CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125320/S-007

Trade Name: **XGEVA**

Generic Name: **Denosumab**

Sponsor: **Amgen, Incorporated**

Approval Date: November, 18, 2010

Indications: Xgeva is a RANK ligand (RANKL) inhibitor indicated for:

• Prevention of skeletal-related events in patients with bone metastases from solid tumors

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/7

SUPPLEMENT BLA APPROVAL
November, 18, 2010

Amgen, Incorporated
Attention: John Bergan
Senior Manager, Regulatory Affairs and Safety
One Amgen Center Drive
Mail Stop 38-4C
Thousand Oaks, CA 91320-9978

Dear Mr. Bergan:

Please refer to your Supplemental Biologics License Application (sBLA), dated May 14, 2010, received May 19, 2010, submitted under section 351 of the Public Health Service Act for denosumab.

We acknowledge receipt of your amendments dated May 14, 2010, July 23, 2010 (2), July 28, 2010, July 29, 2010, August 5, 2010, August 16, 2010, August 23, 2010 (2), August 24, 2010 (2), August 31, 2010, September 7, 2010, September 10, 2010, September 22, 2010, October 11, 2010, October 22, 2010, October 27, 2010 (4), October 28, 2010 (2), October 29, 2010, November 11, 2010, November 15, 2010, and November 18, 2010.

This "Prior Approval" efficacy supplement to your BLA provides for a new indication to include the prevention of skeletal-related events in patients with bone metastases from solid tumors to be marketed under a new proprietary name, Xgeva. We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

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

CM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125320/7**."
Also within 14 days, amend all pending supplemental applications for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

The SPL will be accessible via publicly available labeling repositories.

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125320/7**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are deferring submission of your pediatric studies because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B (a)(3)(B) of the FDCA. These required studies are listed below.

1. To conduct a phase 1, open-label, dose-finding pharmacokinetic, pharmacodynamic, and safety study in pediatric patients ages 0 to 18 years who are diagnosed with solid tumors metastatic to bone. The study will determine whether a safe dose can be administered to patients in subsequent phase 2 and phase 3 studies.

   The timetable you submitted on October 29, 2010 states that you will conduct this study according to the following schedule.

   Final Protocol Submission: December 30, 2011

Study Completion Date: March 31, 2014
Final Report Completion: September 30, 2014

2. To conduct a phase 2, open-label, single-arm study in pediatric patients ages 0 to 18 with solid tumors with bone metastases to determine the safety, including effects on growing bones, and activity of denosumab in the prevention of skeletal related events.

   The timetable you submitted on October 29, 2010 states that you will conduct this study according to the following schedule.

   This study must not be initiated until at least one month after you have submitted the complete final report for postmarketing requirement 1.

   Final Protocol Submission: September 30, 2014
   Study Completion Date: September 30, 2018
   Final Report Submission: March 31, 2019

3. To conduct a randomized and controlled pediatric study to evaluate the efficacy and safety of denosumab for the prevention of skeletal related events in pediatric patients ages 0 to 18 years with solid tumors and bone metastases.

   This study must not be initiated until at least one month after you have submitted the complete final report for post marketing requirements 1 and 2.

   The timetable you submitted on October 29, 2010 states that you will conduct this study according to the following schedule.

   Final Protocol Submission: March 31, 2019
   Study Completion Date: March 31, 2025
   Final Report Submission: September 30, 2025

Submit final reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment(s)**."

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since denosumab was approved on June 1, 2010, we have become aware of the increased risk of severe hypocalcemia in patients with renal insufficiency from the clinical trial data submitted for approval of this application using the 120 mg dose of denosumab. Therefore, we consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of hypocalcemia in patients with severe renal insufficiency.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of hypocalcemia in patients with severe renal insufficiency

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4. To conduct a clinical trial to determine the safety of Xgeva (denosumab) 120 mg administered every four weeks by subcutaneous injection in patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) and in patients receiving dialysis. The number of patients enrolled in the trial and the frequency and duration of plasma sampling will be sufficient to estimate the incidence and severity of hypocalcemia, hypomagnesemia, and hypophoshatemia in this patient population. The final report should include the primary and derived datasets using the CDISC and ADaM data models and the analysis programs used to generate the safety and laboratory analyses.

   The timetable you submitted on October 29, 2010 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 31, 2011
Trial Completion Date:	June 30, 2012
Final Report Submission:	December 31, 2012

Submit the protocol to your IND 9838, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment in your submission dated October 29, 2010. This commitment is listed below.

5. To submit a final report that includes updated results for overall survival for trials 20050103 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer;" 200050136 entitled "A Randomized, Double-blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects With Advanced Breast Cancer;" and 20050244 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma." The final report should also include the primary and derived datasets and analysis programs used to generate the overall survival results reported.

   The original protocol for clinical trial 20050103 was submitted to FDA on January 12, 2006, and began patient accrual on May 12, 2006. The original protocol for clinical trial 20050136 was submitted to FDA on January, 13, 2006, and began patient accrual on April 27, 2007. The original protocol for clinical trial 20050244 was submitted to FDA on May 2, 2006, and began patient accrual on June 21, 2006.

   The timetable you submitted on October 07, 2010 states that you will conduct the trials according to the following schedule:

   Final Report Submission: October 01, 2012.

Submit clinical protocols to your IND 9838 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager, at (301) 796-1273.

Sincerely,

/ Patricia Keegan, M.D./
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

LABELING

Denosumab

XGEVA Label (PDF)

Prolia Label (PDF)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XGEVA™ safely and effectively. See full prescribing information for XGEVA.

Xgeva (denosumab)
injection, for subcutaneous use
Initial US Approval: 2010

---------- INDICATIONS AND USAGE----------
Xgeva is a RANK ligand (RANKL) inhibitor indicated for:
- Prevention of skeletal-related events in patients with bone metastases from solid tumors (1.1)

Important limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen (2.1)
- Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- 120 mg/1.7 mL (70 mg/mL) single-use vial (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypocalcemia: Severe hypocalcemia can occur in patients receiving Xgeva. Correct hypocalcemia prior to initiating Xgeva. Monitor calcium levels and adequately supplement all patients with calcium and vitamin D (5.1)
- Osteonecrosis of the jaw can occur in patients receiving Xgeva. Perform an oral examination prior to starting Xgeva. Monitor for symptoms. Avoid invasive dental procedures during treatment with Xgeva (5.2)

----------ADVERSE REACTIONS----------
- The most common adverse reactions in patients receiving Xgeva (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (6.1)

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

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy Surveillance Program available (8.1)
- Nursing mothers: May impair mammary gland development and lactation. Discontinue drug or nursing (8.3)
- Pediatric patients: Safety and efficacy not established (8.4)
- Renal impairment: Patients with creatinine clearance less than 30 mL/min or receiving dialysis are at risk for hypocalcemia. Adequately supplement with calcium and vitamin D (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bone Metastasis from Solid Tumors

Xgeva is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

1.2 Important Limitation of Use

Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma *[see Clinical Trials (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen.

Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia *[see Warnings and Precautions (5.1)]*.

2.2 Preparation and Administration

Visually inspect Xgeva for particulate matter and discoloration prior to administration. Xgeva is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored or cloudy or if the solution contains many particles or foreign particulate matter.

Prior to administration, Xgeva may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm Xgeva in any other way *[see How Supplied/Storage and Handling (16)]*.

Use a 27-gauge needle to withdraw and inject the entire contents of the vial. Do not re-enter the vial. Discard vial after single-use or entry.

3 DOSAGE FORMS AND STRENGTHS

120 mg/1.7 mL (70 mg/mL) single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypocalcemia

Xgeva can cause severe hypocalcemia. Correct pre-existing hypocalcemia prior to Xgeva treatment. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when Xgeva is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare professional for symptoms of hypocalcemia *[see Adverse Reactions (6.1) and Patient Counseling Information (17)]*.

Based on clinical trials using a lower dose of denosumab, patients with a creatinine clearance less than 30 mL/min or receiving dialysis are at greater risk of severe hypocalcemia compared to patients with normal renal function. In a trial of 55 patients, without cancer and with varying degrees of renal impairment, who received a single dose of 60 mg denosumab, 8 of 17 patients with a creatinine clearance less than 30 mL/min or receiving dialysis experienced corrected serum calcium levels less than 8.0 mg/dL as compared to 0 of 12 patients with normal renal function. The risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance less than 30 mL/min or receiving dialysis.

5.2 Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) can occur in patients receiving Xgeva, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials, 2.2% of patients receiving Xgeva developed ONJ; of these patients, 79% had a history of tooth extraction, poor oral hygiene, or use of a dental appliance *[see Adverse Reactions (6.1)]*.

Perform an oral examination and appropriate preventive dentistry prior to the initiation of Xgeva and periodically during Xgeva therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with Xgeva.

Patients who are suspected of having or who develop ONJ while on Xgeva should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

6 ADVERSE REACTIONS

The following adverse reactions are discussed below and elsewhere in the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.2)]*

The most common adverse reactions in patients receiving Xgeva (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (see Table 1).

The most common serious adverse reaction in patients receiving Xgeva was dyspnea.

The most common adverse reactions resulting in discontinuation of Xgeva were osteonecrosis and hypocalcemia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

The safety of Xgeva was evaluated in three randomized, double-blind, double-dummy trials *[see Clinical Trials (14)]* in which a total of 2841 patients with bone metastasis from prostate cancer, breast cancer, or other solid tumors, or lytic bony lesions from multiple myeloma received at least one dose of Xgeva. In Trials 1, 2, and 3, patients were randomized to receive either 120 mg of Xgeva every 4 weeks as a subcutaneous injection or 4 mg (dose adjusted for reduced renal function) of zoledronic acid every 4 weeks by intravenous (IV) infusion. Entry criteria included serum calcium (corrected) from 8 to 11.5 mg/dL (2 to 2.9 mmol/L) and creatinine clearance 30 mL/min or greater. Patients who had received IV bisphosphonates were excluded, as were patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure. During the study, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

The median duration of exposure to Xgeva was 12 months (range: 0.1 – 41) and median duration on-study was 13 months (range: 0.1 – 41). Of patients who received Xgeva, 46% were female. Eighty-five percent were White, 5% Hispanic/Latino, 6% Asian, and 3% Black. The median age was 63 years (range: 18 – 93). Seventy-five percent of patients who received Xgeva received concomitant chemotherapy.

Table 1. Per-patient Incidence of Selected[a] Adverse Reactions of Any Severity (Trials 1, 2, and 3)

Body System	Xgeva n = 2841 %	Zoledronic Acid n = 2836 %
GASTROINTESTINAL		
Nausea	31	32
Diarrhea	20	19
GENERAL		
Fatigue/Asthenia	45	46
INVESTIGATIONS		
Hypocalcemia[b]	18	9
Hypophosphatemia[b]	32	20
NEUROLOGICAL		
Headache	13	14
RESPIRATORY		
Dyspnea	21	18
Cough	15	15

[a] Adverse reactions reported in at least 10% of patients receiving Xgeva in Trials 1, 2, and 3, and meeting one of the following criteria:

- At least 1% greater incidence in Xgeva-treated patients, or

- Between-group difference (either direction) of less than 1% and more than 5% greater incidence in patients treated with zoledronic acid compared to placebo (US Prescribing Information for zoledronic acid)

[b] Laboratory-derived and below the central laboratory lower limit of normal [8.3 – 8.5 mg/dL (2.075 – 2.125 mmol/L) for calcium and 2.2 – 2.8 mg/dL (0.71 – 0.9 mmol/L) for phosphorus]

Severe Mineral/Electrolyte Abnormalities

- Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) occurred in 3.1% of patients treated with Xgeva and 1.3% of patients treated with zoledronic acid. Of patients who experienced severe hypocalcemia, 33% experienced 2 or more episodes of severe hypocalcemia and 16% experienced 3 or more episodes *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

- Severe hypophosphatemia (serum phosphorus less than 2 mg/dL or less than 0.6 mmol/L) occurred in 15.4% of patients treated with Xgeva and 7.4% of patients treated with zoledronic acid.

Osteonecrosis of the Jaw

In the primary treatment phases of Trials 1, 2, and 3, ONJ was confirmed in 1.8% of patients in the Xgeva group and 1.3% of patients in the zoledronic acid group *[see Warnings and Precautions (5.2)]*. When events occurring during an extended treatment phase of approximately 4 months in each trial are included, the incidence of confirmed ONJ was 2.2% in patients who received Xgeva. The median time to ONJ was 14 months (range: 4 – 25).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescent bridging immunoassay, less than 1% (7/2758) of patients with osseous metastases treated with denosumab doses ranging from 30-180 mg every 4 weeks or every 12 weeks for up to 3 years tested positive for binding antibodies. No patient with positive binding antibodies tested positive for neutralizing antibodies as assessed using a chemiluminescent cell-based *in vitro* biological assay. There was no evidence of altered pharmacokinetic profile, toxicity profile, or clinical response associated with binding antibody development.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody (including neutralizing antibody) test result may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug-drug interaction trials have been conducted with Xgeva.

In clinical trials in patients with breast cancer metastatic to bone, Xgeva was administered in combination with standard anticancer treatment. Serum denosumab concentrations at 1 and 3 months and reductions in the bone turnover marker uNTx/Cr (urinary N-terminal telopeptide corrected for creatinine) at 3 months were similar in patients with and without prior intravenous bisphosphonate therapy.

There was no evidence that various anticancer treatments affected denosumab systemic exposure and pharmacodynamic effect. Serum denosumab concentrations at 1 and 3 months were not altered by concomitant chemotherapy and/or hormone therapy. The median reduction in uNTx/Cr from baseline to month 3 was similar between patients receiving concomitant chemotherapy and/or hormone therapy *[see Clinical Pharmacology (12.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Category C

There are no adequate and well-controlled trials of Xgeva in pregnant women. Use Xgeva during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who become pregnant during Xgeva treatment to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

In an embryofetal developmental study, cynomolgus monkeys received subcutaneous denosumab weekly during organogenesis at doses up to 6.5-fold higher than the recommended human dose of 120 mg every 4 weeks, based on body weight (mg/kg). No evidence of maternal toxicity or fetal harm was observed. However, this study only assessed fetal toxicity during the first trimester, and fetal lymph nodes were not examined. Potential adverse developmental effects resulting from exposures during the second and third trimesters have not been assessed in animals *[see Nonclinical Toxicology (13.2)]*.

In genetically engineered mice in which the gene for RANK ligand (RANKL) has been deleted (a "knockout mouse"), the absence of RANKL caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice also showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum *[see Use in Specific Populations (8.3)]*.

8.3 Nursing Mothers

It is not known whether Xgeva is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Xgeva, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Maternal exposure to Xgeva during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway that have shown altered maturation of the maternal mammary gland, leading to impaired lactation postpartum *[see Nonclinical Toxicology (13.2)]*.

8.4 Pediatric Use

The safety and effectiveness of Xgeva in pediatric patients have not been established. Treatment with Xgeva may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

In neonatal rats, inhibition of RANKL with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses less than or equal to 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent monkeys dosed with denosumab at 5 and 25 times (10 and 50 mg/kg dose) higher than the recommended human dose of 120 mg subcutaneously every 4 weeks (based on body weight mg/kg) had abnormal growth plates *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of patients who received Xgeva in Trials 1, 2, and 3, 1260 (44%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

In a trial of 55 patients without cancer and with varying degrees of renal function who received a single dose of 60 mg denosumab, patients with a creatinine clearance of less than 30 mL/min or receiving dialysis were at greater risk of severe hypocalcemia with denosumab compared to patients with normal renal function. The risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance of less than 30 mL/min or receiving dialysis *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no experience with overdosage of Xgeva.

11 DESCRIPTION

Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Xgeva is a sterile, preservative-free, clear, colorless to pale yellow solution.

Each single-use vial of Xgeva contains 120 mg denosumab, 4.6% sorbitol, 18 mM acetate, Water for Injection (USP), and sodium hydroxide to a pH of 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Xgeva binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Xgeva prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases.

12.2 Pharmacodynamics

In patients with breast cancer and bone metastases, the median reduction in uNTx/Cr was 82% within 1 week following initiation of Xgeva 120 mg administered subcutaneously. In Trials 1, 2, and 3, the median reduction in uNTx/Cr from baseline to month 3 was approximately 80% in 2075 Xgeva-treated patients.

12.3 Pharmacokinetics

Following subcutaneous administration, bioavailability was 62%. Denosumab displayed nonlinear pharmacokinetics at doses below 60 mg, but approximately dose-proportional increases in exposure at higher doses. With multiple subcutaneous doses of 120 mg every 4 weeks in patients with cancer metastatic to the bone, up to 2.8-fold accumulation in serum denosumab concentrations was observed and steady state was achieved by 6 months. At steady state, the mean ± SD serum trough concentration was 20.5 ± 13.5 mcg/mL at the recommended Xgeva dose, and the mean elimination half-life was 28 days.

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. Denosumab clearance and volume of distribution were proportional to body weight. The steady-state exposure following repeat subcutaneous administration of 120 mg every 4 weeks to 45 kg and 120 kg subjects were, respectively, 48% higher and 46% lower than exposure of the typical 66 kg subject.

Specific Populations
The pharmacokinetics of denosumab were not affected by age, gender, and race. The pharmacokinetics of denosumab in pediatric patients have not been assessed.

Hepatic Impairment: No clinical trials have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab.

Renal Impairment: In a trial of 55 subjects with varying degrees of renal function, including subjects on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
The carcinogenic potential of denosumab has not been evaluated in long-term animal studies.

Mutagenicity
The genotoxic potential of denosumab has not been evaluated.

Impairment of Fertility
Denosumab had no effect on female fertility or male reproductive organs in monkeys at exposures that were 6.5- to 25-fold higher than the observed human dose of 120 mg subcutaneously administered once every 4 weeks (based on body weight mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Denosumab is an inhibitor of osteoclastic bone resorption via inhibition of RANKL. Adolescent nonhuman primates treated with monthly doses of denosumab greater than 5 times the recommended human dose of 120 mg had abnormal growth plates. Because the biological activity of denosumab in animals is specific to nonhuman primates, evaluation of genetically engineered (knockout) mice or use of other biological inhibitors of the RANK/RANKL pathway, OPG-Fc and RANK-Fc, provided additional safety information on the inhibition of the RANK/RANKL pathway in rodent models. A study in 2-week-old rats given the RANKL inhibitor OPG-Fc showed reduced bone growth, altered growth plates, and impaired tooth eruption. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued. Neonatal RANK/RANKL knockout mice also exhibited reduced bone growth and lack of tooth eruption. RANK/RANKL knockout mice also exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) *[see Use in Specific Populations (8.3, 8.4)]*.

14 CLINICAL TRIALS

The safety and efficacy of Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three international, randomized (1:1), double-blind, active-controlled, noninferiority trials comparing Xgeva with zoledronic acid. In all three trials, patients were randomized to receive 120 mg Xgeva subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30 mL/min were excluded. In each trial, the main outcome measure was demonstration of noninferiority of time to first skeletal-related event (SRE) as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE; testing for these outcome measures occurred if the main outcome measure was statistically significant. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Trial 1 enrolled 2046 patients with advanced breast cancer and bone metastasis. Randomization was stratified by a history of prior SRE (yes or no), receipt of chemotherapy within 6 weeks prior to randomization (yes or no), prior oral bisphosphonate use (yes or no), and region (Japan or other countries). Forty percent of patients had a previous SRE, 40% received chemotherapy within 6 weeks prior to randomization, 5% received prior oral bisphosphonates, and 7% were enrolled from Japan. Median age was 57 years, 80% of patients were White, and 99% of patients were women. The median number of doses administered was 18 for denosumab and 17 for zoledronic acid.

Trial 2 enrolled 1776 adults with solid tumors other than breast and castrate-resistant prostate cancer with bone metastasis and multiple myeloma. Randomization was stratified by previous SRE (yes or no), systemic anticancer therapy at time of randomization (yes or no), and tumor type (non-small cell lung cancer, myeloma, or other). Eighty-seven percent were receiving systemic anticancer therapy at the time of randomization, 52% had a previous SRE, 64% of patients were men, 87% were White, and the median age was 60 years. A total of 40% of patients had non-small cell lung cancer, 10% had multiple myeloma, 9% had renal cell carcinoma, and 6% had small cell lung cancer. Other tumor types each comprised less than 5% of the enrolled population. The median number of doses administered was 7 for both denosumab and zoledronic acid.

Trial 3 enrolled 1901 men with castrate-resistant prostate cancer and bone metastasis. Randomization was stratified by previous SRE, PSA level (less than 10 ng/mL or 10 ng/mL or greater) and receipt of chemotherapy within 6 weeks prior to randomization (yes or no). Twenty-six percent of patients had a previous SRE, 15% of patients had PSA less than 10 ng/mL, and 14% received chemotherapy within

6 weeks prior to randomization. Median age was 71 years and 86% of patients were White. The median number of doses administered was 13 for denosumab and 11 for zoledronic acid.

Xgeva delayed the time to first SRE following randomization as compared to zoledronic acid in patients with breast or castrate-resistant prostate cancer (CRPC) with osseous metastases (Table 2). In patients with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, Xgeva was noninferior to zoledronic acid in delaying the time to first SRE following randomization.

Overall survival and progression-free survival were similar between arms in all three trials. Mortality was higher with Xgeva in a subgroup analysis of patients with multiple myeloma (hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n = 180).

Table 2. Efficacy Results for Xgeva Compared to Zoledronic Acid

	Trial 1 Metastatic Breast Cancer		**Trial 2 Metastatic Solid Tumors or Multiple Myeloma**		**Trial 3 Metastatic CRPC[a]**	
	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid
N	1026	1020	886	890	950	951
First On-study SRE						
Number of Patients who had SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
Radiation to Bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
Pathological Fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
Surgery to Bone	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)
Spinal Cord Compression	9 (0.9)	7 (0.7)	24 (2.7)	21 (2.4)	26 (2.7)	36 (3.8)
Median Time to SRE (months)	NR[b]	26.4	20.5	16.3	20.7	17.1
Hazard Ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Noninferiority p-value	< 0.001		< 0.001		< 0.001	
Superiority p-value[c]	0.010		0.060		0.008	
First and Subsequent SRE[d]						
Mean Number/Patient	0.46	0.60	0.44	0.49	0.52	0.61
Rate Ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)	
Superiority p-value [e]	0.001		0.145		0.009	

[a]CRPC = castrate-resistant prostate cancer.
[b]NR = not reached.
[c]Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid within trial.
[d]All skeletal events postrandomization; new events defined by occurrence ≥ 21 days after preceding event.
[e]Adjusted p-values are presented.

16 HOW SUPPLIED/STORAGE AND HANDLING

Xgeva is supplied in a single-use vial.

120 mg/1.7 mL	1 vial per carton	NDC 55513-730-01

Store Xgeva in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, Xgeva must not be exposed to temperatures above 25°C/77°F or direct light and must be used within 14 days. Discard Xgeva if not used within the 14 days. Do not use Xgeva after the expiry date printed on the label.

Protect Xgeva from direct light and heat.

Avoid vigorous shaking of Xgeva.

17 PATIENT COUNSELING INFORMATION

Advise patients to contact a healthcare professional for any of the following:

- Symptoms of hypocalcemia, including paresthesias or muscle stiffness, twitching, spasms, or cramps *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*
- Symptoms of ONJ, including pain, numbness, swelling of or drainage from the jaw, mouth, or teeth *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- Persistent pain or slow healing of the mouth or jaw after dental surgery *[see Warnings and Precautions (5.2)]*
- Pregnancy or nursing *[see Use in Specific Populations (8.1, 8.3)]*

Advise patients of the need for:

- Proper oral hygiene and routine dental care
- Informing their dentist that they are receiving Xgeva
- Avoiding invasive dental procedures during treatment with Xgeva

Advise patients that denosumab is also marketed as Prolia™. Patients should inform their healthcare provider if they are taking Prolia.

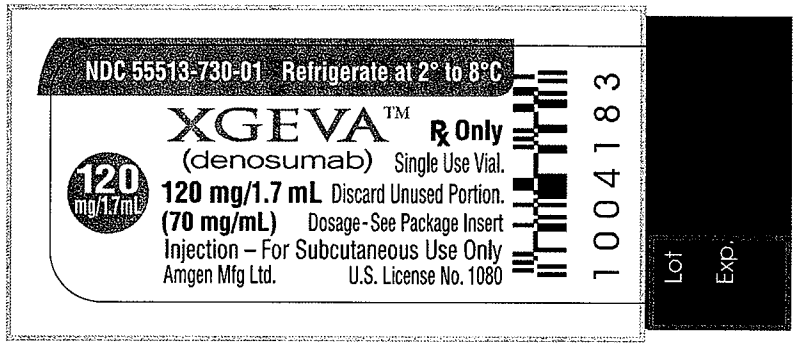
AMGEN®

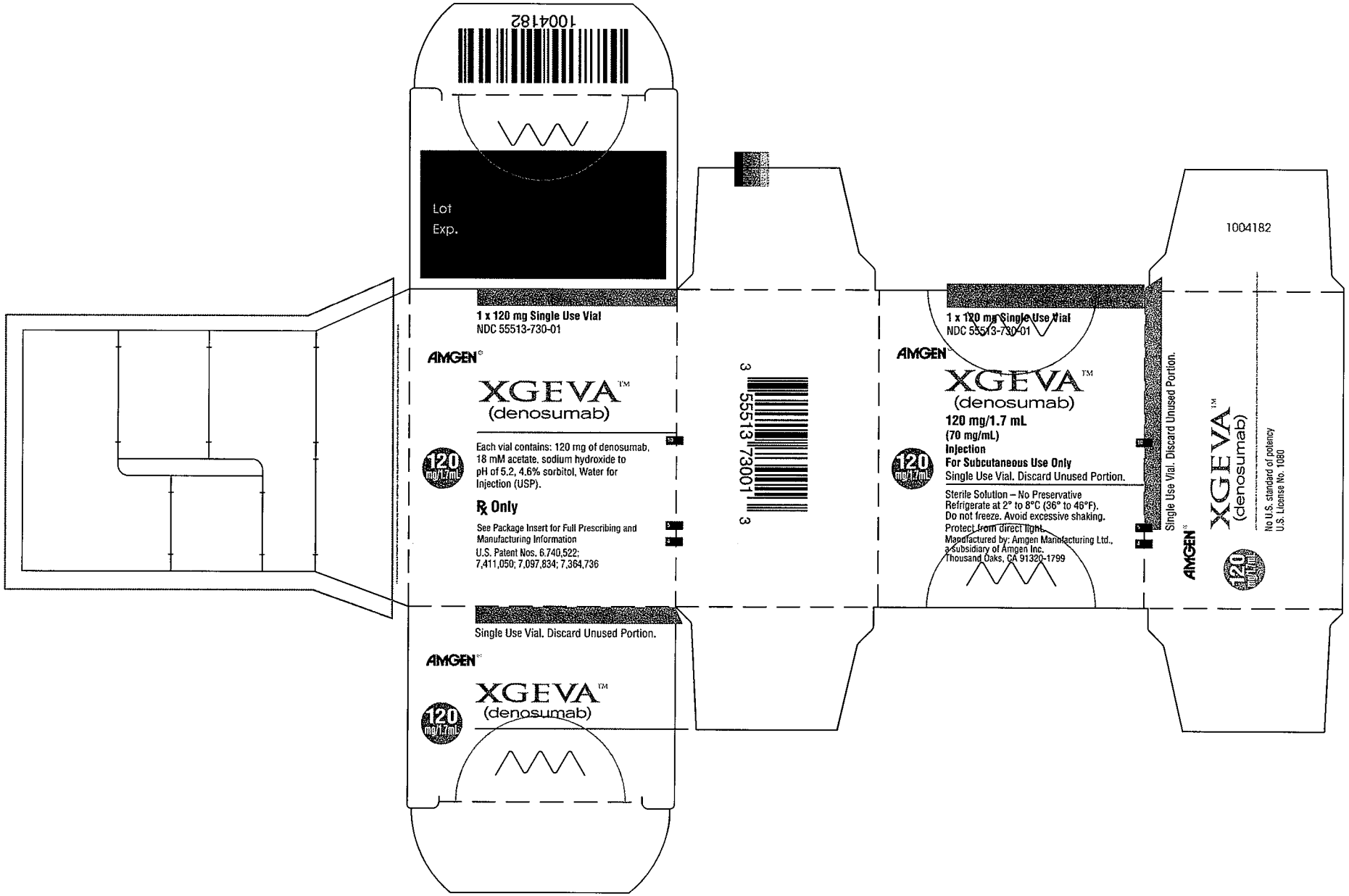
Xgeva™ (denosumab)

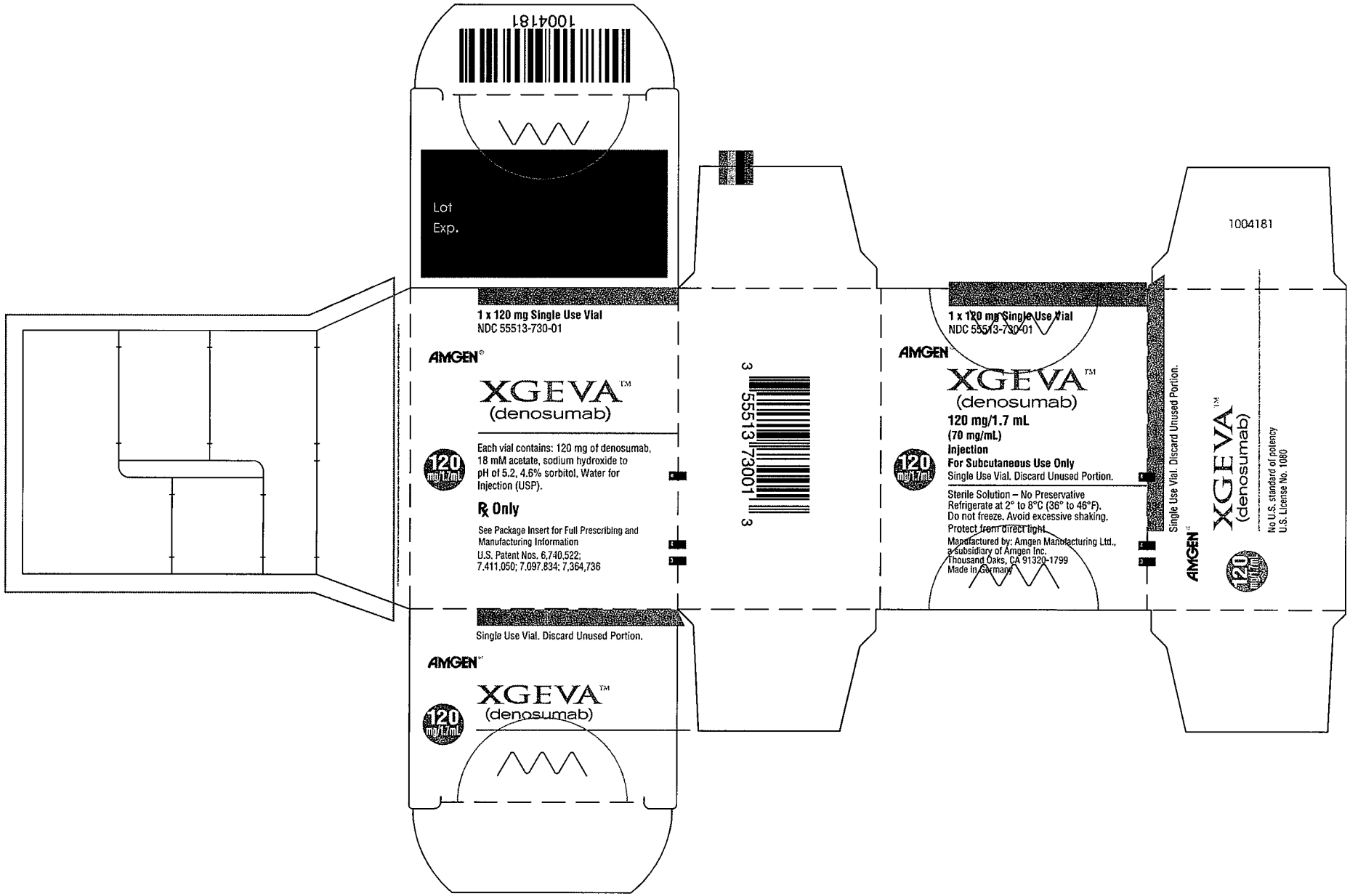
Manufactured by:
Amgen Manufacturing Limited, a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

This product, its production, and/or its use may be covered by one or more US Patents, including US Patent Nos. 6,740,522; 7,411,050; 7,097,834; and 7,364,736, as well as other patents or patents pending.

1xxxxx – v1







CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 18, 2010
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
BLA Supplement #	STN BL 125320/7
Applicant Name	Amgen, Inc.
Date of Submission	May 19, 2010
PDUFA Goal Date	November 18, 2010
Proprietary Name / Established (USAN) Name	Xgeva/ Denosumab
Dosage Forms / Strength	Solution in vials; 120 mg/1.7 mL
Proposed Indication(s)	(b) (4)
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Melanie Pierce
Medical Officer Review	Shan Pradhan & Michael Axelson
Statistical Review	Vivian Yuan & Jenny Zhang
Pharmacology Toxicology Review	Michael Orr
Supervisory Toxicology Review	Anne Pilaro
CMC Review/OBP Review	Sarah Kennett
Facilities Reviewer (DS)	Kalavati Suvarna
Facilities Reviewer (DP)	Don Obenhuber
Clinical Pharmacology Review	Stacey Shord
Biopharmaceutics Review	Bahru Habtemariam
DDMAC	Carole Broadnax
DSI	Lauren Iacono-Connors
CDTL Review	Steven Lemery
OSE/DMEPA	Carlos Mena-Grillasca; Judy Park; Latonia Ford
OSE/DRISK	Elizabeth Donohoe & Suzanne Robottom
OSE/Division of Epidemiology	Fatmatta Kuyateh
Maternal Health Team	Jeanine Best

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DS- drug substance
DP= drug product

Division Director Summary Review

1. Introduction

Denosumab is a human monoclonal IgG2 kappa antibody produced from genetically-engineered CHO cells. Denosumab binds specifically to the D-E loop of the human RANKL [Receptor Activator of Nuclear factor Kappa B ligand] and also cross-reacts with the RANKL in non-human primates. Upon binding to RANKL, denosumab prevents the binding of the ligand to RANK, which is expressed on osteoclasts and osteoclast precursors. By preventing this interaction, denosumab inhibits the formation, function and survival of osteoclasts which results from the RANKL- RANK binding. The resulting inhibition of osteoclast function (bone resorption) results in an increase in bone density.

Denosumab significantly inhibits bone resorption as determined by reduction in the Type 1 C-telopeptide (CTX1). The pharmacodynamic activity of denosumab can also be assessed through measurement of urinary N-terminal telopeptide, corrected for urinary creatinine (uNTx/uCr). The dose selected for clinical development in the proposed indication is based on a dose projected to result in complete saturation of RANKL binding and sustained inhibition of bone turnover as measured by uNTx/uCr.

This application is an efficacy supplement to a recently approved new molecular entity. Prolia® (denosumab) was approved on June 1, 2010 for the treatment of post-menopausal women with osteoporosis at high-risk for fracture at a recommended dose of 60 mg as a subcutaneous injection every 6 months. The approval for this indication was based on demonstration of significant reduction in the risk of vertebral fractures of three years.

All members of the review team recommended approval of this efficacy supplement and there are no unresolved issues which preclude approval. The proposed claim was for the (b) (4) (b) (4) however at FDA's request, the indication has been revised to accurately reflect the treatment effect on primary endpoint of the clinical efficacy trials (time-to-first skeletal-related event). The indication agreed-upon with Amgen is "for the prevention of skeletal-related events in patients with bone metastases from solid tumors."

The application was submitted on May 14, 2010 and received by FDA on May 19, 2010. The efficacy supplement is supported by the results of three randomized, multicenter, active-controlled trials conducted by Amgen, Inc., listed below.

- Protocol 20050103 entitled, "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer", which enrolled 1904 patients across 342 centers in 39 countries.

- Protocol 20050136 entitled, "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects with Advanced Breast Cancer", which enrolled 2049 patients across 322 centers in 35 countries.

- Protocol 20050244 entitled, "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma", which enrolled 1779 patients across 321 centers in 33 countries.

These trials were designed to demonstrate that denosumab is not inferior to zoledronic acid (Zometa®, an active control) for the composite efficacy endpoint of time-to-first skeletal-related event (SRE).

FDA granted marketing approval for two bisphosphonates (Aredia and Zometa) based on demonstration of a reduction in the incidence of skeletal-related events (SREs) and reduction in the time to an SRE in patients with multiple myeloma or solid tumors metastatic to bone. The composite endpoint of SRE is defined by the following events: radiation to metastatic lesions in the bone, pathological fracture, surgery for metastatic lesions in the bone, or spinal cord compression due to osseous metastases. In studies supporting approval of Aredia and Zometa as well as provided in this application, radiation to bone and pathological fractures were the most common SRE events.

The two issues to be discussed further in section 7 of this review are the use of a composite endpoint for demonstration of efficacy and the approach to demonstration of non-inferiority in the major efficacy studies.

2. Background

Two IND applications for denosumab were submitted on May 22, 2001: IND 9837 for the denosumab clinical development program for the treatment of osteoporosis in post-menopausal women and IND 9838 for the treatment of bone disease associated with cancer.

Clinical Development Program for denosumab for Treatment of Post-Menopausal Osteoporosis

The clinical development program conducted under IND 9837. On December 19, 2008, Amgen submitted a Biologics License Application (STN BL 125320) for denosumab for the following proposed indications:

- Treatment and prevention of osteoporosis in postmenopausal women
- Treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast and prostate cancer

The original BLA (STN BL 125320/0) was approved for the treatment of post-menopausal women with osteoporosis at high-risk for fracture. Other proposed claims (prevention of

osteoporosis in post-menopausal women, treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer, and treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer) will be reviewed under separate efficacy supplements to STN BL 125320.

The efficacy and safety of Prolia was demonstrated in a 3-year, randomized, double-blind, placebo-controlled trial that enrolled 7808 women who had a baseline BMD T-score between -2.5 and -4.0 at either the lumbar spine or total hip. These studies demonstrated that Prolia significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years. A Risk Evalaution and Mitigation Strategy (REMS), consisting of a Medication Guide, communication plan, and timetable for submission of assessments, was required due to the risks of serious infections including serious skin infections, dermatologic adverse events, and over-suppression of bone turnover. In addition, the following post-marketing trials were required:

- A retrospective cohort study to determine the incidence of serious skin infections, dermatologic adverse events, and over-suppression of bone turnover in women with post-menopausal osteoporosis.
- A long-term observational study to prospectively evaluate the incidence of serious skin infections, dermatologic adverse events, and over-suppression of bone turnover in post-menopausal women receiving Prolia.
- A long-term surveillance study to prospectively evaluate the incidence of serious skin infections, dermatologic adverse events, and over-suppression of bone turnover in post-menopausal women receiving Prolia.

Prior Approvals Based on the Composite Endpoint of Skeletal-Related Events

On July 16, 1996, Aredia® was approved for the expanded indication "Aredia is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. The Aredia treatment effect appeared to be smaller in the study of breast cancer patients receiving hormonal therapy than in the study of those receiving chemotherapy, however, overall evidence of clinical benefit has been demonstrated." Approval was based on a randomized, placebo-controlled trial in patients with multiple myeloma and two randomized, placebo-controlled trials in patients with breast cancer metastatic to the bone (MBC) receiving concurrent chemotherapy or concurrent hormonal therapy, respectively.

All three trials demonstrated a reduction in the incidence of SREs for the palmidronate arm compared to placebo for patients with multiple myeloma (24% vs. 41%; $p < 0.001$), MBC receiving concurrent chemotherapy (46% vs. 65%; $p < 0.001$), and MBC receiving concurrent hormonal therapy (55% vs. 63%, $p = 0.094$). There was also a consistent delay in time-to-first SRE in patients with MBC receiving concurrent chemotherapy (13.9 mos vs. 7.0 mos, $p<0.001$) or hormonal therapy (10.9 mos vs 7.4 mos; p-0.118).

On February 22, 2002, Zometa® was approved for the expanded indication "for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have

progressed after treatment with at least one hormonal therapy". The approval was based on the results of a randomized, active-controlled (palmidronate) trial conducted in patients with breast cancer metastatic to bone and in patients with multiple myeloma and two randomized, placebo-controlled trials in patients with prostate cancer who had documentation of previous bone metastases and 3 consecutive rising PSAs while on hormonal therapy and in patients with solid tumor study with bone metastases from malignancies other than breast cancer and prostate cancer. Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in antineoplastic therapy due to increased pain was an SRE in the prostate cancer study only. Planned analyses included the proportion of patients with an SRE during the study (the primary endpoint) and time to first SRE. In the breast cancer /myeloma trial, efficacy was determined by a non-inferiority analysis comparing Zometa to pamidronate 90 mg for the proportion of patients with an SRE. The estimation of the treatment effect of pamidronate was based on historical data in 3 randomized placebo-controlled trials of palmidronate that enrolled a total of 1128 patients. The reduction in the proportion of patients with an SRE among palmidronate-treated patients was estimated to be 13.1% (95% CI: 7.3%, 18.9%).

The two placebo-controlled trials revealed a consistent reduction in the proportion of patients with an SRE for the zoledronic acid arm compared to controls that was significant in patients with prostate cancer (33% vs 44%, p=0.21) but not significant for patients with solid tumors other than breast or prostate cancer (38% vs. 44%, p=0.13). In both trials there was a delay in the time-to-first SRE for the for the zoledronic acid arm compared to controls in both the prostate cancer trial (HR 0.67; p=0.11, median time-to-first SRE not reached in Zometa arm vs. 321 days in control) and the solid tumor trial (HR 0.73; p=0.023, median times to first SRE 230 days vs. 163 days).

In the active-controlled trial, the proportion of patients with an SRE as 44% for patients in the zoledronic acid arm as compared to 46% in the palmindronate arm, with a difference in incidence of -2% (95% CI around the difference -7.9% and 3.7%); based on these results, more than half of the estimated treatment effect of palmidronate (13% reduction in proportion of patients with SREs) was retained. The time to first SRE was not different with median times to first SRE of 373 days for the zoledronic acid arm and 363 days for the palmidronate arm, [HR 0.92 (95% CI : 0.77, 1.09)].

Clinical Development Program for denosumab for Prevention of Skeletal-Related Events

On September 20, 2005, an end-of-Phase 2 meeting was held to discuss the adequacy of Protocols 20050103 and 20050136 to support labeling claims for denosumab for the proposed indication of "(b) (4) ". With regard to claims for prevention of SREs, FDA stated that the primary endpoint should be the time-to-first on-study SRE, that Amgen's proposed primary analysis method (the synthesis method for non-inferiority, was acceptable as was the proposed to use the Hochberg procedure for control of Type I error rate for secondary endpoints. FDA further agreed that if non-inferiority was demonstrated on the primary endpoint, then testing for superiority on time-to-SRE would be

acceptable. However FDA cautioned that in order to demonstrate a robust effect on the primary endpoint, the results of the NI analyses in the intent-to-treat and per-protocol populations should be similar. With regard to the proposed non-inferiority margins for Protocols 20050103, FDA stated agreement with the margin but for Protocol 20050136, FDA noted that they could not duplicate the calculations provided but agreed that a protocol with 80% power, at a denosumab vs. zoledronic acid hazard ratio of 0.9, to rule out with at least 97.5% confidence that the denosumab vs. zoledronic acid hazard ratio is 1.11 or greater would be acceptable. (b) (4)

On Nov. 1, 2006, FDA provided written advice regarding the additional clinical protocol (Protocol 20050244 submitted on May 2, 2006. FDA advised that they "[did] not object to using a synthesis method for the primary analysis. However, the meta-analysis used to estimate the zoledronate effect uses patients having a wide variety of diseases. Direct and indirect comparisons were also used to determine the zoledronate effect. The patient population for which the estimate from the meta-analysis is unbiased and valid may not be the same as the patient population used for study 20050244. It is not clear that the estimate of the zoledronate effect from the meta-analysis is directly transferable to the current trial. A quality assessment should be done of the transferability to this trial of the estimated pamidronate versus placebo effect on the time to first skeletal-related event. Such an assessment cannot be made until after study 20050244 is complete. Also, the reproducibility of the effectiveness of denosumab would need to be studied from the results of trials comparing Denosumab with zoledronate and studying the reproducibility of the zoledronate effect. The robustness of the results should also be evaluated in a determination of efficacy."

Amgen met with FDA on December 8, 2006 and on July 8, 2008 to reach agreements regarding the comparability data necessary to support a new concentration (70 mg/mL) and dosage strength (120 mg per 1.7 mL) and the stability and analytical assessments necessary to support a new presentation (prefilled syringe). The new dosage strength, concentration, and presentation were to be used only for the proposed indication of prevention of skeletal-related events.

