b) (4).
- Summary report and results from bioburden and endotoxin test methods qualification performed for (b) (4) the drug substance (3.2.S.4). In addition, the test methods should be described.
- If the formulation contains polysorbate, the effect of hold time on endotoxin recovery should be assessed (b) (4) (b) (4). The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated (3.4.S.4).

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the aseptic process and sterility assurance. For guidance on the type 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" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

Provide the following information in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

- Description of the manufacturing areas and fill line, including air classifications.
- Description of the environmental and personnel monitoring programs.
- Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.

- [redacted]
- Parameters for filling and stoppering.
- Processing and hold time limits [redacted]

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- [redacted] retention study [redacted].
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program. For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.
- In-process microbial controls and hold times. Three successful [redacted] hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- [redacted] bioburden limits should be monitored and should be less than [redacted] CFU/100 mL.
- [redacted].
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.
- A description of the routine environmental monitoring program.
- Shipping validation studies, including container closure integrity data. Additionally for PFS, the difference in air pressures during air shipment may cause movement of the plunger which may breach the sterility of PFS. Include results to demonstrate that the PFS plunger movement during air transportation does not impact product sterility.

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 initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the PFS should be included. Container closure integrity methods 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 [redacted] until expiry (3.2.P.8.2).

- Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed (b) (4) (if applicable) and the drug product, as appropriate. In addition, the test methods should be described.

- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13 (b).

- Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed (b) (4) (b) (4) and (b) (4) then testing for recoverable endotoxin over time. These studies should be conducted in the containers in which the product and samples are held prior to endotoxin testing.

Discussion at the Meeting:
There was no further discussion at the meeting.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 29, 2016, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

Discussion at the Meeting:

- The content of a complete application was discussed. Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: the 6-month time point stability data for the commercial (b) (4) PFS lots.

  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 the Agency will determine the need for a REMS during the review of the application.

- Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  NDA/BLA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

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 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- 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 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item 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 submission in the format described, the Applicant can describe location or provide a link 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 (Attachment 1, 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 submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA 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 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 for each site by site

3. Please include the following information in a tabular format in the NDA 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 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 Organization (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.

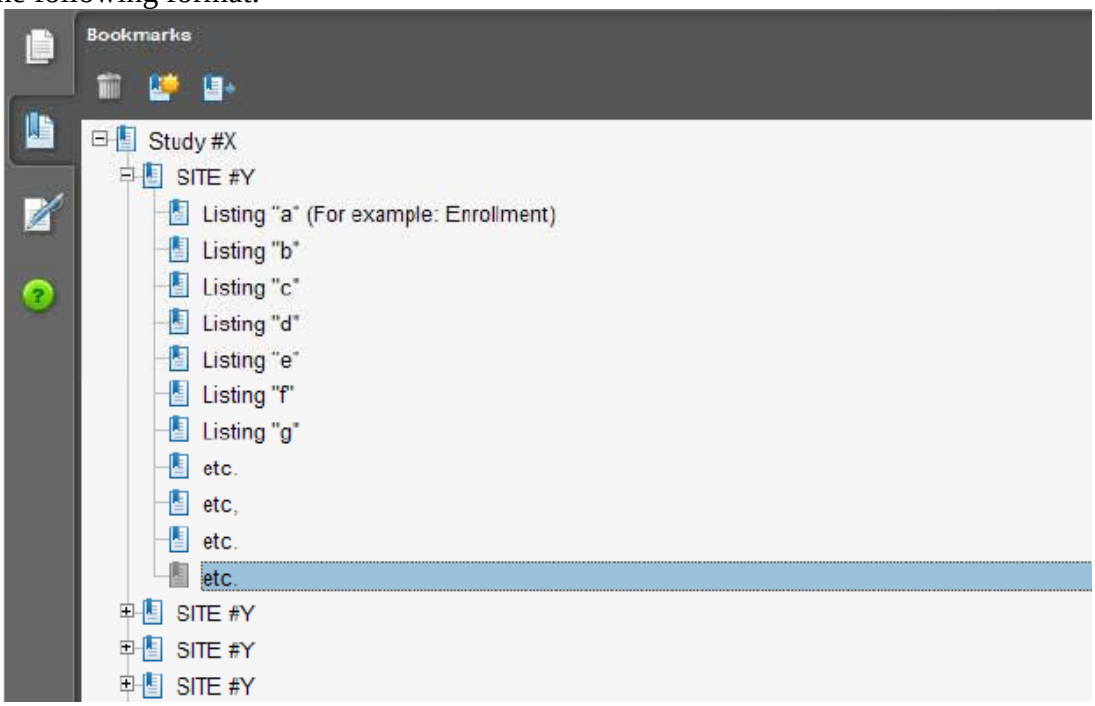
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere 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 line listings for:
   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, 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.

Attachment 1

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."

DSI 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

There were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	June 17, 2016

6.0 ATTACHMENTS AND HANDOUTS

IND 100391 18 May 2016 Type B Romosozumab Pre-BLA Meeting Presentation

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

/s/

THERESA E KEHOE
06/09/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100391

MEETING MINUTES

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

Dear Ms. Mattheson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG 785.

We also refer to the End of Phase 2 (CMC) meeting that was scheduled for November 22, 2011. On November 17, 2011, we provided you with Preliminary Comments that contained responses to the questions in your meeting package. After reviewing the Preliminary Comments, you informed us on November 21, 2011, that the meeting could be cancelled because the responses in the Preliminary Comments had adequately addressed the questions in the meeting package and no additional discussion was required.

The enclosed Memorandum of Meeting Minutes contains the comments we conveyed to you in the Preliminary Comments as well as your responses to those comments and serves as the official minutes of your End of Phase 2 (CMC) meeting. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Senior Regulatory Project Manager at (301) 796-0928.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical Team Leader
Division of Reproductive and Urologic
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Phase 2 (CMC)
Meeting Date and Time:	November 22, 2011 [This meeting was cancelled by the Sponsor after reviewing the Division's Preliminary Comments]
Application Number:	IND 100391
Product Name:	AMG 785
Indication:	Treatment of postmenopausal osteoporosis women with osteoporosis at high risk for fracture
Sponsor/Applicant Name:	Amgen, Inc.

1.0 BACKGROUND

AMG 785 is a high-affinity IgG2 monoclonal antibody generated by humanizing m13C7, a mouse monoclonal antibody that neutralizes the bone formation inhibitor sclerostin. The protein product of the SOST gene, sclerostin is secreted by osteocytes and is thought to act by binding to low-density lipoprotein receptor-related proteins 4, 5, and 6 (LRP4, LRP5, and LRP6), thereby inhibiting Wnt signaling and reducing osteoblast-mediated bone formation. AMG 785 stimulates bone formation by binding to sclerostin and preventing its inhibitory action.

Amgen, Inc., the sponsor of IND 100391, has completed a nonclinical package of pharmacology, pharmacokinetics, and toxicology studies, as well as Phase 1 clinical studies for AMG 785. In addition, the 12-month primary analysis is complete for a phase 2 dose-ranging study (Study 20060326) in postmenopausal women with low BMD. The sponsor requested this Type B End of Phase 2 (CMC) meeting to discuss the proposed AMG 785 development program for the indication of treatment of postmenopausal women with osteoporosis at high risk for fracture.

The objectives for this meeting are to discuss and obtain input from the Division regarding:

- the proposed data package required to support registration and commercialization of a new drug product presentation.
- blinding and testing plans for the comparator, Fosamax 70 mg Tablets, and placebo.

On November 17, 2011, the Division provided the Sponsor with Preliminary Comments that responded to the questions contained in the Sponsor's meeting package. After reviewing the Preliminary Comments, the Sponsor informed the Division on November 21, 2011, that the meeting could be cancelled because the responses in the Preliminary Comments had adequately addressed the questions in their meeting package and no additional discussion was required. This Memorandum of Meeting Minutes documents the responses contained in the Preliminary Comments.

2. DISCUSSION

Question 1:
Amgen intends to conduct a single dose bioequivalence study (Protocol 20101180) to support registration of a new drug product presentation, (b) (4) PFS. In addition, a multiple dose clinical study will be conducted to gain further clinical experience with this presentation (Protocol 20110252). The study designs are presented in Section 9 of the meeting package.

Does the Agency agree that the above noted clinical data package, coupled with analytical comparability that will demonstrate comparability between the clinical and proposed commercial material, is sufficient to obtain commercial registration of this drug product presentation at time of initial market application?