A pre-BLA meeting was held on January 30, 2009, to discuss the content of an application for the use of denosumab (proposed trade name AMGIVA™) in (b) (4) (b) (4)
This supplemental application was to be based on the results of Protocols 20050136 and 20050244 which were expected to be available by Q2 2009 and Q3 2009, respectively. If available at the time of the 120-day update, Amgen proposed to also provide the results from the primary analysis of Study 20050103. Since the data were not available, the meeting focused on issues of organization of integrated safety and efficacy analyses and extent of safety data to be provided. FDA agreed that Amgen would not be required to submit individual radiologic images and that submission of datasets in CDISC was acceptable. FDA also agreed that the supplemental application should include only the drug substance and drug product information that would be required for registration of the 70 mg/ml vial presentation and requested that the supplement clearly delineate CMC information unique to this supplement and that which was identical to information contained in STN 125320. At FDA's

request, Amgen agreed to include a complete dossier of the available nonclinical data and to clearly identify new information (not contained in the original BLA) and information previously submitted in support of the post-menopausal osteoporosis and hormonal ablation therapy indications.

The data cut-off dates for the final analysis of Protocol 20050136 occurred in March 2009, for Protocol 20050244 in April 2009, and for Protocol 20050103 in October 2009.

On April 13, 2010, Amgen provided a meeting package summarizing the quality, nonclinical, and clinical content of the BLA to be based on the results of studies 20050136, 20050244, and 20050103 for the [redacted] (b) (4). Amgen confirmed their intent to submit a stand-alone biologics license application for denosumab under the proprietary name AMGIVA™ for the treatment of patients with bone metastases from solid tumors. FDA and Amgen reached agreement on the proposed content and structure of the BLA submission. In addition, Amgen agreed to provide the clinical study reports incorporating data from the ongoing extension phase for study 20050103 once that phase is complete. Amgen also agreed to provide the results from both the Cox and log-rank tests in the summary of efficacy as well as integrated datasets. With regard to the requirement for a REMS (Medication Guide and communication plan), FDA stated that the need for a medication guide will be a review issue.

The application was submitted on May 14, 2010 and received by FDA on May 19, 2010; it was assigned the submission tracking number (STN) BL 125355, however upon approval of denosumab for the treatment of post-menopausal osteoporosis on June 1, 2010, under STN BL 125320, the application that is the subject of this review was re-coded as a supplement (STN BL 125320/7) to the approved BLA.

The application was designated as a priority review based on the claims of an advance over available therapy [zoledronic acid (Zometa®)] reported for two of the three major efficacy trials in the supplement. The application was filed on July 16, 2010.

The application was amended multiple times (July 26 and 29, 2010; August 5, 18, 23, 24, 25 and 31, 2010; September 8, 10, and 22, 2010, and October 12, 22, 27, 28, and 29, 2010) during the review for administrative reasons and in response to information requests from FDA.

3. CMC/Device

I concur with the conclusions reached by the quality reviewer and the facilities reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. All manufacturing site inspections were acceptable. The supplement relied primarily on quality data provided in the original BLA supporting approval of denosumab solution at a concentration of 60 mg/mL supplied in vials and pre-filled syringes and on comparability of quality characteristics for the current strength (120 mg) and concentration (70 mg/mL) to that approved in original BLA. Additional information to support minor manufacturing changes. Stability testing supports the proposed expiry dating for this strength. Amgen's request for

waiver for categorical exclusion from environmental assessment was granted. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology or toxicology issues that preclude approval. There were no new nonclinical toxicology or safety pharmacology data provided in this supplement. The OPG-Fc (osteoprotegrin-Fc) rodent animal model was used to investigate the effects of RNAK-L inhibition, as denosumab-binding is restricted to human and non-human primates. This OPG-Fc rodent model has been determined to be an appropriate surrogate for denosumab. Nonclinical studies using OPG-Fc alone or in combination with chemotherapy in human xenograft tumor models and investigative studies of OPG-Fc and vascular endothelial growth factor B in rats were provided in the supplement. Studies of OPG-Fc in the nude mouse/tumor xenograft model indicated that inhibition of RANKL does not inhibit tumor growth but did decrease the size of osteolytic lesions at sites of bone metastases. Rodent studies with OPG-Fc and VEGF conducted to investigate effects of RANKL inhibition on the cornea were inconclusive in determining whether such inhibition results in corneal pathology, as observed in toxicology studies in cynomolgus monkeys treated with denosumab.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology and biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

Data supporting the original BLA noted that pharmacokinetics were best characterized by a two-compartment model and the exposure increased in a linear, dose-proportional manner over a range of 60-210 mg. Clearance mediated by target antigen (RANKL)-binding was more rapid at lower concentrations, indicated saturation of binding at denosumab concentrations above 1 mcg/mL.

Denosumab significantly inhibits bone resorption as determined by reduction in serum levels of Type 1 C-telopeptide (CTX1). The onset of action is rapid with 70% reduction of CTX1 levels from pretreatment levels within 6 hours of administration of 60 mg of denosumab as a SC injection. The reduction in serum CTX1 is persistent for up to 6 months.

The dose of denosumab, 120 mg administered every four weeks, utilized in clinical studies supporting the proposed new indication (prevention of SREs) is higher than the recommended dose approved for Prolia for the treatment of osteoporosis. In dose-finding, tolerability and activity-estimating clinical trials, doses of 30 to 180 mg administered at 4- week and 12-week intervals were determined to be tolerable and active, however the Amgen tested doses ranging from 30 mg to 180 mg administered subcutaneously (SC) every 4 weeks or every 12 weeks. The maximum tolerated dose was not reached. Amgen states that the dose (120 mg every 4 weeks) used in pivotal efficacy trials for prevention of SRE was selected based on maximal

reduction of bone turnover using the biomarker urinary N-terminal telopeptide, corrected for urinary creatinine (uNTx/uCr). Amgen determined that the every 12 week dosing schedule did not result in sustained reductions in uNTx/Cr.

The pharmacokinetics data of denosumab were also evaluated in dose-ranging, activity estimating study in 255 women with breast cancer metastatic to bone. Patients were randomized to one of six arms: denosumab at doses of 30 mg, 120 mg, or 180 mg SC every four weeks or densoumab at 60 mg or 180 mg SC every 12 weeks) or zoledronic acid every four weeks. Based on these data, the mean C_{max} following a 120 mg dose of denosumab was 13.5 mcg/mL, and the terminal elimination half-life was 28.8 days following multiple doses.

In a population PK analysis conducted in patients enrolled in the major efficacy trials, bioavailability was estimated to be 62% and the beta elimination half-life was 38 days (at higher doses) once non-linear target mediated clearance was saturated. The population PK analysis also demonstrated an inverse relationship between exposure (estimated from trough concentrations) and BSA and weight as well as difference in exposure based on tumor type (higher clearance resulting in lower exposure in patients with multiple myeloma) but did not identify differences in exposure based on gender, race, or age (adults < 65 yrs compared to adults ≥ 65 years)

The clinical pharmacology reviewer concluded that there is evidence of an exposure-response (ER) relationship for effectiveness based on subset analyses of the major efficacy trials in which trough concentrations for denosumab were obtained in 183 patients. In exploratory analyses, the probability of development an SRE decreased with increasing denosumab trough concentrations; this relationship appeared to be linear across quartiles defined by trough concentrations (46 patients per quartile over a trough concentrations ranging from approximately 10,000 ng/mL to approximately 30,000 ng/mL). In this subset analysis, patients with trough levels above the median for the study population had longer time-to-first SRE than the overall experience in the control population, however those with trough concentrations below the median appeared to have a similar time-to-first SRE as compared to the control population, based on visual inspection of figure 3 in the clinical pharmacology review. The clinical pharmacologists concluded that no modifications for pharmacokinetically-guided or weight-adjusted dosing appear necessary. I concur with these conclusions, given the small numbers of patients in the subset, the exploratory nature of the analysis and comparison, the consistency of effect on biomarkers of bone resorption across a very broad dose range (30-180 mg every 4 weeks), and inspection of the curves that suggest that patients with lower denosumab exposure (below the median) have a time-to-first SRE that is similar to the active control. It is also notable that in exploration of exposure-response relationships in clinical trials of denosumab for the treatment of post-menopausal osteoporosis demonstration that body weight was a covariate for clearance however body weight did not appear to be an important factor in characterizing the exposure-response relationship with regard to incidence of new verterbral fractures over 3 years or change in bone mineral density.

With regard to ER relationships for toxic effects, based on assessments from the 183-patient subset from the major efficacy trials, there was no evidence of an exposure-response for the risk of hypocalcemia. An assessment of effects on cardiac conduction through serial ECG

assessments was obtained in 255 women with metastatic breast cancer enrolled in the dose-ranging, active controlled trial (20040113), there was no evidence of an effect on QTc interval.

6. Clinical Microbiology

There was no clinical microbiology review conducted or required for review of this application. Microbial sterility was conducted as part of the CMC evaluation of this application and is discussed in section 3 of this review.

7. Clinical/Statistical-Efficacy

The clinical development program establishing safety and efficacy is supported by three large, multinational, randomized (1:1), double-blind, double-dummy, active-controlled trials. FDA concurred with the acceptability of the trial designs and analysis plans prior to initiation of the trials, with caveats to be discussed with the efficacy results. The reduction in the incidence of the composite clinical endpoint, skeletal-related events, has been previously determined by FDA to be a direct measure of clinical benefit; this composite endpoint was used as the primary basis for approval of two bisphosphonates (Zometa and Aredia) based on demonstration of reduction in the proportion of patients with a skeletal-related event. The trials were well-conducted and as a whole, provide substantial evidence of efficacy for denosumab.

In general, the trials were very similar in design and differed primarily in eligibility criteria for underlying disease and stratification factors for randomization specific to the underlying primary cancer. Eligibility for Protocol 20050103 was restricted to patients with castrate-resistant prostate cancer, eligibility to Protocol 20050136 was restricted to patients with breast cancer, and eligibility to Protocol 20050244 excluded enrollment of patients with either breast or prostate cancer, but permitted enrollment of patients with other solid tumors and patients with multiple myeloma.

All trials required that patients have radiological evidence of at least one osseous metastasis or a lytic lesion from multiple myeloma, creatinine clearance $\geq$ 30 mL/min, and corrected (for serum albumin level) serum calcium of $\geq$ 8 mg/dL. Patients with hypercalcemia, prior intravenous bisphosphonate use, planned radiation or surgery to bone, osteonecrosis of the jaw, active dental condition requiring surgery, or a planned invasive dental procedure during the course of the study. Patients who received prior oral bisphonates for prevention of skeletal-related events were eligible.

Treatment consisted of denosumab 120 mg by subcutaneous (SC) injection and IV placebo for zoledronic acid every four weeks or zoledronic acid (dose reduced for reduced renal function) 4 mg intravenously (IV) and SQ placebo for denosumab every four weeks until toxicity or study termination. Patients were encouraged to continue taking the investigational products following the first skeletal-related event, in order to assess the durability of the treatment effect

beyond the first event. In order to maintain the study blind, dose modification rules were based on the presumption that all patients were receiving zoledronic acid and denosumab; both drug/placebo were held for ≥ Grade 3 toxicity attributed by the investigators to study drug and IV zoledronic acid/placebo were held for renal toxicity.

Supplementation with oral calcium and vitamin D was recommended but not required.
The primary endpoint of the three efficacy studies was non-inferiority in time-to-first on-study SRE, as determined by an independent radiology review committee assessed radiographs to confirm pathological fractures and spinal cord compression events. Events included in the composite endpoint were radiation to bone, pathological fracture, surgery to bone, or spinal cord compression. If more than one event occurred on the same date, the SRE-defining event was identified according to the following protocol-specified, hierarchal order:spinal chord compression, surgery, fracture, radiation.

Secondary endpoints included

- Superior time-to-first SRE
- Time to first and subsequent SRE

The statistical analysis plans for each protocol identified two secondary endpoints that were to be tested only if denosumab was found to be non-inferior to zoledronic acid in the primary efficacy analysis. The SAPs specified that the Hochberg procedure would be used to adjust for multiplicity to maintain an overall significance level of 0.05, two-sided.

Additional analysis included a comparison of overall survival and a comparison of progression-free survival for safety purposes (to evaluate for potential adverse consequences).

With regard to acceptability of the non-inferiority comparisons, FDA agreed that the synthesis approach was acceptable but expressed concerns regarding the reliability of the estimated treatment effect of zoledronic acid. These concerns are included

- Uncertainty with regard to the precision (or variability) of the estimate of zoledronic acid effect derived from the meta-analysis of clinical trials which were not optimal or designed for estimating this effect.

  The estimated zoledronic acid treatment effect used in Protocol 20050136 for determination on the NI margin for time to first on-study SRE of placebo versus zoledronic acid was based on four historical trials conducted in patients with advanced breast cancer: the Novartis 010, Novartis 019, and Novartis 018 trials and the Japan 1501 trial. Only one of these trials, the Japan 1501 trial, compared the treatment effect of zoledronic acid against a placebo control using a multiple events analysis. Novartis 019 and 018 did not utilize zoledronic acid, and the Novartis 010 trial was a non-inferiority comparison of palmidronate and zoledronic acid. Amgen employed a step-wise procedure to first estimate the pamidronate treatment effect relative to placebo in the Novartis 019 and 018 trials. The second step was to combine this information with the Novartis 010 trial results in order to estimate the zoledronic acid treatment effect relative to placebo.

Since three of the four trials did not directly assess the zoledonic acid treatment effect relative to placebo, one of the four trials relied on non-inferiority, and individual trials were generally small (small sample size), the pooled hazard ratio 1.58 of placebo relative to zoledronic acid with a 95% CI (1.23, 2.02) lacks precision, reliability and robustness.

The estimated zoledronic acid treatment effect used in Protocol 20050244 for determination on the NI margin for time to first on-study SRE of placebo versus zoledronic acid was based on three historical trials: the Novartis 010, Novartis 011, and Novartis 012 trials. Novartis 011 compared the treatment effect of zoledronic with placebo in patients with solid tumors and Novartis 012 trial established the treatment effect of pamidronate with placebo in patients with multiple myeloma, while the Novartis 010 trial was a non-inferiority comparison of palmidronate and zoledronic acid conducted in patients with breast cancer. Amgen again employed a step-wise procedure with sequential pooling of data beginning with Novartis 012, then Novartis 010, and finally including data from Novartis 011 in order to estimate the zolendromic acid treatment effect Since only one of three trials (Novartix 011) directly compared the zoledronic acid treatment effect to placebo, one trial relied on non-inferiority and the individual trials were generally small, the pooled hazard ratio 1.40 of placebo relative to zoledronic acid with a 95% CI (1.11, 1.77) was also considered not to be well-estimated, and lacking in precision, reliability and robustness.

The estimated zoledronic acid treatment effect used in Protocol 20050103 for determination on the NI margin for time to first on-study SRE of placebo versus zoledronic acid was based on a single historical trials: Novartis 039 trial, which compared zoledronic acid with placebo in patients with prostate cancer, in which the hazard ratio for time-to-first SRE was 1.477 (95% CI:1.10, 1.98) for placebo relative to zoledronic acid. Since there is only a single trial, there is no objective assessment of study-to-study variability.

- A second issue with regard to acceptability of applications based on non-inferiority trials is establishing that the constancy assumption (that effect size remains constant between historical trials and the NI trial) is correct. Since this can generally not be proven, NI trials should attempt to control for factors that might alter the effect size by utilizing the same trial design features (patient eligibility criteria, adjunctive treatment, same method and timing of assessments) in the NI trial as the historical trials. Evidence that the NI trials differ from historical trials in patient characteristics or patient management undermines confidence in the constancy assumption.

- The third issue with regard to acceptability of applications based on non-inferiority trials is the approach to selection of a non-inferiority margin that preserves a clinically meaningful effect. In this application, using the synthesis method, all three trials planned to preserve at least 50% of zoledronic acid effect. The synthesis method is designed to directly address the question of whether the test product would have been superior to a placebo had a placebo been in the NI trial as well as to assess the fraction of the zelodronic acid treatment effect that is preserved in denosumab-treated patients. In the synthesis approach, the NI margin is not predetermined and the synthesis method can not generate a fixed margin, therefore evaluation of the percentage of zelodronic acid treatment effect that is retained occurs after the trial is completed. Because zelodronic acid effects were not well-estimated, use of the

synthesis method rather than pre-selection of an appropriate margin was considered by FDA to be an acceptable methodology for comparisons of the two treatment arms.

- The fourth issue with regard to acceptability of applications based on non-inferiority trials is the ability to demonstrate that the treatment effect is robust. Where there is uncertainty about the historical effect size, more than one NI trial should be provided to support effectiveness.

Although some of these issues were adequately addressed, FDA raised concerns in presubmission meetings and communcations regarding lack of confidence in an accurate and robust estimation of the treatment effect for purposes of establishing non-inferiority. FDA stated that a conclusion that substantial evidence of efficacy was established would be contingent on the trial results.

Efficacy Results

Protocol 20050103 enrolled 1904 patients with metastatic prostate cancer from 342 centers in 39 countries. Patients were accrued between May 12, 2006 and December 18, 2008. The data cut-off date for the primary efficacy analysis was October 30, 2009.

Protocol 20050136 enrolled 2049 patients with metastatic breast cancer from 322 centers in 35 countries between April 27, 2006 and December 31, 2008. The data cut-off date for the primary efficacy analysis was April 30, 2009.

Protocol 20050244 enrolled Bone Metastases in Subjects with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma", which enrolled 1779 patients with solid tumor metastatic to bone or multiple myeloma from 321 centers in 33 countries. Patients were accrued between June 21, 2006 and May 16, 2008. The data cut-off date for the final efficacy analysis was March 6, 2009.

Key demographics and baseline tumor characteristics are summarized in the next two tables (abstracted from the Clinical Review). The three trials differed with regard to patient population in that those in Protocol 20050103 were all male and were generally older than in the other two trials while those in Protocol 20050136 were nearly all female. The populations also differed in the type of osseous metastases, with 20050103 having the highest proportion of patients with osteoblastic disease and those in 20050244 having the highest proportion of osteolytic disease, as might be predicted by the underlying cancer primary (prostate and multiple myeloma).

Demographics	Trial 103		Trial 136		Trial 244		Total All Studies
	D	ZA	D	ZA	D	ZA	D and ZA
	n=950 (%)	n=951 (%)	n=1026 (%)	n=1020 (%)	n=886 (%)	n=890 (%)	n=5732 (%)
Age (years)							
Min	40	38	27	24	18	22	18
Median	71	71	57	56	60	61	63
Max	93	91	91	90	89	87	93
Age ≥75	(35.6)	(36.5)	(5.9)	(6.2)	(8.4)	(8.3)	(16.7)
Age ≥ 65	(73.4)	(77.3)	(26.8)	(26.1)	(33.7)	(37.6)	(45.5)
Gender							
Male	(100.0)	(100.0)	(0.8)	(0.9)	(66.4)	(61.9)	(53.3)
Female	0	0	(99.1)	(99.0)	(33.6)	(37.8)	(46.4)
Race							
White	(87.3)	(85.2)	(80.0)	(79.6)	(86.9)	(86.2)	(83.9)
Hispanic or Latino	(4.7)	(6.0)	(5.8)	(5.8)	(5.5)	(4.0)	(5.3)
Asian	(2.3)	(2.7)	(3.1)	(3.6)	(4.1)	(4.9)	(3.4)
Black	(4.0)	(3.7)	(2.5)	(2.5)	(2.3)	(3.3)	(3.0)
Japanese	(0.0)	(0.0)	(6.8)	(6.8)	(0.3)	(0.1)	(2.5)
Other	(1.6)	(2.3)	(1.6)	(1.6)	(0.9)	(0.9)	(1.5)
Native Hawaiian or Other Pacific Islander	(0.1)	(0.1)	(0.1)	(0.1)	(0.0)	(0.0)	(0.1)
American Indian or Alaska Native	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.2)	(0.0)
Region							
Europe	(55.2)	(53.1)	(52.1)	(51.1)	(55.4)	(53.8)	(53.3)
North America	(17.9)	(17.8)	(18.9)	(18.4)	(22.2)	(23.4)	(19.6)
Latin America	(20.3)	(21.1)	(16.9)	(17.3)	(16.5)	(14.6)	(17.8)
Other	(6.6)	(8.0)	(12.0)	(13.1)	(5.9)	(7.9)	(9.0)

Disease Characteristics	Trial 103		Trial 136		Trial 244		Subjects
	D	ZA	D	ZA	D	ZA	
	n= 950 (%)	n= 951 (%)	n=1026 (%)	n=1020 (%)	n=886 (%)	n=890 (%)	n=5732 (%)
History of SRE							
N	(74.0)	(74.0)	(59.5)	(58.1)	(49.3)	(45.5)	(60.2)
Y	(26.0)	(26.0)	(40.4)	(41.8)	(50.7)	(54.2)	(39.5)
Lesion Type							
Osteoblastic	(63.3)	(56.5)	(27.4)	(27.9)	(17.0)	(14.6)	(34.6)
Not Seen	(19.8)	(23.4)	(32.7)	(32.8)	(43.1)	(43.5)	(32.3)
Mixed	(13.5)	(15.8)	(24.8)	(25.1)	(17.5)	(17.4)	(19.2)
Osteolytic	(3.4)	(4.1)	(14.8)	(13.6)	(22.1)	(23.6)	(13.4)
Unable to Evaluate	(0.1)	(0.2)	(0.3)	(0.4)	(0.2)	(0.6)	(0.3)
ECOG							
1	(48.8)	(48.4)	(44.0)	(43.5)	(57.3)	(55.3)	(49.2)
0	(44.0)	(44.8)	(49.1)	(47.8)	(27.1)	(26.5)	(40.3)
2	(7.2)	(6.8)	(6.6)	(8.0)	(15.3)	(17.6)	(10.0)
Missing	(0.0)	(0.0)	(0.1)	(0.3)	(0.2)	(0.2)	(0.1)
3	(0.0)	(0.0)	(0.1)	(0.2)	(0.0)	(0.0)	(0.1)
Visceral Mets							
N	(83.1)	(81.0)	(46.2)	(48.4)	(46.5)	(49.6)	(59)
Y	(16.9)	(19.0)	(53.7)	(51.5)	(53.5)	(50.1)	(41)
Gleason Score							
2-6	(18.4)	(18.9)					
7	(28.7)	(29.4)					
8-10	(41.5)	(42.9)					
Missing	(11.4)	(8.7)					
Menopause Status							
Y			(81.8)	(81.6)	(27.8)	(32.9)	
Missing			(0.3)	(0.2)	(66.8)	(62.4)	
N			(16.6)	(16.9)	(4.7)	(4.4)	
N/A			(1.4)	(1.4)	(0.7)	(0.3)	

All three studies met the primary endpoint, demonstrating that denosumab is non-inferior to zoledronic acid in the time-to-first skeletal-related event. In addition, two of the trials (20050103 and 20050136) demonstrated that denosumab significantly delayed the time to first SRE as compared to zoledronic acid. For the third trial, the p-value, adjusted by the Hochberg procedure for multiple testing, did not demonstrate superiority at a two-sided 0.05 level, however the unadjusted p-value was less than 0.05 (p= 0.03, unadjusted). The consistency of the findings with demonstration of superior results in two of the three studies are sufficient to establish the clinical benefit without the need to characterize or rely upon preservation of the treatment effect of zoledronic acid. In addition, the effects on the primary endpoint are supported by a significant prolongation in the time to first and subsequent SRE as well as the lower proportion of patients with an SRE in the denosumab arm compared to the zoledronic acid arm across all three studies. The efficacy results are summarized in the following table.

Table 2. Efficacy Results for Xgeva Compared to Zoledronic Acid in Patients with Advanced Malignancies Involving Bone

	Trial 1 Metastatic Breast Cancer		Trial 2 Metastatic Solid Tumors or Multiple Myeloma		Trial 3 Metastatic CRPC[a]	
	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid
N	1026	1020	886	890	950	951
First On-study SRE						
Number of Patients who had SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
Radiation to Bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
Pathological Fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
Surgery to Bone	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)
Spinal Cord Compression	9 (0.9)	7 (0.7)	24 (2.7)	21 (2.4)	26 (2.7)	36 (3.8)
Median Time to SRE (months)	NR[b]	26.4	20.5	16.3	20.7	17.1
Hazard Ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Noninferiority p-value	< 0.001		< 0.001		< 0.001	
Superiority p-value[c]	0.010		0.060		0.008	
First and Subsequent SRE[d]						
Mean Number/Patient	0.46	0.60	0.44	0.49	0.52	0.61
Rate Ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)	
Superiority p-value[c]	0.001		0.145		0.009	

[a]CRPC = castrate-resistant prostate cancer.
[b]NR = not reached.
[c]Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid within trial.
[d]All skeletal events postrandomization; new events defined by occurrence ≥ 21 days after preceding event.
[e]Adjusted p-values are presented.

8. Safety

The application contained sufficient safety data to adequately characterize the risks to the indicated population. The primary source of safety supporting the recommended dose of 120 mg subcutaneously every 4 weeks, which is both a higher dose and more frequent schedule than in the initial approval, was derived from 2841 denosumab-treated patients enrolled in the three randomized, double-dummy, active-controlled trials which established efficacy;. In all three studies, the dose of denosumab was 120 mg administered subcutaneously (SC) every 4 weeks and the active control was zoledronic acid at a dose of 4 mg intravenously every 4 weeks.

Key eligibility criteria for these studies included a requirement for creatinine clearance of ≥30 mL/min, corrected serum calcium of 8-11.5 mg/dL, no prior history of bisphosphonate use, no prior history of osteonecrosis of the jaw (ONJ), and no planned or recently completed dental surgery.

The median duration of exposure to denosumab varied from 7 months in Protocol 2050244 to 12 months in Protocol 20050103 to 17 months in Protocol 20050136. Among the 2841 patients treated with one or more doses of denosumab, 46% were female, 85% were White, 5% Hispanic/Latino, 6% Asian, and 3% Black. The median age was 63 years (range 18 – 93). Seventy-five percent of denosumab-treated patients also received concomitant chemotherapy.

The attribution of adverse reactions to denosumab were based on occurrence of the event at an higher incidence in denosumab-treated patients compared to zoledronic acid-treated patients or at the same incidence as adverse reactions of zoledronic acid as listed in the Zometa product label. The most common adverse reactions of denosumab, occurring in greater than 10% of patients were fatigue (46%), hypophosphatemia (32%), nausea (31%), dyspnea (21%), diarrhea (20%), hypocalcemia (18%), cough (15%), and headache (13%). The most serious adverse reactions of denosumab were dyspnea and ONJ.

Adverse reactions occurring at a clinically important higher rate in denosumab-treated patients were hypocalcemia (18% vs. 9%), hypophosphatemia (32% vs. 20%), and ONJ (1.8% vs. 1.3%). Severe hypocalcemia, defined as corrected serum calcium of < 7 mg/dL and severe hypophosphatemia (<2 mg/dL) were also more common in denosumab-treated patients [(3.1% vs. 1.3%, severe hypocalcemia) and (15.4% vs. 7.4%, severe phosphatemia)]. Based on pharmacokinetic studies conducted in patients with various levels of renal insufficiency, the risks of hypocalcemia appears to be increased in patients with creatinine clearances of less than 30 mL/min; this finding is not due to difference in pharmacokinetics of denosumab in patients with renal impairment.

While the incidence of ONJ was higher in denosumab-treated patients, the requirement for surgical management of ONJ was similar in the denosumab- and zoledronic acid-treated patients.

As noted by in the clinical review and CDTL reviews, exploratory analyses of progression-free survival and overall survival were conducted to evaluate for possible risks. The design of these studies was not optimal for assessment of progression-free survival since eligibility criteria did not limit entry for all relevant prognostic characteristics nor did the randomization plan stratify for all relevant variables for a given tumor type. With these caveats, there was no evidence of an adverse effect on tumor growth rate or impairment of PFS among denosumab-treated patients compared to the control arm. Similarly, analyses of overall survival did not suggest adverse impact on survival with one exception. In an exploratory subset analysis conducted in 180 patients with multiple myeloma enrolled in Protocol 20050244, the results suggested poorer survival for patients receiving denosumab with a hazard ratio of 2.26 (95% CI: 1.13, 4.50). These findings are not considered definitive due to the exploratory nature of the analysis. However, as noted below, pending more definitive data, product labeling includes a limitation of use stating that Xgeva is not indicated for the prevention of SRE in patients with multiple myeloma.

A total of 2758 patients were evaluated for evidence of an immune response to denosumab. The rate of development of a binding antibodies directed against denosumab was approximately 1%, as detected by a sensitive electrochemiluminescent bridging immunoassay. Among patients with evidence of binding antibodies, no patient developed neutralizing antibodies to denosumab. The development of binding antibodies did not appear to alter the pharmacokinetics or pharmacodynamic effects of denosumab and did not appear to result in increased rate of adverse reactions to denosumab.

Specific safety concerns that were addressed in product labeling are

- A limitation of use for patients with multiple myeloma, pending adequately designed trials that demonstrate that overall survival is not impaired in patients with this primary cancer.
- Product labeling contains a subsection under Warnings and Precautions, describing the incidence and severity of hypocalcemia, the potential for higher risks in patients with severe renal dysfunction, recommendations for use of supplementation which may mitigate this risk and recommendations for patient management in the event of severe or serious hypocalcemia.
- Product labeling contains a subsection under Warnings and Precautions, describing the risks of osteonecrosis of the jaw and precautions to be taken to mitigate these risks.
- Based on non-clinical studies and on the known mechanism of action of denosumab, the potential exists for impairment of normal bone growth in children. Information is included under Use in Specific Populations describing potential risks to the developing fetus based on non-clinical studies. In addition, the Pediatric subsection notes that the safety and effectiveness of denosumab in children has not been established.

The DRISK consultant concurred with the clinical review team's recommendation that a REMS should not be required, based on the availability of other drugs for this indication with similar risks that have been safely administered outside of a REMS. The DRISK consultant noted that given the frequency of administration (every 4 weeks), patients will be closely monitored and that the prescribing medical subspecialists (oncologists) are experienced in the administration of toxic therapy and in risk communication of therapy.

The clinical review team and the DRISK consultant agreed that revised labeling adequately communications risks of hypercalcemia and ONJ in the *Warnings and Precautions* and the *Adverse Reactions* sections of the labeling. Given the lack of safety or efficacy data in patients with multiple myeloma and the findings of unplanned subset analyses which cannot rule out potential safety concerns (shortened survival), the *Indications and Usage* section of the label notes that denosumab is not indicated for the treatment of patients with multiple myeloma as a limitation of use. The results of an additional trial which will either confirm or rule out such risks are pending.

Post-marketing requirements have been identified for pediatric studies and for characterization of the risks of hypocalcemia in patients with severe renal dysfunction who receive denosumab according to the recommended dose for this indication (120 mg every 4 weeks), which will result in substantially greater exposure than the original approval (60 mg every six months). Additional non-clinical studies are ongoing to more fully assess the risks of denosumab with regard to normal bone growth. Studies to be conducted in children will be designed, considering the findings in the non-clinical studies.

9. Advisory Committee Meeting

This supplement was not referred to an advisory committee for advice because the application presented no controversial issues. The results of three large, well-conducted clinical trials provided substantial evidence of effectiveness. No new safety issues were identified in this application as compared to the original BLA and the acceptability of the risks in light of the

benefits for this supportive care agent is similar to those considered for the approved indication under the original BLA. The safety of denosumab for the treatment of post-menopausal osteoporosis was discussed at the Advisory Committee convened to provide advice on the original BLA for Prolia in August 2009.; based on the advice of that Committee, the risks of denosumab do not outweigh the benefits for patients with post-menopausal osteoporosis (PMO), however based on differences in the incidence of malignancy which was higher on the denosumab arms in the PMO trials, the AC recommended that additional trials were needed to establish the safety of denosumab in patients with cancer, specifically addressing the risk of adverse effect on tumor growth manifesting in a shortening of progression-free survival or in an increased incidence of second primary cancers. The results the three trials reviewed under this efficacy supplement did not provide signals that denosumab impairs tumor control or increases the rate of second malignancies.

10. Pediatrics

The requirement to conduct pediatric studies for the initial approval of denosumab (Prolia) was waived because the condition (post-menopausal osteoporosis) does not occur in children.

Amgen requested a deferral for the conduct of pediatric studies for the proposed indication in this efficacy supplement; the Division concurred that a deferral was appropriate. The applicant's request for deferral under this supplement was presented to the PeRC on September 22, 2010. The PeRC agreed with the Division to grant a deferral because the product is ready for approval in adults.

The deferral request included Amgen's plans to conduct dose-tolerability (phase 1) and activity-estimating (phase 2) studies in patients ages birth to 18 years. Two nonclinical studies in a human neuroblastoma tumor cell line-nude mouse xenograft model will be conducted prior to initiation of studies in children with cancer to assess proof-of-concept and safety (effects on bone growth). The PeRC suggested that submission of the non-clinical data could be required under a PMR and that a broad PMR be required for this supplemental indication to assess safety and efficacy in children. In addition, the PeRC noted the Division's plans to seek advice from the Pediatric subcommittee to the Oncologic Drugs Advisory Committee on Nov. 30, 2010. Based on the advice from the Pediatric subcommittee, the Division could issue a requirement for a new PMR(s) and release the original PMR(s). The PeRC also noted that, based on the available non-clinical data regarding effects on bone growth and development and/or advice from the Pediatric subcommittee regarding applicability to this population, a waiver for the youngest age cohort might be appropriate.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues. Financial disclosure statements were provided by the applicant; the potential for bias is limited by the study design (double-blind, double-dummy) and was also assessed to a limited extent through clinical site inspections.

The applicant provided assurances that the clinical trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practices.

Six clinical were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811). Sites were chosen based upon analysis of site-specific efficacy data, number and types of protocol deviations, patient enrollment per site, and self-identified investigator financial conflict of interest.

The contract research organization (CRO), (b) (4), responsible for independent confirmation of the skeletal-related events was inspected in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810). This CRO was responsible for central review of primary efficacy endpoint components for the three major efficacy trials.

The inspectional findings for the CRO and the clinical investigators indicate that the data appear generally reliable and may be used to support this efficacy supplement. .

12. Labeling

Includes:

- Proprietary name
  Amgen requested a new proprietary name for denosumab for this proposed indication. Concerns were raised by DRISK regarding potential safety issues with use of a second proprietary name, resulting in possible overdosage due to concurrent dosing with denosumab under both proprietary names. However based on Phase 1 studies, single doses of up to 180 mg were tolerable, thus safety risks alone were not sufficient to support rejection of the second name. FDA rejected Amgen's first proposed proprietary name (b) (4) due to risks of medication error based on orthographic similarities to another approved drug (Cimzia). The Division of Medication Errors and the Division of Biologic Oncology Products found the proposed proprietary name of Xgeva acceptable.

- Physician labeling
  There were no unresolved issues regarding physician labeling. Disagreements among various FDA review staff were resolved by discussion during internal labeling meetings. Major revisions to Amgen's proposed labeling requested by FDA staff are summarized below:
  - The proposed indication was modified to reflect the clinical benefit of Xgeva (prevention of SRE); (b) (4) (b) (4)
  - A limitation of use was added to state that Xgeva is not indicated for patients with multiple myeloma, based on the uncertainty regarding safety in this population and the possibility that the risk:benefit ratio is not favorable as suggested by the exploratory subset analyses of Protocol 20050244.

- Dosage and Administration sections edited for brevity and "command language". [redacted] was deleted; there were not data provided in the application to support that this limitation is necessary to ensure safe and effective use.
- Amgen did not propose Contraindications and the clinical review staff in DBOP and I concur with this approach. The acceptable risks for the proposed use are different than for treatment of post-menopausal osteoporosis given the high incidence of SRE in patients with cancer. In addition, patients with cancer will be closely monitored for their underlying cancer by subspecialists who are experienced in the administration and management of drugs which carry risks of electrolyte abnormalities (e.g., cetuximab, cisplatin).
- The proposed Warnings and Precautions subsection titled [redacted] was deleted as there is no evidence that [redacted].
- The proposed Warnings and Precautions subsection titled [redacted] was deleted due to [redacted].
- The proposed [redacted] was deleted in favor of a specific limitation of use. The overall survival data in this exploratory analysis are included in Section 14 of the product label.
- Editorial changes to the Warnings and Precautions subsections titled "Hypocalcemia" and "Osteonecrosis of the Jaw (ONJ)". These sections were also amended to include the incidence of the risks, in accordance with FDA Guidance for this section of product labeling.
- The proposed table in the Adverse Reactions section was modified to include percentages (rather than numbers of patients) and to include only those reactions occurring at a higher incidence in the denosumab-treated patients or at the same incidence as the control arm for adverse reactions of zoledronic acid (based on the product label for Zometa).
- The Immunogenecity subsection was modified to include data obtained in patients treated at the recommended dose for Xgeva, [redacted].
- Drug Interactions section modified to include available data on possible drug-interactions between chemotherapy and denosumab and between prior bisphosphonate therapy and denosumab.
- Pregnancy category (Category C) added to subsection 8.1 and information re-ordered to place information relevant to human subjects first.
- Subsection 8.4 modified to characterize dosing in non-clinical studies as a fraction of the recommended dose in adults rather than as a [redacted].
- Subsection 8.6 modified to delete the statement that [redacted].

[redacted] (b) (4)
" was replaced with the statement "The risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance of less than 30 mL/min or receiving dialysis."
- [redacted] (b) (4)
- The Description section was modified to include additional information on the composition of the excipients and to remove potentially promotional wording.
- Section 12.1 (Mechanism of Action) was modified to delete [redacted] (b) (4)
- Sections 12.2 (Pharmacodynamics) and 12.3 (Pharmacokinetics) extensively edited for brevity and to include only essential information. [redacted] (b) (4)
- Section 13 modified to relate non-clinical doses to the recommended human doses rather than exposure. Section 13.2 extensively edited for brevity and to include only essential information (deletion of [redacted] (b) (4)
- Section 14 modified to include additional details regarding the protocol design and characteristics of the patient population. [redacted] (b) (4) deleted from the table summarizing efficacy results. [redacted] (b) (4) deleted as redundant (information provided in tabular format)
- Section 16 modified to with regard to protecting vials from direct sunlight and to correct the maximum duration of storage (14 days rather than 30 days) at room temperature.
- Section 17 modified to advise patients that Xgeva and Prolia contain the same active ingredient, to include a description of the sign and symptoms of hypocalcemia and ONJ for which a healthcare provider should be contacted [redacted] (b) (4)
  Deleted information on [redacted] (b) (4) as the data in this application have not identified this as a risk in this population and administered the direction to healthcare providers regarding missed patient visits.

- Carton and immediate container labels
  Recommended revisions to carton and container labeling made by the DMEPA and DMA were incorporated by Amgen, Inc.
- [redacted] (b) (4)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  Three adequate and well-controlled clinical trials demonstrated that denosumab, when administered at a dose of 120 mg subcutaneously every 4 weeks, delays the time to development of a skeletal-related event. Prevention of the complications of bony metastases has been accepted as a measure of direct clinical benefit due to the substantial morbidity that such events represent. In fact, these studies showed not only that denosumab is effective but is more effective than another agent (zoledronic acid) approved for this same indication. The major toxicities identified in clinical trials of denosumab administered at 120 mg every 4 weeks include hypocalcemia and osteo-necrosis of the jaw (ONJ). These toxicities are uncommon and are also present in alternative treatments (bisphosphonates) although at a slightly lower incidence that with denosumab. These risks have been deemed to be reasonable and acceptable in light of the benefits of agents that reduce the substantial morbidity of bone fracture, spinal cord compression, or severe pain and prevention of the need for radiotherapy for control of pain or to prevent pathologic fracture or of surgical intervention to prevent impending pathologic fracture.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  The clinical review team and DRISK consultant agreed that there are no safety issues identified in the clinical trials supporting this supplement that warrant a REMS for the proposed patient population. The risk profile that is generally acceptable and adequately managed by the medical subspecialists who treat this patient population. Because of these differences, a REMS similar to that required for women with post-menopausal osteoporosis is not considered necessary to ensure safe use.

- Recommendation for other Postmarketing Requirements and Commitments

  Required post-marketing studies under 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA)

  1. To conduct a phase 1, open-label, dose-finding pharmacokinetic, pharmacodynamic, and safety study in pediatric patients ages 0 to 18 years who are diagnosed with solid tumors metastatic to bone. The study will determine whether a safe dose can be administered to patients in subsequent phase 2 and phase 3 studies.

  2. To conduct a phase 2, open-label, single-arm study in pediatric patients ages 0 to 18 with solid tumors with bone metastases to determine the safety, including effects

on growing bones, and activity of denosumab in the prevention of skeletal related events.

3. To conduct a randomized and controlled pediatric study to evaluate the efficacy and safety of denosumab for the prevention of skeletal related events in pediatric patients ages 0 to 18 years with solid tumors and bone metastases.

   This study must not be initiated until at least one month after you have submitted the complete study report for post marketing requirements 1 and 2.

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

There are three post-marketing required studies associated with approval of this supplement that the Division has required under PREA in order to evaluate the safety and efficacy of denosumab for the prevention of skeletal-related events in pediatric patients. Unlike post-menopausal osteoporosis, osseous metastases may occur in pediatric patients with cancer, therefore the requirement for such studies could not be waived or deemed inapplicable at this time.

Submission of the required pediatric studies was deferred because this product is ready for approval for use in adults and the pediatric studies have not been completed.

PMR under 505(o)

4. To conduct a clinical trial to determine the safety of Xgeva (denosumab) 120 mg administered every four weeks by subcutaneous injection in patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) and in patients receiving dialysis. The number of patients enrolled in the trial and the frequency and duration of plasma sampling will be sufficient to estimate the incidence and severity of hypocalcemia, hypomagnesemia, and hypophoshatemia in this patient population. The final report should include the primary and derived datasets using the CDISC and ADaM data models and the analysis programs used to generate the safety and laboratory analyses.

Rationale: Denosumab (at a lower dose than proposed in this efficacy supplement) has been administered to patients with renal insuffciency commonly resulting in hypocalcemia. In the clinical data establishing the safety and efficacy of denosumab for the proposed indication, the incidence of hypocalcemia (18% vs. 9%) and severe hypocalcemia (3.1% vs. 1.3%) defined as corrected serum calcium levels of < 7 mg/dL) were higher for denosumab-treated patients compared to zoledronic acid-treated patients. In addition, in a trial of 55 patients, without cancer and with varying degrees of renal impairment, who received a single dose of 60 mg denosumab, 8 of 17 patients with a creatinine clearance less than 30 mLlmin or

receiving dialysis experienced corrected serum calcium levels less than 8.0 mg/dL as compared to 0 of 12 patients with normal renal function.

For the current indication, it will be necessary to assess the safety of denosumab at this dose and dosing schedule in patients with severe renal insufficiency (i.e., creatinine clearance less than 30 mL/min).

SIGNATURES PAGE

/Patricia Keegan/ November 18, 2010

Patricia Keegan, M.D. Date
Director, Division of Biologic Oncology Products
Office of Oncology Drug Products
OND/CDER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: 125320/7

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Axelson, Michael
Best, Jeanine
Feibus, Karen
Fuchs, Chana
Ford, LaTonia
Garnette, Christine
Habtemariam
He, Kun
Hughes, Patricia
Jones, Karen
Karwoski, Claudia
Keegan, Patricia
Kennett, Sarah
Lemery, Steven
Mathis, Lisa
Mena-Grillasca, Carlos
Orr, Michael
Park, Judy
Pierce, Melanie
Pilaro, Anne
Pradhan, Shan
Purohit-Sheth, Tejashri
Robottom, Suzanne
Shord, Stacey
Sridhara, Rajeshwari
Suvarna, Kalavati
Yuan, Vivian
Zhang, Jenny
Zhao, Hong

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	11/17/2010
From	Steven Lemery
Subject	Cross-Discipline Team Leader Review
BLA #	sBLA# 125320/7
Applicant	Amgen, Inc.
Date of Submission	May 14, 2010 (received May 19, 2010)
PDUFA Goal Date	November 18, 2010
Proprietary Name / Established Name	Xgeva (denosumab)
Dosage forms / Strength	120 mg denosumab (70 mg/mL) solution in a single-use vial
Proposed Indication(s)	(b) (4)
Recommended:	*Approval*

Table of Contents

Table of Figures

Table of Tables

1. Introduction

FDA received a new Biologics License Application (STN 125355/0) from Amgen for denosumab (trade name Xgeva) on May 19, 2010, for [redacted] (b) (4) [redacted] (b) (4) Following the approval of denosumab with the proprietary name Prolia (osteoporosis indication, STN 125320/0) on June 1, 2010, FDA administratively re-designated BLA 125355/0 as an efficacy supplement under BLA 125320, assigned STN 125320/7 (Table 2). FDA did not change the original PDUFA goal date as a result of this administrative action.

To support this sBLA, the Applicant primarily relied on the results of three randomized trials: Study 20050103 (103) evaluated the effects of denosumab in preventing skeletal related events (SREs) in men with castrate-resistant prostate cancer metastatic to bone; Study 20050136 (136) evaluated the effects of denosumab in preventing SREs in patients with breast cancer metastatic to bone; and Study 20050244 (244) evaluated the effects of denosumab in preventing SREs in patients with solid tumors metastatic to bone or in patients with multiple myeloma and bone involvement. Amgen designed all three studies as randomized (1:1), international, double-blind, double-dummy, non-inferiority studies that evaluated the effects of denosumab and zoledronic acid in preventing SREs. The primary endpoint for all three studies was non-inferiority (NI) in the time to first on-study SRE. The statistical analysis plans for the three studies allowed for testing of superiority if the primary endpoint was achieved.