Division response:
Insufficient information regarding the commercial manufacturing process for AMG 785 is presented to allow us to assess whether additional clinical or non-clinical data will be necessary.

Your proposed comparability study (Protocol 20101180) is acceptable in general. However, we strongly recommend that you assess the comparability of the drug products using both AUC and Cmax as primary parameters.

> **Sponsor Response:**
> Amgen has considered the Agency's recommendation to include C_{max} as a primary endpoint consistent with the FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations (March 2003). Since AMG 785 is a subcutaneously administered long acting antibody, the relationship between drug concentrations and effects on bone turnover markers and bone mineral density is indirect. For this reason, Amgen considers that exposure based on AUC correlates better with PD response, and is thus more clinically relevant as primary endpoint. Based on this information, would the Agency agree that C_{max} is acceptable as a secondary endpoint? If the agency still believes that C_{max} should be a primary endpoint, would the Agency provide additional insight into this recommendation?
>
> **Division Comment:**
> For comparability assessments between two formulations, the Agency would not differentiate primary and secondary pharmacokinetic endpoints between AUC and Cmax. The Agency would consider both parameters in totality. In addition, there are no sufficient data to conclude that Cmax does not have an impact on PD responses of efficacy as well as safety.

Our understanding from the meeting package is that Amgen intends to use clinical process 2 of the 70mg/mL PFS presentation to manufacture AMG 785 for the phase 3 clinical trials intended to support safety and efficacy for the purposes of product registration, with additional comparability and clinical data collected for the (b) (4) PFS presentation manufactured by the clinical process 2. There is no information in the meeting package on the intended commercial process that will be used for manufacturing AMG 785, and only very high level

information on the analytical comparability approach planned for the commercial product. If Amgen does not intend to include clinical data using product manufactured by the commercial process, the BLA should include a comprehensive package to address the understanding of quality attributes and their linkage to parameters impacting product safety and efficacy.

Sponsor Response:
Amgen agrees there is insufficient information regarding the commercial manufacturing process for AMG 785 to allow FDA to assess whether additional clinical or non-clinical studies will be necessary. Our intent of providing the high level CMC information was to inform the Agency that there will be a comprehensive analytical package generated to support the site transfer to the commercial facility. Amgen intends to return to the Agency once data has been generated from the commercial facility to discuss the acceptability of those data.

Amgen has not submitted any questions regarding the comparability studies between products manufactured by the clinical and the commercial processes; however, based on the information that was provided, we have the following comments:

1. We note that current Drug Substance and Drug Product lot release assays (section 8, tables 3 and 4 of the briefing package) do not include a non-reducing SDS assay to monitor product purity. As pointed out in ICH Q6b, the assessment of purity may be highly method-dependent and overall product purity, and product-related substances/impurities are usually evaluated by a combination of analytical methods. It is therefore recommended that a non-reduced separation assay be included in the drug substance and drug product lot release and stability specifications. If a non-reduced separation assay is not used to monitor product quality at lot release and on stability, the rationale with supporting data should be provided demonstrating analytical methods that monitor quality attributes that would be detected by a non-reducing separation assay. Appropriate justification will need to be submitted in the BLA to support the selected analytical methods used for release and stability testing of both drug substance and drug product. Lack of appropriate testing of lots used in the major efficacy trial could present a significant BLA review challenge.

   Sponsor Response:
   Amgen acknowledges the Agency's feedback regarding the importance of appropriate analytical method for both release and stability testing. Amgen is evaluating the appropriateness of using non-reduced SDS. Data will be provided in the marketing application justifying whether or not the non-reduced SDS will be included as a release assay.

   Division Response:
   Please collect the data from non-reduced SDS-PAGE analyses to include in the BLA.