The primary regulatory consideration of this application was whether the results from three non-inferiority studies could support the determination that denosumab is effective for the intended indication. The following section presented in a "question and answer" format describes the NI design and results issues pertaining to this application.

1. *Were non-inferiority studies appropriate?* NI studies were acceptable for this application for the following reasons:

   - It is unlikely that patients or clinicians would accept randomization to a placebo controlled arm. Bisphosphonates are established and prevent skeletal related events including fractures and need for radiation (to bone) in patients with cancer metastatic to bone.

     A retrospective study evaluated 718 patients with metastatic breast cancer (Domchek et al., Cancer, 2000) prior to the use of bisphosphonates and showed that skeletal complications frequently occur in women with breast cancer: skeletal complications occurred in 80% of women with bone metastases. Additionally, the authors described other reports that estimated a 20-57% fracture rate in women with breast cancer metastatic to bone.

   - National guidelines recommend bisphosphonate treatment for the prevention of SREs in patients with malignancies metastatic to bone (i.e., http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf).

- An add-on design would not be appropriate because the addition of denosumab to bisphosphonates may cause excessive over-suppression of bone turnover.
- Sufficient evidence did not exist to have expected *a priori* that denosumab would be superior to zoledronic acid for the prevention of SREs in patients with solid tumors metastatic to bone. Additionally, denosumab appeared to cause less renal insufficiency than bisphosphonates, potentially justifying the NI design.

2. *Is there sufficient historical evidence of sensitivity to drug effects (HESDE) regarding zoledronic acid for the prevention of SREs in patients with solid tumors metastatic to bone?*

   As stated in the 2010 draft NI Guidance Document, *HSEDE means that appropriately designed and conducted trials in the past that used a specific active treatment (generally the one that is to be used in the new NI study or, in some cases, one or more pharmacologically closely related drugs) regularly showed this treatment to be superior to placebo (or some other treatment).*

   Results from multiple large randomized studies demonstrated beneficial effects of zoledronic over placebo or compared to pamidronate in patients with solid tumors metastatic to bone or in patients with multiple myeloma. The hazard ratios for two large placebo controlled studies were 0.67 and 0.3 (zoledronic acid USPI) favoring zoledronic acid. Additionally, zoledronic acid decreased the SRE rate ratio at one year compared to placebo in a Japanese study (Kohno et al., JCO, 2005). Other studies submitted by the Applicant showed beneficial effects of pamidronate (a different bisphosphonate drug) on SREs providing consistent evidence from multiple clinical trials that bisphosphonates prevent SREs in patients with cancer metastatic to bone.

3. *Was there sufficient assay sensitivity in the three NI studies (i.e., could these studies have distinguished an effective from an ineffective drug)? As stated in 21 CFR 314.126(a)(2)(iv), the analysis of a study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.*

   Because two of the three studies demonstrated superiority (as described in Section 7 below) against zoledronic acid, these studies demonstrated *de facto* assay sensitivity. Accordingly, the FDA draft NI Guidance states the following: *ICH E-9 and FDA policy has been that a superiority finding arising in a NI study can be interpreted without adjustment for multiplicity. Showing superiority to an active control is very persuasive with respect to the effectiveness of the test drug, because demonstrating superiority to an active drug is much more difficult than showing superiority to placebo.*

   One of the three studies (Study 244) failed to demonstrate statistical superiority against zoledronic acid; however, the HR point estimate of 0.84 favoring denosumab (0.71, 0.98) for time to first on-study SRE was similar to the HR point estimates of 0.82 in Studies 136 and 103. The 95% CI excluded 1 for Study 244 for the HR of time to first on-study SRE. Statistical significance was not achieved despite the unadjusted superiority p value of 0.03 because the procedure to control multiplicity set the alpha of 0.025 using the Hochberg procedure for this analysis. The FDA draft NI Guidance states that *in most cases, a successful NI study supports effectiveness of the test drug, but it only rarely will support a conclusion that the drug is "equivalent" or "similar" to the active control, a concept that has not been well-*

defined for these situations. Such similarity might be concluded, however, if the point estimate of the test drug favored it over the control and the upper bound of the 95% CI for C-T was close to showing superiority. Thus, overall, the results of the three studies support the overall effectiveness of denosumab for the claimed indication.

4. *Were there other considerations supporting the results of the NI studies?*

   As discussed in the FDA NI Guidance, *where there is uncertainty about the historical effect size because of variability or reliance on a single historical study, it will usually be necessary to have more than one NI study to support effectiveness.*

   As previously stated, Amgen submitted the results of three randomized NI studies, two of which showed superiority. Consistent results across studies support the conclusion that the treatment effect observed in the three denosumab studies is a true treatment effect.

5. *Was the constancy assumption satisfied for the three studies?*

   This CDTL reviewer was not convinced that the three studies satisfied the constancy assumption. In general, as shown in Table 1 (data obtained from statistical reviews), patients receiving zoledronic acid enrolled into the (Amgen) denosumab studies experienced a longer median time to first SRE compared to the historical studies evaluating zoledronic acid. Despite similarities in the overall study designs and enrollment criteria compared to the historical studies (as described in the clinical and statistical reviews), differences in treatment effects might have occurred due to improved treatments for the underlying malignancies or improved supportive care (or to unknown factors in the overall study populations).

Table 1 Analysis of Constancy Assumption for Zoledronic Acid Compared to Historically Controlled Studies

Study	Median time to first SRE on ZA in pivotal denosumab studies (months)	Median time to first SRE in historical control studies of ZA (months)
103	17.1	12*
136	26.4	12*
244	16.3	**

*from USPI; **difficult to evaluate as there was not a historically controlled study that solely evaluated all solid tumors (except prostate and breast cancer) and multiple myeloma

Even though this reviewer shares the statistical reviewers' concerns regarding the constancy assumption, the overall conclusions based on the results of the studies are valid because of the following reasons:

- Demonstration of superiority in Studies 103 and 136 (constancy assumption not required for superiority analyses, and thus the assay sensitivity criterion was established for these studies).
- Results in Study 244 were largely consistent with the 103 and 136 studies (see Item #3 above). A sensitivity analysis conducted by the statistical reviewer indicated that although the results were not statistically superior, numerically the median time to first on-study SRE and HR for first on-study SRE favored denosumab.

- Median time to first SRE for patients treated with zoledronic acid in the denosumab studies was longer compared to the historically controlled studies. Although not conclusive, the longer time to first SRE in the newer studies likely represented a true treatment effect of the control zoledronic acid arms compared to a theoretical placebo.

6. *Was an appropriate NI margin selected and was an appropriate analysis performed in the three studies?*

   Even though the primary endpoint for the denosumab studies differed from the historically controlled studies (i.e., proportion of patients with an SRE in historical zoledronic acid studies versus time to first on-study SRE in the denosumab studies), margins could be selected based on the historical studies as time to first on-study SRE was considered a secondary endpoint in the historical studies. Amgen designed the denosumab studies using a synthesis approach to demonstrate that denosumab preserved at least 50% of the treatment effect of zoledronic acid compared to (a theoretical) placebo.

   Irrespective of whether the margin was appropriate, the overall study results (superiority in two studies, and preserving much more than 50% of the treatment effect of zoledronic acid in the third study) established the effectiveness of denosumab. Amgen reached agreement regarding the NI margin with the Agency prior to conducting the studies. The synthesis method used for the analyses was considered acceptable according to the draft FDA NI Guidance Document. According to the NI Guidance Document, *the synthesis method is designed to directly address the question of whether the test product would have been superior to a placebo had a placebo been in the NI study, and also to address the related question of what fraction of the active comparator's effect is maintained by the test product.*

7. *Was the study of acceptable design to allow for the NI study to be interpretable?*

   The FDA draft NI Guidance states the following: *In non-inferiority trials, many kinds of problems fatal to a superiority trial, such as non-adherence, misclassification of the primary endpoint, measurement problems (i.e., "noise"), or many dropouts can bias toward no treatment difference (success) and undermine the validity of the trial, creating apparent non-inferiority where it did not really exist.*

   - Because two of the studies demonstrated superiority, it is likely that the studies were of sufficient quality so that the effects were not biased towards the null hypothesis.
   - Additionally, the studies were double-blind and double-dummy in design. Furthermore, because toxicities were similar, patients or physicians were unlikely to be able to guess their assigned treatment arm. These design elements strengthened the validity of the overall study results.

2. Background

Denosumab is a monoclonal human IgG2 antibody that binds to human RANKL and is manufactured using genetically engineered Chinese hamster ovary cells. The RANK/RANKL (receptor activator for nuclear factor κ B ligand) pathway is involved in the formation, function, and survival of osteoclasts (responsible for bone resorption). Amgen developed denosumab as a biological drug to inhibit this pathway and prevent skeletal related events in patients with cancer metastatic to bone.

The Applicant proposed that denosumab (as Xgeva) be indicated for [redacted] (b) (4). Amgen requested approval of this sBLA based on a treatment effect on the prevention of skeletal related events (SREs) in three randomized studies with a NI design with zoledronic acid as the active control. FDA approved the bisphosphonate drugs based on the treatment effect of preventing SREs in patients with advanced cancer and bone metastases (although the exact analyses differed). SRE, a composite endpoint, consists of any of the following: radiation to bone, pathological fracture, surgery to bone, or spinal cord compression. In general, in both historically controlled (zoledronic acid) studies and in the pivotal denosumab studies, radiation to bone and pathological fractures were the two most commonly occurring events making up the composite endpoint (refer to Section 7 below for additional discussion of the primary endpoint).

In addition to bisphosphonates (zoledronic acid and pamidronate), FDA approved two other drugs for more limited indications involving bone metastases. FDA approved strontium-89 chloride injection to treat bone pain in cancer patients with painful skeletal metastases. Samarium SM 153 lexidronam injection is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scans.

Table 2 summarizes the pertinent regulatory history of denosumab prior to this sBLA submission. Amgen and FDA held a meeting on September 20, 2005 to discuss proposed phase 3 protocols [redacted] (b) (4) (b) (4) (b) (4). FDA and Amgen discussed two of the protocols during the September 20, 2005 meeting that were reviewed as part of this efficacy supplement. The third protocol (Study 20050147) was entitled "A Randomized, Double Blind, Placebo Controlled, Multicenter Phase 3 Study of Denosumab on Prolonging Bone Metastases-Free Survival in Men with Hormone Refractory Prostate Cancer."

During the September 20, 2005 meeting, FDA stated that protocols 20050103 and 20050136 were adequate to support licensure; however, FDA recommended that Amgen revise the primary endpoint to "time to first on-study SRE." FDA stated that the Agency will consider other endpoints including overall survival, proportion of patients with SREs, and time to first symptomatic SRE during the review of a licensing application. FDA agreed to the overall non-inferiority design using a synthesis approach and the plan to allow testing for superiority if denosumab established non-inferiority to zoledronic acid in the studies. To consider approval, FDA expected that the results of the per-protocol analysis would be similar to the results of the ITT analysis. Additionally, during the meeting, Amgen agreed to increase the number of documented examinations of the oral cavity (during the proposed studies); conduct assessments for anti-denosumab antibodies; provide data to FDA that denosumab does not cause infusion reactions (to justify not increasing the frequency of vital sign measurements); clarify rules for withdrawing patients from protocols 20050103 and 20050136; include PK assessments in a subset of patients with breast and prostate cancer; provide a detailed description of censoring rules in the statistical analysis plans for protocols 20050103 and 20050136; and provide information concerning EKG monitoring in the denosumab drug-

development program. Refer to Table 2 below for additional issues addressed during the meeting.

Subsequent to the September 20, 2005 meeting held to discuss protocols 20050103 and 20050136, Amgen submitted clinical protocol 20050244 to IND 9838 on May 2, 2006. FDA sent Amgen an advice and information letter on November 1, 2006 regarding protocol 20050244. In the letter, FDA noted an issue regarding the meta-analysis used to estimate the zoledronic treatment effect for patients with multiple different cancers. In the letter, FDA stated that "a quality assessment should be done of the transferability to this trial of the estimated pamidronate versus placebo effect on the time to first skeletal-related event. Such an assessment cannot be made until after study 20050244 is complete. Also, the reproducibility of the effectiveness of denosumab would need to be studied from the results of trials comparing denosumab with zoledronate and studying the reproducibility of the zoledronate effect. The robustness of the results should also be evaluated in a determination of efficacy." Additionally, the letter stated that Amgen should also conduct a non-inferiority analysis using the results from the per-protocol population and that Amgen should conduct the multiple endpoints analysis (i.e., time to first and subsequent SRE) using an Andersen Gill analysis supported by a statistically significant result from an appropriate multiple events analysis of Amgen's choice.

Prior to obtaining the results from Studies 20050136 and 20050244, Amgen held a pre-BLA meeting with FDA on January 30, 2009 with the intent to submit a BLA (b) (4) (b) (4) as early as December 2009. In the meeting briefing package, Amgen expected that the results of Study 20050103 would be available following the BLA submission. Based on the assumption that Amgen would submit a BLA supported by Studies 20050136 and 20050244, FDA agreed to Amgen's proposal to submit CSRs form Studies 20050136 and 20050244 as well as "non-pivotal" studies 20040113 and 20040114. FDA requested and Amgen agreed to submit safety analyses from the pooled study populations and from each individual study. Additionally, during the meeting, Amgen agreed to provide a Summary of Clinical Safety (including bone loss information as appropriate) in Module 2 of the BLA; provide CRFs from phase 2 and 3 advanced cancer studies for all subjects who died on study, for all subjects who withdrew from investigational product or from the study due to an adverse event, and for all subjects with a serious adverse event; provide locations of SAS datasets and programs to get every value that will appear in product labeling; and to provide only DS and DP information required for registration of the 70 mg/mL vial presentation.

During the January 30, 2009 meeting, FDA agreed with the following Amgen proposals: not to submit radiology images to the BLA; submission of datasets using CDISC format; submission of seven custom SDTM domains; and to remap MedDRA terms to a single consistent version. FDA disagreed with Amgen's original proposal to omit certain non-clinical studies from the BLA. However, during the meeting, Amgen agreed to provide the requested non-clinical study results to the BLA. Also, FDA informed Amgen that the request for two proprietary names for denosumab was under review.

FDA and Amgen held an additional pre-BLA meeting on April 13, 2010. The briefing package contained a summary of key data from Studies 20050136 and 20050244 that were

discussed during the January 30, 2009 meeting. Additionally, Amgen presented key results from Study 20050103. During the meeting, Amgen informed the agency of the intent to submit a BLA for denosumab for the treatment of patients with bone metastases from solid tumors.

During the April 13, 2010 meeting, FDA informed Amgen that the proposed clinical data from the three identified studies appeared adequate to support a BLA submission for the proposed advanced cancer indication. During the meeting, Amgen agreed to provide analysis datasets for all three studies and include flags to identify data from the double-blind extension phase and the open-label phase. Amgen agreed to provide full CSRs containing the completed primary analyses for Studies 20050136, 20050244, and 20050103. Amgen agreed to provide supportive information including results from the double-blind, extension phase for Studies 20050136 and 20050244 in the synopsis CSRs. Amgen stated that the results from the extension phase for Study 20050103 would be provided at a later time. Amgen confirmed that all efficacy data for the primary analyses for Studies 20050136, 20050244, and 20050103 and all safety data for these studies will be complete upon submission of the BLA.

Additionally, during the April 13, 2010 meeting, FDA agreed to Amgen's plan to provide synopsis CSRs and case narratives for all clinically significant adverse events for studies 20050136, 20050244 and 20050103 in the 120-day safety update report. FDA also agreed to Amgen's plan not to provide case narratives in the BLA for patients who withdrew from a study for reasons not related to adverse events. FDA informed Amgen that the determination of whether the application will receive priority status will be made after Amgen submits the BLA.

Table 2 Summary of Pertinent Regulatory History of Denosumab (as Xgeva)

Date	Nature of Regulatory Activity	Issues Described in Meeting, Submission, Letter, or Action
May 22, 2001	IND 9837 submitted	IND application submitted for studies of women with post-menopausal osteoporosis.
May 22, 2001	IND 9838 submitted	IND application submitted for studies of patients with bone disease associated with cancer.

Date	Nature of Regulatory Activity	Issues Described in Meeting, Submission, Letter, or Action
April 14, 2004	Type B pre-phase 3 meeting to discuss CMC issues (under IND 9837)	• If pre-filled syringes will be used to distribute drug product, Amgen will need stability data in the to-be-marketed container closure system. • Additional information deemed necessary by FDA to establish the comparability of the CP1 (initial) manufacturing process with the CP2 manufacturing process. • Bridging studies might be required if compatibility between manufacturing methods not established. • Discussion held regarding product specification criteria for DS and DP and that the specifications proposed would not allow for an accurate measurement or control of aggregates. • FDA requested additional information regarding the methods to determine potency for DP and DS stability testing. • Amgen planned to assess the risk of TSE/BSE according to EMEA guidelines and Amgen agreed to provide a complete list of raw materials with identification of materials of animal origin. • FDA requested information regarding the working cell bank, purification process, and viral clearance. • Amgen agreed to validate in-process hold times prior to licensure.
April 20, 2004	Type B pre-phase 3 meeting to discuss the pharmacology-toxicology program and overall development plan including future phase 3 studies (under IND 9837)	• Because denosumab does not cross react with non-primate RANKL, FDA agreed that rat long term bone quality studies were unnecessary. • FDA agreed to Amgen's overall plan to conduct non-clinical studies in cynomologus monkeys to evaluate the effects of long term dosing on cortical and cancellous bone mass. • FDA would work with Amgen to determine if there were any potential deficiencies in the non-clinical package prior to the completion of phase 3 clinical studies. • Based on data submitted in the briefing package, FDA recommended additional dose exploration prior to the conduct of phase 3 studies. • FDA provided advice regarding studies designed to support the post-menopausal osteoporosis indication (refer to BLA 125320/0).
September 21, 2004	Follow-up teleconference regarding CMC issues discussed during the April 14, 2004 CMC meeting (under IND 9837)	• FDA considered the HTRF test method acceptable for release and stability testing. • FDA requested the certificate of analysis and integrated CEX results for CP1 and CP2 lots used in the animal PK study.

Date	Nature of Regulatory Activity	Issues Described in Meeting, Submission, Letter, or Action
September 20, 2005	Pre-phase 3 meeting (IND 9838)	• FDA recommended time to first on-study SRE as the primary endpoint. • The results of the NI analyses should be similar in the full analysis sets and the per protocol populations. • FDA agreed on Amgen's plan to use the synthesis method to test for non-inferiority. • FDA considered the Hochberg procedure as acceptable for the control of type 1 error rate (for secondary endpoints). • Testing for superiority could be performed if the results were shown to be non-inferior. • FDA considered the proposed NI margin as acceptable for studies 20050103 and 20050136. • FDA expressed concern regarding Amgen's plans for testing and analysis of quality-of-life endpoints. • FDA agreed to Amgen's plan to study immunogenicity.
November 1, 2006	Letter to Amgen (IND 9838) regarding new clinical protocol 20050244	• FDA recommended that Amgen perform a quality assessment regarding the transferability to this trial of the estimated pamidronate versus placebo effect on time to first skeletal-related event. The 20050244 study results should reproduce the results of other denosumab studies. • The multiple events analysis for the secondary endpoint should be tested using the Andersen Gill approach supported by a statistically significant result from an additional multiple endpoints analysis.
December 8, 2006	Type C CMC meeting (under IND 9837)	• Amgen discussed with FDA issues regarding the registration of DS manufactured at the Amgen Colorado site. • Amgen discussed with FDA issues regarding comparability to DS at BI Pharma including stability data and analytical assessments. • Prefilled syringe comparability issues were discussed. • 70 mg/mL vial comparability issues were discussed.
July 8, 2008	Type B CMC meeting (under IND 9837)	• Data submitted by Amgen may support comparability between ACO and BI Pharma manufactured denosumab; however, final conclusions will be a review issue. • Discussion held regarding Amgen's risk based approach to setting bioburden limits. • Amgen could update stability data during an FDA review of a marketing application. • The applicability of the 70 mg/mL presentation would be determined during the BLA review. • FDA and Amgen discussed the use of the HTRF receptor-ligand binding assay to determine potency.
December 19, 2008	BLA 125320/0 submitted (Prolia)	BLA was submitted for the following indications: • Treatment and prevention of osteoporosis in postmenopausal women. • Testament and prevention of bone loss associated with hormone ablation therapy in patients with breast and prostate cancer.

Date	Nature of Regulatory Activity	Issues Described in Meeting, Submission, Letter, or Action
January 30, 2009	Type B pre-BLA meeting (IND 9838)	• Amgen agreed to provide safety data from each individual study in addition to the pooled results from the pivotal SRE studies. • **FDA agreed to Amgen's plan to submit the Integrated** Summary of Safety in Module 2 of the BLA. • **FDA agreed to Amgen's position to include CRFs from phase** 2 and advanced cancer studies for all patients who discontinued denosumab due to an adverse event or experienced an SAE. • **FDA agreed to Amgen's proposal regarding submission of the** imaging charter and not to submit individual radiological images to the BLA. • **FDA agreed to Amgen's plan to submit datasets using CDISC** format. • Only CMC information pertinent to DS and DP required for the 70 mg/mL vial should be submitted to the BLA. • Amgen agreed to provide information regarding non-clinical studies requested by FDA.
October 16, 2009	CR letter issued for BL 125332/0	CR letter issued from ODE III, Division of Reproductive and Urologic Products.
October 19, 2009	CR letter issued for BL 125332/0	CR letter issued from DBOP, OODP.
April 13, 2010	Pre-BLA meeting (IND 9838)	• Meeting held to discuss an upcoming BLA submission including the results of two studies identified during the January 30, 2009 meeting (20050136 and 20050244) and the results of a third study 20050103. • Amgen proposed submitting a stand alone BLA with a new trade name. FDA stated that the new trade name was under review. • FDA and Amgen reached agreement on the proposed content and structure of the BLA submission.
May 14, 2010	BLA 125355/0	• BLA 125355/0 submitted in support of denosumab for the treatment of patients with bone metastases from solid tumors. • BLA received on May 19, 2010.
April 15, 2010	Proposed trade name rejected	FDA rejected Amgen's original proposed trade-name (b) (4) for the (b) (4) due to look-alike and sound-alike attributes with an already approved drug.
June 1, 2010	BLA 125320/0	BLA 125320/0 approved for the following indication: *Prolia is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.*
July 2, 2010	Amgen request for new proprietary name	Proposed new trade name: Xgeva.
July 16	Letter to Amgen describing administrative refilling of BLA-	• Following approval of BLA 125320 (Prolia application) on June 1, 2010, FDA re-designated BLA 125355/0 (submitted prior to the approval) as an efficacy supplement under BLA 125320 (new STN# 125320/7). • Original PDUFA goal date did not change following this action.

3. CMC

The CMC review team (OBP/DMA) recommended approval of the 70 mg/mL 1.7 mL single use denosumab vial. The review team concluded that the product manufactured under this formulation is pure, potent, and free from endogenous and adventitious infections agents sufficient to meet parameters recommended by the Agency.

3.1 General product quality considerations

Denosumab is a full-length human monoclonal kappa light-chain containing IgG2 antibody that binds specifically to the D-E loop of the human receptor activator for nuclear factor κ B ligand (refer to DMA review for specifics regarding the structure and properties of denosumab). DMA reviewed drug substance (DS) information during the submission of the original BLA (125320/0). No major manufacturing changes were submitted based on DS to this efficacy supplement (this CDTL review will thus not comment on DS issues).

The presentation of the drug product (DP) in this application differs from the DP currently approved under the Prolia trade-name (60 mg/mL vial and 60 mg/mL pre-filled syringe). The concentrations of acetate and sorbitol differ between the two formulations due to (b) (4) (b) (4) The new formulation contains 18 mM acetate and 4.6% sorbitol at a pH of 5.2.

To assess the formulation used in the advanced cancer studies, Amgen conducted an analytical comparability and bioequivalence study (20060446) using DP from the 60 mg/mL and 70 mg/mL vials. DMA analyzed DP characteristics using the results of lot release testing and stability data (the 70 mg/mL DP is stable through 36 months under recommended storage conditions). The DMA reviewer concluded that these formulations were found to be comparable. Differences between these formulations included (b) (4)

Finally, the DMA review team recommended (b) (4) (b) (4)

3.2 Facilities review/inspection

The Division of Manufacturing and Product Quality (DMPQ) review team recommended approval of this supplement from a CMC microbiology quality perspective.

Manufacturing of drug product occurs at the Amgen (ACO) facility in Boulder, Colorado and Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma) facility in Germany.

Denosumab formulation, fill/finish, and packaging (and storage) of drug product is performed at Amgen Manufacturing Limited (AML site) in Juncos, Puerto Rico.

Denosumab drug product storage and distribution occurs at the Amgen (LDC) site in Louisville, Kentucky and the Amgen (ATO) site in Thousand Oaks, California. Additionally, DP lot release and stability testing occurs at the AML and ACO sites.

Denosumab container closure testing for stability occurs at the Amgen (AFR site) in Fremont, California.

Table 3 shows the summary of inspection results from sites related to the manufacturing, stability testing, and release of denosumab as of 10/18/2010. No sites inspected received a classification of OAI. No follow-up inspection items were required in association with this supplement to the BLA.

Table 3 DMPQ Inspection Summary (Adapted from Dr. Suvarna's Review)

Establishment	Inspection Date(s)	Classification
Amgen Inc. (ACO) LakeCentre Facility Boulder, CO	August 23-September 3, 2010	VAI
Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma) Biberach an der Riss Germany	May 15-26, 2010	VAI
Amgen Inc. (ACO) Longmont Facility Longmont, CO	August 23-September 9, 2010	VAI
Amgen Manufacturing Limited Juncos, Puerto Rico	May 19-27, 2010	NAI
(b) (4)		

4. Nonclinical Pharmacology/Toxicology

The primary non-clinical reviewer stated in his review that the non-clinical data support the approval of denosumab, provided that the clinical review team determines a positive risk-benefit profile based on the studies conducted in humans.

New animal studies submitted in support of this efficacy supplement were primarily pharmacology studies to support the potential mechanism of action of denosumab in the intended indication. Amgen also submitted secondary pharmacodynamics studies to assess effects of OPG-Fc on neovascularization in the rat-corneal disk implant model of angiogenesis.

The non-clinical reviewer stated that the non-clinical studies in different tumor models were designed to evaluate the effects of inhibition of RANKL on tumor growth and animal survival. However, in rodent models, OPG-Fc was used as a surrogate (for denosumab) because denosumab does not recognize rodent RANKL. The non-clinical review describes studies Amgen conducted showing that inhibition of RANKL by rodent OPG-Fc alone can reduce osteolysis in syngeneic murine breast, prostate, and lung tumor models. Additionally, the non-clinical review describes data showing that the combination of OPG-Fc and docetaxel displayed apparent, additive inhibition of osteolysis relative to either agent alone in the *in vivo* H1299 mouse human tumor xenograft model.

The non-clinical reviewer concluded that the findings in the rat-corneal disk studies using rodent OPG-Fc were equivocal. One study did not replicate the findings of increased VEGF-induced angiogenesis following the administration of OPG-Fc in combination with VEGF in the rat-corneal disk implant model.

4.1 General nonclinical pharmacology/toxicology considerations

4.1.1 Safety pharmacology assessments

FDA reviewed the results of the safety pharmacology studies at the time of the original BLA submission (STN 125320/0).

4.1.2 Repeat-dose toxicology studies

FDA reviewed the results of the general toxicology studies at the time of the original BLA submission (STN 125320/0).

4.1.3 Genetic-toxicology studies

Amgen did not submit data from genetic toxicology studies in this efficacy supplement.

4.2 Carcinogenicity

The non-clinical review stated that carcinogenicity risk has not been evaluated due to the lack of an appropriate model.

4.3 Reproductive toxicology

FDA reviewed the results of reproductive and developmental toxicology studies at the time of the original BLA submission (STN 125320/0).

4.4 Other notable issues (resolved or outstanding)

None; no new additional non-clinical studies are required at this time.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology review staff from the Clinical Pharmacology 5 Division of OCP stated that the clinical pharmacology and biopharmaceutics data submitted by Amgen support the approval of this efficacy supplement.

5.1 General clinical pharmacology/biopharmaceutics considerations

5.1.1 Dose selection

The dose of denosumab 120 mg every four weeks proposed in this efficacy supplement [redacted] (b)(4) is higher that the dose approved for osteoporosis (Prolia indications). Amgen selected the dose based on a finding of maximal reduction of bone turnover using the biomarker urinary N-terminal telopeptide corrected for urinary creatinine (uNTx/uCr). Amgen tested doses ranging from 30 mg to 180 mg and schedules of one dose every four weeks or every 12 weeks. Amgen determined that the every 12 week dosing schedule did not result in sustained reductions in uNTx/Cr.

5.1.2 Pharmacokinetics

OCP reviewed pharmacokinetics data from a study that randomized 255 women with breast cancer metastatic to bone to one of five dosing schedules of denosumab (30 mg, 130 mg, or 180 mg every four weeks or 60 mg or 180 mg every 12 weeks) or to zoledronic acid every four weeks. As described in the OCP review, mean C_{max} following a 120 mg dose of denosumab was 13.5 mcg/mL (SD 6.1), and terminal elimination half-life was 28.8 (SD 9.5) days following multiple doses of denosumab (120 mg).

Additionally (as determined in the OCP review), in a population PK analysis including data from 20 clinical trials, bioavailability was estimated to be 62%, distribution half-life was 15 hours, and the beta-elimination half-life was 38 days (at higher doses) once non-linear target mediated clearance was saturated. Steady state exposure (AUC) was higher following repeated administration of 120 mg denosumab in lower weight patients compared to normal or higher weight patients.

5.1.3 Comparability of formulations

OCP review staff determined that the 70 mg/mL formulation was comparable to the 60 mg/mL formulation based on a randomized PK study conducted in 116 healthy volunteers. These study results permitted OCP and non-clinical reviewers to rely on the safety and PK data from clinical trials that used the 60 mg/mL formulation.

5.2 Drug-drug interactions

OCP determined that concomitant anticancer therapy did not appear to influence the pharmacokinetics or pharmacodynamics of denosumab. Additionally, prior IV bisphosphonate therapy did not appear to affect denosumab concentrations (at one and three months post dosing) or uNTx/Cr concentrations (evaluated in studies 20040114 and 20040113).

5.3 Immunogenicity

A total of 7 of 2758 patients developed binding anti-denosumab antibodies (in an evaluation of studies not previously submitted to the BLA). None of these patients developed neutralizing antibodies.

5.4 Demographic interactions/special populations

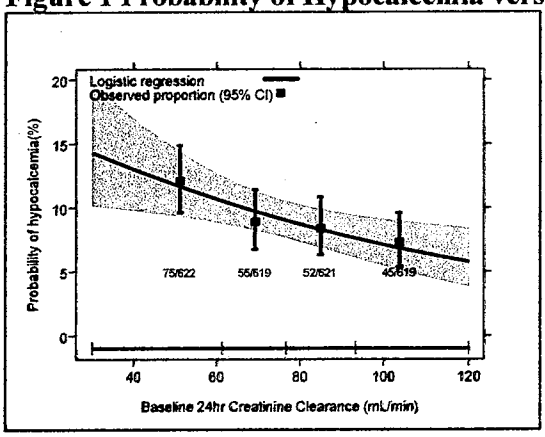
5.4.1 Body weight

Amgen's population pharmacokinetic analysis showed that patients with lower body weights experienced higher exposures to denosumab. An analysis of time to first on-study SRE by BSA quartile showed that patients with a lower body surface area experienced a prolonged time to first on-study SRE compared to patients with a higher body surface area. This same pattern; however, was also observed in patients treated with zoledronic acid; thus no conclusions can be made with respect to an interaction between weight, BSA, or denosumab concentrations and treatment effect.

5.4.2 Renal insufficiency

The pharmacodynamic effect of denosumab-induced hypocalcemia appeared to be exacerbated in patients with renal insufficiency (PKs appeared unaffected). The analysis in Figure 1, copied from Dr. Shord's review, shows a higher probability of hypocalcemia in patients with reduced creatinine clearance. Data did not replicate this effect in patients treated with zoledronic acid (note that dose-reduction recommendations exist for zoledronic acid based on reduced creatinine clearance).

Figure 1 Probability of Hypocalcemia versus Baseline Creatinine Clearance



5.4.3 Other demographic populations

No differences in pharmacokinetic effects were observed in patients older than 65 years treated with denosumab. Clearance values of denosumab were higher in Black and Hispanic patients treated with denosumab compared to Asian and White patients; however, these differences were within the reported PK variability at high denosumab concentrations estimated from phase 2 and 3 studies.

The safety and efficacy of denosumab has not been studied in children treated with denosumab. However, neonatal rats exposed to OPG-Fc exhibited greater reductions in skeletal growth and inhibited incisor growth. In a long term recovery study, rats exhibited modest epiphyseal growth plate changes after discontinuing OPG-Fc and bone size was decreased when compared to control vehicle group. A separate study report showed that weekly OPG-Fc caused osteopetrosis-like changes in rats at the 10mg/kg dose level.

Histopathological assessment of the tibia showed disorganized growth plate morphology. Amgen concluded from non-clinical studies that denosumab carries potential risks (in patients with rapidly growing bones) from widened growth plates, decreased long bone growth, and impaired dentition.

5.5 Thorough QT study or other QT assessment

During the review of the original BLA (STN 125320/0), QT-IRT determined that ECG evaluations were adequate and that denosumab did not appear to prolong QTc intervals across a dosing spectrum up to 210 mg. QT-IRT did not require any new studies to support this efficacy supplement.

6. Clinical Microbiology

This section is not applicable to this indication.

7. Clinical/Statistical- Efficacy

The clinical reviewers (Shan Pradhan and Michael Axelson) recommended approval of this sBLA based on the results from studies 20050103 (103), 20050136 (136), and 20050244 (244). The statistical reviewers summarized that the data from the three studies supported the claimed treatment effect.

7.1 Background of clinical program

This sBLA was primarily supported by the results from three randomized controlled trials comparing the effects on skeletal related events (SREs) of denosumab against zoledronic acid. Table 4, copied from Dr. Pradhan's review, summarizes the three studies submitted in support of the proposed new indication. Amgen designed all three studies to demonstrate non-inferiority of denosumab as compared to zoledronic acid (in time to first on-study SRE).

Table 4 Studies Submitted by Amgen supporting the Efficacy of Denosumab for the Proposed Indication

Trial	Disease	Study Design	Primary Objective	Regimen*	Subjects Enrolled	Status
103	Prostate cancer	Randomized, double-blind, double-dummy	To determine if denosumab is non-inferior to zoledronic acid with respect to first on-study occurrence of an SRE	Denosumab SC and zoledronic acid placebo IV Q4w, or zoledronic acid IV and denosumab placebo SC Q4w	1901	Open label treatment phase ongoing
136	Breast cancer				2046	
244	Solid tumors (excluding breast and prostate cancer) and multiple myeloma				1776	Survival follow-up ongoing

*SC = subcutaneous; IV = intravenous

FDA and Amgen held a pre-phase 3 meeting on September 20, 2005 to discuss the overall design of studies intended to demonstrate the safety and efficacy of denosumab for the prevention of skeletal related events in patients who have tumors metastatic to bone. Amgen

initiated the first of the three studies (20050103) in May 2006. Table 5 copied from Dr. Pradhan's review shows the dates of study initiation for the three pivotal trials and primary data cutoff dates.

Table 5 Study Initiation and Data Cutoff Dates

	Study Initiation	Primary Analysis Cutoff Date
103	May 2006	October 2009
136	April 2006	March 2009
244	June 2006	April 2009

7.2 Design of efficacy studies

The three studies submitted in support of this sBLA were randomized (1:1), international, double-blind, double-dummy, non-inferiority studies. Study 103 enrolled men with castrate-resistant prostate cancer and bone metastases, Study 136 enrolled patients with breast cancer and bone metastases, and Study 244 enrolled patients with solid tumors and bone metastases or patients with multiple myeloma and bone disease.

7.2.1 Primary endpoint

The primary endpoint of the three pivotal efficacy studies was time to first on-study SRE (NI analysis). FDA agreed to the appropriateness of this endpoint in a pre-phase 3 meeting on September 20, 2005. SRE, a composite endpoint, consisted of any of the following: radiation to bone, pathological fracture, surgery to bone, or spinal cord compression. FDA considered this endpoint as the basis for approval of zoledronic acid. This reviewer believes that a double-blind study design is necessary for the consideration of this endpoint because radiation to bone (and surgery to bone) can be subject to different standards and potential bias (as judgment is necessary regarding who should receive radiation versus opiates or other pain control). Pathological fracture and spinal cord compression cause severe pain and frequently, decreased function, and as such, are surrogates for worse quality of life.

7.2.2 Secondary endpoints

The protocols and statistical analysis plans described two secondary endpoints that were to be tested only if denosumab was found to be non-inferior to zoledronic acid for the time to first on-study SRE analysis. The sponsor designated the Hochberg procedure to test for the two secondary endpoints simultaneously. The significance level was set at 0.05. If the larger of the two p values was not significant, the other secondary endpoint could be tested at a significance level of 0.025. The two secondary endpoints tested were time to first on-study SRE (superiority analysis) and time to first-and-subsequent on-study SRE (superiority analysis using the Andersen-Gill approach).

7.2.3 Exploratory endpoints

The sponsor conducted multiple additional exploratory endpoint analyses. This review will focus on the results for PFS and OS. Amgen did not utilize an independent radiology review to determine PFS; however, adequate blinding minimized the potential for bias.

7.2.4 Common eligibility criteria

Refer to Table 4 above for study enrollment criteria by disease. Patients were eligible if they had radiological evidence of at least one osseous metastasis or a lytic lesion from multiple myeloma. Additionally, patients must have had a creatinine clearance ≥ 30 mL/min and albumin-adjusted calcium of ≥ 8 mg/dL. Patients enrolled into Study 103 (prostate cancer) were castrate resistant. Exclusion criteria included hypercalcemia, prior intravenous bisphosphonate use (or oral bisphosphonates if used to treat osseous metastases), planned radiation or surgery to bone, osteonecrosis of the jaw, active dental condition requiring surgery, or a planned invasive dental procedure during the course of the study.

7.2.5 General study design/treatment plan

In general, the three pivotal studies were of similar design. The following describes major design components. Refer to Section 5 of the clinical review and the statistical reviews for a more complete description of the individual clinical studies.

- All studies were randomized (1:1), international, double-blind, double-dummy studies.
- Patients received denosumab 120 mg by subcutaneous (SC) injection and intravenous (IV) placebo for zoledronic acid every four weeks *or* zoledronic acid (dose reduced for reduced renal function) 4 mg IV and SQ placebo for denosumab every four weeks.
- The protocols *recommended* supplementation with at least 500 mg calcium and 400 IU vitamin D.
- The protocols encouraged patients to continue receiving investigational products following a skeletal related event.
- Study drugs were held for ≥ Grade 3 toxicity considered related to investigational product; IV investigational products (zoledronic acid or placebo) were withheld for renal deterioration.
- The protocols required visits for laboratory monitoring every four weeks from study day 1 to week 49.
- Study investigators monitored patients for SREs and progression events.
- An independent radiology review committee assessed radiographs to confirm pathological fractures and spinal cord compression events.
- A DMC reviewed safety and efficacy data at regular intervals.

7.2.6 Statistical design and analysis issues

Stratification Factors

- Study 103 was stratified by history of previous SRE (yes or no), PSA level (< 10 ng/mL or ≥ 10 ng/mL), and current chemotherapy [defined as occurring within 6 weeks before randomization (yes or no)].
- Study 136 was stratified by history of previous SRE (yes or no), prior oral bisphosphonate use (yes or no), current chemotherapy [defined as occurring within 6 weeks before randomization (yes or no)], and region (Japan or other).
- Study 244 was stratified by tumor type (non-small cell lung cancer, multiple myeloma, or other), previous SRE (yes or no), and systemic anticancer therapy (yes or no).

Endpoints

- Refer to Sections 7.2.1 and 7.2.2 above.

Determination of Sample Size

- Refer to statistical reviews for discussion of the historical studies used for the estimation of the zoledronic acid effect sizes *[This CDTL shares the statistical reviewer's concern regarding the estimate of the historical zoledronic acid effect size for Study 244; ultimately, however, the results of the three studies (Section 1) supported the efficacy of denosumab in preventing SREs].*
- Amgen designed the three studies to assess non-inferiority against zoledronic acid in the time to first on-study SRE with a HR of 0.9, based on a synthesis approach.
- Amgen designed the three studies to demonstrate that denosumab perseveres at least 50% of the effect of zoledronic acid compared to the (historical) placebo effect. For the primary analysis, Study 244 was designed with 97% power, Study 103 was designed with 90% power, and Study 136 was designed with 97% power to detect non-inferiority.
- The final analyses for all three studies were planned to occur when 745 patients were to have experienced at least one SRE following randomization.

Analyses

- For the primary analysis, if a patient had not experienced an SRE, the patient was censored at the data cutoff date or the end of study date on the CRF (whichever came first).
- For the secondary endpoint "time to first and subsequent on-study SRE," only new events occurring at least 21 days after the previous SRE were counted as a subsequent event.
- Amgen and the statistical reviewers conducted the primary analyses using the intent-to-treat populations. Sensitivity analyses were conducted using the per-protocol populations (see statistical reviews for details).
- Amgen conducted the primary analyses using a synthesis approach with a Cox model that used the stratification factors to test for non-inferiority of the primary endpoint (time to first on-study SRE).
- Testing for the two secondary endpoints, superiority for time to first on-study SRE and superiority for time to first-and-subsequent on-study SRE, was permitted using the Hochberg procedure if non-inferiority was demonstrated. Testing for superiority used a stratified log-rank test and testing for time to first-and-subsequent on-study SRE used the Andersen and Gill approach.

7.3 Study results

This application was primarily supported by the results of three large randomized controlled trials demonstrating that denosumab is non-inferior to zoledronic acid in regards to time to first on-study SRE. Section 1 of this review contains a detailed discussion regarding the NI study considerations that supported this application. Two of the randomized trials demonstrated superiority of denosumab against zoledronic acid in prolonging the time to first on-study SRE. Overall, analyses of progression free survival (PFS) and overall survival (OS) showed no apparent trends indicating worse PFS or OS following denosumab treatment. OS was worse for denosumab in a subgroup of patients with multiple myeloma [HR 2.26 (1.13, 4.50)]; however, there were few events in both arms. The OS analyses should be interpreted with some caution as the power to detect small differences (i.e., a HR of 0.95 with an alpha of 0.05) in OS was low, even when combining the study results.

7.3.1 Study 103 (prostate cancer)

Demographics and Disposition

As described and presented in the statistical review, randomization was generally balanced between the two treatment arms (Table 6: data obtained from statistical review). Median age in both arms was 71 years and most patients (> 85% in both arms) were White.

Table 6 Baseline Disease Characteristics and Stratification Factors from Study 103

	Denosumab (N=950)	Zoledronic Acid (N=951)
Previous SRE:		
Yes	232 (24.4%)	231 (24.3%)
No	718 (75.6%)	720 (75.7%)
PSA level:		
<10 ng/mL	145 (15.3%)	145 (15.2%)
≥10 ng/mL	805 (84.7%)	806 (84.8%)
Current chemotherapy:		
Yes	132 (13.9%)	132 (13.9%)
No	818 (86.1%)	819 (86.1%)
ECOG performance status:		
0	418 (44.0%)	426 (44.8%)
1	464 (48.8%)	460 (48.4%)
2	68 (7.2%)	65 (6.8%)
Distant metastasis at diagnosis:		
M0	410 (43.2%)	422 (44.4%)
M1	326 (34.3%)	336 (35.3%)
Mx	214 (22.5%)	192 (20.2%)
Missing	0 (0.0%)	1 (0.1%)
# of metastatic lesions in bone at baseline – by central read:		
≤ 2	632 (66.5%)	623 (65.5%)
> 2	318 (33.5%)	328 (34.5%)
Type of bone lesion at baseline:		
Osteoblastic	601 (63.3%)	537 (56.5%)
Osteolytic	32 (3.4%)	39 (4.1%)
Mixed	128 (13.5%)	150 (15.8%)
Unable to evaluate	1 (0.1%)	2 (0.2%)
Not seen	188 (19.8%)	223 (23.4%)
Visceral metastases:		
Any	161 (16.9%)	181 (19.0%)
Liver	16 (1.7%)	20 (2.1%)
Lung	26 (2.7%)	32 (3.4%)
Other	141 (14.8%)	153 (16.1%)

In general, reasons for treatment discontinuation were similar for the two treatment arms. More patients withdrew due to an adverse event in the denosumab arm. Few patients were considered lost to follow-up (9 in the denosumab arm and 13 in the zoledronic acid arm).

Results

Table 7 presents results of the primary and secondary analyses from the statistical review (Dr. Zhang) using data submitted by the Applicant. In Study 103, denosumab was both non-inferior to and superior to zoledronic acid in the analysis of time to first on-study SRE. These results demonstrated the efficacy of denosumab in preventing or delaying SREs compared to zoledronic acid when taken into context with the results of Studies 136 and 244. Figure 2, copied from the statistical review, shows a proportional hazard for each KM curve throughout the study and that the KM curves appear to separate between months 3 and 6. The curves remain separate throughout the course of the study.

Table 7 Prostate Cancer (103) Study: Results of Primary and Secondary Analyses

Endpoint	Median time to SRE in Months		HR (95% CI)	p-value
	D	ZA		
1st SRE (NI)	20.7	17.1	0.82 (0.71, 0.95)	0.0002*
1st SRE (superiority)	20.7	17.1	0.82 (0.71, 0.95)	0.0082#
1st and subsequent SRE (Superiority)	NA	NA	0.82 (0.71, 0.94)	0.0088$

*Cox-model synthesis method; #Log-rank, adjusted; $Cox-model, adjusted

Figure 2 Time to First on-Study SRE, Study 103

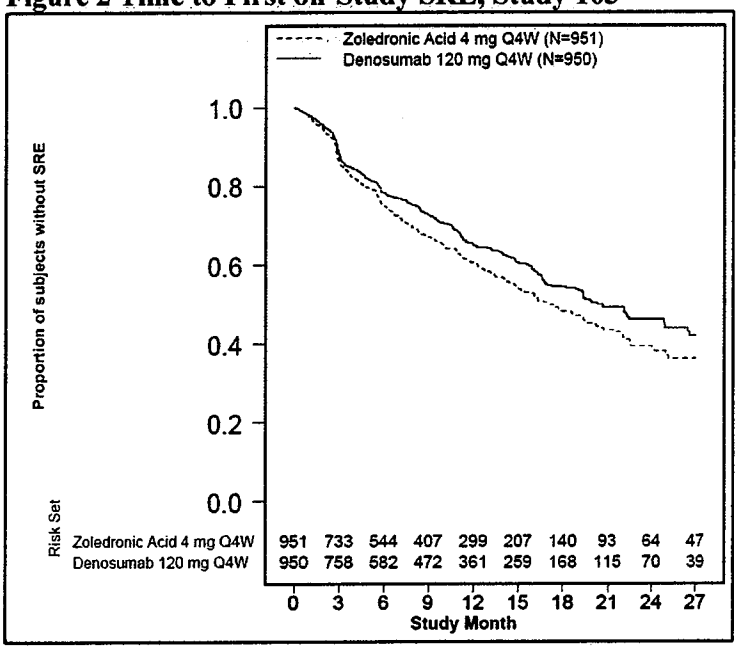


Table 8 shows the components of the first on-study SREs as determined by the statistical reviewer. Overall, pathological fractures and radiation to bone comprised most of the SREs. Few patients required surgery to bone.

Table 8 Components of First on-Study SREs

SRE	Denosumab (N=950)	Zoledronic acid (N=951)
Pathologic fracture	137 (14.4%)	143 (15.0%)
Radiation to bone	181 (18.6%)	207 (21.4%)
Surgery to bone	1 (0.1%)	4 (0.4%)
Spinal cord compression	26 (2.7%)	36 (3.8%)
Total	341 (35.9%)	386 (40.6%)

Table 9 shows the results obtained from the FDA statistical review of exploratory endpoints of Study 103. The point estimates for the HRs for first SRE or HCM (hypercalcemia of malignancy) and first symptomatic SRE were consistent with the results of the primary and secondary endpoints. The point estimate for OS favored zoledronic acid slightly (median difference of 0.4 months); however, this result was not consistent in the other two studies.

Table 9 Exploratory Endpoints for Study 103 (Prostate Cancer)

Endpoint	Number of events (%)		Median (in mos.)		HR (95% CI)
	D	ZA	D	ZA	
1st SRE or HCM	340 (35.8)	384 (40.4)	20.7	17.1	0.83 (0.72, 0.96)
OS	474 (49.9)	461 (48.5)	19.4	19.8	1.05 (0.91, 1.20)
Progressive Disease in bone	387 (40.7)	402 (42.3)	13.7	11.1	0.93 (0.80, 1.08)
PFS	767 (80.7)	735 (77.3)	8.1	8.0	1.03 (0.92, 1.14)
1st symptomatic SRE	241 (25.4)	289 (30.4)	NR	24.2	0.78 (0.66, 0.93)

7.3.2 Study 136 (breast cancer)

Demographics and Disposition

As described and presented in the statistical review, randomization was generally balanced between the two treatment arms (Table 10: data obtained from statistical review). Median age in the denosumab arm was 57 years, and median age in the zoledronic acid arm was 56 years. A total of 17 patients were men (8 in the denosumab arm and 9 in the zoledronic acid arm). Most patients were White (80%); approximately 10% of patients were of Asian ethnicity.

Table 10 Baseline Disease Characteristics and Stratification Factors from Study 136

	Denosumab (N=1026)	Zoledronic Acid (N=1020)
Previous SRE:		
Yes	378 (36.8%)	373 (36.6%)
No	648 (63.2%)	647 (63.4%)
Prior oral bisphosphonate use:		
Yes	42 (4.1%)	38 (3.7%)
No	984 (95.6%)	982 (96.3%)
Current chemotherapy:		
Yes	410 (40.0%)	408 (40.0%)
No	616 (60.0%)	612 (60.0%)
Region:		
Japan	69 (6.7%)	67 (6.6%)
Others	957 (93.3%)	953 (93.4%)

	Denosumab (N=1026)	Zoledronic Acid (N=1020)
ECOG Performance Status:		
0	504 (49.1%)	488 (47.8%)
1	451 (44.0%)	444 (43.5%)
2	68 (6.6%)	82 (8.0%)
3	1 (0.1%)	2 (0.2%)
Missing	2 (0.2%)	4 (0.4%)
ER/PR status:		
Negative	163 (15.9%)	163 (16.0%)
Positive	740 (72.1%)	726 (71.2%)
Unknown	121 (11.8%)	129 (12.6%)
Missing	2 (0.2%)	2 (0.2%)
Her-2 status:		
Negative	518 (50.5%)	472 (46.3%)
Positive	183 (17.8%)	194 (19.0%)
Unknown	321 (31.3%)	350 (34.3%)
Missing	4 (0.4%)	4 (0.4%)
# of metastatic lesions in bone at baseline – by central read:		
≤ 2	784 (76.4%)	780 (76.5%)
> 2	242 (23.6%)	240 (23.5%)
Type of bone lesion at baseline:		
Osteoblastic	285 (27.8%)	281 (27.5%)
Osteolytic	139 (13.5%)	152 (14.9%)
Mixed	256 (25.0%)	254 (24.9%)
Unable to evaluate	4 (0.4%)	3 (0.3%)
Not seen	336 (32.7%)	336 (32.9%)
Visceral metastases:		
Any	552 (53.8%)	525 (51.5%)
Liver	211 (20.6%)	182 (17.8%)
Lung	216 (21.1%)	210 (20.6%)
Other	369 (36.0%)	369 (36.2%)

In general, reasons for treatment discontinuation were similar for the two treatment arms. More patients withdrew due to an adverse event in the zoledronic acid arm. Few patients were considered lost to follow-up (8 in the denosumab arm and 7 in the zoledronic acid arm).

Results

Table 11 presents results of the primary and secondary analyses from the statistical review (Dr. Zhang) using data submitted by the Applicant. In Study 136, denosumab was both non-inferior to and superior to zoledronic acid in the analysis of time to first on-study SRE. These results demonstrated the efficacy of denosumab in preventing or delaying SREs compared to zoledronic acid when taken into context with the results of Studies 103 and 244. Figure 3, copied from the statistical review, shows a (near) proportional hazard for each KM curve throughout the study and that the KM curves appear to separate prior to the sixth month time-point. The curves remain separate throughout the course of the study.

Table 11 Breast Cancer (136) Study: Results of Primary and Secondary Analyses

Endpoint	Median time to SRE in Months		HR (95% CI)	p-value
	D	ZA		
1st SRE (NI)	NR	26.4	0.82 (0.71, 0.95)	< 0.0001*
1st SRE (superiority)	NR	26.4	0.82 (0.71, 0.95)	0.0097#
1st and subsequent SRE (Superiority)	NA	NA	0.77 (0.66, 0.89)	0.0012$

*Cox-model synthesis method; #Log-rank, adjusted; $Cox-model, adjusted

Figure 3 Time to First on-Study SRE, Study 136

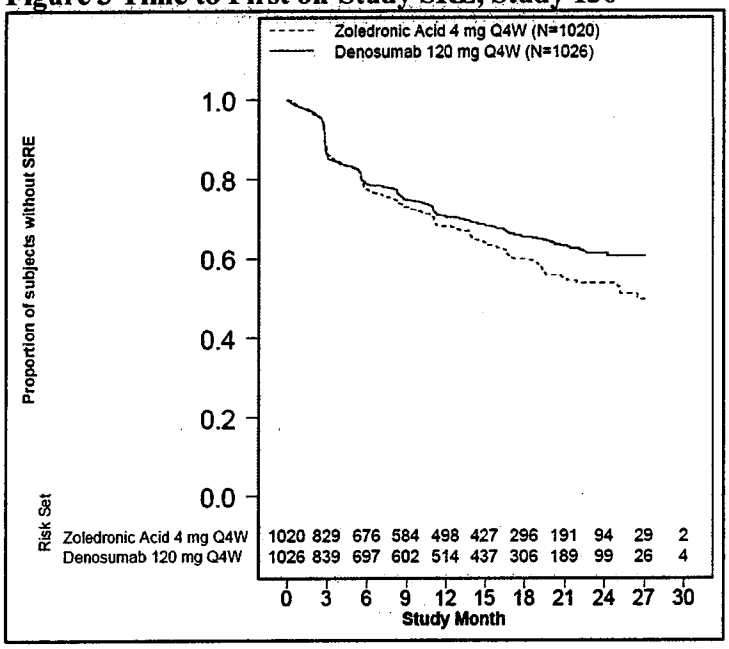


Table 12 shows the components of the first on-study SREs as determined by the statistical reviewer. Overall, pathological fractures and radiation to bone comprised most of the SREs. Fractures occurred more frequently in the breast cancer study compared to the prostate cancer study.

Table 12 Components of First on-Study SREs

SRE	Denosumab (N=1026)	Zoledronic Acid (N=1020)
Pathologic fracture	212 (20.7%)	238 (23.3%)
Radiation to bone	82 (8.0%)	119 (11.7%)
Surgery to bone	12 (1.2%)	8 (0.8%)
Spinal cord compression	9 (0.9%)	7 (0.7%)
Total	315 (30.7%)	372 (36.5%)

Table 13 shows the results obtained from the FDA statistical review of exploratory endpoints of Study 136. The point estimates for the HRs for first SRE or HCM (hypercalcemia of

malignancy) and first symptomatic SRE were consistent with the results of the primary and secondary endpoints. The point estimate for OS favored denosumab slightly.

Table 13 Exploratory Endpoints for Study 136 (Breast Cancer)

Endpoint	Number of events (%)		Median (in mos.)		HR (95% CI)
	D	ZA	D	ZA	
1st SRE or HCM	323 (31.5)	383 (36.5)	NR	25.2	0.82 (0.70, 0.95)
OS	301 (29.3)	305 (29.9)	29.4	NR	0.96 (0.82, 1.13)
PD in bone	446 (43.5)	449 (44.0)	16.6	16.4	0.99 (0.87, 1.13)
PFS	683 (66.6)	698 (68.4)	11.8	11.7	1.01 (0.91, 1.13)
1st symptomatic SRE	156 (15.2)	198 (19.4)	NR	NR	0.76 (0.61, 0.93)

7.3.3 Study 244 (solid tumors and multiple myeloma)

Demographics and Disposition

As presented in the statistical review (Dr. Yuan), randomization was generally balanced between the two treatment arms (Table 14: data obtained from statistical review). More patients were older than 65 years in the zoledronic acid arm (37.8% versus 33.7% in the denosumab arm), and there were more men in the denosumab arm (66.4% versus 62% in the zoledronic acid arm). In general, reasons for treatment discontinuation were similar between the two treatment arms.

Table 14 Baseline Disease Characteristics and Stratification Factors from Study 244

	Denosumab (N=886)	Zoledronic Acid (N=890)
Stratum: Tumor Type (assigned*)		
Multiple Myeloma	86 (9.7%)	93 (10.4%)
Non-Small Cell Lung Cancer	343 (38.7%)	345 (38.8%)
Other	457 (51.6%)	452 (50.8%)
Stratum: Previous SRE		
Yes	440 (49.7%)	446 (50.1%)
No	446 (50.3%)	444 (49.9%)
Stratum: Systemic Anti-Cancer Treatment		
Yes	746 (84.2%)	747 (83.9%)
No	140 (15.8%)	143 (16.1%)
ECOG Performance Status at Baseline		
0	240 (27.1%)	236 (26.5%)
1	508 (57.3%)	492 (55.3%)
2	136 (15.3%)	157 (17.6%)
Missing	2 (0.2%)	5 (0.6%)
Number of Metastatic Bone Lesions		
≤ 2	749 (84.5%)	746 (83.8%)
> 2	137 (15.5%)	144 (16.2%)
Time from Cancer Diagnosis to 1st Bone Metastasis (Months)		
Mean (St. Dev.)	13.3 (28.7)	14.3 (32.0)
Median (Q1, Q3)	2.1 (0.0, 15.0)	2.9 (0.0, 14.5)

*Note that this number differs from *verified* tumor types in Table 15 below

Table 15 (using data from the Applicant's CSR) shows that the distribution of patients with the most common tumor types was similar in the two arms.

Table 15 Most Frequent Tumor Types (≥ 2% in either arm) Enrolled In Study 244

	Denosumab (N=886)	Zoledronic Acid (N=890)
Non-small cell lung cancer	350 (39.5%)	352 (39.6%)
Multiple myeloma	87 (9.8%)	93 (10.4%)
Renal	70 (7.9%)	85 (9.6%)
Small cell lung cancer	61 (6.9%)	48 (5.4%)
Unknown primary	31 (3.5%)	27 (3.0%)
Colon	30 (3.4%)	29 (3.3%)
Bladder	28 (3.2%)	35 (3.9%)
Rectal	25 (2.8%)	35 (3.9%)
Head and neck	24 (2.7%)	19 (2.1%)
Gastric	19 (2.1%)	16 (1.8%)
Cervix	18 (2.0%)	25 (2.8%)

Results

Table 16 presents results of the primary and secondary analyses from the statistical review (Dr. Yuan) using data submitted by the Applicant. In Study 244, denosumab was non-inferior to zoledronic acid in the analysis of time to first on-study SRE. Denosumab was not superior (statistically) to zoledronic acid in time to first on-study SRE or time to first and subsequent on-study SRE. Sensitivity analyses of non-inferiority including the per-protocol analysis and an analysis using verified strata supported the overall study results. Additionally, a sensitivity analysis conducted by the statistical reviewer indicated that although the results were not statistically superior, numerically the median time to first on-study SRE and HR for first on-study SRE favored denosumab.

Figure 4, copied from the statistical review, shows a proportional hazard for each KM curve throughout the study and that the KM curves appear to separate prior to month five. The curves remain separate throughout the course of the study.

Table 16 Solid Tumors and Multiple Myeloma (244) Study: Results of Primary and Secondary Analyses

Endpoint	Median time to SRE in Months		HR (95% CI)	p-value
	D	ZA		
1st SRE (NI)	20.5	16.3	0.84 (0.71, 0.98)	0.0007*
1st SRE (superiority)	20.5	16.3	0.84 (0.71, 0.98)	0.060#
1st and subsequent SRE (Superiority)	NA	NA	0.90 (0.77, 1.04)	0.145$

*Cox-model synthesis method; #Log-rank, adjusted; $Cox-model, adjusted

Figure 4 Time to First on-Study SRE, Study 244

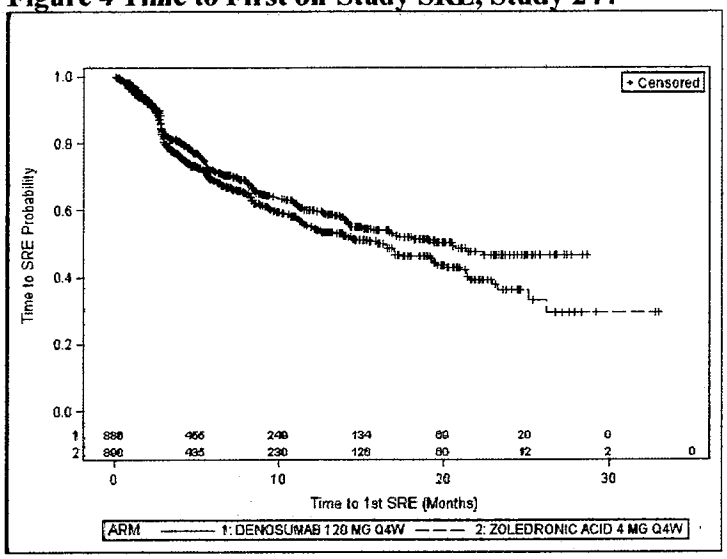


Table 17 shows the components of the first on-study SREs as determined in the statistical review. Overall, as occurred in Studies 103 and 136, pathological fractures and radiation to bone comprised most of the SREs.

Table 17 Components of First on-Study SREs

SRE	Denosumab (N=1026)	Zoledronic Acid (N=1020)
Pathologic fracture	119 (13.4%)	144 (16.2%)
Radiation to bone	122 (13.8%)	139 (15.6%)
Surgery to bone	13 (1.5%)	19 (2.1%)
Spinal cord compression	24 (2.7%)	21 (2.4%)
Total	278 (31.4%)	323 (36.3%)

Table 18 shows the results obtained from the FDA statistical review of exploratory endpoints. The point estimates for the HRs for first SRE or HCM (hypercalcemia of malignancy) and first symptomatic SRE were consistent with the results of the primary and secondary endpoints. The point estimate for the HR for OS favored denosumab slightly although median overall survival was slightly longer in the zoledronic acid arm. The KM curves for OS, in general, appeared superimposed between the two treatment arms.

Table 18 Exploratory Endpoints for Study 244 (Solid Tumors and Multiple Myeloma)

Endpoint	Number of events (%)		Median (in mos.)		HR
	D	ZA	D	ZA	(95% CI)
1st SRE or HCM	287	336	19.0	14.4	0.83 (0.71, 0.97)
OS	479	474	12	12.6	0.95 (0.84, 1.08)
PD in bone	283	292	13.9	13.6	0.98 (0.83, 1.16)
PFS	687	679	5.4	5.5	1.01 (0.91, 1.12)
1st symptomatic SRE	200	228	NE	28.3	0.84 (0.69, 1.02)

A subgroup analysis of Study 244 revealed a potential concern regarding a negative effect of denosumab for patients diagnosed with multiple myeloma. The hazard ratio point-estimate for this subgroup was worse for denosumab-treated patients diagnosed with multiple myeloma in regards to time to first on-study SRE (Table 19: copied from the statistical review). More concerning to this reviewer was the effect on overall survival (Table 20: copied from the statistical review). The point estimate for the HR was 2.26 (worse for denosumab-treated patients) and the confidence interval excluded one.

Overall, few events occurred in the multiple myeloma subgroup analysis, so the results should be interpreted with caution. At this time, however, this reviewer recommends excluding patients with multiple myeloma from the overall indication statement (i.e., with a limitation of use). Nevertheless, because of the uncertainty regarding the subgroup effect, it may be reasonable to allow additional studies to determine whether denosumab may benefit patients with multiple myeloma (assuming adequate informed consent, close monitoring, and DSMB oversight).

Table 19 Results of Time to First on-Study SRE Analysis – Multiple Myeloma Subgroup

	Denosumab	Zoledronic Acid
	N = 87	N = 93
Number of Events (%)	44 (50.6%)	46 (49.5%)
Median Time to 1st SRE (95% CI)	14.2 (8.4, NE)	16.6 (9.5, 25.2)
HR (95% CI)	1.03 (0.68, 1.57)	

Table 20 OS Analysis – Multiple Myeloma Subgroup

	Denosumab	Zoledronic Acid
	N = 87	N = 93
Number of Deaths (%)	23 (26.6%)	13 (14.0%)
Median Survival (95% CI)	NE	NE (28.4, NE)
HR (95% CI)	2.26 (1.13, 4.50)	

8. Safety

8.1 Adequacy of database, major safety findings

This reviewer considered the size of the safety database as adequate. A total of 2,841 patients received denosumab in Studies 103, 136, and 244 at the dosing schedule proposed in product labeling (in addition to additional safety information submitted to the original BLA). As described in the safety review, median cumulative exposure to denosumab was 12 months in Study 103, 16 months in Study 136, and 7 months in Study 244. Key safety findings included increased mortality in a subgroup of patients with multiple myeloma (n = 180) in Study 244; hypocalcemia; and osteonecrosis of the jaw.

Table 21, copied from Dr. Pradhan's review, summarizes denosumab and zoledronic exposure information from each trial. In general, patients in both arms received investigational product for similar durations. Exposure was probably of shorter duration in Study 244 because patients in this study were diagnosed with more aggressive malignancies.

Table 21 Exposure Summary by Trial

	103 (Prostate)		136 (Breast)		244 (Other)	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=943	n=945	n=1020	n=1013	n=878	n=878
Median # of doses	13	10	18	17	7	7
Mean study duration (months)	13.2	12.6	15.9	15.9	9.7	9.7

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

8.2.1 Deaths

In general, the incidence rates of fatal events were balanced between the two treatment groups. As described in the safety review, investigators reported a total of 1,638 fatal adverse events in Studies 104, 136, and 244 (both treatment groups). In the pooled analysis of the three studies (Table 22, data obtained from Dr. Pradhan's review) no single preferred term (fatal event analysis) occurred with a 0.5% or higher incidence rate in the denosumab group as compared to the zoledronic acid group. One case of sudden death was reported in a patient diagnosed with Grade 4 hypocalcemia during the same day. In general, the safety reviewer found that disease progression caused most events described as "respiratory failure," during an audit of selected "respiratory failure" events.

In the HLT analysis (refer to Dr. Pradhan's review), the largest difference between groups (with a higher incidence rate for denosumab) was for hepatic failure and associated disorders (1.2% versus 7%). Liver metastases or disease progression in the liver primarily caused hepatic failure in these patients.

Table 22 Incidence Rate of Most Common Fatal Adverse Events (Pooled Analysis of Studies 103, 136, and 244)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Malignant neoplasm progression	93	3.3	84	3.0
Respiratory failure	66	2.3	55	1.9
Metastases to central nervous system	38	1.3	31	1.1
General physical health deterioration	35	1.2	44	1.6
Multi-organ failure	32	1.1	31	1.1
Hepatic failure	30	1.1	19	0.7
Cardiac failure	27	1.0	24	0.9
Metastases to liver	27	1.0	28	1.0
Dyspnea	22	0.8	18	0.6
Prostate cancer	21	0.7	43	1.5
Death	19	0.7	19	0.7
Cachexia	15	0.5	21	0.7

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Cardio-respiratory arrest	15	0.5	17	0.6
Pneumonia	15	0.5	14	0.5
Cardiac arrest	14	0.5	9	0.3
Disease progression	14	0.5	21	0.7
Metastases to bone	13	0.5	7	0.3
Metastasis	12	0.4	7	0.3
Breast cancer	11	0.4	14	0.5
Cardiopulmonary failure	11	0.4	18	0.6
Pulmonary embolism	10	0.4	8	0.3
Cerebrovascular accident	8	0.3	7	0.3
Sepsis	8	0.3	9	0.3
Myocardial infarction	7	0.3	6	0.2
Prostate cancer metastatic	7	0.3	13	0.5

8.2.2 SAEs

In general, the incidence rates of most serious adverse events were balanced between the two treatment groups. Osteonecrosis and hypocalcemia were clear treatment related adverse reactions caused by denosumab. SAEs due to fatigue occurred at a 0.9% higher incidence rate in the denosumab group compared to the zoledronic acid group (1.6% versus 0.7%). In the pooled analysis, CVAs (preferred term) occurred more frequently in patients treated with denosumab (0.8% versus 0.3%); however, this difference primarily occurred in Study 103 and was not consistent in the other two studies.

Table 23 shows the per-patient incidence rate (using data obtained from Dr. Pradhan's review) of SAEs occurring in the pooled analysis of Studies 103, 136, and 244. The table only includes SAEs occurring at a per-patient incidence rate > 1% in the denosumab arm. Refer to the clinical review for a more complete list of SAEs and the SAE analyses from the individual studies.

Table 23 Incidence Rate of Most Common Serious Adverse Events (Pooled Analysis of Studies 103, 136, and 244)

SAE PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Anemia	160	5.6	163	5.8
Dyspnea	144	5.1	120	4.2
Pneumonia	112	3.9	93	3.3
Malignant neoplasm progression	111	3.9	110	3.9
Metastases to central nervous system	104	3.7	96	3.4
Respiratory failure	89	3.1	74	2.6
Dehydration	84	3	77	2.7
Vomiting	76	2.7	77	2.7
General physical health deterioration	75	2.6	81	2.9
Asthenia	70	2.5	59	2.1
Pyrexia	66	2.3	65	2.3
Pleural effusion	59	2.1	61	2.2

SAE PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Spinal cord compression	57	2	67	2.4
Back pain	52	1.8	69	2.4
Pulmonary embolism	50	1.8	52	1.8
Metastases to liver	49	1.7	46	1.6
Fatigue	46	1.6	21	0.7
Febrile neutropenia	46	1.6	61	2.2
Bone pain	45	1.6	62	2.2
Diarrhea	45	1.6	42	1.5
Urinary tract infection	44	1.6	48	1.7
Nausea	43	1.5	53	1.9
Abdominal pain	41	1.4	43	1.5
Hypocalcaemia	41	1.4	17	0.6
Neutropenia	40	1.4	29	1
Osteonecrosis	39	1.4	19	0.7
Thrombocytopenia	39	1.4	39	1.4
Cardiac failure	37	1.3	35	1.2
Multi-organ failure	37	1.3	35	1.2
Renal failure	37	1.3	50	1.8
Hepatic failure	36	1.3	26	0.9
Urinary retention	36	1.3	44	1.6
Prostate cancer	34	1.2	56	2
Pain	32	1.1	26	0.9
Hematuria	31	1.1	39	1.4
Decreased appetite	30	1.1	28	1
Sepsis	30	1.1	26	0.9

8.2.3 Drop-outs and discontinuations due to adverse events

Most adverse events cited by investigators as reasons for discontinuation of study drug occurred at similar frequencies irrespective of study arm (see Table 24 using data obtained from Dr. Pradhan's review). Osteonecrosis and hypocalcemia were adverse reactions directly attributable to denosumab that caused drug discontinuation (or study drop-out) in 1.1% and 0.7% of patients, respectively.

Table 24 Incidence Rate of Adverse Events Leading to Drug Discontinuation (Pooled Analysis of Studies 103, 136, and 244)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Malignant neoplasm progression	42	1.5	43	1.5
Osteonecrosis	32	1.1	20	0.7
General physical health deterioration	27	1.0	29	1.0
Hypocalcaemia	20	0.7	1	0.0

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Fatigue	19	0.7	15	0.5
Metastases to central nervous system	19	0.7	24	0.9
Asthenia	18	0.6	24	0.9
Dyspnea	17	0.6	13	0.5
Renal failure	14	0.5	13	0.5
Metastases to liver	11	0.4	12	0.4
Respiratory failure	10	0.4	6	0.2
Spinal cord compression	10	0.4	10	0.4

8.2.4 Common adverse events

Attribution of adverse events was difficult for this application for two reasons: no placebo arm, and frequent co-administration of anti-cancer therapies that resulted in additional toxicities (i.e., nausea, diarrhea). For inclusion in product labeling, the review team agreed to include adverse reactions reported in at least 10% of denosumab-treated patients and occurring either with at least 1% greater incidence in the denosumab group, or with a between-group difference of less than 1% and more than 5% greater incidence in patients treated with zoledronic acid compared to placebo (per the US Prescribing Information for zoledronic acid). The review team recommended inclusion of osteonecrosis of the jaw in product labeling despite a per-patient incidence rate of < 10% because osteonecrosis is serious and is a rare event in the absence of drugs that inhibit bone turnover. As shown in Table 25 adapted from Dr. Pradhan's review, most adverse events occurred at the same (or near the same) per-patient incidence rate irrespective of treatment arm (refer to Dr. Pradhan's review for individual analyses from the three studies). Hypocalcemia (and severe hypocalcemia) occurred more frequently in denosumab-treated patients as compared to zoledronic acid-treated patients.

Table 25 Incidence Rate of Most Common Adverse Events (Pooled Analysis of Studies 103, 136, and 244)

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=2841	n=2836	n=2841	n=2836
	%	%	%	%
Nausea	31	32	2	3
Anemia	27	30	11	12
Fatigue	27	27	7	6
Back pain	25	26	5	7
Decreased appetite	23	25	3	3
Asthenia	21	22	6	6
Constipation	21	24	1	2
Dyspnea	21	18	8	7
Diarrhea	20	19	3	2
Arthralgia	20	22	3	3

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=2841	n=2836	n=2841	n=2836
	%	%	%	%
Vomiting	20	20	3	3
Bone pain	20	23	6	6
Pain in extremity	18	19	3	4
Edema peripheral	17	16	1	1
Cough	15	15	1	1
Pyrexia	14	20	1	1
Headache	13	13	1	1
Musculoskeletal pain	13	14	2	2
Weight decreased	12	12	1	1
Insomnia	11	11	0	0
Abdominal pain	10	10	2	2
Neutropenia	10	10	7	7
Alopecia	9	9	0	0
Hypocalcaemia	9	5	4	2
Chest pain	9	9	2	2
Dizziness	8	9	1	1
Pain	8	9	2	2
Urinary tract infection	8	9	1	2
Thrombocytopenia	8	7	4	4
Anxiety	7	6	1	0
Rash	7	7	0	0
Depression	7	6	0	1
Musculoskeletal chest pain	7	7	1	1
Dehydration	6	6	3	3
Paresthesia	6	7	0	0
Abdominal pain upper	6	6	1	1
Leucopenia	6	6	3	3
Rib fracture	6	6	0	0

8.2.5 Laboratory tests

The safety review showed that hypocalcemia and hypophosphatemia (including severe events) occurred more frequently in patients treated with denosumab compared to patients treated with zoledronic acid. A total of 3% of patients with Grade 0 hypocalcemia at baseline developed ≥ Grade 3 hypocalcemia in the denosumab arm. Based on these analyses, DBOP recommended revising the label to include information describing hypocalcemia using laboratory derived values.

Elevated creatinine levels occurred more frequently in patients treated with zoledronic acid compared to patients receiving denosumab.

8.3 Immunogenicity

Refer to Section 5.3 above.

8.4 Special safety concerns

Dr. Pradhan conducted additional analyses of hypocalcemia, osteonecrosis of the jaw, injection-related reactions, cardiac events, renal toxicity, infections, malignancies, and acute phase reactions.

In the pooled analyses of the three studies, the per-patient incidence rates for cardiac events, infections, and new malignancies were balanced between the treatment arms. Acute phase reactions were uncommon with both drugs; however, fever occurred more frequently with zoledronic acid than denosumab. Renal toxicity also occurred more frequently in patients receiving zoledronic acid.

As described in the laboratory section of this review, hypocalcemia occurred more frequently following denosumab. The proposed label includes a warning describing hypocalcemia. Osteonecrosis of the jaw also occurred more frequently following denosumab compared to zoledronic acid (1.8% and 1.3%, respectively). Approximately half of positively adjudicated ONJ events required surgery; and three denosumab-treated patients required bone resection. Most patients diagnosed with ONJ in both treatment groups had a potential additional risk factor for ONJ including tooth extraction, poor oral hygiene, or use of a dental appliance.

8.5 Discussion of primary reviewer's comments and conclusions

Overall, Dr. Pradhan concluded that denosumab has an acceptable risk-benefit profile for the prevention of skeletal related events in patients with bone metastases from solid tumors. The two major safety concerns for this application were hypocalcemia and osteonecrosis of the jaw. Oncologists can manage hypocalcemia through frequent monitoring and calcium repletion. Osteonecrosis of the jaw can be more difficult to manage and required surgery in approximately half of patients who developed ONJ. The per-patient incidence rate of positively adjudicated ONJ occurring during the primary analysis phases of the three studies was 0.5% higher in the denosumab group compared to the zoledronic acid group (1.8% versus 1.3%, respectively). This 0.5% incidence rate translates into 1 additional ONJ event occurring above the background zoledronic acid ONJ rate for every 200 patients treated with denosumab.

8.6 Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed

There were no major differences between the CDTL and the primary review team regarding this section of the application.

9. Advisory Committee Meeting

An advisory committee meeting was not held regarding this supplemental BLA. Consistent results across the three studies confirmed the robustness of the findings regarding this application. An advisory committee meeting was previously held regarding the original denosumab BLA submission.

10. Pediatrics

In the sBLA submission, Amgen requested a deferral of PREA requirements for all age groups. Amgen stated in the sBLA that the denosumab pediatric development plan is predicated on the determination of a positive benefit-risk profile in adult patients with solid tumors and bone metastases based on the data submitted in the advanced cancer marketing application and completion of two nonclinical studies in models of pediatric neuroblastoma. In the Amgen pediatric submission, Amgen cited results from non-clinical studies suggesting that the use of denosumab in children (with growing bones) may result in widened growth plates, decreased long bone growth, and impaired dentition.

In the pediatric document sent to the RPM on July 16, 2010, the DBOP clinical review team informed the PeRC that Amgen requested a deferral of PREA requirements, based on the indication sought for this efficacy supplement. The document described specific safety concerns in children based on denosumab-related effects on bone growth and remodeling. Specifically the concern is for skeletally immature children who are receiving anti-cancer therapy with curative intent. In the neonatal study (Report 20080340), RANKL inhibitor OPG-Fc treated rats exhibited greater reductions in skeletal growth and exhibited inhibited incisor growth along with prevention of molar eruption. In a longer term recovery study (20090070), rats exhibited modest epiphyseal growth plate changes after discontinuing OPG-Fc and decreased bone size when compared to the control vehicle group. Report 20090282 showed that weekly OPG-Fc caused osteopetrosis-like changes in rats at the 10mg/kg dose level. Additionally, histopathological assessments of the tibia showed disorganized growth plate morphology. Amgen concluded from non-clinical studies that denosumab carries risks (in patients with rapidly growing bones) from widened growth plates, decreased long bone growth, and impaired dentition. The pediatric document informed the PeRC that Amgen will conduct two additional pharmacology studies in mice using a neuroblastoma model.

The PeRC met on 9/22/2010 and agreed that deferral of the PREA requirements was justified. During the meeting, the PeRC recommended the institution of a broad PREA PMR (refer to Section 13.4 below); however, reconsideration of PREA PMRs, and the potential risk-benefit profile of denosumab in children, will be made by FDA following the pediatric subcommittee of the ODAC meeting tentatively planned during the forth quarter of 2010. Specifically, FDA will consider the safety of denosumab in children with rapidly growing bones and whether the endpoint of SREs is applicable for pediatric patients with solid tumors.

In the PeRC meeting minutes, the PeRC recommended that the Division consider making "wanted" preclinical data as a PREA PMR. Because Amgen will conduct the additional non-clinical studies in neuroblastoma models rather than solid tumor models, the Division believes that these non-clinical pharmacology studies may not be applicable to the current application. Additionally, FDA expects that Amgen will submit any findings from these studies in laboratory animals that suggest a significant risk for human subjects in accordance with 21 CFR 312.32.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

Based on the review of CRFs by the clinical reviewer and preliminary inspection findings of study sites by DSI (verbally communicated during an internal review-team meeting), the primary data submitted to this application were found to be reliable for the primary analyses of safety and efficacy. The Applicant certified that no services were rendered in connection with this application by any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act.

11.2 Financial disclosures

Section 3.3 of the clinical review describes investigators and sub-investigators with financial conflicts of interest who participated in the conduct of the three trials supporting this efficacy supplement. Ultimately, the design of the studies minimized the chance that these investigators unduly influenced the outcomes of the studies (double-blind, double-dummy, large international studies).

11.3 GCP issues

The clinical study reports submitted to the sBLA contained statements that the respective studies were conducted under ICH GCP guidelines. Amgen submitted accompanying Audit Certificates (for sites audited) to the sBLA.

11.4 DSI audits

DSI completed the clinical inspection summary for this application on 11/8/2010. The review division and DSI chose clinical sites for inspection based on the size of the enrolled study population, number of major protocol violations, financial conflicts of interest, or high rate of treatment responders. DSI also conducted inspections of the CRO, (b) (4)

Table 26 shows the interim DSI inspection results at each site. No sites received an interim classification of OAI. Overall, DSI determined that based on the preliminary inspection findings, data from these sites were reliable and could be used in support of the efficacy supplement.

Table 26 DSI Inspection Results by Site

Site	Protocols	Number Subjects at Site	Inspection Dates	Interim Classification
Dr. Ronaldo Damiao Hospital Universitario Pedro Ernesto Rio de Janeiro, Brazil	20050103	42	9/27/2010 - 9/30/2010	NAI
Dr. Karim Fizazi Institut Gustave Roussy Villejuif, France	20050103	42	10/11/2010 - 10/15/2010	VAI
Dr. Alexey Manikhas City Oncology Dispensary Saint Petersburg, Russia	20050136	25	9/27/2010 - 10/1/2010	NAI

Site	Protocols	Number Subjects at Site	Inspection Dates	Interim Classification
Dr. Jose R. Pereira Instituto do Cancer Arnaldo Sao Paulo, Brazil	20050244	40	9/20/2010 - 9/24/2010	NAI
Dr. Maciej Krzakowski Instytut im. M. Sklodowskiej-Cuire-Centurm Onkologii Warszawa, Poland	20050244	27	10/4/2010 - 10/8/2010	VAI
Dr. Veena Charu Pacific Cancer Center Anaheim, CA 92801	20050103 20050244	6/15	8/19/2010 - 8/26/2010	NAI
[redacted]				(b) (4)

11.5 Other discipline consults

11.5.1 Maternal Health Team

The MHT recommended the addition of a pregnancy category classification and other "minor revisions" to the pregnancy subsection of the label. Based on the MHT recommendations, "Pregnancy Category C" was added to product labeling.

11.5.2 DRISK

DRISK concluded that "after review of the comparison of the risk management approaches for drugs with similar risks and/or similar indications, it is reasonable not to require additional risk mitigation measures to address the risks of dermatologic adverse events, infection, hypocalcemia, use in severe CKD/ESRD, and ONJ."

12. Labeling

12.1 Proprietary name

DMEPA notified DBOP by email on October 20, 2010 that the proposed trade name Xgeva was acceptable from a look-alike and sound-alike perspective.

12.2 Labeling issues raised by DDMAC

The following labeling issues were raised in the DDMAC review.

- Update the Highlights Section to be consistent with the Full Prescribing Information *(DBOP's intent was to revise the highlights section when the Full Prescribing Information was near completion).*
- DDMAC raised the issue whether malignancies should be designated as "advanced" in the indication statement. *Comment: This CTDL reviewer considers any patient with solid tumors metastatic to bone to have an "advanced" malignancy (especially patients with common tumors including breast cancer, castrate-resistant prostate cancer, and lung cancer); thus it is not necessary to use the word "advanced" in the indication statement.*

- DDMAC recommended changes to the Warnings and Precautions Section regarding multiple myeloma. *Comment:* (b) (4) (b) (4) *The review team recommended including this information in Section 14 with a limitation of use in the Indication statement.*
- DDMAC recommended removing the statement (b) (4) (b) (4) (b) (4) *Comment: DBOP agreed with this recommendation.*
- DDMAC recommended against inclusion of p-values for secondary endpoints unless there was a clear rule for alpha spending. *Comment: As described in Section 7, the protocols pre-specified clear rules for alpha spending and thus, these claims were adequately supported.*

12.3 Physician labeling

In general, DBOP revised all sections of the label for brevity and clarity. Command language was preferred as directed by the PLR. The remainder of this section of the review will only focus on high-level issues regarding the label submitted by Amgen. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections (for example, if only minor edits were made to a section). This CDTL agreed with the recommendations made by the review teams that are described below.

1. Indications and Usage

Because the treatment effect of denosumab involves prevention of SREs, DBOP recommended revision of the indication statement to highlight this effect rather than the indication proposed by the Applicant (b) (4)

The review team recommended that the indication statement include a limitation of use for patients with multiple myeloma based on data presented in Section 7.3.3 of this review.

2. Dosage and Administration

Consistent with guidance from the PLR, the statement (b) (4) (b) (4)

4. Contraindications

No change was made to the proposed contraindication section. This reviewer comments that Prolia contains a contraindication for hypocalcemia and the proposed Xgeva label does not. Similarly, Zometa (zoledronic acid—skeletal related events and hypercalcemia indication) does not have a contraindication for hypocalcemia whereas the Reclast (zoledronic acid—osteoporosis indications) label contains a contraindication for hypocalcemia. In the oncology setting, physicians are trained to monitor patients frequently and manage severe toxicities. Oncologists may consider a contraindication statement as forbidding treatment with denosumab for any patient with a previous history of hypocalcemia. The Warnings and Precautions section of the label instructs physicians that denosumab can cause severe hypocalcemia and to correct hypocalcemia prior to treatment.

5. Warnings and Precautions

- DBOP recommended removal of the Warning for skin infections as skin infections occurred at nearly the same incidence rate in both arms in the pooled analysis of the advanced cancer studies (0.9% versus 0.7% with zoledronic acid).
- (b) (4)
  (b) (4)
  Additionally, DBOP review staff recommended inclusion of a limitation of use to the indication statement.

6. Adverse Reactions

- DBOP added statements as to the most common serious adverse reactions and most common adverse reactions resulting in denosumab discontinuation.
- DBOP removed from the Adverse Reactions table any adverse events that could not be considered related to denosumab as described in the PLR Labeling Guidance.
- DBOP recommended inclusion of additional information (using laboratory derived data) regarding severe mineral and electrolyte (i.e., hypocalcemia and hypophosphatemia) abnormalities.

8. Use in Specific Populations

- DBOP and OCP revised the label to include additional information regarding the risk of hypocalcemia in patients with renal impairment based on a study of 55 patients without cancer and with varying degrees of renal function who received a single dose of 60 mg denosumab.
- (b) (4)

13. Clinical Pharmacology

(b) (4)

14. Clinical Studies Section

- DBOP added additional information describing the study designs and included demographic information (as recommended by the PLR guidance).
- (b) (4)
- Information regarding the specific components of the composite SRE endpoint was added to the label (as recommended in PLR guidance).

12.4 Carton and immediate container labels

DMEPA and OBP agreed that the final version of the carton and container labels were acceptable.

12.5 Patient labeling/Medication Guide

Because denosumab as Xgeva will be administered to patients by oncologists who are trained to consent patients prior to administering therapies and to adequately monitor patients, a specific Medication Guide was not required in the oncology setting. Similarly Zometa (zoledronic acid) does not have a MedGuide.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This Cross Discipline Team Leader recommends approval of BLA STN 125320/7 submitted under section 351 of the Public Health Service Act. All review teams recommended approval or have reported that there were no findings that would prevent approval.

13.2 Risk-benefit assessment

This CDTL reviewer recommends approval of this efficacy supplement (STN 125320/7) based on consistent results from three studies showing that denosumab delays the occurence of SREs in patients with solid tumors and osseous metastases. Prevention of SREs, especially reduction of pathological fractures, is an important clinical effect in patients with solid tumors metastatic to bone and treatment with bisphosphonates is currently considered standard therapy for these patients.

Two studies (breast and prostate cancer) demonstrated the superiority of denosumab over zoledronic acid in prolonging the time to first on-study SREs. In Study 103, median time to first on-study SRE was 17.1 months for zoledronic acid and 20.7 months for denosumab (HR = 0.82: superiority p-value 0.008). In Trial 136, median time to first on-study SRE was 26.4 months for zoledronic acid and was not reached for denosumab (HR = 0.82: superiority p-value 0.010). Additionally, the HRs (for the exploratory endpoint) of time to first *symptomatic* SRE were 0.78 and 0.76 in Studies 103 and 136, respectively (95% CIs excluded 1 in both studies). The symptomatic events analyses in the double-blinded trials provided additional evidence that denosumab provided clinical benefit to patients diagnosed with solid tumors metastatic to bone. Finally, Study 244 demonstrated non-inferiority in the time to first on-study SRE compared to zoledronic acid. The HR of 0.84 was similar to the HRs of 0.82 in the breast and prostate cancer studies. The 95% CI for the HR (for time to first on-study SRE) excluded 1; however, superiority was not demonstrated over zoledronic acid because of the pre-specified method to control type I error.

Overall the safety profile of denosumab was similiar to that of zoledronic acid. The incidence of hypocalcemia was higher for denosumab-treated patients and close monitoring of hypocalcemia will be required. The incidence rate of osteonecrosis of the jaw was slightly higher for denosumab-treated patients compared to those treated with zoledroinc acid. The per-patient incidence rate of positively adjudicated ONJ occurring during the primary analysis phases of the three studies was 0.5% higher in the denosumab group compared to the zoledronic acid group (1.8% versus 1.3%, respectively). This 0.5% incidence rate translates into 1 additional ONJ event occurring above the background zoledronic acid ONJ rate for every 200 patients treated with denosumab. This compares to the benefit of an improvement in the mean number of SREs per patient (in the first and subsequent on-study SRE analysis) of

0.14, 0.05, and 0.09 in Studies 136, 244, and 103, respectively. Thus, denosumab (compared to zoledronic acid) prevents more SREs compared to the additional number of ONJ events caused by denosumab.