2. The meeting package identifies that the cell-based bioassay is intended to be used for release and stability testing of Drug Substance and Drug Product as well as comparability. We note that the current potency assay for AMG 785 is a binding ELISA assay. Prior to replacing the binding assay with the cell based bioassay, Amgen should provide a comprehensive package consisting of studies assessing the equivalency of the cell-based bioassay and the antigen

binding assay. The information to be included should identify whether the two assays are equivalent, or whether any of the two assays is superior to the other in parameters such as detection of changes in stability under stressed conditions such as exposure to temperature, light, and other potential degradation pathways. Data should also be included to identify how the product potency achieved through use of the ELISA assay for lots at release or on stability would be linked in a meaningful way to the potency of lots using the cell-based assay. The additional information and data requested should be provided for review and concurrence prior to replacing the binding assay with the cell based bioassay. Until that time, both assays may concurrently be used in release and stability assessment to accumulate the information that will be needed to justify specifications in the BLA.

Sponsor Response:
Amgen notes your recommendation regarding the replacement of the antigen binding assay with a cell-based bioassay. We would like to direct your attention to the IND amendment submitted on 7 October 2011, that provides the data to support the change to the cell-based bioassay (IND 100391,SN 0118 [Section S.4.3]). Based on the data presented in the IND amendment, Amgen feels that the replacement of the antigen binding assay with the cell-based bioassay is justified.

Division Response:
We have received and reviewed the referenced amendment. The data in the amendment do not provide sufficient justification for dropping the antigen binding assay from the release and stability specifications at this time. This action would require additional information as delineated in comment two of our reply under question one of the meeting package.

3. The comparability package should include detailed descriptions of the analytical methods used for testing AMG 785. For example, in Table 4, the differences between the two CEX-HPLC methods and the purity parameters that each would identify should be clearly described.

4. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of anti-drug antibodies (ADA). The qualification results should include data demonstrating that the assay is specific, sensitive, and reproducible, and should include information on the sensitivity of the assay to product interference. The validated assay should be capable of sensitively detecting ADA responses in the presence of drug levels that are expected to be present at the time of patient sampling. Information on the expected product levels that will be present in patient samples should be included to support use of the assay. An assay should also be developed that is able to delineate neutralizing ADA responses. Until an assay (s) has been developed and validated, patients samples should be banked under appropriate storage conditions. If such information has already been submitted to the IND, please indicate the submission where it can be found.

Sponsor Response:
Regarding the anti-drug antibodies (ADA) assay, anti-AMG 785 antibodies are being detected in subjects' serum using a sensitive and specific immunoassay which uses electrochemiluminescence as detection. Samples that are positive in the immunoassay are

also tested in a bioassay to determine if antibodies are neutralizing. The bioassay measures binding of AMG 785 to its target sclerostin. Both immunoassay and bioassay have been validated and are specific, sensitive and reproducible. Drug product interference has been studied during assay validation and was included in the method validation reports. Antibody sampling time points for clinical studies have been selected based on an expected concentration of drug product that will not interfere with sensitive ADA detection. Methods and method validation reports will be submitted to the IND.

Question 2:
Amgen intends to obtain Fosamax 70 mg tablets, marketed for use in the United States, for use in the active controlled Phase 3. Specific details regarding blinding and testing for Fosamax and the corresponding placebo are provided in Section 10 of the meeting package.

Does the Agency agree with the blinding and testing strategy of the small molecule comparator and the corresponding placebo?

Division response:
Your blinding and testing strategy for the Fosamax comparator and corresponding placebo appear appropriate. Provide CMC information on the (b) (4) either in the IND or by cross-reference to a DMF with the appropriate Letter of Authorization provided in the IND.

Sponsor Response:
It is anticipated that the IND amendment will be submitted by the end of this year and will include the DMF reference for the (b) (4).

Additional Comments:

1. Clinical Pharmacology:
   The drug product you propose to use in your Phase 3 study is different from the drug product used in the dose-ranging Phase 2 study. The differences include product presentation (liquid in vial vs. prefilled syringe), addition of a new excipient (b) (4) and proportion of the remaining excipients. In order to bridge data from the dose-ranging Phase 2 study, it will be beneficial for you to conduct a comparative PK study to demonstrate that the PK profiles of these two products are similar, before you start your Phase 3 program.
2. Clinical:
   Serum magnesium, PTH, and urinary calcium should be followed in Protocol 20110252. The enrolled population in Protocol 20110252 should reflect the target population for this drug (patients with osteoporosis at high risk for fracture).

Sponsor Response:
Amgen also acknowledges the Agency's additional clinical pharmacology and clinical comments and will take those comments under advisement.

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

/s/

THERESA E KEHOE
12/21/2011