No trends indicating a potential overall survival difference (or difference in PFS) were observed when evaluating the OS data submitted to this application.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

Review staff did not recommend any new postmarketing Risk Evaluation and Management Strategies for the population of patients with advanced cancer and osseous metastases.

13.4 Recommendation for other postmarketing requirements and commitments

The review team in consultation with PeRC proposed the following postmarketing requirements (PMRs) and postmarketing commitments (PMCs). The exact language (including dates) of the PMRs is pending final sign-off at the Division, Office, and OND levels.

The first three PMRs are PREA requirements. The PeRC committee recommended a broad PMR on 9/22/2010; however, due to the concerns regarding the safety of denosumab in children with immature skeletons and whether the endpoint "skeletal related event" is applicable to pediatric patients with solid tumors, both the PeRC and DBOP review staff acknowledged that changes may need to be made to these PREA PMRs post-approval. Because of the complex issues related to the safety of denosumab in pediatric patients with advanced cancer, Amgen has agreed to participate in a discussion of denosumab for the prevention of SREs in children with solid tumors at a meeting of the Pediatric Subcommittee of the Oncology Drugs Advisory Committee scheduled during the fourth quarter of 2010. Following the meeting, DBOP review staff will reassess the risk-benefit consideration of denosumab in pediatric patients with solid tumors and determine whether some or all components of PREA should be waived in children.

DBOP recommended the fourth PMR to determine whether denosumab can be safely administered to patients with severe renal insufficiency. Amgen excluded these patients from the advanced cancer studies because of the risk of renal failure related to zoledronic acid (in these patients). Based on the pharmacodynamic profile of denosumab, review staff expects hypocalcemia to be the major safety concern for this population.

Finally, FDA requested a PMC in order to collect all survival information that will be collected from Trials 103, 136, and 244. The review Division intends to confirm the results submitted to the sBLA showing that no concerning trends regarding OS are present when taking the totality of the data into context.

1. A phase 1, open-label, dose-finding pharmacokinetic, pharmacodynamic, and safety study in pediatric patients ages 0 to 18 years who are diagnosed with solid tumors metastatic to bone. The study will determine whether a safe dose can be administered to patients in subsequent phase 2 and phase 3 studies.

The timetable you submitted on October 29, 2010 states that you will submit this study report according to the following timetable.

Final Protocol Submission: December 30, 2011
Study Completion Date: March 31, 2014
Final Report Completion: September 30, 2014

2. A phase 2, open-label, single-arm study in pediatric patients ages 0 to 18 with solid tumors with bone metastases to determine the safety, including effects on growing bones, and activity of denosumab in the prevention of skeletal related events.

   The timetable you submitted on October 29, 2010 states that you will submit this study report according to the following timetable.

   This study must not be initiated until at least one month after you have submitted the complete study report for post marketing requirement 1.

   Final Protocol Submission: September 30, 2014
   Study Completion Date: September 30, 2018
   Final Report Submission: March 31, 2019

3. A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of denosumab for the prevention of skeletal related events in pediatric patients ages 0 to 18 with solid tumors and bone metastases.

   This study must not be initiated until at least one month after you have submitted the complete study report for post marketing requirements 1 and 2.

   The timetable you submitted on October 29, 2010 states that you will submit this study report according to the following timetable

   Final Protocol Submission: March 31, 2019
   Study Completion Date: March 31, 2025
   Final Report Submission: September 30, 2025

4. To conduct a clinical trial to determine the safety of denosumab 120 mg administered every four weeks by subcutaneous injection in patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) and in patients receiving dialysis. The number of patients enrolled in the trial and the frequency and duration of plasma sampling will be sufficient to estimate the incidence and severity of hypocalcemia, hypomagnesemia, and hypophosphatemia in this patient population. The final report should include the primary and derived datasets and analysis programs used to generate the safety and laboratory analyses.

   The timetable you submitted on October 29, 2010 states that you will conduct this trial according to the following schedule:

   Final Protocol Submission: March 31, 2011
   Trial Completion Date: June 30, 2012
   Final Report Submission: December 31, 2012

5. To submit a final report that includes updated results for overall survival for trials 20050103 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer;" 200050136 entitled "A Randomized, Double-blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects With Advanced Breast Cancer;" and 20050244 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma." The final report should also include the primary and derived datasets and analysis programs used to generate the overall survival results reported.

The original protocol for clinical trial 20050103 was submitted to FDA on January 13, 2006 and began patient accrual on May 12, 2006. The original protocol for clinical trial 20050136 was submitted to FDA on January 13, 2006 and began patient accrual on April 27, 2006. The original protocol for clinical trial 20050244 was submitted to FDA on May 2, 2006 and began patient accrual on June 21, 2006.

The timetable you submitted on October 07, 2010 states that you will conduct the trials according to the following schedule:

Final Report Submission: October 1, 2012.

Signature:

_____ 11/17/2010

Steven Lemery, M.D., M.H.S.
Cross Discipline Team Leader
OODP/DBOP

Cross Discipline Team Leader Review

Signature:

Steven Lemery 11/17/2010 11/17/2010

Steven Lemery, M.D., M.H.S.
Cross Discipline Team Leader
OODP/DBOP

PMC/PMR Development Templates

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A phase 1, open-label, dose-finding pharmacokinetic, pharmacodynamic, and safety study in pediatric patients ages 0 to 18 years who are diagnosed with solid tumors metastatic to bone. The study will determine a whether a safe dose can be administered to patients in subsequent phase 2 and 3 studies.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	12/30/2011
Study/Clinical trial Completion Date:	03/31/2014
Final Report Submission Date:	9/30/2014
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☒ Theoretical concern
- ☒ Other

Deferred PREA study. There is also a safety concern related to bone growth in skeletally immature patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Satisfy PREA requirement.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Phase 1, dose-finding, study to deterimine if a safe dose can be adminstered to pediatric patients.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☒ Other (provide explanation)

PREA study

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Summe

_____

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A phase 2, open-label, single-arm study in pediatric patients ages 0 to 18 with solid tumors with bone metastases to determine the safety, including effects on growing bones, and activity of denosumab in the prevention of skeletal related events.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	9/30/2014
Study/Clinical trial Completion Date:	09/30/2018
Final Report Submission Date:	03/31/2019
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☒ Theoretical concern
- ☒ Other

Deferred PREA study. There is also a safety concern related to bone growth in skeletally immature patients. Phase 2 study will deterimine additional safety data including effects on growing bones and whether there is sufficient justification to intiate a phase 3 study to determine the safety and efficacy of denosumab for the pediatric population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Satisfy PREA requirement.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☒ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Phase 2, single-arm study in pediatric patients to determine whether there is sufficient justification to initiate a phase 3 study to determine the safety and efficacy of denosumab for the pediatric population.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☒ Other (provide explanation)
  PREA study

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Summer

_____

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of denosumab for the treatment of pediatric patients ages 0 to 18 with solid tumors and bone metastases in the prevention of skeletal related events.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	03/31/2019
Study/Clinical trial Completion Date:	03/31/2025
Final Report Submission Date:	09/30/2025
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☒ Theoretical concern
- ☒ Other

Deferred PREA study to determine safety and efficacy. There is also a safety concern related to bone growth in skeletally immature patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Satisfy PREA requirement.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☒ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Phase 3 randomized study to determine safety and efficacy in pediatric patients.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
PREA study

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Simmer

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: To conduct a clinical trial to determine the safety of denosumab in patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) and in patients receiving dialysis. The number of patients enrolled in the trial and the frequency and duration of plasma sampling will be sufficient to estimate the incidence and severity of hypocalcemia, hypomagnesemia, and hypophoshatemia in this patient population

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	03/31/2011
Study/Clinical trial Completion Date:	06/30/2012
Final Report Submission Date:	12/31/2012
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Denosumab (at a lower dose than proposed in this efficacy supplement) has been administered to patients with renal insufficiency commonly resulting in hypocalcemia. In a trial of 55 patients, without cancer and with varying degrees of renal impairment, who received a single dose of 60 mg denosumab, 8 of 17 patients with a creatinine clearance less than 30 mL/min or receiving dialysis experienced corrected serum calcium levels less than 8.0 mg/dL as compared to 0 of 12 patients with normal renal function.

For the current indication, it will be necessary to assess the safety of denosumab at this dose and dosing schedule in patients with severe renal insufficiency (i.e., creatinine clearance less than 30 mL/min).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The risk to be assessed is ~~severe~~ hypocalcemia and other electrolyte abnormalties (hypomagnesemia and hypophosphatemia).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The trial will be conducted in a subpopulation (of patients with severe renal insufficiency) to determine the incidence of ~~severe~~ electrolyte abnormalties including hypocalemia and whether denosuamb at the proposed dose and schedule can safely be adminstered to pateints with hypocalcemia.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Summer

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: PMC

To submit a final report that includes updated results for overall survival and datasets for overall survival for trials 20050103 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer;" 200050136 entitled "A Randomized, Double-blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects With Advanced Breast Cancer;" and 20050244 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma."

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	N/A
Study/Clinical trial Completion Date:	N/A
Final Report Submission Date:	10/01/2012
Other: _____	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Confirm the results submitted to the sBLA based on long-term follow-up that there does not appear to be a survival difference for patients who receive denosumab compared to those who recive zoledronic acid.

Note that these studies have completed enrollment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Confirm overall survival results based on extended follow-up.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Follow-up from three trials are ongoing. We are requesting results from extended follow-up.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Extended follow-up of ongoing Trials.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

MEDICAL REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 17, 2010
To:	Patricia Keegan, M.D. Director, Division of Biologic Oncologic Products
Through:	Judy Staffa, Ph.D, R.Ph. Emarilyn Vega for Judy staffa Acting Director, Division of Epidemiology
Through:	Rita Ouellet-Hellstrom, Ph.D., M.P.H Team Leader, Division of Epidemiology
From:	Fatmatta Kuyateh, M.D., M.S. Medical Officer, Division of Epidemiology
Subject:	Memo to File: DEPI review of Amgen's Response to ONJ Case Registry Information Request.
Drug Name:	Denosumab
Application Type/Number:	BLA 125320/7/5
Applicant/sponsor:	Amgen Incorporated
OSE RCM #:	2010-1884

1 INTRODUCTION

This memorandum is a review of Amgen Inc's response to recommendations made by Division of Epidemiology (DEPI) regarding their proposed Osteonecrosis of the Jaw (ONJ) Registry protocol.

Denosumab is a human IgG2 monoclonal antibody that inhibits receptor activator of nuclear factor kappa B ligand (RANKL). It inhibits the formation, activation, and survival of osteoclasts and consequently reduces bone resorption. Amgen Inc. (the sponsor) submitted a biologic licensing application to FDA on May 14, 2010 seeking licensure to market denosumab (under the proposed trade name Xgeva) for the (b) (4) (b) (4) Denosumab is currently approved under the trade name Prolia for treatment of postmenopausal women with osteoporosis at high risk for fracture.

Because denosumab suppresses bone turnover, there is biologic plausibility to support a possible association with ONJ. In clinical trials of denosumab patients with advanced cancer, all events reported as ONJ or corresponding to a prespecified list of MedDRA adverse event preferred terms suggesting ONJ were reviewed and adjudicated by an independent adjudication committee. Based on results of three phase-3 randomized clinical trials, ONJ occurred with similar frequency during treatment with denosumab as during treatment with the comparator zoledronic acid (a bisphosphonate) in patients with cancer. Consequently, the sponsor proposed an ONJ case registry of cancer patients (regardless of exposure to denosumab) as part of the denosumab post-marketing pharmacovigilance program. DEPI reviewed the protocol (b) (4), (b) (5)

(b) (4), (b) (5)

2 MATERIAL REVIEWED

- Response to Proposed ONJ Case Registry Information Request, Denosumab (AMG162), submitted to FDA on October 29, 2010.

3 DISCUSSION

In our review dated September 23, 2010, we made the following recommendations for the sponsor to consider:

For the purpose of meeting the stated objective, this reviewer recommends the following changes be made to the protocol:

(b) (4), (b) (5)

In their response the sponsor agreed to all of the recommendations and states that the changes will be reflected in the final protocol.

4 CONCLUSIONS AND RECOMMENDATIONS

The sponsor has agreed to amend the final protocol to incorporate the recommended changes. If done, the final protocol will be adequate to meet the sponsor's stated objectives for the registry.

Fatmatta Kuyateh, MD, MS

Medical Officer, Division of Epidemiology

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125320/7 (formerly BLA 125355)
Priority or Standard	Priority
Submit Date	May 14, 2010
Received Date	May 19, 2010
PDUFA Goal Date	November 18, 2010
Division / Office	Division of Biologic Oncology Products/Office of Oncology Drug Products
Reviewer Name(s)	Shan Pradhan, MD Michael Axelson, MD
Review Completion Date	November 17, 2010
Established Name	Denosumab
(Proposed) Trade Name	Xgeva
Therapeutic Class	Human monoclonal antibody
Applicant	Amgen, Inc.
Formulation	120 mg denosumab (70 mg/mL) in 1.7 mL solution, single-use vial
Dosing Regimen	120 mg administered as a single subcutaneous injection

Proposed Indication(s)	every 4 weeks (b) (4)
Intended Population(s)	Patients with bone metastases from solid tumors

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment (S. Pradhan, except as noted)

1.1 Recommendation on Regulatory Action

(S. Pradhan)

This reviewer recommends approval of supplemental Biologic License Application (sBLA) 125320/7 for the prevention of skeletal related events in patients with bone metastases from solid tumors.

The primary basis for this application consists of three international, randomized (1:1), double-blind, double-dummy, non-inferiority trials that compared denosumab to zoledronic acid and enrolled a total of 5,723 patients with advanced malignancies involving bone. Trial 20050103 (Trial 103) enrolled patients with castrate-resistant prostate cancer, Trial 20050136 (Trial 136) enrolled patients with breast cancer, and Trial 20050244 (Trial 244) enrolled patients with solid tumors other than breast or prostate cancer and patients with multiple myeloma. Patients were randomized to receive either 120 mg of denosumab every 4 weeks by subcutaneous injection or 4 mg (dose-adjusted for renal function) of zoledronic acid every 4 weeks by intravenous infusion. Prior intravenous bisphosphonate therapy was not permitted. The primary endpoint in each trial was non-inferiority in time to first on-study skeletal related event (SRE) as compared to zoledronic acid. An SRE was defined as a pathologic fracture, need for radiation or surgery to bone, or cord compression. Secondary endpoints in each trial were superiority in time to first on-study SRE and superiority in time to first-and-subsequent on-study SRE. Superiority testing was performed after demonstration of non-inferiority within the respective trial as compared to zoledronic acid. Overall survival was included in each trial as an exploratory endpoint.

The clinically relevant composite SRE endpoint was the basis for approval of zoledronic acid and of pamidronate for patients with cancer and bone metastases.

Results from Trials 103 and 136 demonstrated superiority over zoledronic acid in delaying time to first SRE and first- and-subsequent SRE in patients with prostate cancer and patients with breast cancer. In Trial 103, median time to SRE was 17.1 months for zoledronic acid and 20.7 months for denosumab (superiority p-value 0.009). In Trial 136, median time to SRE was 26.4 months for zoledronic acid and was not reached for denosumab (superiority p-value 0.010). Results from Trial 244 demonstrated non-inferiority compared to zoledronic acid in delaying time to first SRE,

in patients with other solid tumors or multiple myeloma (non-inferiority p-value < 0.001). Overall survival was similar between arms in each trial, though mortality was higher with denosumab in a subgroup analysis of patients with multiple myeloma in Trial 244. This reviewer recommended the inclusion of an Important Limitation of Use in the Indications and Usage section of the product labeling regarding patients with multiple myeloma (see Section 9.2 Labeling Recommendations).

Overall, results from Trials 103, 136, and 244 demonstrate a consistent, robust treatment effect for denosumab across tumor types in the prevention of SREs. No inconsistency in effectiveness was observed across individual components of the SRE endpoint or across relevant subpopulations.

(M. Axelson)

This clinical reviewer recommends approval of supplemental Biologic License Application (sBLA) STN 125320/7 for the prevention of skeletal related events in patients with bone metastases from solid tumors.

The assessment of benefit in this application is based on the endpoint of time to first on-study SRE, a composite endpoint of pathologic fracture, spinal cord compression, radiation to bone, and surgery on bone. The recommendation is based on the review of the clinical data, which supports the conclusion that denosumab is non-inferior to zoledronic acid in patients with solid tumors including breast cancer and prostate cancer with bone metastases and that denosumab is superior to zoledronic acid in patients with breast or prostate cancer and bone metastases for the endpoint of time to first on-study skeletal related event (SRE). Trials 20050103 (103) [HR 0.82 (0.71, 0.95), p=0.0101] and 20050136 (136) [HR 0.82 (0.71, 0.95) p=0.0085] demonstrated superiority of denosumab over zoledronic acid for first on-study SRE; Trial 20050244 (244) [HR 0.84 ((0.71, 0.98) p=0.0007; superiority p=0.0619] demonstrated non-inferiority for first on-study SRE. The median time to first SRE for denosumab could not be determined for Trial 136; the difference in median time to first SRE was 3.6 months for Trial 103, and 4.3 months for Trial 244. Consistent effects on time to SRE were observed regardless of baseline age, sex, stratification factors, and individual SRE events.

1.2 Risk Benefit Assessment

(S. Pradhan)

Trials 103, 136, and 244 included a total of 2,841 patients who received denosumab at the dose and dosing schedule proposed in this application and 2,836 patients who received zoledronic acid. Overall, the profile of adverse events, serious adverse events, and fatal adverse events reported with denosumab was similar to that of zoledronic acid

and consistent over time for exposure periods of up to 41 months and across tumor types and relevant subgroups. There was no evidence of increased risk for infections (including serious skin infections), new primary malignancies, or tumor promotion (growth of pre-existing cancers). There was no evidence of injection-related reactions, as can occur with administration of a monoclonal antibody, that appeared causally or temporally related to denosumab administration. Overall survival was similar between treatment groups in each trial. See Section 1.1 (under S. Pradhan) regarding higher mortality with denosumab in a subgroup of patients with multiple myeloma in Trial 244, and this reviewer's related labeling recommendations.

Hypocalcemia and osteonecrosis of the jaw (ONJ), two adverse reactions associated with antiresorptive agents, occurred at higher incidence with denosumab compared to zoledronic acid. Severe hypocalcemia (≥ CTCAE Grade 3) occurred in 3.1% of patients in the denosumab group and 1.3% of patients in the zoledronic acid group. The incidence of positively adjudicated ONJ was 1.8% in the denosumab group and 1.3% in the zoledronic acid group. Approximately half of patients who developed ONJ in each treatment group underwent surgical treatment for ONJ. Few patients in either treatment group required bone resection.

The incidence of adverse events related to worsening renal function and laboratory findings indicative of changes in renal function was higher for zoledronic acid compared to denosumab. The incidence of adverse events indicative of acute-phase reaction, including pyrexia, was also higher for zoledronic acid compared to denosumab.

This reviewer concludes that denosumab has an acceptable risk-benefit profile for the prevention of skeletal related events in patients with bone metastases from solid tumors. Refer to Section 1.4 for recommendations regarding postmarketing requirements.

(M. Axelson)

The sBLA was supported by the results of three, randomized, active control, double blinded non-inferiority trials in patients with multiple myeloma or solid tumors with osseous metastases: Trial 103 in 1901 patients with castrate-resistant prostate cancer; Trial 136 in 2046 patients with breast cancer; Trial 244 in 1776 patients with multiple myeloma or advanced solid tumors other than breast or prostate cancer. The assessment of risk-benefit in this application is based on the endpoint of time to first on-study SRE, a composite endpoint of pathologic fracture, spinal cord compression, radiation to bone, and surgery on bone and review of the adverse event data. The recommendation is based on the review of the clinical data, which supports the conclusion that denosumab is non-inferior to zoledronic acid in patients with solid tumors other than breast or prostate cancer and bone metastases and that denosumab is superior to zoledronic acid in patients with breast or prostate cancer and bone metastases for the endpoint of time to first on-study SRE.

The results of Trials 103, 136, and 244 provide evidence of a clinically meaningful prolongation in the time to SRE in patients with cancer and bone metastases. SRE is a clinically meaningful endpoint as the individual components represent events associated with neurologic or functional detriment, pain, or need for prolonged or intensive treatment. Two of the three trials, 103 and 136, demonstrated statistically significant superiority of denosumab over zoledronic acid in prolonging the time to first SRE. The third trial, 244, demonstrated non-inferiority to zoledronic acid.

Important safety concerns for denosumab include use in patients with multiple myeloma, osteonecrosis of the jaw (ONJ), and hypocalcemia. Overall survival was worse in an exploratory subgroup analysis of patients with multiple myeloma [HR 2.22 (1.11, 4.46), P=0.021)] among patients who received denosumab compared to zoledronic acid. Labeling will indicate the worse survival in this subgroup of patients. The rate of ONJ was 1.8% in patients receiving denosumab compared to 1.3% of patients receiving zoledronic acid. Lastly, the rate of severe, corrected hypocalcemia (<7 mg/dL) was higher in the denosumab treated patients (3.1%) compared to patients treated with zoledronic acid (1.4%); hypocalcemia of any grade was also higher (18% versus 9%) in the denosumab treated patients compared to the zoledronic acid patients. Supplementation of calcium and vitamin D was not mandated in Trials 103, 136, and 244, but lack of supplementation alone would not be expected to account for this difference. The risk of hypocalcemia also appeared to be worse in patients with severe renal impairment (creatinine clearance < 30 mL/min). The exclusion of patients with severe renal impairment, consistent with the zoledronic acid label, however, limits the analysis of this safety concern.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This reviewer recommended an Important Limitation of Use for the Indications and Usage Section of the product labeling regarding patients with multiple myeloma (refer to Section 9.2 Labeling Recommendations).

(b) (4)

1.4 Recommendations for Postmarket Requirements and Commitments

- This reviewer recommended the following postmarketing requirement regarding the risk of hypocalcemia in patients with a creatinine clearance less than 30 mL/min or receiving dialysis (refer to Section 7.3.5 'Submission Specific Primary Safety Concerns' for further detail):

  To conduct a clinical trial to determine the safety of denosumab 120 mg administered every four weeks by subcutaneous injection in patients with severe renal insufficiency (creatinine clearance less than 30 mL/min) and in patients receiving dialysis. The number of patients enrolled in the trial and the frequency and duration of plasma sampling will be sufficient to estimate the incidence and severity of hypocalcemia, hypomagnesemia, and hypophosphatemia in this patient population. The final report should include the primary and derived datasets and analysis programs used to generate the safety and laboratory analyses.

  The Applicant submitted the following timetable:
  - Final Protocol Submission: March 31, 2011
  - Study Completion: June 30, 2012
  - Final Report Submission: December 31, 2012

- The clinical review team also recommended the following postmarketing requirement regarding updated survival results for Trials 103, 136, and 244:

  To submit a final report that includes updated results for overall survival for (Trial 103), (Trial 136), and (Trial 244). The final report should also include the primary and derived datasets and analysis programs used to generate the overall survival results reported.

  The Applicant submitted the following timetable:
  - Final Report Submission: October 1, 2012

- The clinical review team recommended the following postmarketing requirements under the Pediatric Research Equity Act (PREA) (refer to Section 7.6.3 'Pediatrics and Assessment of Effects on Growth' for further detail):

  Conduct a phase 1, open-label, dose-finding, pharmacokinetic, pharmacodynamic, and safety study in pediatric patients ages 0 to 18 years who are diagnosed with solid tumors metastatic to bone. The study will determine whether a safe dose can be administered to patients in subsequent phase 2 and phase 3 studies.

The Applicant submitted the following timetable:
- Final Protocol Submission: December 30, 2011
- Study Completion: March 31, 2014
- Final Report Completion: September 30, 2014

Conduct a phase 2, open-label, single-arm study in pediatric patients ages 0 to 18 with solid tumors with bone metastases to determine the safety, including effects on growing bones, and activity of denosumab in the prevention of skeletal related events. The study must not be initiated until at least one month after you have submitted the complete study report for post-marketing requirement 1.

The Applicant submitted the following timetable:
- Final Protocol Submission: September 30, 2014
- Study Completion: September 30, 2018
- Final Report Submission: March 31, 2019

Conduct a randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of denosumab for the prevention of skeletal related events in pediatric patients ages 0 to 18 with solid tumors and bone metastases. The study must not be initiated until at least one month after you have submitted the complete study report for post-marketing requirements 1 and 2.

The Applicant submitted the following timetable:
- Final Protocol Submission: March 31, 2019
- Study Completion: March 31, 2025
- Final Report Submission: September 30, 2025

Introduction and Regulatory Background (M. Axelson)

Denosumab is an IgG_2, fully human monoclonal antibody to receptor activator for nuclear factor-kB ligand (RANKL). Denosumab blocks the binding of RANKL to RANK, limiting terminal differentiation and activation of osteoclasts.

The prevalence of bone metastases in patients with cancer represents a frequent cause of morbidity and is estimated to be present in up to 1.5 million patients with cancer (Coleman and Brown 2005). In patients with advanced metastatic cancer, the incidence of bone metastases in patients with breast cancer is 73%, prostate cancer is 68%, and lung cancer is 36% (Gralow 2009). Complications of bone metastases include pain requiring narcotics or local procedures (surgery or XRT) to treat the pain, fractures, and spinal cord compression. Prior to initiation of bisphosphonate therapy, skeletal related complications were common. In one retrospective study (Domchek 2000),

approximately 80% of patients with bone limited disease at the time of diagnosis developed a skeletal related complication.

Table 1 contains pooled data from four long term follow-up trials involving bisphosphonate therapy, showing the prevalence of skeletal related events (SREs) including fractures, need for radiation or surgery to the bone, and spinal cord compression for common tumors that affect the bone.

Table 1: Prevalence of SRE Components by Tumor Type

	Fracture (%)	XRT (%)	Surgery (%)	Spinal Cord Compression (%)
Breast	52	43	11	3
Prostate	25	33	4	8
Multiple Myeloma	37	34	5	3
NSCLC and other solid tumors	22	34	5	4

Table adapted from Gralow et al 2009.

Drugs approved for bone metastases include the bisphosphonates zoledronic acid and pamidronate, and the radiopharmaceuticals strontium-89 chloride (Metastron) and samarium SM-153 lexidronam (Quadramet). Other treatments include surgery and external beam radiation.

For bisphosphonates, the primary regulatory endpoint for treatment of bone metastases was the incidence of skeletal related events (SREs) and time to first SRE; though the endpoint for the two radiopharmaceutical drugs was pain reduction. Trials supporting approval of zoledronic acid and pamidronate used SREs defined as pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Placebo was the comparator in the trials supporting pamidronate; trials supporting zoledronic acid used either placebo or pamidronate, the latter of which was a non-inferiority trial.

2.1 Product Information

Table 2: Denosumab Product Information

Generic Name:	Denosumab
Trade Name:	Xgeva
Pharmacological Category:	Receptor activator for nuclear factor-kB ligand (RANKL) antagonist
Drug Class:	Recombinant humanized monoclonal antibody
Route of Administration:	Subcutaneous injection
Storage:	Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton
Drug Product:	Single-use vial containing 120 mg denosumab, 4.6% sorbitol, 18mM acetate, Water for Injection (USP), and sodium hydroxide to a pH of 5.2 (total vial size 1.7 mL solution)
Dose and Regimen:	120 mg subcutaneously every four weeks
Populations Studied:	Subjects with cancer with osseous metastases, including subjects with cancer of the breast, prostate, lung, and other solid tumors, as well as multiple myeloma.

2.2 Tables of Currently Available Treatments for Proposed Indications

(b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Denosumab is marketed in the United States as Prolia. The current application is an efficacy supplement to the original BLA.

2.4 Important Safety Issues With Consideration to Related Drugs

Patients with cancer and osseous metastases receive bisphosphonates to prevent and delay SREs associated with the malignancy. Bisphosphonates can cause several complications that are serious and require careful attention and monitoring, specifically, hypocalcemia, renal toxicity, fetal harm, bone pain, and osteonecrosis of the jaw (ONJ).

Hypocalcemia can occur in patients treated with bisphosphonates when the compensatory mechanisms of the body, most importantly secretion of parathyroid hormone, are dysfunctional because of a history of parathyroidectomy, low levels of Vitamin D, renal insufficiency or hypomagnesemia. Periodic monitoring of serum magnesium, calcium and phosphate during therapy is recommended during treatment with bisphosphonates.

Nephrotoxicity in patients receiving bisphosphonates is dose and infusion-time dependent and may require treatment and dose modification as appropriate. Nephrotoxicity may be more common in patients with impaired renal function.

ONJ with bisphosphonate therapy is most common in patients with underlying malignancies who are receiving intravenous bisphosphonates. Risk factors include dental extraction, poor dental hygiene during treatment, monthly sequential therapy with pamidronate or zoledronic acid, longer duration of treatment, older age at diagnosis, and certain concomitant medications (e.g., corticosteroids). Both prevention and conservative treatment strategies (limited debridement, antibiotics, and good oral hygiene) are recommended for patients who experience ONJ.

Additionally, RANKL inhibition has immune system effects because RANK is expressed on dendritic cells and activated B and T cells. Treatment with denosumab could lead to an increased risk of susceptibility to infections, especially in certain high risk groups of patients (e.g., patients receiving chemotherapy). Denosumab is currently approved as Prolia for the treatment of postmenopausal women with osteoporosis at high risk for facture at a dose of 60 mg every 6 months as a subcutaneous injection. The Prolia label includes hypocalcemia, serious infections including skin infections, dermatologic reactions, ONJ, and suppression of bone turnover as warnings and precautions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 4: Regulatory History

Meeting Date	Meeting Purpose
July 17, 2001	IND 9838 may proceed letter issued
April 14, 2004	Type B Pre-IND pre phase 3 meeting to discuss CMC issues
September 21, 2004	Follow up on CMC issues
April 20, 2005	FDA comments to Amgen on PK study in subjects with renal dysfunction
September 20, 2005	Pre-Phase 3 meeting

Meeting Date	Meeting Purpose
November 1, 2006	FDA comments on 20050244 SAP
December 8, 2006	Type C CMC meeting
July 8, 2008	Pre-BLA CMC meeting
December 19, 2008	BLA application submitted for Prolia (under BLA STN 125320/0)
January 30, 2009	Discuss proposed structure and format of Denosumab marketing application
April 13, 2010	pre-BLA meeting
May 19, 2010	BLA received
June 1, 2010	Denosumab approved as Prolia for treatment of osteoporosis

SRE Endpoint

Approvals for drugs intended to treat patients with bone metastases have established the regulatory precedent for the aggregate endpoint, skeletal related events (SRE). Prevention of the components of the endpoint, including fractures and radiation to bone, is considered clinical benefit. For example, fractures are associated with severe pain, limitation in mobility, and increased risks for venous thrombosis. Both pamidronate and zoledronic acid registration trials used SRE as the primary efficacy endpoint for the treatment indication of patients with cancer and bone metastases.

In the January 31, 2002 Oncology Drug Advisory Committee (ODAC) meeting, SREs were not questioned as an acceptable endpoint. Based on the regulatory history of SRE as an endpoint in the zoledronic acid and pamidronate approvals, SREs represent an acceptable efficacy measure for new drug approvals (assuming adequate treatment effect size and acceptable safety profile of the drug). The zoledronic acid registration trials used non-inferiority designs and trials for both zoledronic acid and pamidronate investigated patients with different individual tumor types to support a broad bone metastases indication.

In subjects with multiple myeloma, pamidronate reduced the proportion of subjects developing any SRE (24% vs. 41%, P<0.001) and the mean skeletal morbidity rate (#SRE/year) compared to subjects on placebo. In subjects with metastatic breast cancer, pamidronate reduced the proportion of subjects developing any SRE (46% vs. 65%, P<0.001) and prolonged the median time to SRE in months (13.9 vs. 7, P<0.001) compared to placebo.

In subjects with prostate cancer, zoledronic acid reduced the proportion of subjects with an SRE (33% vs. 44%, P=0.02) compared to placebo; in subjects with solid tumors, the reduction was 7% (38% vs. 44%, P=0.13). In subjects with breast cancer and myeloma, zoledronic acid was non-inferior to pamidronate for the proportion of subjects with an SRE (44% vs. 46%, P=0.46)

Meeting Agreements

The following are clinical regulatory agreements or issues pertinent to the drug development of denosumab for the SRE indications.

20 September 2005: pre-phase 3 meeting
FDA had the following comments:

- That demonstration of clinical benefit in Studies 20050103 and 20050136 would be adequate to support licensure.
- Time to first on-study SRE is an acceptable primary endpoint.
- Use of a primary non-inferiority analysis would be acceptable pending review of the final SAP. Studies 20050103 and 20050136 should demonstrate that denosumab preserves at least 50% of the effect of zoledronic acid on the time to first on-study SRE.

1 November 2006
FDA commented on the SAP for Study 20050244:

- FDA did not object to the use of a synthesis method for the primary analysis. FDA stated that the estimated effect of zoledronic acid from trials of subjects who have a wide variety of diseases may not be the same as the patient population used for study 20050244.
- The pursuit of a secondary endpoint labeling claim based on a multiple event analysis is acceptable provided an Andersen Gill analysis demonstrates a statistically significant result that is supported by a statistically significant result from an appropriate multiple events analysis.

30 January 2009 pre-BLA Meeting
FDA had the following comments:

- The proposal to submit CSRs for studies 20050136 and 20050244 was acceptable.
- CRFs should be submitted for all subjects who died on study, for all subjects who withdrew from the investigational product or the study due to an adverse event, and for all subjects who experienced a serious adverse event.
- The plan for independent review of radiographs was acceptable.

Amgen stated that the submitted datasets will be compliant with the CDISC SDTM Implementation Guide 3.1.1 for tabulation data and observe the CDISC ADaM 1.0 for analysis data. This was acceptable to FDA.

FDA did not agree that the proposed primary analysis, which integrated the phase 3 trials, was "acceptable to support a broad labeling claim [redacted] (b) (4) Instead, for each study, substantial evidence should be provided on the efficacy of denosumab. Each comparison may be supportive of each other. Integrated analyses may be supportive."

13 April 2010 Type B pre-BLA Meeting
FDA had the following comments:

- The proposed clinical data from the three phase 3 trials (20050136, 20050244, and 20050103) as well as the data summarized from the overall development program were adequate to support a BLA submission for the proposed cancer with osseous metastases indications.
- The primary evaluation of efficacy and safety and label claims will be based on the results from the primary analysis phase of the three randomized pivotal trials.
- The analysis for the superiority test should employ a stratified log-rank test.
- The plan for the 120-day safety update was acceptable.

2.6 Other Relevant Background Information

Amgen initially requested the proprietary name, (b) (4) on January 22, 2009. The FDA stated (b) (4) was not acceptable due to orthographic similarities to (b) (4) as well as sharing dosage forms, route of administration, frequency of administration, and availability in a single strength. Amgen submitted an alternative proprietary name, Xgeva, which was found to be acceptable to FDA on October 22, 2010.

Amgen currently markets denosumab under the trade name Prolia, approved on June 1, 2010. Prolia does not have required pediatric assessments under Pediatric Research Equity Act (PREA) because the osteoporosis indication does not occur in the pediatric population. Required post marketing requirements (PMRs) under Section 505(o) of the Federal Food, Drug and Cosmetic Act (FDCA) include:

1. A retrospective cohort study using multiple existing observational databases to collect data from a 5-year period prior to the availability of denosumab. This study will be designed to identify women with post-menopausal osteoporosis and determine the prevalence of serious infection including skin infection, dermatological adverse events, and over-suppression of bone turn-over.
2. A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered Prolia (denosumab).
3. A long-term surveillance study in postmenopausal women administered Prolia (denosumab) to prospectively evaluate the incidence of serious infection including skin infections, dermatologic adverse events, and over-suppression of bone turnover.
4. An *in vivo* drug-drug interaction clinical trial with a CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis to characterize the potential risk of drug interactions of Prolia (denosumab) with CYP3A4 substrates.

Under Section 506(b) of the Federal Food, Drug and Cosmetic Act, Amgen committed to conduct the following post marketing commitments (PMCs):

1. To confirm validation of the updated SE-HPLC method (MET-001208). The method was revised to add column conditioning using material containing the high molecular weight species.
2. To submit proposed revisions to the breakloose and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method after 15 commercial manufacturing runs.
3. To submit proposed revisions to the breakloose and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method to reflect increased manufacturing experience.

Lastly, the approval of denosumab as Prolia has Risk Evaluation and Mitigation Strategy (REMS) requirements under Section 505-1 of the Federal Food, Drug and Cosmetic Act "to ensure that the benefits of [denosumab] outweigh the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover." The REMS assessment plan was to include:

1. An evaluation of healthcare providers' understanding of the serious risks of Prolia (denosumab), including the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover, and how to select patients who are appropriate for treatment.
2. An evaluation of patients' understanding of the serious risks of Prolia (denosumab), including the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.
3. An evaluation of whether patients receive the Medication Guide and actions taken to ensure that patients receive the Medication Guide.
4. A summary of all reported serious infections including skin infection, dermatologic adverse events, and events possibly related to over-suppression of bone turnover, with analysis of adverse event reporting by prescriber type (e.g., endocrinologist, rheumatologist, primary care physician), when available.
5. Provide the following details in the evaluation of the communication plan implementation: launch date of communication plan, number of recipients emailed the DHCP letter, number of recipients included in mass mailing of DHCP letter, dates of mailings (United States Postal mail and email), and a copy of the documents included in mailing.

Amgen's current REMS for Prolia includes a Medication Guide for health care providers to dispense to each patient who receives Prolia and a communication plan.

3 Ethics and Good Clinical Practices (S. Pradhan)

3.1 Submission Quality and Integrity

The submission was of adequate quality and integrity to allow for review of the clinical trials pertaining to the proposed indication. Electronic datasets were submitted in CDISC format as requested by the Division. Adverse events from a subset of case report forms and case narratives for each of Trials 103, 136, and 244 were reviewed and compared to the datasets in order to confirm adequacy of the data transfer. To confirm the overall adequacy of AE coding, verbatim terms all Grade 4 or 5 (NCI CTCAE v3.0) adverse events (AEs) in the 3 trials and all Grade 3 AEs in Trial 244 were compared to the corresponding MedDRA lower level term.

3.2 Compliance with Good Clinical Practices

The submission contained a statement that clinical trials were conducted under Good Clinical Practices as described in International Conference on Harmonization (ICH) E6 (ICH, 1996), under the principles of the Declaration of Helsinki.

Based upon analyses of site-specific efficacy data, numbers and types of protocol deviations, patient enrollment per site, and investigator financial conflict of interest disclosures, a DSI consult was requested for the clinical inspection of 6 trial sites and of the CRO responsible for central review of components of the primary efficacy endpoint.

Table 5 DSI Clinical Inspections

Site Number	PI / Site	Trial	Number of Patients
686	Dr. Ronaldo Damiao Hospital Universitario Pedro Ernesto BRAZIL	103	42
503	Dr. Karim Fizazi Institut Gustave Roussy FRANCE	103	42
115 (Trial 103) 107 (Trial 244)	Dr. Veena Charu Pacific Cancer Center USA	103, 244	6 (Trial 103) 15 (Trial 244)
346	Dr. Alexey Manikhas City Oncology Dispensary RUSSIA	136	25
672	Dr. Jose R. Pereira Instituto do Cancer BRAZIL	244	40

Site Number	PI / Site	Trial	Number of Patients
386	Dr. Maciej Krzakowski Instytut im. M. Sklodowskiej-Cuire-Centurm Onkologii POLAND	244	27
(b) (4)			

Clinical inspection results were not available at the time of completion of this review.

3.3 Financial Disclosures

The Applicant submitted lists of investigators having disclosable financial arrangements and of investigators who did not provide financial disclosure information. Statements of Actions to Minimize Bias were submitted for investigators having disclosable financial interests and the actions taken were acceptable. Additionally, bias was minimized by the double-blind, double-dummy study designs and the large size of the clinical trials, precluding these sites from unduly influencing the overall results.

Table 6 Disclosable Financial Conflicts of Interest

(b) (6)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines (S. Pradhan)

4.1 Chemistry Manufacturing and Controls

Denosumab is a full-length human monoclonal IgG2 antibody that binds to the D-E loop of human receptor activator of nulear factor kappa B ligand. The Office of Biotechnology Products/Division of Monoclonal Antibodies reviewed the data regarding the manufacture of drug substance (DS) with the original denosumab BLA submission (STN 125320). Amgen submitted no major manufacturing changes regarding drug substance to this efficacy supplement. Additionally Amgen made no clinically significant changes to manufacturing process development or to drug substance characterization or control.

In this sBLA, Amgen submitted data to support a new presentation of the drug product (DP) in a 70 mg/mL vial. DMA concluded that the manufacture of the 70 mg/mL denosumab DP is well-controlled and leads to product that is pure and potent. The DP meets parameters recommended by FDA for endogenous and adventitious infectious agents. Amgen sufficiently validated the conditions used in the manufacturing process.

The application contained information to support commercial production of denosumab DS at Amgen Colorado (ACO) [Boulder, Colorado] and Boehringer Ingelheim Pharma (BIP) [Biberach an der Riss, Germany] and DP manufacture at Amgen Manufacturing Limited (AML) [Puerto Rico]. The Sections of the sBLA pertaining to microbial control of the drug substance manufacturing process were reviewed by the DMPQ/BMT reviewer, who recommended approval of the sBLA from a CMC microbiology standpoint. Inspections of drug substance manufacturing and release and stability testing sites was completed, with no pending or ongoing compliance actions preventing approval of the sBLA.

4.2 Preclinical Pharmacology/Toxicology

Adolescent nonhuman primates treated with denosumab at doses more than 5 times higher than the recommended human dose of 120 mg experienced abnormal skeletal growth plates. Amgen conducted safety studies in rodents using OPG-Fc as a surrogate for denosumab because denosumab does not recognize rodent RANKL. A study in 2-week-old rats given OPG-Fc showed reduced bone growth, altered growth plates, and impaired tooth eruption. Changes were partially reversible when RANKL inhibitor dosing was discontinued. Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. RANK/RANKL knockout mice also exhibited absence of lymph node formation, as well as absence of lactation due to inhibition of mammary gland maturation.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

Denosumab binds RANKL, a protein involved in the formation, function, and survival of osteoclasts. Denosumab prevents RANKL from activating its receptor on the surface of osteoclasts and their precursors. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in bone metastases from solid tumors.

4.3.2 Pharmacodynamics

In patients with breast cancer and bone metastases, the median reduction in uNTx (urinary N-terminal telopeptide)/Cr was 82% within 1 week following initiation of denosumab 120 mg administered subcutaneously. In Trials 103, 136, and 244, the median reduction in uNTx/Cr from baseline to month 3 was approximately 44% in 2,560 denosumab-treated patients.

4.3.3 Pharmacokinetics

Following subcutaneous administration, denosumab bioavailability was 62%. Denosumab displayed nonlinear pharmacokinetics (PK) at doses below 60 mg, but approximately dose-proportional increases in exposure at higher doses. With multiple subcutaneous doses of 120 mg every 4 weeks in patients with cancer and bone metastases, up to 2.8-fold accumulation in serum denosumab concentrations was observed and steady-state was achieved by 6 months. At steady-state, the mean ± standard deviation serum trough concentration was 20.5 ± 13.5 mcg/mL at the recommended denosumab dose and the mean terminal half-life was 28 days.

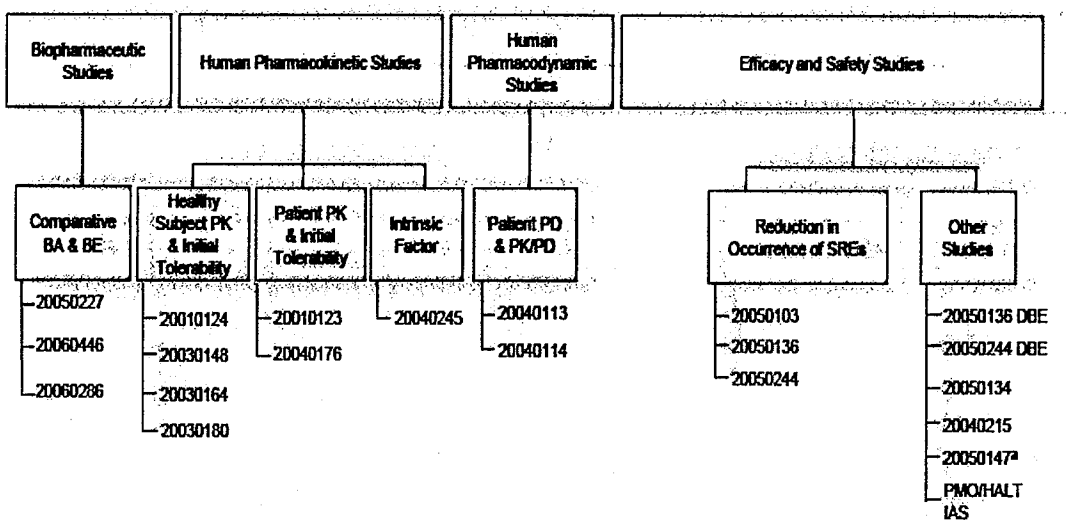
A population PK analysis was performed to evaluate the effects of demographic characteristics on the PK profile of denosumab. Denosumab clearance and volume of distribution were proportional to body weight. Steady-state exposure following repeat subcutaneous administration of 120 mg every 4 weeks in 45 kg and 120 kg patients was, respectively, 48% higher and 46% lower than exposure in the typical 66 kg patient. (b) (4)

The PK of denosumab was not affected by age, gender, or race. Amgen did not study the PK of denosumab in pediatric patients. In a trial of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the PK of denosumab. (b) (4)

5 Sources of Clinical Data (S. Pradhan)

5.1 Tables of Studies/Clinical Trials

Figure 1 Clinical Trials Included in the Marketing Application (excerpted from the sBLA)



[a] blinded demographic and safety data only

BA = bioavailability, BE = bioequivalence, DBE = double-blind extension, HALT = hormone ablation therapy, IAS = integrated analysis of safety, PD = pharmacodynamics, PK = pharmacokinetics, PMO = postmenopausal osteoporosis, SRE = skeletal-related event.

The primary safety and efficacy analyses in this review include Trials 20050103, 20050136, and 20050244 only; hereon, these trials are referred to as Trials 103, 136, and 244, respectively.

Trials 20050134, 20040215, and 20050147 were outside the indication sought in this application. Trial 20050147 enrolled patients with hormone-refractory prostate cancer, studied bone-metastasis-free survival and utilized the same denosumab dosing regimen as Trials 103, 136, and 244; the primary treatment phase for trial 20050147 is ongoing and only a synopsis report of blinded SAE and limited demographic data was submitted.

Table 7 Trials Included in the Primary Safety and Efficacy Analyses

Trial	Disease	Study Design	Primary Objective	Regimen*	Subjects Enrolled	Status
103	Prostate cancer	Randomized, double-blind, double-dummy	To determine if denosumab is non-inferior to zoledronic acid with respect to first on-study occurrence of an SRE	Denosumab SC and zoledronic acid placebo IV Q4w, or zoledronic acid IV and denosumab placebo SC Q4w	1901	Open label treatment phase ongoing
136	Breast cancer				2046	
244	Solid tumors (excluding breast and prostate cancer) and multiple myeloma				1776	Survival follow-up ongoing

*SC = subcutaneous; IV = intravenous

5.2 Review Strategy

Dr. Pradhan was primarily responsible for review of safety and has written Sections 1 (except as noted within Section 1), 3, 4, 5, 7, 8 and 9 of this review. Dr. Axelson was responsible for review of efficacy, has written Sections 2 and 6, and has documented his overall conclusions and recommendations in a subsection of Section 1.

Safety and efficacy data including clinical study reports, CRFs, and electronic datasets for Trials 103, 136, and 244 were reviewed. These 3 trials enrolled 5,723 patients in total, were of parallel design, utilized the denosumab dosing regimen proposed in the application, and encompassed the application's intended population. DBE ("double-blind extension") datasets were submitted in addition to the primary analysis datasets and included an approximately 4-month treatment phase extension for each of the 3 trials. Dr. Pradhan also reviewed the clinical study report for Trial 2004245. Other trials submitted to the sBLA included relatively few patients each (range 19-255), populations outside that proposed in this application, or varied denosumab dosing regimens.

For the safety review, adverse event reporting in a subset of case report forms and case narratives for each of Trials 103, 136, and 244 was reviewed and compared to the datasets in order to confirm adequacy of the data transfer. Additional case report forms and case narratives were examined as necessary through the course of the safety review. The safety review included review of Trials 103, 136, and 244 both individually and via pooled analysis of the 3 trials (utilizing SDTM tabulation and AdaM datasets for each of the 3 trials and the integrated summary of safety datasets). Safety databases were analyzed at all levels of the MedDRA hierarchy and using standardized MedDRA queries (SMQs). The safety review also included separate investigations for submission-specific safety concerns.

Section 5.3 contains a description of the design of Trials 103, 136, and 244 and brief descriptions of Trials 20040245 (renal impairment/PK study pertinent to the Review of Safety) and 20040113 (dose-finding study pertinent to the Review of Efficacy).

5.3 Discussion of Individual Studies/Clinical Trials

Trials 103, 136, and 244

Trials 103, 136, and 244 are international, randomized, double-blind, double-dummy trials of parallel design that together form the primary basis for the application. The trials encompass different tumor types, in support of the single proposed indication for (b) (4)

Table 8 Trials 103, 136, and 244

103	Hormone-refractory prostate cancer
136	Breast cancer
244	Solid tumors (other than breast and prostate cancer) and multiple myeloma

Each trial compared denosumab to zoledronic acid with respect to the following endpoints:

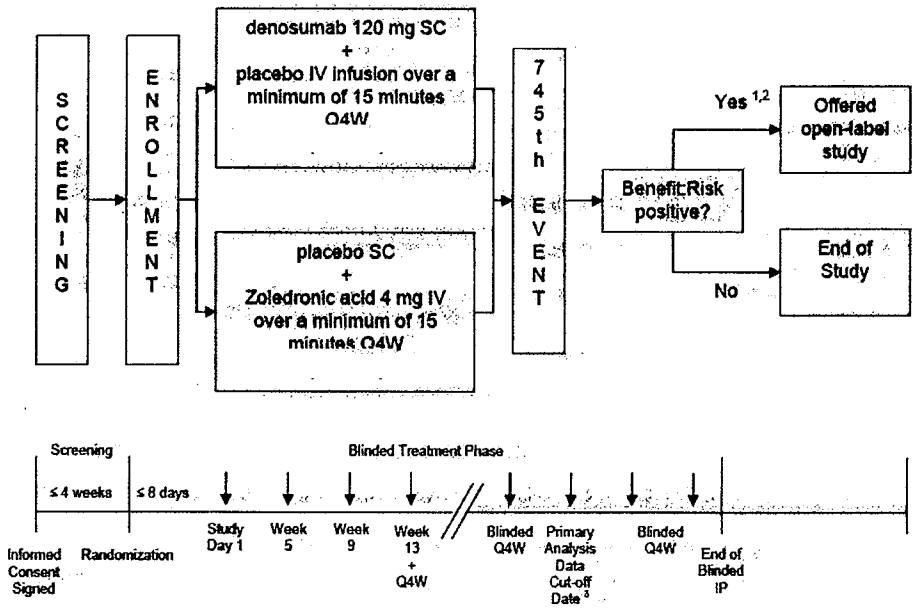
- Primary
  - Time to first on-study SRE ***(non-inferiority)***
- Secondary (tested only if denosumab was found to be non-inferior to zoledronic acid with respect to time to first on-study SRE)
  - Time to first on-study SRE ***(superiority)***
  - Time to first-and-subsequent on-study SRE
    - Multiple event analysis
    - To be considered a subsequent event, the SRE must have occurred at least 21 days after the previous SRE
- Exploratory endpoints included OS and PFS

A skeletal-related event (SRE) was defined as any of the following:
- Pathologic fracture (vertebral or non-vertebral)

- Radiation therapy to bone (including the use of radioisotopes)
- Surgery to bone
- Spinal cord compression

Patients were randomized 1:1 to receive denosumab 120 mg by subcutaneous injection every 4 weeks or zoledronic acid 4 mg (dose-reduced for reduced renal function) by IV infusion every 4 weeks, in a blinded fashion until approximately 745 patients experienced at least 1 on-study SRE.

Figure 2 Treatment Schema for Trials 103, 136, and 244 (adapted from the sBLA)



1. **End of Blinded Investigational Product: If positive benefit:risk confirmed, all subjects may be offered open-label denosumab in a separate protocol. If positive benefit:risk not confirmed, all subjects will be followed for survival for 2 years**
2. **Subjects not participating in the open-label treatment protocol will be followed for survival for 2 years**
3. **Primary Analysis Data Cut-off Date: data cut-off date for the primary efficacy analysis in anticipation of approximately 745 subjects having experienced at least one on-study SRE**

For patients ending study participation before the end of the blinded treatment phase, follow-up survival data was to be collected every 12 weeks for 2 years from the last dose of blinded IP.

Table 9 Trial Initiation/Cutoff Dates

	Trial Initiation	Primary Analysis Cutoff Date
103	May 2006	October 2009
136	April 2006	March 2009
244	June 2006	April 2009

Randomization was stratified within each trial as shown below.

Table 10 Randomization Stratification

Stratification Factor		103 (Prostate)	136 (Breast)	244
Previous SRE	y vs. n	X	X	X
PSA	< 10 vs. ≥ 10	X		
Current chemotherapy	y vs. n	X	X	
Prior oral bisphosphonate	y vs. n		X	
Region	Japan vs. other		X	
Tumor type	NSCLC vs. MM vs. other			X
Systemic anti-cancer therapy	y vs. n			X

*PSA = prostate specific antigen; NSCLC = non small cell lung cancer; MM = multiple myeloma

It was recommended, not required, that patients receive daily supplementation with at least 500 mg calcium and at least 400 IU of vitamin D unless documented hypercalcemia developed during the study.

A data monitoring committee reviewed safety and efficacy data at regular intervals (approximately twice yearly) during the blinded treatment phases. See Section 6 for further detail regarding the DMC including review of the DMC charter.

Important Inclusion Criteria (modified from the protocols)

- Current or prior radiographic (X-ray, CT, or MRI) evidence of at least one bone metastasis (or lytic bone lesion from multiple myeloma)
- CrCl ≥ 30 mL/min
- Serum calcium (albumin-adjusted) ≥ 8 mg/dL and ≤ 11.5 mg/dL
- For Trial 103 only:
    - Failure of at least 1 hormonal therapy as evidenced by a rising PSA

- Serum testosterone level < 50 ng/dL due to either surgical or chemical castration

Important Exclusion Criteria (modified from the protocols)

- Prior IV bisphosphonate use
- Prior oral bisphosphonate use for the treatment of bone metastases
- Planned radiation or surgery to bone
- History of ONJ/osteomyelitis of the jaw
- Active dental or jaw condition requiring oral surgery
- Non-healed dental/oral surgery
- Planned invasive dental procedure for the course of the study

Administration of blinded IV investigational product (IP) was withheld (SC administration continued) for patients who experienced renal deterioration (as defined in the zoledronic acid USPI) on study. Once the patient's serum Cr returned to within 10% of baseline, the IV IP was re-initiated at the same dose as that prior to treatment interruption.

Administration of both SC and IV IP was withheld for any patient experiencing a Grade 3 or 4 (NCI CTCAE v3.0) adverse event (AE) reported by the investigator to be related to IP. Re-exposure to both IPs could only occur when the AE resolved to Grade 1 or less and the investigator and sponsor agreed that the patient's safety would not be compromised.

See below for a general Schedule of Assessments. In addition, Trial 103 required monitoring of PSA levels every 12 weeks.

An examination of the oral cavity was to be conducted by the investigator or designated healthcare professional at screening, then every 24 weeks (approximately 6 months) during the treatment period, and at the end-of-study visit.

Concomitant Therapies

Investigators could prescribe any concomitant treatments deemed necessary with the exception of those prohibited below. Usual therapy for metastatic cancer was allowed, including chemotherapy or hormonal therapy for metastatic breast or prostate cancer.

Prohibited Therapies

- Bisphosphonates (oral and IV, other than the IV IP)
- (Unapproved) investigational products other than denosumab

The protocols contained the statement that "If an SRE occurs on study, every effort should be made to continue the subject on investigational products". All patients who experienced an SRE on study were to receive treatment for the SRE as determined by their physician, which may have included radiation, surgery, chemotherapy, and/or the

administration of bisphosphonates. If administration of bisphosphonates was chosen, the patient was to be discontinued from further administration of IP but was to continue with all other study assessments every four weeks.

Figure 3 Schedule of Assessments

(excerpted from the BLA)

	Screening[1]		Blinded Treatment Period[3]: in weeks - Study Day 1 - Week 49 (Visits every 4 weeks)												
*Informed Consent must be obtained before any study assessments are performed unless it is standard of care	≤ 28 days	≤ 14 days	Study Day 1[2]	W5	W9	W13	W17	W21	W25	W29	W33	W37	W41	W45	W49[18]
	Before Randomization														
Medical History[4]	x														
Physical Examination[5] and ECOG Assessment	x					x			x			x			x
Oral Examination[6]	x								x						x
CENTRAL LABORATORY															
Serum Chemistry[7]		x[7]		x	x	x	x	x	x	x	x	x	x	x	x
Hematology[8]		x[8]		x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy Test[9]		≤ 7 days													
Urine Collection[10]			x			x									
Bone Specific Alk. Phos.			x			x									
Anti-Denosumab Antibody			x						x						x
Denosumab Concentration (subset of 150 subjects)			x	x	x	x			x						x
LOCAL LABORATORY															
Serum Creatinine[11]			x	x	x	x	x	x	x	x	x	x	x	x	x
INVESTIGATIONAL PRODUCT ADMINISTRATION[12] - Subcutaneous injection is to be administered before IV infusion															
Denosumab/placebo (SC)			x	x	x	x	x	x	x	x	x	x	x	x	x
Zoledronic acid/placebo (IV)			x	x	x	x	x	x	x	x	x	x	x	x	x
IMAGING															
Skeletal Survey (X-rays)[13]	x					x			x			x			x
OTHER ASSESSMENTS															
Skeletal Event Recording[14]			x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Event Collection[15]			x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications[16]			x	x	x	x	x	x	x	x	x	x	x	x	x
PROs			footnote[17]	x	x	x	x	x	x	x	x	x	x	x	x
Healthcare Utilization			x	x	x	x	x	x	x	x	x	x	x	x	x
Survival Data															

	Blinded Treatment Period[4] in weeks (Visits every 4 weeks)																
[3]Informed Consent must be obtained before any study assessments are performed unless it is standard of care	W53	W57	W61	W65	W69	W73	W77	W81	W85	W89	W93	W97	W101	W105	W109	End of Study Visit[20]	Follow Up[39] (Q12W)
Medical History[5]																	
Physical Examination[6] and ECOG Assessment			x			x			x			x			x	x	
Oral Examination[7]						x						x				x	
CENTRAL LABORATORY																	
Serum Chemistry[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Hematology[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Pregnancy Test[9]																	
Urine Collection[10]																x	
Bone Specific Alk. Phos.																x	
Anti-Denosumab Antibody												x				x	x[21]
Denosumab Concentration (subset of 150 subjects)						x						x				x	
LOCAL LABORATORY																	
Serum Creatinine[11]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
INVESTIGATIONAL PRODUCT ADMINISTRATION[12] - Subcutaneous injection is to be administered before IV infusion																	
Denosumab/placebo (SC)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Zoledronic acid/placebo (IV)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
IMAGING																	
Skeletal Survey (X-rays)[13]			x			x			x			x			x	x	
OTHER ASSESSMENTS																	
Skeletal Event Recording[14]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Event Collection[15]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medications[16]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
PROs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Healthcare Utilization	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Survival Data																	x

Footnotes for Schedules of Subject Assessments
1. Screening: All screening assessments must be completed and results obtained (eg, chemistry, hematology) before randomization into the study. Assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the screening windows specified. Randomization must occur no more than 8 calendar days before planned study day 1.
2. Study day 1: The first day that investigational product is administered will be study day 1.
3. Blinded Treatment Phase: The treatment phase will end when the benefit: risk analysis has been completed
4. Medical History: Includes detailed history of cancer and metastatic bone disease, history of other disease processes (active or resolved) and concomitant illnesses including SREs and/or HCM.
5. Physical Examination: A routine physical examination by the investigator (or designated physician) will include height (screening only), weight, and vital signs. ECOG performance status will be assessed with each physical examination.
6. Oral Examination: A visual examination of the oral cavity, including teeth, mucosa and jaws will be conducted at screening to establish baseline oral health conditions and subsequently to identify any new abnormalities or changes in pre-existing conditions.
7. Serum Chemistry: Organ function including monitoring of calcium levels. A complete listing of tests can be found in Section 7.8.1. Screening values, provided by the central laboratory, will be used as baseline values.
8. Hematology: Red blood cell count, hemoglobin, hematocrit, platelet count, and white blood cell count with differential. Screening values, provided by the central laboratory, will be used as baseline values.
9. Pregnancy Test: Serum or urine test must be performed for all women of childbearing potential no more than 7 days before randomization. Must be repeated (locally) if the result is more than 7 days before randomization.
10. Urine Collection: Study day 1, week 13, and end of study, urine must be collected from the 2nd void of the day (before 12:00pm) for urine creatinine and urinary N-telopeptide (uNTx) analysis.
11. Serum Creatinine: To determine creatinine clearance at baseline in order to calculate the dose of IV investigational product, using the Cockcroft-Gault formula provided in the Zometa® prescribing information. Serum creatinine must be obtained using a local laboratory, preferably on the day of, and no more than 14 days before, each administration of IV investigational product to monitor for renal insufficiency. Refer to Section 6.1.3 for dose stopping rules.
12. Investigational Product Administration: Denosumab will be administered at a dose of 120 mg SC Q4W and zoledronic acid will be administered IV at a dose of 4 mg (equivalent creatinine clearance-adjusted dose in patients with baseline creatinine clearance ≤ 60 mL/min) as a single, minimum 15-minute infusion Q4W in a blinded manner. Subcutaneous injection must be administered first, followed by IV infusion. Both (SC and IV) investigational products must be withheld for related Grade 3 or 4 AEs. IV investigational product must be withheld (SC will continue) for renal toxicity (refer to Section 6.1.3 for dose withholding rules).
13. Skeletal Survey: Radiograph of skull, spine, chest, pelvis, upper extremities shoulder to elbow, lower extremities hip to knee. Blinded hard copy films or digitized films will be sent for each radiologic assessment to a central reader after local reading and reporting, including any unplanned x-rays.
14. Skeletal Related Event (SRE) Recording: SREs include pathologic fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression. Pathological fracture(s) will be obtained through skeletal surveys, analyzed by the central imaging reader. Spinal cord compression will be confirmed using radiographic imaging (eg, MRI) and sent to the central imaging reader. Radiation to bone and surgery to bone SREs are to be documented on the respective CRF(s).
15. Adverse Events: Adverse events must be assessed and documented at each scheduled clinic visit. Subjects must be followed for adverse events for 30 days after the last dose of investigational product, or until all investigational product-related toxicities and ongoing serious adverse events have resolved or are considered stable, whichever is later.
16. Concomitant Medications/Treatments: Information regarding type and timing of concomitant medications and treatments will be collected. Calcium and Vitamin D supplements will be recorded as concomitant medications.

Footnotes for Schedule of Subject Assessments
17. PROs: The PROs will be administered on days 1, 8 (completed at home or in clinic), 29 (week 5) and then every visit (Q4W) thereafter. Forms are to be completed by the subject before any other study procedures are conducted for each visit.
18. Blinded Treatment After Week 49: Subjects continuing on treatment after week 49 will continue on a Q4W schedule with investigational product administration and blood sample collection and a Q12 week schedule for physical examinations, oral examinations and skeletal surveys, until the end of study. Serum for anti-denosumab antibody assay will be collected once every 53 weeks after Week 49, until the end of study.
19. End of Study Visits in the blinded treatment phase will be completed at any point a subject discontinues participation. If the benefit: risk is not positive, all subjects will be given approximately 4 weeks to complete the end of study visit. All end of study assessments must be completed if not done in the last week, except skeletal surveys which do not need to be repeated if completed within the last 12 weeks.
20. Follow up: Follow up survival data will be collected approximately every 12 weeks for each subject 2 years after the subject's end of study visit.
21. Follow up Anti-denosumab Antibody Sample: One follow up serum sample for anti-denosumab antibody (binding and neutralizing) assay will be collected from each subject, 24 weeks (approximately 6 months) after the subject's last dose of investigational product.

Skeletal-Related Events

- Skeletal surveys were sent from the site to the central imaging vendor for central reading. See Section 6 for further details regarding the central imaging review and IRC.
- Surgery to bone included procedures used to set or stabilize a fracture or to prevent an imminent fracture or cord compression.
- Radiation therapy to bone included radiation for pain control, to treat or prevent pathologic fractures, or to treat or prevent cord compression.
- Cord compression events were to be confirmed using MRI or CT scans which were to be submitted to the central imaging reader for review.
- All scheduled and non-scheduled x-rays were to be submitted to the central imaging vendor for review.

Disease Progression

- Overall disease progression was to be assessed and documented by the investigator on the CRF based on clinical observations.

Statistical Considerations

- See Section 6 for review of the statistical analysis plans including sample size assumptions and analysis of primary and secondary endpoints.
- Early stopping
    - No trial was to be stopped early based on evidence of non-inferiority.
    - For superiority, no trial was to be stopped unless a p-value of 0.0005 was achieved.
- The protocol specified that the Applicant would monitor the rate of SREs by treatment group and if this was lower than expected, may choose to modify the sample size.

Important Protocol Amendments

- Trial 103
    - The sample size was increased from 1700 to 1870 patients.
- Trial 136
    - The sample size was increased from 1400 to 1680 patients.
    - The sample size was increased from 1680 to 1960 patients.

Trial 20040245

Trial 20040245 was an open-label, single-dose PK study in patients without cancer and with varying degrees of renal function, using a 60-mg dose of denosumab. A total of 55 patients were enrolled and assigned to 1 of 5 renal function groups based on CrCl:

- Group 1 – CrCl > 80 mL/min
- Group 2 – CrCl 50-80 mL/min

- Group 3 – CrCl 30-49 mL/min
- Group 4 – CrCl < 30 mL/min
- Group 5 – requiring hemodialysis

Patients with hypocalcemia at screening were excluded from trial entry, as were patients with a CrCl of 15 – 30 mL/min who had iPTH levels > 110 pg/mL, patients with a CrCl less than 15 mL/min or receiving dialysis who had iPTH levels > 300 pg/mL, and patients with a CrCl less than 30 mL/min who had 1,25-OH-vitamin D levels < 30 pg/mL (other than those receiving hemodialysis and receiving calcium or vitamin D analogs). These criteria excluded patients with severe CKD or ESRD having abnormal vitamin D or iPTH levels at screening.

Trial 20040113

Trial 20040113 was an international, randomized, multidose, active-controlled study in patients with breast cancer with bone metastasis who had not previously received IV bisphosphonates. Patients were randomized to receive 1 of 5 dose schedules of denosumab (30, 120, or 180 mg Q4W; or 60 or 180 mg Q12W) or open-label IV bisphosphonate therapy. The trial enrolled 255 women (212 denosumab, 43 IV bisphosphonate). Duration of treatment was 25 weeks of IP administration followed by a 32-week post-treatment follow-up. The primary endpoint was percentage change in uNTX/Cr from baseline to week 13.

6 Review of Efficacy (M. Axelson)

Efficacy Summary

The efficacy conclusions for this application are based on the analyses of efficacy data submitted from three randomized, active-controlled, non-inferiority trials, Trial 20050103 (103), Trial 20050136 (136), and Trial 20050244 (244). All three trials compared zoledronic acid (ZA) to denosumab with first on-study skeletal-related event (SRE) as the primary endpoint. SRE, a composite endpoint of spinal cord compression, surgery to bone, fracture, and radiation to bone, has been accepted as a regulatory endpoint for the bisphosphonate class of products. The primary endpoint in Trials 103, 136, and 244 was time to first on-study SRE (non-inferiority). As a result, demonstration of clinical benefit for the primary indication for the treatment of patients with bone metastases from solid tumors comes from the efficacy data submitted for Trials 103, 136, and 244.

Trials 103, 136, and 244 were multinational, multicenter, double-blind, active-controlled trials involving 5,723 subjects, 1,901 with metastatic, castrate resistant prostate cancer, 2,046 with metastatic breast cancer, and 1,776 with multiple myeloma or metastatic solid tumors other than breast or prostate cancer, respectively. Subjects were

randomized (1:1) to denosumab or zoledronic acid and received denosumab or zoledronic acid every 4 weeks until the date when approximately 745 subjects were expected to have an on-study SRE (number of events required for the primary analysis). Use of daily calcium (≥ 1 g/day) and vitamin D (≥ 400 IU/day) supplementation throughout the trial was encouraged but not required. Stratification factors for Trials 103, 136, and 244 included previous SRE and current chemotherapy. Additional protocol-specific stratification factors included PSA level < 10 ng/mL ≥ 10 ng/mL (103); prior oral bisphosphonate use and Japanese race (136); and Tumor Type [Multiple Myeloma, Non-Small Cell Lung Cancer (NSCLC), or other] (Trial 244). All three trials included a double-blind extension (DBE) period that allowed subjects to receive open-label denosumab for up to 2 years or until commercial availability of denosumab, whichever came first and followed subjects for survival for 2 years after the last dose of blinded investigational product. The results of the DBE studies for 136 and 244 were available at the time of the sBLA submission; the sponsor submitted results for Trial 103 on 08/23/2010.

As previously described, the primary efficacy endpoint was time to first on-study SRE (non-inferiority). Key secondary endpoints were time to first on-study SRE (superiority) and first-and-subsequent on-study SRE. Neoplastic disease assessments were required during the trials including imaging every 12 weeks to assess disease progression. Additionally, the protocols mandated telephone contact every 12 weeks for 2 years after the end-of-study visit to assess overall survival.

Trials 103 [HR 0.82 (0.71, 0.95), p=0.0101] and 136 [HR 0.82 (0.71, 0.95) p=0.0085] demonstrated superiority of denosumab over zoledronic acid for first on-study SRE; Trial 244 [HR 0.84 ((0.71, 0.98) p=0.0007; superiority analysis p=0.0619] demonstrated non-inferiority for first on-study SRE. The median time to first SRE for denosumab could not be determined for Trial 136; the difference in median time to first SRE was 3.5 months for Trial 103, and 4.2 months for Trial 244. Consistent effects on time to SRE were observed regardless of baseline age, sex, stratification factors, and individual SRE events.

As previously described, Trials 103, 136, and 244 used a non-inferiority analysis for the primary pre-specified analysis with zoledronic acid as the active comparator in each trial. In general, the registration trials comparing denosumab to zoledronic acid were similar in design and conduct to the trials that established the effectiveness of zoledronic acid. The inclusion criteria for Trials 103, 136, and 244 were similar to zoledronic acid trials. Additionally, the demographics of subjects enrolled into the denosumab trials were similar to the demographics of subjects in the zoledronic acid trials. Trials 103, 136, and 244 did not allow for prior bisphosphonate use. In the zoledronic acid registration trials, prior bisphosphonate use was restricted to 12 months prior to the screening visit.

The effectiveness of zoledronic acid for the prevention of SREs was established by two placebo controlled studies in prostate and solid tumors and a non-inferiority active controlled study versus pamidronate in subjects with breast cancer and multiple myeloma. Two pre-specified analyses were included in product labeling: analysis of proportion of subjects with an SRE and time to first SRE. For time to first SRE, the HR for the prostate cancer study was 0.67 (0.49, 0.91), and the HR for the "solid tumors" study was 0.73 (0.55, 0.96).

The median time to first SRE was not reached in the zoledronic prostate cancer study comparing zoledronic acid to placebo [the point estimate for the median time to first SRE in the placebo arm was 321 days with a HR of 0.67 favoring zoledronic acid (extrapolating out to an estimated median time to first SRE of 479 days in the zoledronic acid arm)]. The median control (zoledronic acid) arm SRE effect size was 521 days in Trial 103 (denosumab study). *Reviewer's Comment: This effect size was similar to the estimated (extrapolated) effect size of 479 days in the placebo controlled study, and in general consistent with the constancy of effect requirements for non-inferiority studies.*

The median time to first SRE was 230 days in the zoledronic acid arm of the study comparing zoledronic acid to placebo versus a placebo effect size of 163 days. The median time to first SRE was longer in Trial 244 compared to the historical study demonstrating the effectiveness of zoledronic acid (496 days versus 230 days).

In the breast cancer and multiple myeloma study, the HR (first SRE) for zoledronic acid compared to pamidronate was 0.92 (0.77, 1.09). As described in product labeling for zoledronic acid, historical data from 1,128 subjects in three pamidronate placebo-controlled trials demonstrated that pamidronate decreased the proportion of subjects with SRE by 13.1% (7.3, 18.9). The median number of days to first SRE in the zoledronic acid arm was 373 days in the zoledronic acid-pamidronate study versus 806 days for zoledronic acid in Trial 136.

The dosing of zoledronic acid in registration trials was every 3 or 4 weeks compared to every 4 weeks in the denosumab trials. A review of the literature did not reveal evidence of differences in treatment effects between three and four week dosing. Planned analyses in the historical zoledronic acid trials included the proportion of subjects during a specified time period who did not have an SRE and time to first SRE. *The individual components of the SRE endpoint were similar when comparing the denosumab trials to the zoledronic acid registration trials.*

The differences in the demographics (prior bisphosphonate use), trial design (comparator), and primary endpoint (time to SRE vs. proportion of subjects with SRE) between Trials 103, 136, and 244 to the zoledronic acid registration trials were minimal enough to be reasonably assured that the effect size of zoledronic acid could be replicated in Trials 103, 136, and 244, i.e. the constancy assumption.

6.1 Indication

The proposed indication for this application is [redacted] (b) (4) There is regulatory precedent establishing that the aggregate endpoint SRE represents an adequate efficacy measure. *Reviewer's Comment: Pathologic facture and spinal cord compression are associated with functional and neurological detriment, as well as pain; a reduction of these events is clinically meaningful. Surgery or radiation to bone often is performed to relieve pain or prevent an impending fracture. This reviewer agrees that a reduction in or delay in time to SREs constitutes clinical benefit.*

Furthermore, there is regulatory precedent establishing a broad indication for drugs intended to treat SREs in patients with cancer of different tumor types provided the trials encompass the most common solid tumor types and are large enough to detect meaningful differences in overall survival and disease progression to ensure the supportive beneficial effect is not offset by worsening of the underlying cancer.

6.1.1 Methods

Figure 4 summarizes the trial design and study objectives from the key clinical trials supporting the cancer with osseous metastases indication.

Figure 4: Trial Design and Objectives for Key Trials, Cancer with Osseous Metastases Indication (copied from the Amgen sBLA submission)

Study No.	Study Design	Study Population	Study Objectives	Region	Number of Randomized Subjects	Duration of Treatment
20050136	Phase 3, randomized, double-blind, active-controlled	Adult (men included) with histologically or cytologically confirmed breast adenocarcinoma; current or prior radiographic (ie, x-ray, CT, or MRI) evidence of at least 1 bone metastasis	Primary: to determine if denosumab was noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE Secondary: to determine if denosumab was superior to zoledronic acid with respect to the first on-study SRE and the first-and-subsequent on-study SRE (using multiple-event analysis), and to assess the safety and tolerability of denosumab compared to zoledronic acid	North America, Europe, Latin America, Japan, India, Australia, South Africa	2046 (1026 denosumab 120 mg Q4W, 1020 zoledronic acid)	Event driven: double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~745 subjects experienced an initial on-study SRE, followed by a 2-year survival follow-up period or a 2-year open-label extension period[a].
20050244	Phase 3, randomized, double-blind, active-controlled	Adult with histologically or cytologically confirmed advanced cancers including solid tumors (excluding breast and prostate), multiple myeloma, and lymphoma; current or prior radiographic (ie, x-ray, CT, or MRI) evidence of at least 1 bone metastasis (or lytic bone lesion from multiple myeloma)	Primary: to determine if denosumab was noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE Secondary: to determine if denosumab was superior to zoledronic acid with respect to the first on-study SRE and the first-and-subsequent on-study SRE (using multiple-event analysis), and to assess the safety and tolerability of denosumab compared to zoledronic acid	North America, Europe, Latin America, India, Australia, South Africa	1778 (886 denosumab 120 mg Q4W, 890 zoledronic acid)	Event driven: double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~745 subjects experienced an initial on-study SRE, followed by a 2-year survival follow-up period.

Study No.	Study Design	Study Population	Study Objectives	Region	Number of Randomized Subjects	Duration of Treatment
20050103	Phase 3, randomized, double-blind, active-controlled	Adult men with histologically confirmed prostate cancer; current or prior radiographic (ie, x-ray, CT, or MRI) evidence of at least 1 bone metastasis; documented failure of at least one hormonal therapy as evidenced by a rising PSA[a]; serum testosterone level of < 50 ng/mL due to either surgical or chemical castration	Primary: to determine if denosumab was noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE Secondary: to determine if denosumab was superior to zoledronic acid with respect to the first on-study SRE and the first-and-subsequent on-study SRE (using multiple-event analysis), and to assess the safety and tolerability of denosumab compared to zoledronic acid	North America, Europe, Latin America, India, Australia, South Africa, New Zealand	1901 (950 denosumab 120 mg Q4W, 951 zoledronic acid)	Event driven: double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~745 subjects experienced an initial on-study SRE, followed by a 2-year survival follow-up period or a 2-year open-label extension period[b].

Page 2 of 2

CT = computed tomography; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; SRE = skeletal-related event
[a] defined as 3 consecutive determinations, taken at least 2 weeks apart from one another. The third measurement must be ≥ 0.4 ng/mL and be taken within 8 weeks prior to randomization
[b] For subjects at all study centers, except in the United Kingdom and Czech Republic, the open-label phase is being conducted under the respective protocol number (20050136 or 20050103); in the United Kingdom and Czech Republic, the open-label extension phase is being conducted under protocol number 20080540 per Health Authority request.

Definition of Endpoints for All Studies (adapted from Amgen's CSR):

SRE was defined as one or more of the following: pathological fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression.

- Pathological fractures were those bone fractures that occurred spontaneously or resulted from trivial trauma. The nature of the trauma, whether trivial or otherwise, was to be determined by the investigator. Vertebral fractures included compression fractures.
- Surgery to bone included procedures to set or stabilize a fracture, or to prevent an imminent fracture or spinal cord compression.
- Radiation therapy to bone included radiation for pain control, to treat or prevent pathologic fractures, or to treat or prevent spinal cord compression. These events were to be captured on the CRF.
- Spinal cord compression events were to be confirmed using appropriate radiographic imaging (e.g., MRI or CT scans) and submitted to the central imaging reader for review.

The composite SRE endpoint was the same endpoint that served as the basis for zoledronic acid and pamidronate approvals.

Primary Data Analyses for Pivotal Studies:

- The primary analysis of efficacy used a synthesis approach for non-inferiority testing of the full analysis set incorporating the stratification variables.
- A proportional hazards model with treatment groups as the independent variable and stratified by randomization stratification factors was used to analyze time to first SRE.
- Patients were censored at the time of death if they died without experiencing the primary endpoint.
- A sensitivity analysis was to be performed using a per-protocol analysis set.

- Secondary endpoints (superiority in time to first SRE and time to first and subsequent SREs) were to be tested using the Hochberg procedure to control Type 1 error.
  - The Wald test from the proportional hazards model was used to test for superiority.
  - The Andersen and Gill model with robust variance estimate stratified by randomization stratification factors was used to test for superiority in time to first-and-and subsequent SRE (based on regulatory feedback the AG model was used rather than the Prentice, Williams, and Peterson model).

Independent Review Committee Procedures; (adapted from Amgen CSR):
Independent review consisted of three bodies:

- the Independent Eligibility Review (IER) to review eligibility criteria of current or prior radiographic evidence of at least one bone metastasis;
- the Independent Review Committee (IRC) to assess the study occurrences of fractures, spinal cord compression, and evaluate progression of disease in bone as determined by the presence of a new bone lesion; and,
- the SRE Reconciliation Committee (SRERC) to review discrepancies in the SRE findings identified between the investigative sites and (b) (4), an independent imaging core laboratory that provided independent radiology review.

The IER consisted of a pool of ten radiologists with one radiologist arbitrarily assigned to a given subject.

The IRC consisted of the same two radiologist reviewers who were to read all exams for a particular subject. IRC members were blind to treatment arm and site assessment and did not communicate the results to study sites. The reviewers, instead, sent their reviews to Amgen, as described in the protocol Data Transfer Plan, so Amgen had the ability to compare blinded (b) (4) results to blinded site results on a per-subject basis. An adjudicating radiologist reviewed discordant information and chose one of the two reads that he or she believed most accurately represented the subject's SRE profile up until the time of the first SRE.

The SRERC reviewed discrepancies between sites and (b) (4) For each discrepant case, Amgen sent the SRERC subject identification, identification of the time point at which the discrepancy occurred, and the location code of the SRE in question. The SRERC consisted of 4 radiologists not involved in the reading of any on-study images for the cases in question during the conduct of the study who re-reviewed the results provided by (b) (4) and the site and determined by Committee consensus which result was correct. The outcome of the review by the SRERC was binary, agreeing or disagreeing with the (b) (4) (IRC) assessment.

Interlaboratory Standardization Methods and Quality Assurance Procedures defined vertebral fracture as ≥ 20% reduction in vertebral height (anterior, middle, or posterior),

non-vertebral fracture as present or not, and MRI/CT scan or myelogram confirmation of spinal cord compression. *The published report (Saad et al. 2002) which served as the basis for the non-inferiority margin and one of the trials supporting zoledronic acid approval used ≥ 25% reduction in vertebral height. The lower cut-off in the 103 study could lead to a higher event rate and overestimation of the treatment effect.*

Review of Data Monitoring Committees:
The DMC charters indicated that the committee would not stop the trials early based on "on overwhelming evidence of non-inferiority," but "for superiority, the study should not stop unless the result for the primary endpoint achieves a p-value of 0.0005." The DMCs had access to each subject's individual treatment assignments, but could not have any direct contact with the study site personnel or subjects. The DMC was to communicate major safety concerns and recommendations regarding study modification or termination to Amgen Inc., senior management.

The DMC reviewed the following results for safety and toxicity of treatment for all protocols:
- Subject incidence of treatment-emergent adverse events
- Changes in laboratory values
- Subject incidence of anti-denosumab antibody formation
- Change from baseline in bone turnover markers

Results to be reviewed for efficacy for protocols 20050103, 20050136, and 20050244:
- Time to the first on-study SRE
- Time to first-and-subsequent-SRE
- Time to first on-study radiation to bone (including the use of radioisotopes)
- Other clinical outcomes (i.e., overall survival, progression of disease in bone, and overall progression of disease)
- Time to first on-study SRE or HCM

Additional discussion of Issues Related to Sample Size and Study Design

Study 103: Prostate Cancer Study

Study 20050103 was a double blind, randomized (1:1) non-inferiority trial comparing denosumab to zoledronic acid intending to demonstrate that denosumab preserves at least 50% of the effect of zoledronic acid on the time to first on-study SRE in subjects with hormone-refractory (castrate-resistant) prostate cancer and bone metastases. Stratification factors for randomization were previous SRE (yes or no), PSA level (< 10 ng/mL or ≥ 10 ng/mL), and current chemotherapy [defined as within 6 weeks before randomization (yes or no)]. Randomization was equally allocated (1:1) within each stratum. A trial comparing zoledronic acid to placebo in subjects with metastatic prostate cancer served as the basis for estimating the treatment effect of zoledronic

acid; the hazard ratio (HR) in that trial was 1.477 (1.101, 1.980) for placebo (Saad 2004).

Data were to be collected on all subjects from the randomization date to the primary analysis cut-off date [when approximately 745 subjects were anticipated to have experienced an on-study SRE (primary analysis data cutoff date) and the primary efficacy and safety analyses were completed]. The analysis of the primary and secondary endpoints was hierarchical with significance level for the primary endpoint at 0.05 and testing of the primary secondary endpoint, superiority of time to first on-study SRE, to occur if the primary endpoint reached statistical significance. The trial was an event driven trial to end 4 weeks after the 745th subject's first on-study SRE occurred.

The study was designed to detect non-inferiority based on the true HR of at least 0.9 and 90% power based on a synthesis approach (Hung 2003). A total of 1700 subjects were to be enrolled for a target event rate of 745. The study was designed with 90% power to detect a HR 0.8 for the secondary endpoints of time to first on-study SRE (superiority) and time to first-and-subsequent on-study SRE (superiority), and a correlation coefficient of 0.6 between the two endpoints.

The Applicant amended the protocol on May 5, 2008 to increase the sample size from 1700 to 1870 due to a lower than expected overall SRE rate.

The non-inferiority design was consistent with FDA's current guidance on non-inferiority. The sponsor amended the protocol to increase the sample size from 1700 subjects to 1870 subjects (increase of 10%) due to a lower than expected SRE rate, pooled by treatment group; the approach to revise the sample size was pre-specified in the protocol.

Study 136: Breast Cancer Study

Study 20050136 was a double blind, randomized (1:1) non-inferiority trial comparing denosumab to zoledronic acid intending to demonstrate that denosumab preserves at least 50% of the effect of zoledronic acid on the time to first on-study SRE in subjects with advanced breast cancer and bone metastases. Stratification factors for randomization were previous SRE (Yes or No), prior oral bisphosphonate use (Yes or No), current (defined as within 6 weeks before randomization) chemotherapy (Yes or No), and region (Japan or other countries). Subjects were randomized (1:1) with equal allocation into each stratum. Prior trials in non-Japanese subjects comparing pamidronate to placebo and zoledronic acid to pamidronate, as well as a trial conducted in Japan comparing zoledronic acid to placebo served as the basis for estimating the treatment effect of zoledronic acid. Due to limited data comparing zoledronic acid to placebo, the sponsor used a 3-step approach (copied from Amgen CSR):

1. Data from 2 trials comparing pamidronate with placebo in subjects with breast cancer receiving either chemotherapy (Hortobagyi 1996) or hormone therapy

(Theriault 1999) were combined in order to estimate the hazard ratio [95% confidence interval (95% CI)] for placebo relative to pamidronate [1.36 (1.10, 1.67)].

2. The results of step 1 were combined with the results of a trial comparing zoledronic acid with pamidronate in subjects with breast cancer receiving either chemotherapy or hormone therapy (Rosen 2004a; Rosen 2001) in order to estimate the hazard ratio (95% CI) for placebo relative to zoledronic acid in non-Japanese subjects [1.53 (1.13, 2.06)].
3. The results of step 2 were combined with the results of a trial comparing zoledronic acid with placebo in Japanese subjects (Kohno 2005) to obtain an overall estimate of the hazard ratio (95% CI) of placebo relative to zoledronic acid (1.58 [1.23, 2.02]).

The primary analysis was to occur when approximately 745 subjects were anticipated to have experienced an on-study SRE. The study was designed with 97% power to assess for non-inferiority using a synthesis approach (Hung 2003) based on the true HR of at least 0.9. The study was designed with 90% power to detect superiority of denosumab to zoledronic acid for at least one of the two secondary endpoints, assuming a true hazard ratio of 0.8 for both secondary endpoints and a correlation coefficient of 0.6 between the two endpoints.

The sponsor amended the protocol on April 2, 2007 to increase the sample size from 1,400 to 1,680 due to a lower than expected overall SRE rate and again on August 15, 2007 to 1,960 subjects after a review "of baseline characteristics indicated that subjects enrolled had an earlier disease state than subjects in the historical study (Novartis 010)" used to estimate the SRE rate.

Ultimately, the study was concluded with a primary cut-off date of March 6, 2009. At this time, 687 subjects experienced a confirmed first on-study SRE (rather than the pre-specified 745 subjects). The applicant justified this cut-off as follows:

- The number of new subjects experiencing an SRE each month was low (< 10 subjects).
- The approximate treatment duration specified by the protocol had been reached.
- With 687 subjects experiencing an SRE, the study had approximately 96% power for non-inferiority and 87% power for superiority.
- As a result, the study was considered appropriately powered to assess the primary and secondary endpoints with the data available as of 06 March 2009.

Because the study design was double-blind, this reviewer did not object to the applicant's justification.

Study 244: Other Solid Tumors and MM Study

Study 20050244 was a double-blind, randomized (1:1) non-inferiority trial comparing denosumab to zoledronic acid intending to demonstrate that denosumab preserves at least 50% of the effect of zoledronic acid on the time to first on-study SRE in subjects with advanced cancer (excluding breast and prostate cancer) and bone metastases (or lytic bone lesions from multiple myeloma). Stratification factors for randomization were tumor type (non-small cell lung cancer or multiple myeloma or other), previous SRE (yes or no), and systemic anti-cancer therapy (yes or no). Subjects were randomized (1:1) with equal allocation within each stratum. Prior trials in subjects with multiple myeloma comparing zoledronic acid and pamidronate (Rosen 2001) and a study in subjects with lung cancer comparing zoledronic acid and placebo (Rosen 2003a) served as the basis for estimating the treatment effect of zoledronic acid. Due to limited data comparing zoledronic acid to placebo, the sponsor used a 3-step approach (copied from Amgen CSR):

1. Zoledronic acid was compared with placebo in Novartis solid tumor trial 011 (Statistical Review and Evaluation of Zometa). In this trial, in subjects with a solid tumor, the hazard ratio for time to first on-study SRE for placebo relative to zoledronic acid was 1.36 with 95% CI (1.04, 1.80).
2. In subjects diagnosed with multiple myeloma, pamidronate was compared with placebo in Novartis trial 12 and zoledronic acid was compared with pamidronate in Novartis trial 10. In Novartis trial 12, the hazard ratio for placebo relative to pamidronate was 1.45 with 95% CI (1.07, 2.0). In Novartis trial 10 the hazard ratio for zoledronic acid relative to pamidronate was 0.97 with 95% CI (0.71, 1.31). By combining data from these two trials, the hazard ratio for placebo relative to zoledronic acid in multiple myeloma subjects was calculated as 1.50 with 95% CI (0.97, 2.32).
3. By combining the results in step 1 with the results of step 2, the hazard ratio for placebo relative to zoledronic acid in subjects with advanced cancer (excluding breast or prostate cancer) or multiple myeloma was calculated as 1.40 with 95% CI (1.11, 1.77).

The primary analysis was to be conducted using data collected from all subjects from the randomization date to the primary analysis cut-off date, when approximately 745 subjects were anticipated to have experienced an on-study SRE.

The same trials that served as the basis of the effect size of zoledronic acid also provided the estimation for sample size. The study was designed with 97% power to detect non-inferiority using a synthesis approach (Hung 2003) based on the true HR of at least 0.9. The study was designed to require seven hundred forty five subjects with at least one SRE among 1,690 planned subjects. The study was designed with 90%

power to detect superiority of denosumab to zoledronic acid for at least one of the two secondary endpoints, assuming a true hazard ratio of 0.8 for both secondary endpoints and a correlation coefficient of 0.6 between the two endpoints.

6.1.2 Demographics

Table 11 contains the key dates for Trials 103, 136, and 244. The full analysis set contained 5723 subjects: 1901 in 103, 2046 in 1306, and 1776 in 244. Table 12 contains the patient characteristics of the ITT population. Randomization was balanced within each study.

Table 11: Study Periods

	Trials		
Study Periods	103	136	224
First Subject Enrollment Date	5/12/2006	4/27/2006	6/21/2006
Last Subject Enrollment Date	12/18/2008	12/31/2007	5/16/2008
Primary Analysis Data Cut-off Date	10/30/2009	4/30/2009	3/6/2009

The ASLBASE dataset was the primary resource for the demographics and disease characteristics shown in Table 12 and Table 13. The median age at enrollment was higher in the 103 study (71 years in both arms) compared to Trial 136 [57 (denosumab) and 56 (ZA)], and Trail 244 [60 (denosumab) and 61 (ZA)]. In Trial 103, over 70% of subjects were ≥ 65 years of age with approximately 36% of subjects in each arm ≥ 75 years of age. In Trials 136 and 244, the percentages of subjects ≥ 65 and ≥ 75 years of age were lower, 26% and 6% for 136 and 36% and 8% for 244, respectively. In Trial 244, 34% and 38% of subjects were women in the denosumab and ZA arms, respectively; Trial 136 enrolled 1% men in each arm. Over 80% of subjects were White and Europe was the most common region of enrollment in all three studies; in each arm over 5% of subjects were either Black or Latino.

Table 12: Demographics

Demographics	Trial 103		Trial 136		Trial 244		Total All Studies
	D	ZA	D	ZA	D	ZA	D and ZA
	n=950 (%)	n=951 (%)	n=1026 (%)	n=1020 (%)	n=886 (%)	n=890 (%)	n=5732 (%)
Age							
Min	40	38	27	24	18	22	18
Median	71	71	57	56	60	61	63
Max	93	91	91	90	89	87	93
Mean	70.5	71	56.8	56.6	60	61	62.4
Age ≥75	(35.6)	(36.5)	(5.9)	(6.2)	(8.4)	(8.3)	(16.7)

Demographics	Trial 103		Trial 136		Trial 244		Total All Studies
	D	ZA	D	ZA	D	ZA	D and ZA
	n=950 (%)	n=951 (%)	n=1026 (%)	n=1020 (%)	n=886 (%)	n=890 (%)	n=5732 (%)
Age ≥ 65	(73.4)	(77.3)	(26.8)	(26.1)	(33.7)	(37.6)	(45.5)
Sex							
M	(100.0)	(100.0)	(0.8)	(0.9)	(66.4)	(61.9)	(53.3)
F	(0.0)	(0.0)	(99.1)	(99.0)	(33.6)	(37.8)	(46.4)
Race							
White	(87.3)	(85.2)	(80.0)	(79.6)	(86.9)	(86.2)	(83.9)
Hispanic or Latino	(4.7)	(6.0)	(5.8)	(5.8)	(5.5)	(4.0)	(5.3)
Asian	(2.3)	(2.7)	(3.1)	(3.6)	(4.1)	(4.9)	(3.4)
Black	(4.0)	(3.7)	(2.5)	(2.5)	(2.3)	(3.3)	(3.0)
Japanese	(0.0)	(0.0)	(6.8)	(6.8)	(0.3)	(0.1)	(2.5)
Other	(1.6)	(2.3)	(1.6)	(1.6)	(0.9)	(0.9)	(1.5)
Native Hawaiian or Other Pacific Islander	(0.1)	(0.1)	(0.1)	(0.1)	(0.0)	(0.0)	(0.1)
American Indian or Alaska Native	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.2)	(0.0)
Region							
Europe	(55.2)	(53.1)	(52.1)	(51.1)	(55.4)	(53.8)	(53.3)
North America	(17.9)	(17.8)	(18.9)	(18.4)	(22.2)	(23.4)	(19.6)
Latin America	(20.3)	(21.1)	(16.9)	(17.3)	(16.5)	(14.6)	(17.8)
Other	(6.6)	(8.0)	(12.0)	(13.1)	(5.9)	(7.9)	(9.0)

In the 136 trial over 80% of subjects were post-menopausal; in the 244 trial, post-menopausal status was balanced. There was frequent missing data regarding post-menopausal status, over 50% in each arm. The median ECOG status for all trials was 1. Fewer than 20% of subjects in Trial 103 had visceral metastases; 53% of subjects in the 136 trial and 52% of subjects in the 244 trial had visceral metastases. Baseline disease characteristics and stratification factors were well balanced within each study.

Table 13: Disease Characteristics

Disease Characteristics	Trial 103		Trial 136		Trial 244		Subjects
	D	ZA	D	ZA	D	ZA	
	n= 950 (%)	n= 951 (%)	n=1026 (%)	n=1020 (%)	n=886 (%)	n=890 (%)	n=5732 (%)
History of SRE							
N	(74.0)	(74.0)	(59.5)	(58.1)	(49.3)	(45.5)	(60.2)
Y	(26.0)	(26.0)	(40.4)	(41.8)	(50.7)	(54.2)	(39.5)
Lesion Type							
Osteoblastic	(63.3)	(56.5)	(27.4)	(27.9)	(17.0)	(14.6)	(34.6)
Not Seen	(19.8)	(23.4)	(32.7)	(32.8)	(43.1)	(43.5)	(32.3)
Mixed	(13.5)	(15.8)	(24.8)	(25.1)	(17.5)	(17.4)	(19.2)
Osteolytic	(3.4)	(4.1)	(14.8)	(13.6)	(22.1)	(23.6)	(13.4)
Unable to Evaluate	(0.1)	(0.2)	(0.3)	(0.4)	(0.2)	(0.6)	(0.3)
ECOG							
1	(48.8)	(48.4)	(44.0)	(43.5)	(57.3)	(55.3)	(49.2)
0	(44.0)	(44.8)	(49.1)	(47.8)	(27.1)	(26.5)	(40.3)
2	(7.2)	(6.8)	(6.6)	(8.0)	(15.3)	(17.6)	(10.0)
Missing	(0.0)	(0.0)	(0.1)	(0.3)	(0.2)	(0.2)	(0.1)
3	(0.0)	(0.0)	(0.1)	(0.2)	(0.0)	(0.0)	(0.1)
Visceral Mets							
N	(83.1)	(81.0)	(46.2)	(48.4)	(46.5)	(49.6)	(59)
Y	(16.9)	(19.0)	(53.7)	(51.5)	(53.5)	(50.1)	(41)
Gleason Score							
2-6	(18.4)	(18.9)					
7	(28.7)	(29.4)					
8-10	(41.5)	(42.9)					
Missing	(11.4)	(8.7)					
Menopause Status							
Y			(81.8)	(81.6)	(27.8)	(32.9)	
Missing			(0.3)	(0.2)	(66.8)	(62.4)	
N			(16.6)	(16.9)	(4.7)	(4.4)	
N/A			(1.4)	(1.4)	(0.7)	(0.3)	

The primary individual tumor type of patients enrolled into Trial 244 (Table 14) were similar to the primary individual tumor type of patients in a published report of a zoledronic acid registration trial (Rosen 2003). NSCLC was the most common (39.5%) tumor type followed by renal (8.7%), and small cell lung cancer [SCLC (6%)]. The study prevalence of other malignancies was under 5% for each malignancy.

Table 14: Primary Tumor Type by Arm Trial 244

Primary Tumor Type (Trial 244)	D n=886 (%)	ZA n=890 (%)	Total n=1776 (%)
Non-Small Cell Lung Cancer (NSCLC)	350 (39.4)	352 (39.6)	702 (39.5)
Multiple Myeloma	90 (10.1)	93 (10.4)	183 (10.3)
Renal	70 (7.9)	85 (9.6)	155 (8.7)
Small Cell Lung Cancer (SCLC)	61 (6.9)	48 (5.4)	109 (6.1)
Bladder	28 (3.1)	35 (3.9)	63 (3.5)
Rectal	25 (2.8)	35 (3.9)	60 (3.4)
Colon	30 (3.4)	29 (3.3)	59 (3.3)
Unknown Primary	31 (3.5)	27 (3.0)	58 (3.3)
Cervix	18 (2.0)	25 (2.8)	43 (2.4)
Head and Neck	24 (2.7)	19 (2.1)	43 (2.4)
Gastric	19 (2.1)	16 (1.8)	35 (2.0)
Non-Hodgkin Lymphoma (NHL)	17 (1.9)	15 (1.7)	32 (1.8)
Soft Tissue Sarcoma	18 (2.0)	13 (1.5)	31 (1.7)
Endometrial	16 (1.8)	11 (1.2)	27 (1.5)
Esophageal	10 (1.1)	15 (1.7)	25 (1.4)
Other	14 (1.6)	11 (1.2)	25 (1.4)
Neuroendocrine/Carcinoid	14 (1.6)	10 (1.1)	24 (1.3)
Melanoma	12 (1.3)	11 (1.2)	23 (1.3)
Ovarian	12 (1.3)	7 (0.8)	19 (1.1)
Thyroid	7 (0.8)	6 (0.7)	13 (0.7)
Pancreatic	3 (0.3)	8 (0.9)	11 (0.6)
Renal Pelvis and Ureter	4(0.4)	5 (0.6)	9 (0.5)
GI, Other	4 (0.4)	4 (0.4)	8 (0.4)
Hodgkin's Lymphoma	5 (0.6)	2 (0.2)	7 (0.4)
Liver	1 (0.1)	4 (0.4)	5 (0.3)
Anal	1 (0.1)	2 (0.2)	3 (0.2)
Testicular	2 (0.2)	1 (0.1)	3 (0.2)
Biliary Tract	1 (0.1)	1 (0.1)	2 (0.1)
Skin, Squamous Cell	2 (0.2)	0 (0.0)	2 (0.1)
Total	886 (100.0)	890 (100.0)	1776 (100.0)

The stratification factors shared by the three trials were balanced in each individual trial with the majority of subjects having not experienced a prior SRE, though prior SRE was more common as was receiving current chemotherapy in Trial 244. The individual stratification factors for each trial were evenly balanced, as shown in Table 15.

Table 15: Stratification Factors

Stratification Factors	Trial 103		Trial 136		Trial 244	
	D n=950 (%)	ZA n=951 (%)	D n=1026 (%)	ZA n=1020 (%)	D n=886 (%)	ZA n=890 (%)
Previous SRE						
Y	232 (24.4)	231 (24.3)	378 (36.8)	373 (36.6)	440 (49.7)	446 (50.1)
N	718 (75.6)	720 (75.7)	648 (63.2)	647 (63.4)	446 (50.3)	440 (49.9)
Current Chemotherapy						
Y	132 (13.9)	132 (13.9)	410 (40)	408 (40)	746 (84.2)	747 (83.9)
N	818 (86.1)	819 (86.1)	616 (60)	612 (60)	140 (15.8)	143 (16.1)
Trial Specific Stratification factors						
PSA Level						
< 10 ng/mL	145 (15.3)	145 (15.2)				
≥ 10 ng/mL	805 (84.7)	806 (84.8)				
Prior oral Bisphosphonate						
Y			42 (4.1)	38 (3.7)		
N			984 (95.9)	982 (96.3)		
Japanese						
Y			69 (6.7)	67(6.6)		
N			957 (93.3)	953 (93.4)		
Tumor Type						
Multiple Myeloma					86 (9.7)	96 (10.4)
NSCLC					343 (38.7)	345 (38.8)
Other					457 (51.6)	452 (50.8)

6.1.3 Subject Disposition

Trials 103, 136, and 244 enrolled a total of 5723 randomized subjects who received either denosumab (950, 1026, 886 respectively) or zoledronic acid (951, 1020, and 890, respectively). Patient disposition and reasons for treatment discontinuation were based on all data contained in the ASLINFO database as of the primary analysis data cut-off date. Of the 5723 randomized subjects, 436 on Trial 103, 929 on Trial 136, and 358 on Trial 244 were still receiving treatment at the time of the primary analysis cut-off date. Table 16 and Table 17 contain patient disposition information (reason for ending study) and reason for treatment discontinuation. Patient disposition and reasons for discontinuing study drug was similar, respectively, across all three trials and between arms within each trial.

Table 16: Patient Disposition

Patient Disposition	Trial 103		Trial 136		Trial 244	
	D n=950 (%)	ZA n=951 (%)	D n=1026 (%)	ZA n=1020 (%)	D n=886 (%)	ZA n=890 (%)
Administrative Decision	1 (0.1)	4 (0.4)	14 (1.4)	15 (1.5)	2 (0.2)	1 (0.1)
Adverse Event	56 (5.9)	43 (4.5)	28 (2.7)	43 (4.2)	36 (4.1)	48 (5.4)
Consent Withdrawn	147 (15.5)	164 (17.2)	118 (11.5)	117 (11.5)	124 (14)	143(16.1)
Death	294 (30.9)	269 (28.3)	174 (17)	169 (16.6)	310 35)	316 (35.5)
Disease Progression	117 (12.3)	113 (11.9)	124 (12.1)	124 (12.2)	126 (14.2)	104 (11.7)
Ineligibility Determined	3 (0.3)	2 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)
Lost to Follow-up	9 (0.9)	13 (1.4)	8 (0.8)	7 (0.7)	22 (2.5)	16 (1.8)
Noncompliance	7 (0.7)	14 (1.5)	10 (1)	4 (0.4)	17 (1.9)	15 (1.7)
Ongoing	228 (24)	208 (21.9)	468 (45.6)	461 (45.2)	180 (20.3)	178 (20)
Other	33 (3.5)	42 (4.4)	18 (1.8)	21 (2.1)	44 (5)	36 (4)
Protocol Deviation	3 (0.3)	4 (0.4)	2 (0.2)	0	2 (0.2)	0
Subject Request	52 (5.5)	75 (7.9)	61 (5.9)	57 (5.6)	22 (2.5)	31 (3.5)

In Trial 136, Administrative Decision occurred more frequently than in Trials 103 or 244. According to the ASLINFO dataset, the most common reason was 'Sponsor Decided to End the Study' (7/29) followed by audit findings (4/29).

Table 17: Percentage of Subjects whose Disposition was "Consent Withdrawn" who experienced an SRE

SRE	103		136		244	
	D (%)	ZA (%)	D (%)	ZA (%)	D (%)	ZA (%)
N	110 (74.8)	110 (67.1)	92 (78)	85 (72.6)	95 (76.6)	102 (71.3)
Y	37 (25.2)	54 (32.9)	26 (22)	32 (27.4)	29 (23.4)	41 (28.7)
Total	147	164	118	117	124	143

The majority of subjects who withdrew consent did not have an SRE [>70% (Table 17)]. The numbers of subjects who withdrew consent and who did not have an SRE were similar between the two arms in all three trials. The EOIPSP and EOSSP fields in the ASLINFO datasets contain a variety of reasons for discontinuation; adverse event only occurred in 4 subjects in Trial 244, 2 in Trial 136, and 3 in Trial 103.

Table 18: Reasons for Discontinuing IP by Arm

Reasons for Discontinuing IP	Trial 103		Trial 136		Trial 244	
	D n=950 (%)	ZA n=951 (%)	D n=1026 (%)	ZA n=1020 (%)	D n=886 (%)	ZA n=890 (%)
Administrative Decision	1 (0.1)	4 (0.4)	17 (1.7)	15 (1.5)	3 (0.3)	2 (0.2)
Adverse Event	94 (9.9)	69 (7.3)	57 (5.6)	73 (7.2)	67 (7.6)	81 (9.1)

Reasons for Discontinuing IP	Trial 103		Trial 136		Trial 244	
	D n=950 (%)	ZA n=951 (%)	D n=1026 (%)	ZA n=1020 (%)	D n=886 (%)	ZA n=890 (%)
Consent Withdrawn	114 (12.0)	132 (13.9)	90(8.8)	90(8.8)	109 (12.3)	119 (13.4)
Death	246 (25.9)	239 (25.1)	151(14.7)	139(13.6)	245 (27.7)	247 (27.8)
Disease Progression	141 (14.8)	134 (14.1)	134 (13.1)	145 (14.2)	156 (17.6)	137 (15.4)
Ineligibility Determined	3 (0.3)	2 (0.2)	3 (0.3)	2 (0.2)	0 (0.0)	2 (0.2)
Lost to Follow-Up	8 (0.8)	13 (1.4)	9 (0.9)	6 (0.6)	19 (2.1)	9 (1.0)
Noncompliance	7 (0.7)	13 (1.4)	10 (1.0)	6 (0.6)	19 (2.1)	18 (2.0)
Ongoing	217 (22.8)	197 (20.7)	450(43.9)	443(43.4)	169 (19.1)	168 (18.9)
Other	24 (2.5)	28 (2.9)	13 (1.3)	13 (1.3)	35 (4.0)	31 (3.5)
Protocol Deviation	4 (0.4)	4 (0.4)	4 (0.4)	4 (0.4)	0	0
Protocol-Specified Criteria	2 (0.2)	4 (0.4)	9 (0.9)	9 (0.9)	2 (0.2)	7 (0.8)
Requirement for Alternative Therapy	15(1.6)	13(1.4)	7(0.7)	7(0.7)	12(1.4)	10(1.1)
Subject Request	73 (7.7)	98 (10.3)	69 (6.7)	65 (6.4)	42 (4.7)	47 (5.3)
Total	949 (99.9)	950 (99.9)	1023 (99.7)	1017 (99.7)	878 (99.1)	878 (98.7)
N Missing	1 (0.1)	1 (0.1)	3 (0.3)	3 (0.3)	8 (0.9)	12 (1.3)

The most common protocol deviation in each trial was "administration of investigational product (IP)", see Table 19. The most common IP Administration protocol violations, for each trial were intravenous infusion of investigational product administered in < 15 minutes, intravenous investigational product administered to subjects with renal deterioration (defined in protocol), and infusion interval(s) < 21 days. The most common reasons for entry/eligibility violations were incorrect stratification of subjects within each trial, the most common reason was prior SRE (171 in Trial 103, 141 in Trial 136, 184 in Trial 244).

Table 19: Protocol Violations

Protocol Violations	Trial 103		Trial 136		Trial 244	
	D n=950 (%)	ZA n=951 (%)	D n=1026 (%)	ZA n=1020 (%)	D n=886 (%)	ZA n=890 (%)
Entry/Eligibility	139 (14.6)	115 (12.1)	123 (12)	141 (13.8)	153 (17.3)	156 (17.5)
Exclusionary Medication	5 (0.5)	6 (0.6)	4 (0.4)	11 (1.1)	4 (0.5)	2(0.2)
IP Administration	138 (14.5)	162 (17)	143 (13.9)	145 (14.2)	107 (12.1)	134 (15.1)
Missing Data	6 (0.6)	3 (0.3)	10 (0.1)	9 (0.09)	13(1.5)	14 (1.6)
Total	288(30.3)	286 (30.1)	280 (27.3)	306 (30)	277 (31.3)	306 (34.4)

6.1.4 Analysis of Primary Endpoint(s)

Reviewer's comment: Efficacy analyses presented in the following Section were performed by the Biometrics Division, Biologics and Therapeutics Statistical Staff, Drs Weishi Yan (Trial 244) and Jing Zhang (Trials 103 and 136). Refer to the statistical review for the statistical reviewers' conclusions.

Time to First On-Study SRE (non-inferiority)

The primary efficacy endpoint for Trials 103, 136, and 244 was Time to First On-Study SRE (non-inferiority), defined as the time from randomization until first spinal cord compression (SCC), surgery to bone, pathologic fracture, or radiation to bone. The CRFs captured the SREs and a central imaging vendor (b) (4) the (IRC)] reviewed radiology scans to confirm fracture assessments and SCC. Hierarchal ordering of on-study SREs were SCC, surgery, fracture, and radiation for SREs occurring on the same day. The SAPs specified that Trials 103, 136, and 244 were all time to event trials designed to stop when approximately 745 events had occurred. Trials 103 (727 events), 136 (687 events), and Trial 244 (601 events) did not reach the planned event rate, due to the longer median time to SRE observed compared to prior trials with ZA.

The SAP for each trial, 103, 136, and 244 derived a HR estimate of placebo (P) versus ZA. Table 20 contains the HR for placebo versus zoledronic acid for each trial. For Trial 103, a single trial of placebo versus ZA in subjects with metastatic prostate cancer served as the basis for the HR estimation; the primary endpoint in that trial was not a time to event endpoint. For Trial 136, the synthesis method used to generate the HR estimation included four trials comparing placebo to pamidronate and pamidronate to ZA, as well as a trial of placebo compared to ZA in Japanese subjects to calculate a pooled HR of 1.58 (1.23, 2.02) for placebo compared with zoledronic acid. The primary endpoint of one of the 4 historical trials was time to 1st SRE, the other 3 included skeletal morbidity rate and proportion of subjects experiencing SRE. However, all studies collected the data to estimate the time to 1st SRE as a secondary endpoint. Lastly, for Trial 244, the HR estimation required analysis of the data from three trials comparing pamidronate to placebo and ZA to pamidronate in subjects with multiple myeloma, and one in subjects with other solid tumors comparing ZA to placebo. The primary endpoints in these trials were proportion of subjects with first SRE, but the pre-planned analysis did include the time to event endpoint, first on-study SRE.

Table 20: HR Estimates for NI Margin

Trial	Disease	HR Placebo versus ZA	Number of Trials	Primary Endpoint Comment
103	Prostate	1.48 (1.10, 1.98)	1	Proportion of subjects with first SRE
136	Breast	1.58 (1.23, 2.02)	4	
244	Solid Tumors and Multiple Myeloma	1.4 (1.11, 1.77)	3	Proportion of subjects with first SRE

The trials were designed with a non-inferiority margin (NI) to preserve ≥50% of the effect of ZA compared to placebo using a synthesis method (Hung 2003). Planned enrollment for each trial was 1,700 (103), 1960 (136), and 1690 (244), based on a calculation of 745 events to maintain ≥ 90% power for the primary NI analysis. In each trial, the SAP designated testing of the primary NI endpoint, Time to First On-Study SRE, first. If time to First On-Study SRE was non-inferior, testing for superiority (for Time to First On-Study SRE) and Time to First-and-subsequent On-Study SRE would occur. The Hochberg Procedure governed the testing of the secondary endpoints. Briefly, the p-values for each secondary endpoint were ordered from largest to smallest. If the largest $p \leq 0.05$, both secondary null hypotheses were rejected. If not, the second p-value was compared to 0.025 to determine rejection of the second null hypothesis. The SAP did not specify multiplicity adjustments for other exploratory endpoints.

The SAP for each trial analyzed the first on-study SRE using a Cox proportional hazards model. The independent variables were the treatment groups and the stratification factors balanced the randomization.

Table 21 (analyses performed by the statistical reviewers for this application, Drs Weishi Yan and Jing Zhang, PhD) summarizes the results of the primary FDA statistical analyses (see statistical reviews) of Time to First On-Study SRE for Trials 103, 136, and 244. The full analysis set (FAS) consisted of all subjects randomized to the study. Subjects in this subset were analyzed according to their original randomized treatment assignment, regardless of treatment received. All three trials demonstrated non-inferiority of denosumab to ZA for Time to First On-Study SRE. The respective HRs were 0.82 [(0.71, 0.95), p< 0.0001], 0.82 [(0.71, 0.98), p = 0.0007], and 0.83 [(0.71, 0.95) p 0.0002]. The Kaplan-Meier curves for Time to First On-Study SRE are displayed in Figure 6, Figure 8, and Figure 10.

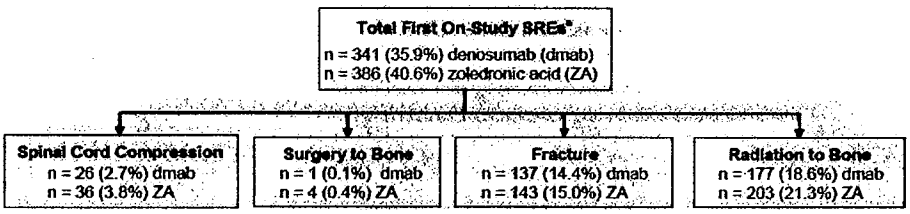
Table 21: Primary End Point for Trials 103, 136, & 244

Endpoint (Time To)	103		136		244	
	HR (95% CI)	p-value (adj.)	HR (95% CI)	p-value (adj.)	HR (95% CI)	p-value (adj.)
1st SRE (non-inferiority)	0.82 (0.71, 0.95)	0.0002	0.82 (0.71, 0.95)	<0.0001	0.84 (0.71, 0.98)	0.0007
	D	ZA	D	ZA	D	ZA
Median (months)	20.7	17.1	NR	26.5	20.5	16.3

Trial 103

Figure 5 shows the components of the first on-study SREs for Trial 103. A total of 341 subjects in the denosumab arm had an SRE and 386 subjects in the ZA arm had an SRE. The make up of the individual components in Trial 103 were consistent with published reports (Saad 2002) with radiation to the bone and pathologic fractures making up the first and second most common events, respectively. The p-value for the homogeneity test for the individual components was 0.7059 indicating the effect of denosumab was consistent in each individual component of the composite SRE.

Figure 5: Total First On-Study SRE Trial 103 (Copied from CSR)



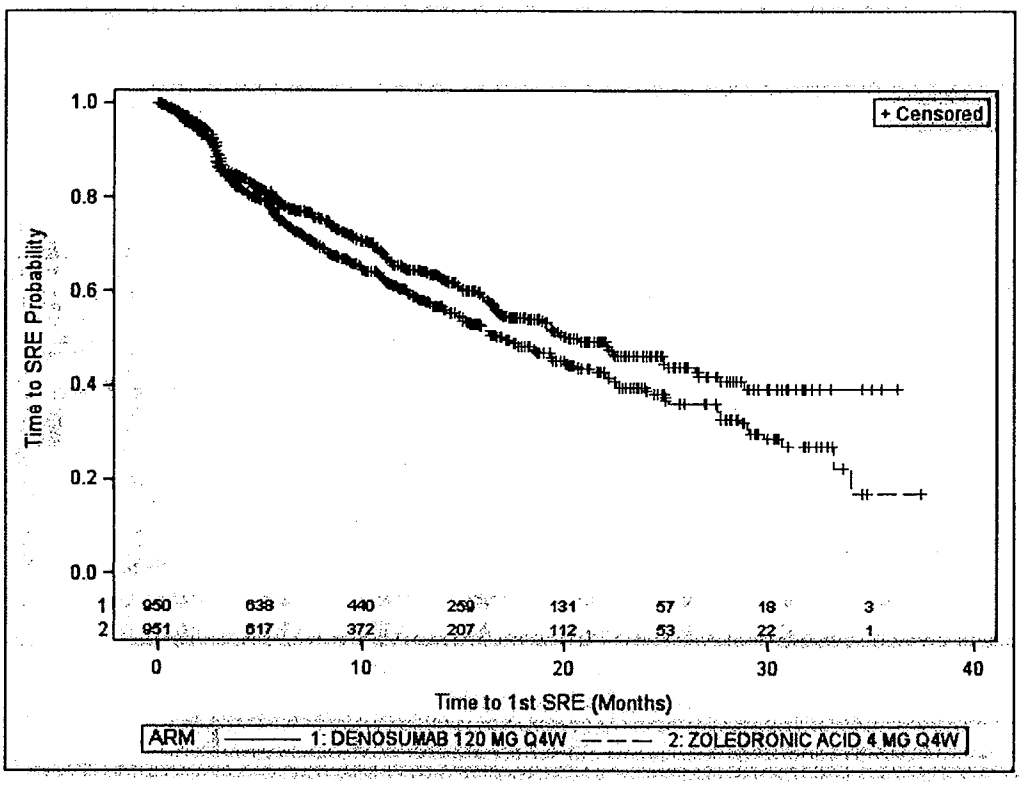
Analysis by the statistical reviewer for Trial 103 using the Wei-Lin-Weissfeld (WLW) homogeneity test yielded a p-value of 0.71 indicating no evidence of inconsistent effects across the SRE components. An analysis of time to each of the individual components of SRE, by the statistic reviewer for Trial 103, showed that the HR favored denosumab for each component, Table 22, (analysis performed by the statistical reviewer for this application, Jing Zhang, PhD).

Table 22: Trial 103 Time to First of each Individual SRE Component

103-Endpoint (Time to 1st event)	Number of events (%)		HR (95% CI)
	D	Z	
Spinal cord compression	26 (2.7)	36 (3.8)	0.74 (0.48, 1.16)
Surgery to bone	1 (0.1)	4 (0.4)	0.60 (0.26, 1.38)
Pathological fracture	137 (14.4)	143 (15)	0.89 (0.71, 1.10)
Radiation to bone	177(18.6)	203 (21.4)	0.78 (0.66, 0.94)

The median time to first on-study SRE for denosumab was 20.7 months compared to 17.1 months for ZA (Figure 6, analysis performed by the statistical reviewer for this application, Jing Zhang, PhD) The HR was 0.82 (0.71, 0.95) with a p-value for non-inferiority of 0.0002.

Figure 6: KM Curve First On-Study SRE Trial 103 (Copied from Statistics Reviewer)

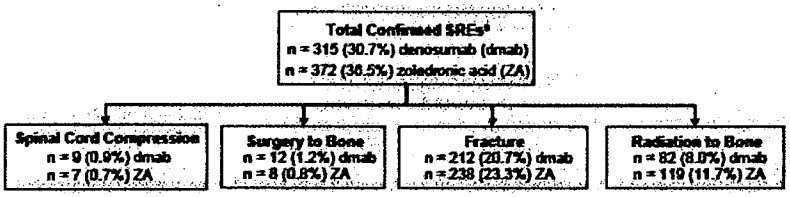


Comment: The results of Trial 103 indicate denosumab is non-inferior to ZA for first on-study SRE. Generally, the conduct and design of Trial 103 do not raise doubts about the constancy assumption. The median time to first on-study SRE in the ZA registration trials was approximately 12 months, however, the median time to first on-study SRE of ZA in Trial 103 was 17.1 months. Although this does not support the constancy assumption, the potential bias would be against the denosumab arm, thus, non-inferiority is still acceptable. The results of the per-protocol analysis were similar to the analysis of the ITT population.

Trial 136

Figure 7 shows the total first on-study SREs for Trial 136. A total of 315 subjects in the denosumab arm had an SRE and 372 subjects in the ZA arm had an SRE. The make up of the individual components in Trial 136 were consistent with published reports (Rosen 2003b; Khono 2005) with pathologic fracture and radiation to the bone making up the first and second most common events, respectively.

Figure 7: Total First On-Study SRE Trial 136 (Copied from CSR)



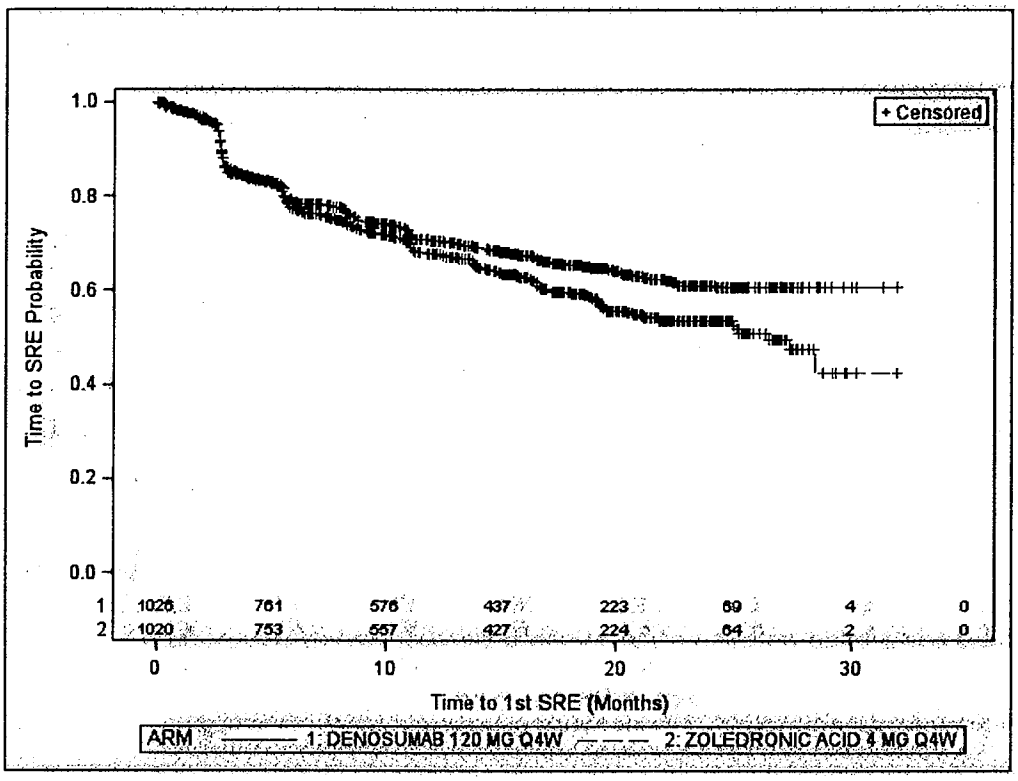
Analysis by the statistical reviewer for Trial 136 using the Wei-Lin-Weissfeld (WLW) homogeneity test yielded a p-value of 0.48 indicating no evidence of inconsistent effects across the SRE components. An analysis of time to each of the individual components of SRE, by the statistical reviewer for 136, showed that the HR favored denosumab for the two most common individual components of SRE, radiation to bone and pathologic fracture in Table 23 (analysis performed by the statistical reviewer for this application, Jing Zhang, PhD).

Table 23: Trial 136 Time to First of each Individual SRE Component

136-Endpoint (Time to 1st event)	Number of events (%)		HR (95% CI)
	D	Z	
Spinal cord compression	9 (0.9)	7 (0.7)	1.25 (0.57, 2.75)
Surgery to bone	12 (1.2)	8 (0.8)	1.01 (0.59, 1.73)
Pathological fracture	212 (20.7)	238 (23.3)	0.83 (0.70, 0.99)
Radiation to bone	82 (8)	119 (11.7)	0.74 (0.59, 0.94)

The median time to first on-study SRE for denosumab was not reached and was 26.4 months in the ZA arm (Figure 8 analysis performed by the statistical reviewer for this application, Jing Zhang, PhD). The HR for first on-study SRE was 0.82 (0.71, 0.95) $p < 0.0001$ indicating denosumab was non-inferior to ZA.

Figure 8: KM Curve First On-Study SRE Trial 136 (Copied from Statistics Reviewer)



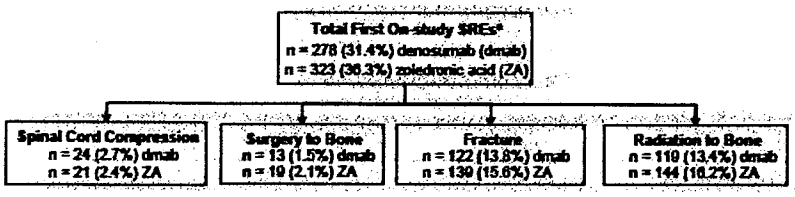
Comment: The results of Trial 136 indicate denosumab is non-inferior to ZA for first on-study SRE. Generally, the conduct and design of Trial 136 do not raise doubts about the constancy assumption. The median time to first on-study SRE in the ZA registration trials was approximately 12 months, however, the median time to first on-study SRE of ZA in Trial 136 was 26.5 months. Although this does not support the constancy assumption, the potential bias would be against the denosumab arm, thus, non-inferiority is still acceptable. The results of the per-protocol analysis were similar to the analysis of the ITT population.

Trial 244

Figure 9 shows the total first on-study SREs for Trial 244. A total of 278 subjects in the denosumab arm experienced an SRE and 328 subjects in the ZA arm experienced an SRE. The individual components of SRE in Trial 244 were consistent with published reports of individual components of SRE in bisphosphonate registration trials (Rosen

2001; Rosen 2003a) with radiation to the bone and pathologic fracture making up the first and second most common events, respectively.

Figure 9: Total First On-Study SRE Trial 244 (Copied from CSR)



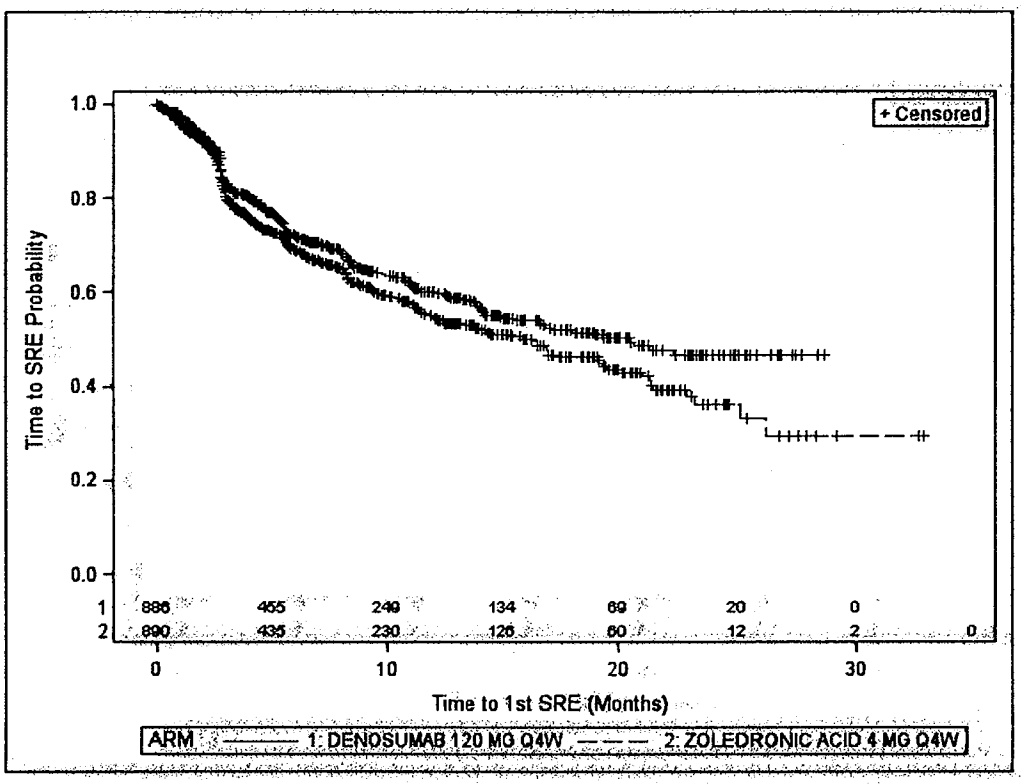
Analysis by the statistical reviewer for Trial 244 using the Wei-Lin-Weissfeld (WLW) homogeneity test yielded a p-value of 0.79 indicating no evidence of inconsistent effects across the SRE components. An analysis of time to each of the individual components of SRE, by the statistical reviewer for Trial 244, showed that the HRs were 1 or less than one for each component, Table 24, (analysis performed by the statistical reviewer for this application, Weishi Yan, PhD).

Table 24: Trial 244 Time to First of each Individual SRE Component

244 Endpoint (Time to 1st event)	Number of events (%)		HR
	D	Z	(95% CI)
Spinal cord compression	24 (2.7)	21 (2.4)	1.00 (0.58, 1.70)
Surgery to bone	13 (1.5)	19 (2.1)	0.86 (0.51, 1.44)
Pathological fracture	122 (13.8)	139 (2.1)	0.87 (0.69, 1.08)
Radiation to bone	119 (13.4)	144 (16.2)	0.78 (0.63, 0.97)

The median time to first on-study SRE for denosumab was 20.5 months and was 16.3 months in the ZA arm (Figure 10 (analysis performed by the statistical reviewers for this application, Weishi Yan, PhD). The HR for first on-study SRE was 0.84 [(0.71, 0.98) p = 0.0007] indicating denosumab was non-inferior to ZA.

Figure 10: KM Curve First On-Study SRE Trial 244 (Copied from Statistics Reviewer)



The analysis using verified strata, a sensitivity analysis, gave a similar HR 0.84 (0.72, 0.99). One hundred eighty subjects in Trials 244 (denosumab 87, zoledronic acid 93) had multiple myeloma and did not appear to benefit from denosumab [HR 1.03 [(0.68, 1.57) P=0.89] compared to those without multiple myeloma (denosumab 799, zoledronic acid 797) [HR0.80 (0.67, 0.96) P=0.012]. *This sensitivity analysis is supportive of the exclusion of subjects with multiple myeloma from the indications and usage Section of the denosumab label, primarily due to an observed detriment in overall survival (See Section 6.1.6.2).*

Comment: The results of Trial 244 indicate denosumab is non-inferior to ZA for first on-study SRE. Generally, the conduct and design of Trial 244 do not raise doubts about the

constancy assumption. The median time to first on-study SRE in the ZA registration trials was approximately 7.5 months, however, the median time to first on-study SRE of ZA in Trial 244 was 16.3 months. Although this does not support the constancy assumption, the potential bias would be against the denosumab arm, thus, non-inferiority is still acceptable. The results of the per-protocol analysis were similar to the analysis of the ITT population.

Overall Comment: This reviewer concurs with the Applicant's assessment of efficacy for denosumab 120 mg subcutaneously every four weeks to treat subjects with advanced solid tumors and bone metastases. Statistical significance was shown for the primary endpoint for a delay in time to first on-study SRE (non-inferiority) for denosumab compared to ZA individually in all three trials. SRE is an acceptable endpoint in evaluating a product for treatment of subjects with advanced solid tumors and bone metastases. In order to support the indication of treatment of subjects with advanced solid tumors and bone metastases, the supporting trials should include the most common types of tumors associated with bone metastases and be efficacious in the individual trials, not just the pooled analysis. The separation of trials into prostate (103), breast (136), and other solid tumors or multiple myeloma (244) allowed for individual assessment of efficacy in each of the most common tumor types associated with bone metastases (prostate and breast) and inclusion of other solid tumors including non-small cell lung cancer (NSCLC).

6.1.5 Analysis of Secondary Endpoints(s)

Statistical testing for secondary endpoints was performed in a step-down manner using a hierarchical testing procedure. Inferential testing was permitted only if time to first on-study SRE (non-inferiority analysis) was significant. To control the overall type I error for multiple comparisons at a significance level of 0.05, the two secondary efficacy endpoints were tested simultaneously using the Hochberg procedure. Briefly, the Hochberg Procedure ordered the p-values from largest to smallest. If the largest p value was ≤ 0.05, then the null hypotheses was rejected; if the p-value was > 0.05, the second largest p value was compared to 0.025 and was rejected if the p value was ≤ 0.025. The testing of first on-study SRE (superiority) used a log-rank test. For time to first-and-subsequent on-study SRE (multiple-event analysis), the Andersen and Gill approach was used.

Time to First On-Study SRE (superiority) and Time to First-and-Subsequent On-Study SRE

Table 25 (analysis performed by the statistical reviewers for this application, Drs Weishi Yan and Jing Zhang, PhD) summarizes the results of time to first on-study SRE (superiority) and time to first-and-subsequent on-study SRE for Trials 103, 136, and 244. The full analysis set (FAS) included all subjects randomized to the study. Subjects

in this subset were analyzed according to their original randomized treatment assignment, regardless of treatment received. Trials 103 and 136 demonstrated statistically significant prolongation of time to first on-study SRE (superiority) and time to first-and-subsequent on-study SRE; Trial 244 did not.

Table 25: Secondary End Point for Trials 103, 136, & 244

Endpoint (Time To)	103		136		244	
	HR (95% CI)	p-value (adj.)	HR (95% CI)	p-value (adj.)	HR (95% CI)	p-value (adj.)
1st SRE (superiority)	0.82 (0.71, 0.95)	0.0082*	0.82 (0.71, 0.95)	0.0097*	0.84 (0.71, 0.98)	0.0604*
1st and subsequent SRE	0.82 (0.71, 0.94)	0.0088	0.77 (0.66, 0.89)	0.0012	0.90 (0.77, 1.04)	0.1447

*log rank superiority test p-value

Trial 103
The NI endpoint, time to first on-study SRE, was statistically significant allowing for testing of the two secondary endpoints, time to first on-study SRE and time to first-and-subsequent on-study SRE. The HR for first on-study SRE was 0.82 [(0.71, 0.94), p=0.0082] and the HR for first and subsequent on-study SRE was 0.82 [(0.71, 0.94), p=0.0088], respectively

Comment: The demonstration of superiority of time to first on-study SRE and first-and-subsequent on-study SRE in Trial 103 was statistically significant and indicates denosumab has efficacy beyond the first SRE.

Trial 136
The NI endpoint, time to first on-study SRE, was statistically significant allowing for testing of the two secondary endpoints, time to first on-study SRE and time to first-and-subsequent on-study SRE. The HR for first on-study SRE was 0.82 [(0.71, 0.95), p=0.0097] and the HR for first and subsequent on-study SRE was 0.77 [(0.66, 0.89), p=0.0012], respectively.

Comment: The demonstration of superiority of time to first on-study SRE and first-and-subsequent on-study SRE in Trial 136 was statistically significant and indicates denosumab has efficacy beyond the first SRE.

Trial 244
The NI endpoint, time to first on-study SRE, was statistically significant allowing for testing of the two secondary endpoints, time to first on-study SRE and time to first-and-subsequent on-study SRE. The HR for first on-study SRE was 0.84 [(0.71, 0.98), p=0.0604] and the HR for first and subsequent on-study SRE was 0.90 [(0.77, 1.04), p=0.1447], respectively. The SAP specified the ordering of the p values, according to the Hochberg procedure, the null hypotheses could not be rejected as the p-value for

first and subsequent on-study SRE was larger than 0.05 and the p-value for first on-study SRE was larger than 0.025.

Comment:
Trial 244 did not demonstrate statistical significance of denosumab over zoledronic acid for time to first on-study SRE and first-and-subsequent on-study SRE.

Overall Comment: This reviewer concurs with the Applicant's assessment of (b) (4) (b) (4) *Trials 103 and 136 demonstrated statistical significance for the secondary endpoints for time to first on-study SRE and first-and-subsequent on-study SRE; Trial 244 did not.* (b) (4)

6.1.6 Other Endpoints

Exploratory endpoints for Trials 103, 136, and 244 included Time to first SRE or HCM; radiation in bone; overall survival (OS); progressive disease (PD) in bone; Progression free survival (PFS); first symptomatic SRE; and "pain scores and analgesic use." The exploratory endpoints will be discussed in three categories, supportive of efficacy, supportive of safety, and supportive of quality of life (QOL). As stated above, the SAP did not control the type I error rate for the exploratory endpoints. Overall, the results of the analyses of exploratory endpoints were consistent with the primary and secondary endpoint analyses; the effect on overall survival, however, was worse in the subgroup of subjects with multiple myeloma in Trial 244. Tables 21 through 27 contain the analyses of exploratory endpoints, and Figures 9 through 11 (Forest Plots, analyses performed by the statistical reviewers for this application, Drs Weishi Yan and Jing Zhang, PhD) contain the results from exploratory analyses for Trials 103, 136, and 244. As there was no control of type 1 error for these endpoints, they must be considered exploratory.

6.1.6.1 Exploratory Endpoints Supportive of Efficacy

The exploratory endpoints time to first on-study SRE or hypercalcemia of malignancy (HCM), time to first on-study radiation to bone, time to first on-study pathological fracture, and skeletal morbidity are supportive of the primary and secondary efficacy endpoints.

Trial 103

Table 26 (analyses performed by the statistical reviewer for this application, Jing Zhang, PhD) shows the HRs for the exploratory endpoints time to first on-study SRE or HCM, first symptomatic SRE, pathologic fracture, and radiation to bone.

Table 26: Exploratory Endpoints-Efficacy Trial 103

103-Endpoint (Time to...)	Number of events (%)		Median (in mos.)		HR (95% CI)
	D	Z	D	Z	
1st SRE or HCM	340 (35.8)	384 (40.4)	20.7	17.1	0.83 (0.72, 0.96)
1st symptomatic SRE	241 (25.4)	289 (30.4)	NR	24.2	0.78 (0.66, 0.93)
Pathologic fracture	158 (16.6)	170 (17.9)	NR	34.0	0.89 (0.71, 1.10)
Radiation in bone	226 (23.8)	273 (28.7)	NR	28.6	0.78 (0.65, 0.93)

Additionally, the Applicant assessed skeletal morbidity rate (SMR) defined as the ratio of the number of occurrences of any SRE for a subject, divided by the subject's time at risk. The mean annual SMR was 0.79 (SD = 3.08) for denosumab and 0.83 (SD = 1.93) for zoledronic acid (analysis performed by the statistical reviewer for this application, Jing Zhang, PhD).

Comments: The point estimates for the HRs (of the exploratory endpoints) for denosumab were less than one when compared to zoledronic acid. These results were consistent with the primary endpoint and support the beneficial effects on skeletal related events in subjects with prostate cancer.

Trial 136

Table 27 (analysis performed by the statistical reviewer for this application, Jing Zhang, PhD) shows the HRs for the exploratory endpoints time to first on-study SRE or HCM, first symptomatic SRE, pathologic fracture and radiation to bone.

Table 27: Exploratory Endpoints Efficacy Trial 136

136-Endpoint (Time to...)	Number of events (%)		Median (in mos.)		HR (95% CI)
	D	Z	D	Z	
1st SRE or HCM	323 (31.5)	383 (36.5)	NR	25.2	0.82 (0.70, 0.95)
1st symptomatic SRE	156 (15.2)	198 (19.4)	NR	NR	0.76 (0.61, 0.93)
Pathologic fracture	226 (22.0)	267 (26.2)	NR	NR	0.83 (0.7, 0.99)
Radiation in bone	123 (12.0)	162 (15.9)	NR	NR	0.74 (0.59, 0.94)

Skeletal morbidity rate, SMR, is the ratio of the number of occurrences of any SRE for a subject, divided by the subject's time at risk. The mean annual SMR was 0.45 (SD = 1.02) for denosumab and 0.58 (SD = 1.34) for zoledronic acid (analysis performed by the statistical reviewer for this application, Jing Zhang, PhD).

Comment: The point estimates for the HRs (of the exploratory endpoints) for denosumab were less than one when compared to zoledronic acid. These results were

consistent with the primary endpoint and support the beneficial effects on skeletal related events in subjects with prostate cancer.

Trial 244

Table 28 (analysis performed by the statistical reviewers for this application, Weishi Yan, PhD) gives the HR for the exploratory endpoints time to first on-study SRE or HCM, first symptomatic SRE, pathologic fracture and radiation to bone.

Table 28: Exploratory Endpoints-Efficacy Trial 244

Endpoint (Time to...)	Number of events (%)		Median (in mos.)		HR(95% CI)
	D	Z	D	Z	
1st SRE or HCM	287 (32.4)	336 (37.8)	19.0	14.4	0.83 (0.71, 0.97)
1st symptomatic SRE	200 (22.6)	228 (25.6)	NE	28.3	0.84 (0.69, 1.02)
Pathologic fracture	144 (16.3)	168 (18.9)	NE	NE	0.87 (0.69, 1.08)
Radiation in bone	157 (17.7)	189 (21.2)	NE	NE	0.78 (0.63, 0.97)

Skeletal morbidity rate, SMR, is the ratio of the number of occurrences of any SRE for a subject, divided by the subject's time at risk. The mean annual SMR was 0.86 (SD = 2.8) for denosumab and 1.04 (SD = 2.76) for zoledronic acid, p value 0.053 (analysis performed by the statistical reviewer for this application, Weishi Yan, PhD).

Comment: The point estimates for the HRs for denosumab were less than one when compared to zoledronic acid. These results were consistent with the primary endpoint and support the beneficial effects on skeletal related events in subjects with prostate cancer.

Individual Components of SRE: Table 29 (analysis performed by the statistical reviewers for this application, Drs Weishi Yan and Jing Zhang, PhD) contains a pooled analysis of the individual components of the primary and secondary endpoints; this analysis was not a pre-specified analysis; however, the results support the results of the primary and secondary endpoints. Radiation to Bone and Fracture were the most commonly occurring components of the composite SRE for Trials 103, 136, and 244 (Table 29) The event rates of XRT to bone, fracture, surgery to bone, and SCC in Trials 103, 136, and 244 were similar to published reports of event rates in published reports of bisphosphonate registration trials (Saad 2002; Rosen 2001; Rosen 2003a; Rosen 2003b; Rosen 2004b, Khono 2005). The point estimate for the HR was 1 or less for each of the individual components of the SRE in the pooled analysis.

Table 29: Analysis of Individual Components of the SRE Endpoint from the Pooled Results from Trials 103, 136, & and 244

Endpoint (Time to...)	Number of events (%)		Median (in mos.)		HR(95% CI)
	D	Z	D	Z	
1st Radiation To Bone	509 (17.8)	625 (21.8)	NE (NE, NE)	33.2 (30.3, NE)	0.78 (0.63, 0.97)
1st Fracture	528 (18.4)	605 (21.1)	NE (NE, NE)	34.0 (33.2, NE)	0.87 (0.69, 1.08)
Time To SCC	76 (2.7)	86 (3.0)	NE (NE, NE)	NE (NE, NE)	1.00 (0.58, 1.70)
Time to Surgery to Bone	63 (2.2)	72 (2.5)	NE (NE, NE)	NE (NE, NE)	0.86 (0.51, 1.44)

Of the individual components of SREs, the timing of radiation to bone has the most potential for the introduction of bias and was the most frequent event in Trials 103 and 244, and the second most frequent event in Trial 136. Generally, patients receive radiation to bone for pain control. Because this component of the endpoint involves subjective decision making at the physician level, this component is potentially subject to bias. In this trial, however, adequate (double) blinding likely mitigated the concern for bias regarding this component of the SRE endpoint.

Comment: The design of the CRFs did not allow for an assessment of the reasons for radiation, except to match pain location or bone metastasis location to radiation location.

The pathologic fracture component of the SRE underwent central radiology review by (b) (4) the independent radiology review committee. If the IRC disagreed with the local investigator's assessment, another review committee, the SRE Review Committee (SRERC) reviewed the films. Section 6.1.1 contains the data analysis plan for documentation of IRC and SRERC. Less than 1% of subjects in each arm of each study required review of SRE by the SRERC, 21 subjects in Trial 103, 41 subjects in 236, and 28 subjects in 244.

The CRFs did not adequately capture information regarding the reasons of discrepancies between local investigators and the IRC, but the overall low incidence of discordance and double binding helped to minimize bias and uncertainty regarding the fracture endpoint. The sensitivity analysis of removing subjects reviewed by the SRERC resulted in trivial changes in the HRs (103 and 136 HR remained at 0.82, the HR changed from 0.84 to 0.82 for study 244).

6.1.6.2 Exploratory Endpoints Supportive of Efficacy

The exploratory endpoints overall survival (OS), progression free survival (PFS), and PD in bone are supportive endpoints for safety. Table 30 (analysis performed by the statistical reviewers for this application, Drs Weishi Yan and Jing Zhang, PhD) contains the HR for these exploratory endpoints in Trials 103, 136, and 244. The HRs for all analyses were close to 1 indicating there was not a major effect in either direction.

Table 30: Exploratory Endpoints-Survival and Disease Progression

Trial	Exploratory Endpoints-Survival and Disease Progression	Number of Events (%)		Median (in months)		HR(95% CI)
		D	Z	D	Z	
103	OS	474 (49.9)	461 (48.5)	19.4	19.8	1.05 (0.91, 1.20)
136	OS	301 (29.3)	305 (29.9)	29.4	NR	0.96 (0.82, 1.13)
244	OS	479 (54.1%)	474 (53.3%)	12.0	12.6	0.95 (0.84, 1.08)
103	PFS	767 (80.7)	735 (77.3)	8.1	8.0	1.03 (0.92, 1.14)
136	PFS	683 (66.6)	698 (68.4)	11.8	11.7	1.01 (0.91, 1.13)
244	PFS	687 (77.5%)	679 (76.3%)	5.4	5.5	1.01 (0.91, 1.12)
103	PD in bone	387 (40.7)	402 (42.3)	13.7	11.1	0.93 (0.80, 1.08)
136	PD in bone	446 (43.5)	449 (44.0)	16.6	16.4	0.99 (0.87, 1.13)
244	PD in bone	283 (31.9)	292 (32.8)	13.9	13.6	0.98 (0.83, 1.16)

A subgroup analysis of OS for patients with multiple myeloma showed that these subjects appeared to have worse survival [HR = 2.22 (1.11, 4.46), p=0.021]. Table 31 (analysis performed by the statistical reviewers for this application, Drs Weishi Yan and Jing Zhang, PhD) shows OS for subjects with multiple myeloma, NSCLC, and other tumors in aggregate.

Table 31: OS by Tumor Type Trial 244

244-OS in Subjects with (Time to...)	Number of events (%)		Median (in mos.)		HR(95% CI)
	D	Z	D	Z	
Multiple Myeloma	23 (26.6)	13 (14.0)	NE	NE	2.22 (1.11, 4.46)
NSCLC	212 (60.6)	238 (67.6)	9.5	8.0	0.78 (0.65, 0.94)
Other tumors	244 (54.3)	223 (50.1)	11.9	12.6	1.08 (0.90, 1.30)

Excluding patients with multiple myeloma, the HR for OS [0.92 (0.81, 1.05) p=0.21] was similar to the overall population for Trial 244 [0.95 (0.84, 1.08],Table 32 (analysis performed by the statistical reviewers for this application, Drs Weishi Yan and Jing Zhang, PhD).

Table 32: Overall Survival Excluding Patients with Multiple Myeloma-Trial 244

244-OS excluding Patients with MM	Denosumab	Zoledronic Acid
	n = 799	n = 797
Number of Events (%)	456 (57.1)	461 (57.8)
Median Time to OS (95% CI)	10.7 (9.2, 11.9)	10.0 (8.7, 11.5)
p-value (Superiority, log-rank)	0.21	
HR (95% CI)	0.92 (0.81, 1.05)	

The OS HR of 2.2, with a 95% CI that excludes 1, in patients with multiple myeloma should result in limiting the indication to exclude patients with multiple myeloma.

Table 33 (analysis performed by the statistical reviewers for this application, Drs Weishi Yan and Jing Zhang, PhD) shows the results of pooled analyses of OS and PFS from Trials 103, 136, and 244. There was no suggestion of worsening survival or progression free survival when pooling the entire population.

Table 33: Pooled Analysis of OS and PFS from Trials 103, 136, and 244

Pooled Survival All Three Trials	Pooled Overall Survival		Pooled PFS	
	Denosumab	Zometa	Denosumab	Zometa
	n = 2862	n = 2861	n = 2862	n = 2861
Number of Events (%)	1254 (43.8%)	1240 (43.3%)	2137 (74.7%)	2112 (73.2%)
Median Survival (95% CI)	22.5 (21.3, 23.6)	22.3 (20.9, 23.5)	8.3 (7.9, 8.5)	8.3 (7.9, 8.5)
HR (95% CI)	0.98 (0.90, 1.06)		1.01 (0.95, 1.07)	

The Kaplan-Meier curves for OS and PFS for the pooled analyses showed no separation of the curves, Figure 11 and Figure 12 (analysis performed by the statistical reviewers for this application, Drs Weishi Yan and Jing Zhang, PhD). The median OS and PFS for denosumab was 22.5 months and 8.3 months, respectively; for ZA the median OS and PFS was 22.3 months and 8.3 months, respectively.

Figure 11: Overall Survival Pooled Data (Copied from Statistics Reviewer)

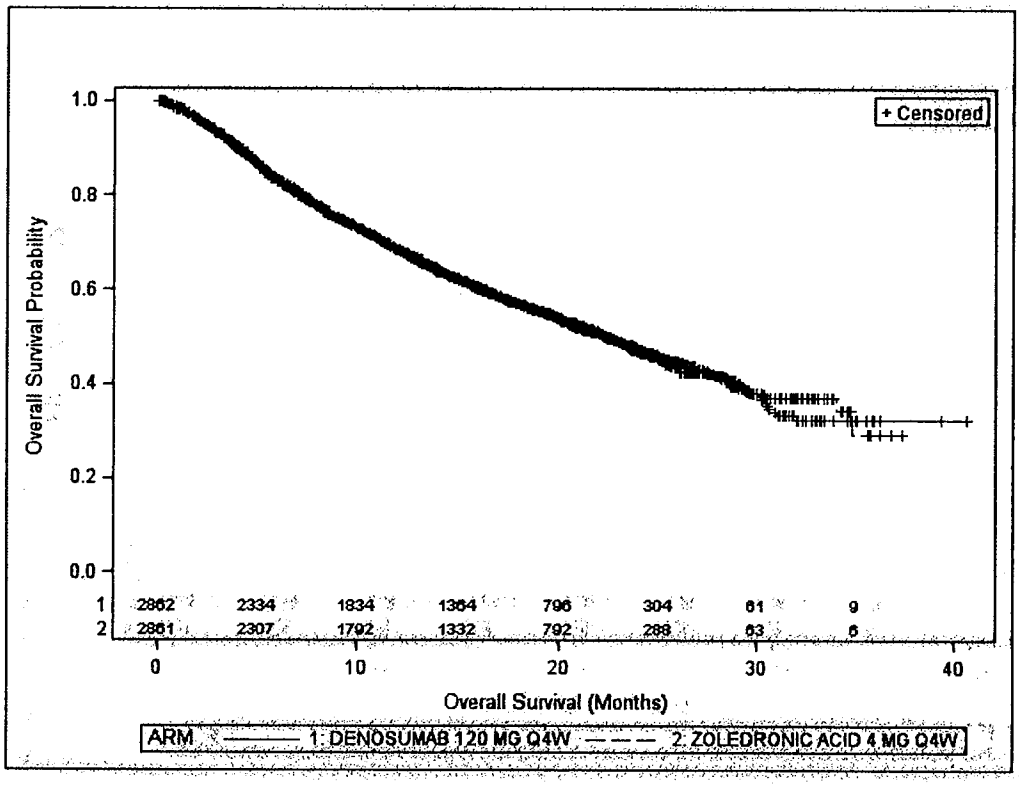
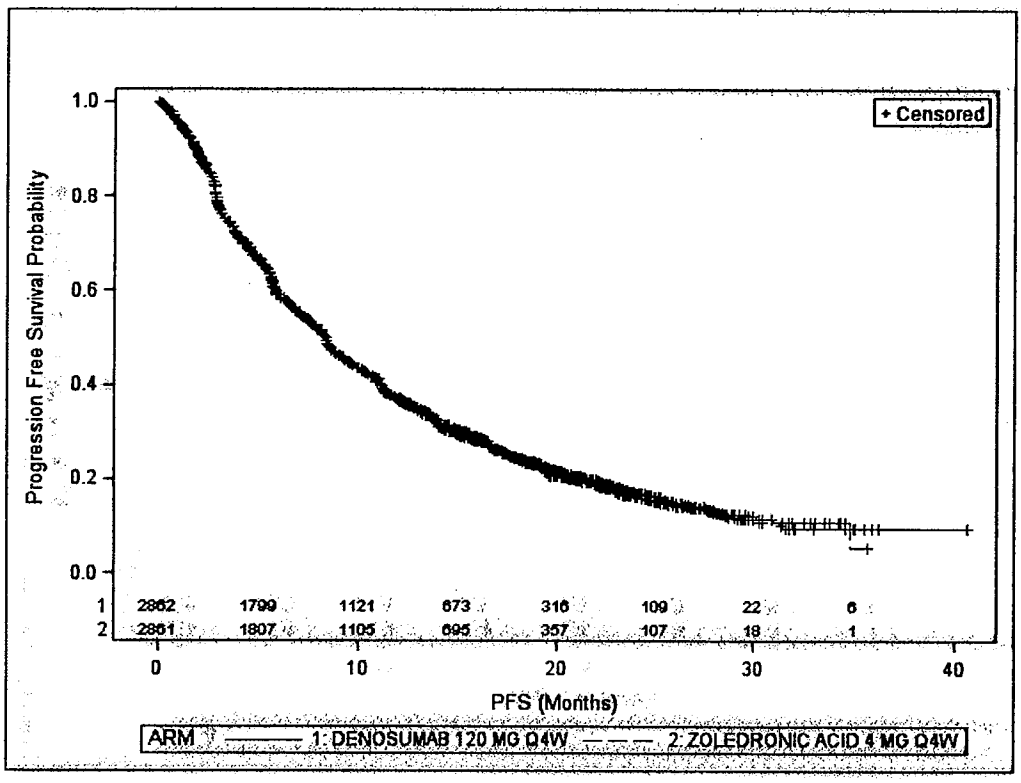


Figure 12: Progression Free Survival Pooled Data (Copied from Statistics Reviewer)



6.1.6.3 Supportive of QOL: Pain Endpoints and Analgesic Use

Results determined by the Applicant where used for consideration of QOL endpoints. For Trial 103, 58% of subjects in the denosumab arm had mild pain or no pain at baseline compared to 59% for zoledronic acid. The mean analgesic score was 1.1 in each arm with no significant difference in analgesic use through week 73 (p=0.2574). The median time to worst pain scored was 86 days for denosumab and 80 days for zoledronic acid (p=0.1677). The time to pain point score endpoints did not differ significantly.

For Trial 136, 56% of subjects in the denosumab arm had mild or no pain at baseline compared to 53% in the zoledronic acid arm. The mean analgesic score was approximately 1 for each arm with no significant difference in analgesic use through week 73 (p=0.07628). The median time to worst pain score was 88 days for denosumab

and 64 days for zoledronic acid (p=0.0094). The time to pain point score endpoints did not differ significantly.

For Trial 244, 41% of subjects in the denosumab arm had mild pain or no pain at baseline compared to 36% in the zoledronic acid arm. Analgesic use at baseline was similar in use 52% (D) and 51% (ZA) in both arms, with a mean analgesic score of 2 for each arm; there was no significant difference in analgesic use through weeks 25 and 45 (p > 0.09). The median time to moderate or severe worst pain score was 57 days for D and 36 days for ZA, but not statistically significant (p=0.1092). The time to pain point score endpoints did not differ significantly.

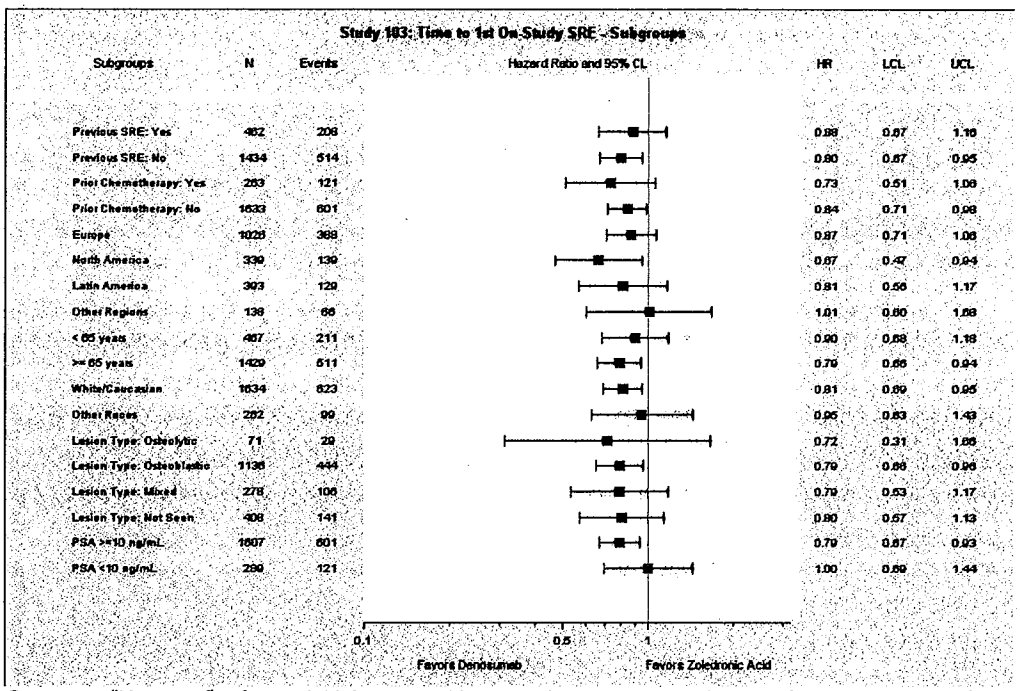
The Applicant used BPI-SF "worst" pain score, a patient reported outcome, and analgesic use as exploratory, quality of life endpoints. The sponsor reported p values and 95% CI for the PRO endpoints, but the statistical analysis plan for these endpoints described the use of descriptive statistics and did not contain a plan to control the type 1 error rate. These endpoints are appropriately considered exploratory endpoints and are not described in the proposed label.

6.1.7 Subpopulations

Time to First On-Study SRE
Multiple exploratory subgroups analyses were performed for each study including region (Europe, Latin America, North America), age, and race (White vs. Other), geographic region, body weight, and gender. In all subgroups, the difference in the time to first on-study SRE was consistent with the results in the overall group (using results of both the pooled analyses and analyses from each individual trial).

Trial 103
Figure 13 (analysis performed by the statistical reviewer for this application, Jing Zhang, PhD) contains the subgroup analyses for Trial 103. The effect of denosumab was maintained in the subgroups defined by the stratifications factors prior SRE, and current chemotherapy. The HR was 1.0 for the subgroup of subjects with PSA less than 10. It cannot be determined if this was a chance effect or related to the (presumed) lower disease burden and fracture rate for this group of subjects. In general, the analyses of all subgroups were supportive of the results in the larger population studied in the trial (with a point estimate for the HR of one or less than one for all subgroups except "other regions").

Figure 13: Subgroup Analyses for Trial 103 (Copied from Statistics Reviewer)

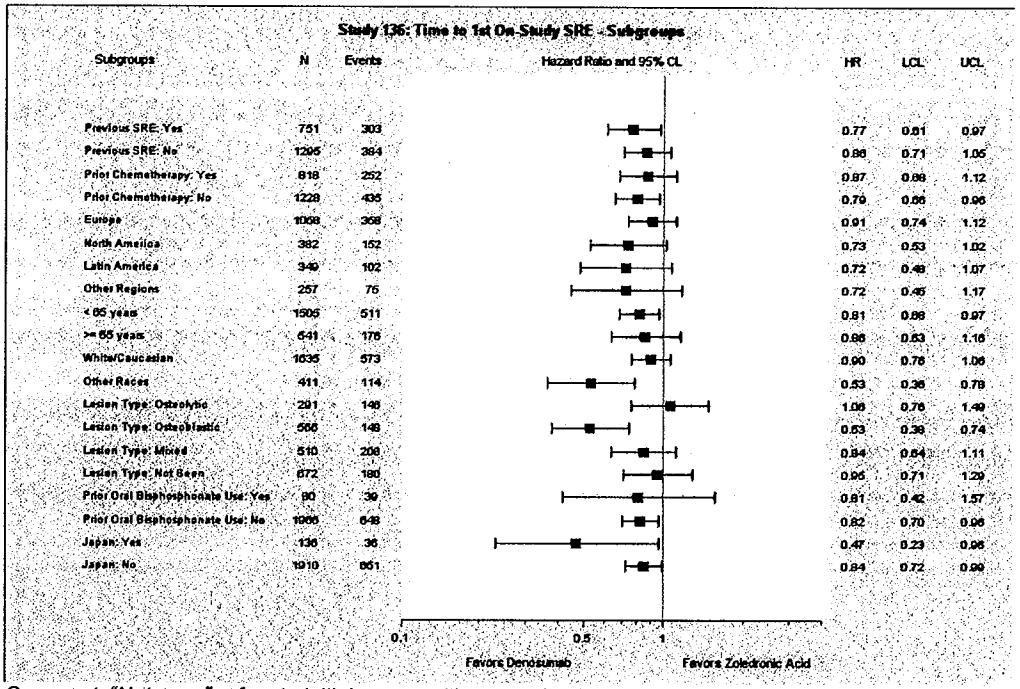


Comment: "Not seen" refers to initial screen with x-rays. Lesion type was later confirmed using MRI, CT Scan or other type of imaging besides plain film x-rays.

Trial 136

Figure 14 (analysis performed by the statistical reviewer for this application, Jing Zhang, PhD) contains a forest plot of the subgroup analyses for Trial 136. The point estimate for the HR was less than one for all subgroups (including subgroups defined by stratification factors) except the subgroup "lesion type: osteolytic."

Figure 14: Subgroups for Trial 136 (Copied from Statistics Reviewer)

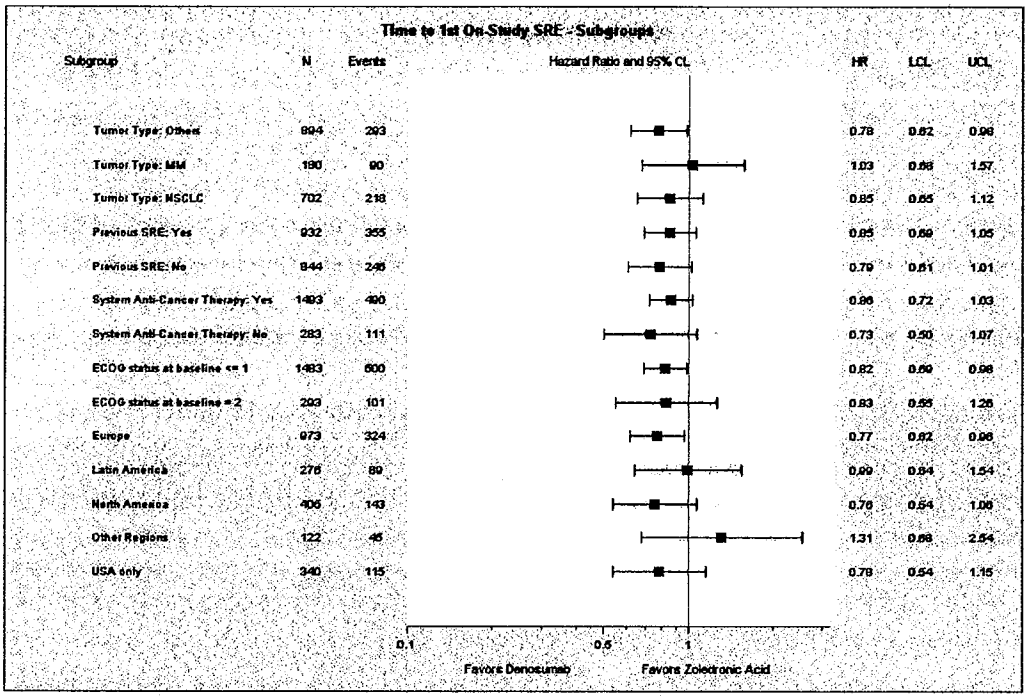


Comment: "Not seen" refers to initial screen with x-rays. Lesion type was later confirmed using MRI, CT Scan or other type of imaging besides plain film x-rays.

Trial 244

Figure 15 (analysis performed by the statistical reviewer for this application, Weishi Yan, PhD) contains the forest plot of the subgroup analyses for Trial 244. The point estimate for the HR was less than one for all subgroups (including subgroups defined by stratification factors) except the subgroups "multiple myeloma", "other region", and "other race." The effects observed in the "other region" and "other race" subgroups were not observed in Trials 103 and 136.

Figure 15: Subgroups for Trial 244 (Copied from Statistics Reviewer)



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Trial 20040113 (113), a randomized phase 2 dose finding study, compared five different subcutaneous doses of denosumab to IV bisphosphonates in 255 subjects with breast cancer and bone metastases. The IV bisphosphonate was open-label and chosen by the patient's physician; however the denosumab cohorts were double-blinded to dose and schedule. Dosing cohorts of denosumab were 30 mg, 120 mg, and 180 mg SC every 4 weeks, and 60 mg and 180mg SC every 12 weeks. Stratification factors included hormonal or chemotherapy treatment and the study duration was "approximately 57 weeks: 25-week treatment period followed by 3 post-treatment visits at weeks 33, 45, and 57," according to the CSR. There were approximately 40 subjects per dosing cohort, for a total of 212 subjects (169 denosumab, 43 bisphosphonate). The study design was adequate to assess week-13 uNTx/Cr, a marker of bone turnover, as a basis of selecting the optimal dose and schedule of denosumab for the phase 3 trials.

The applicant chose 120 mg SC every 4 weeks as the dose for administration in the three Phase 3 trials for treatment of subjects with cancer with osseous metastases (103, 136, 244) based on uNTx/Cr suppression, toxicity data, and maintenance of serum denosumab levels over the dosing interval. Reasons for selecting this dose included (Copied with modifications from the CSR):

- doses higher than 120 mg did not result in greater suppression of uNTx/Cr levels and the 12 week dosing interval did not maintain high serum denosumab levels over the entire dosing interval.
- the 180 mg dose cohort had five CTCAE Grade 2 AEs and one Grade 3 calcium related AE compared to no ≥ Grade 2 calcium related AEs in the 120 mg dose cohort.

Additionally, doses lower than 120 mg did not adequately suppress uNTx/Cr levels.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Time to first-and-subsequent on-study SRE was a pre-specified secondary endpoint in Trials 103, 136, and 244. Demonstration of efficacy in this endpoint in two of the three studies suggests continued activity of denosumab.

7 Review of Safety (S. Pradhan)

Safety Summary

Safety evaluations relevant to the proposed indication included data from a total of 2,841 patients who received denosumab in Trials 103, 136, and 244 at the dosing schedule intended for labeling. Median cumulative exposure to denosumab was 16 months in Trial 136, 7 months in 244, and 12 months in 103. Trials 103, 136, and 244 were analyzed both individually and in pooled analyses of the 3 trials. The safety review includes summaries of deaths and of common, serious, or significant adverse events (AEs) and AEs resulting in dropout from study or discontinuation of investigational product. In addition, AEs of special interest based on the antibody target or on safety signals identified either during development or from experience with other anti-resorptive agents are summarized. Safety laboratory evaluations were performed at regular intervals and these data are also summarized.

Following is a summary of key safety issues pertinent to this application. Hypocalcemia and ONJ are discussed further in Section 7.3.5 Submission Specific Primary Safety Concerns and are included in the Warnings and Precautions Section of the labeling.

Increased Mortality in Patients with Multiple Myeloma in Trial 244

Mortality was higher in the subgroup of patients with multiple myeloma in Trial 244: HR [95% CI] = 2.22 [1.11, 4.46]; n = 180. Therefore, this reviewer recommended the inclusion of an 'Important Limitation of Use' regarding patients with multiple myeloma in the Indications and Usage Section of the labeling. See Section 9.2 Labeling Recommendations.

Hypocalcemia

Hypocalcemia is a known class effect of anti-resorptive agents. At the dosing schedule proposed in this efficacy supplement, denosumab can cause severe (NCI CTCAE v3.0 Grade 3 or 4) hypocalcemia. In Trials 103, 136, and 244, severe hypocalcemia occurred at a higher rate in patients who received denosumab than in patients who received zoledronic acid.

In clinical trials using a lower dose of denosumab (60 mg), there was an increased incidence and severity of hypocalcemia in patients with a creatinine clearance less than 30 mL/min or receiving dialysis compared to patients with normal renal function. In an open label, single dose trial in patients with varying degrees of renal dysfunction, the PK of denosumab was not influenced by renal dysfunction of any severity. The risk of hypocalcemia at the dosing schedule intended for labeling has not been evaluated in patients with a creatinine clearance less than 30 mL/min or receiving dialysis.

ONJ

In the primary analysis phases of Trials 103, 136, and 244, ONJ was positively adjudicated in 1.8% of patients who received denosumab and 1.3% of patients who received zoledronic acid. Median time to ONJ was 14 months (range 4 - 25).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety analyses were conducted using data from Trials 103, 136, and 244. The safety analysis population in these trials consisted of 2,841 patients who received at least one dose of denosumab and 2,836 patients who received at least one dose of zoledronic acid.

7.1.2 Categorization of Adverse Events

Adverse events were coded in Trials 136 and 244 using version 12.0 of the MedDRA dictionary. In Trial 103, adverse events were coded using version 12.1. For the integrated summary of safety, from which all pooled analyses of Trials 103, 136, and

244 in this review are derived, the Applicant re-mapped MedDRA version 12.0 terms to version 12.1.

Toxicity grading was based on the NCI CTCAE version 3.0.

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

Trials 103, 136, and 244 were analyzed both individually and in pooled analyses of the 3 trials. While encompassing different tumor types, these trials were of parallel design and each utilized the denosumab dosing schedule proposed in this efficacy supplement.

7.2 Adequacy of Safety Assessments

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

The following table summarizes IP exposure for each of Trials 103, 136, and 244. Overall exposure was balanced between treatment groups. Consistent with the prognoses of patients with the underlying malignancies, exposure was lower for patients in Trial 244 than for patients in Trials 103 or 136. The size of the overall safety database for Trials 103, 136, and 244 was adequate and is comparable to that described in the zoledronic acid product labeling.

Table 34 Exposure Summary by Trial (Trials 103, 136, and 244)

	103 (Prostate)		136 (Breast)		244 (Other)	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=943	n=945	n=1020	n=1013	n=878	n=878
Median number of doses received	13	10	18	17	7	7
Mean duration on study (months)	13.2	12.6	15.9	15.9	9.7	9.7

There were no significant differences in demographic characteristics between the safety analysis populations and the efficacy analysis populations described in Section 6 of this review. Patient demographics were balanced between treatment groups. Refer to Section 7.5.3 (Drug-Demographic Interactions) for safety analyses by age, sex, and race. Analyses by race were limited by the small number of patients in most non-White subgroups.

7.2.2 Explorations for Dose Response

The following two tables summarize the number of doses of active IP received by treatment group. Few patients in either group received more than 24 doses. Overall, treatment groups were balanced with respect to the number of doses of active IP received.

Table 35 Number of Doses Received by Range (Trials 103, 136, and 244)

Maximum Number of Doses	Denosumab n=2841	Zoledronic Acid n=2836
1 – 6	819 (29%)	905 (32%)
7 – 12	596 (21%)	617 (22%)
13 – 18	546 (19%)	536 (19%)
19 – 24	511 (18%)	454 (16%)
≥ 25	369 (13%)	324 (11%)

Table 36 Number of Doses Received (Trials 103, 136, and 244)

Maximum Number of Doses	Denosumab n=2841	Zoledronic Acid n=2836
1	124 (4.4%)	132 (4.7%)
2	145 (5.1%)	163 (5.7%)
3	135 (4.8%)	160 (5.6%)
4	151 (5.3%)	152 (5.4%)
5	141 (5.0%)	157 (5.5%)
6	123 (4.3%)	141 (5.0%)
7	130 (4.6%)	113 (4.0%)
8	102 (3.6%)	113 (4.0%)
9	106 (3.7%)	119 (4.2%)
10	89 (3.1%)	85 (3.0%)
11	85 (3.0%)	102 (3.6%)
12	84 (3.0%)	85 (3.0%)
13	87 (3.1%)	81 (2.9%)
14	85 (3.0%)	100 (3.5%)
15	88 (3.1%)	79 (2.8%)
16	88 (3.1%)	97 (3.4%)
17	113 (4.0%)	95 (3.3%)
18	85 (3.0%)	84 (3.0%)
19	98 (3.4%)	84 (3.0%)

Maximum Number of Doses	Denosumab n=2841	Zoledronic Acid n=2836
20	98 (3.4%)	75 (2.6%)
21	93 (3.3%)	73 (2.6%)
22	69 (2.4%)	76 (2.7%)
23	90 (3.2%)	76 (2.7%)
24	63 (2.2%)	70 (2.5%)
25	55 (1.9%)	59 (2.1%)
26	62 (2.2%)	52 (1.8%)
27	63 (2.2%)	61 (2.2%)
28	50 (1.8%)	40 (1.4%)
29	36 (1.3%)	15 (0.5%)
30	30 (1.1%)	36 (1.3%)
31	22 (0.8%)	18 (0.6%)
32	14 (0.5%)	11 (0.4%)
33	12 (0.4%)	9 (0.3%)
34	9 (0.3%)	3 (0.1%)
35	4 (0.1%)	5 (0.2%)
36	2 (0.1%)	7 (0.2%)
37	2 (0.1%)	3 (0.1%)
38	3 (0.1%)	2 (0.1%)
39	4 (0.1%)	1 (0.0%)
40	0 (0.0%)	1 (0.0%)
41	0 (0.0%)	1 (0.0%)
44	1 (0.0%)	0 (0.0%)

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical studies with denosumab were limited to non-human primates due to species specificity. Evaluation of knockout mice or the use of other biological inhibitors of the RANK/RANKL pathway, OPG-Fc and RANK-Fc, provided additional safety information on RANK/RANKL pathway inhibition in rodent models. Refer to Section 7.6.3 (Pediatrics and Assessments of Effects on Growth) regarding nonclinical study findings.

7.2.4 Routine Clinical Testing

Overall, routine clinical and laboratory evaluations were adequate to assess the safety of denosumab in Trials 103, 136, and 244. More frequent monitoring of electrolyte levels, however, would have allowed for a more accurate description of the timing of hypocalcemia and other laboratory abnormalities. Refer to Section 5.3 that describes the laboratory schedule of assessments and Section 7.4.2 for details of chemistry, hematology, and other monitoring.

7.2.5 Metabolic, Clearance, and Interaction Workup

Amgen did not conduct hepatic impairment or formal drug interaction studies because denosumab is a monoclonal antibody and does not undergo metabolism and elimination in the manner of small molecule drugs. A renal impairment study (Trial 20040245; see Section 5.3 Discussion of Individual Studies/Clinical Trials) was conducted in patients with varying degrees of renal function. No relationship was observed between denosumab PK and renal function and the Applicant concluded that no dose adjustment is necessary in patients with renal impairment. However, patients with a creatinine clearance of less than 30 mL/min or receiving dialysis were at greater risk of severe hypocalcemia compared to patients with normal renal function. See Section 7.3.5 Submission Specific Primary Safety Concerns, subsection Hypocalcemia, for further detail.

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

Refer to Section 7.3.5 Submission Specific Primary Safety Concerns.

7.3 Major Safety Results

7.3.1 Deaths

A total of 1,638 fatal adverse events occurred in Trials 103, 136, and 244. Fatal adverse events were analyzed by MedDRA preferred term (PT) and high level term (HLT) for each trial and for the 3 trials pooled. For imbalances between treatment groups, case report forms or case narratives were reviewed.

This Section also includes a brief discussion of overall survival in each of the 3 trials and for the subgroup of patients with multiple myeloma in Trial 244.

Table 37 Fatal Adverse Events

103		136		244		Overall	
Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
n=943	n=945	n=1020	n=1013	n=878	n=878	n=2841	n=2836
283	276	204	215	329	331	816	822

Trials 103, 136, and 244 pooled

The following table shows the pooled analysis of deaths at the PT level for the three trials. Events occurring in more than one patient are presented in the table. In general

causes of death were balanced between the treatment groups. Comments regarding specific terms follow the table.

Table 38 Fatal Adverse Events by PT (Trials 103, 136, and 244)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Malignant neoplasm progression	93	3.3	84	3.0
Respiratory failure	66	2.3	55	1.9
Metastases to central nervous system	38	1.3	31	1.1
General physical health deterioration	35	1.2	44	1.6
Multi-organ failure	32	1.1	31	1.1
Hepatic failure	30	1.1	19	0.7
Cardiac failure	27	1.0	24	0.9
Metastases to liver	27	1.0	28	1.0
Dyspnoea	22	0.8	18	0.6
Prostate cancer	21	0.7	43	1.5
Death	19	0.7	19	0.7
Cachexia	15	0.5	21	0.7
Cardio-respiratory arrest	15	0.5	17	0.6
Pneumonia	15	0.5	14	0.5
Cardiac arrest	14	0.5	9	0.3
Disease progression	14	0.5	21	0.7
Metastases to bone	13	0.5	7	0.3
Metastasis	12	0.4	7	0.3
Breast cancer	11	0.4	14	0.5
Cardiopulmonary failure	11	0.4	18	0.6
Pulmonary embolism	10	0.4	8	0.3
Cerebrovascular accident	8	0.3	7	0.3
Sepsis	8	0.3	9	0.3
Myocardial infarction	7	0.3	6	0.2
Prostate cancer metastatic	7	0.3	13	0.5
Performance status decreased	6	0.2	4	0.1
Renal failure acute	6	0.2	4	0.1
Acute myocardial infarction	5	0.2	7	0.3
Febrile neutropenia	5	0.2	0	0.0
Hepatic function abnormal	5	0.2	5	0.2
Pleural effusion	5	0.2	6	0.2

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Renal failure	5	0.2	9	0.3
Respiratory distress	5	0.2	3	0.1
Septic shock	5	0.2	7	0.3
Sudden death	5	0.2	2	0.1
Asthenia	4	0.1	6	0.2
Breast cancer metastatic	4	0.1	10	0.4
Cardiogenic shock	4	0.1	1	0.0
Cerebral haemorrhage	4	0.1	3	0.1
Gastrointestinal haemorrhage	4	0.1	1	0.0
Malignant pleural effusion	4	0.1	0	0.0
Metastases to bone marrow	4	0.1	2	0.1
Metastases to lung	4	0.1	9	0.3
Pulmonary oedema	4	0.1	5	0.2
Subdural haematoma	4	0.1	0	0.0
Acute respiratory distress syndrome	3	0.1	3	0.1
Acute respiratory failure	3	0.1	7	0.3
Anaemia	3	0.1	5	0.2
Bronchopneumonia	3	0.1	1	0.0
Cardiac failure acute	3	0.1	2	0.1
Circulatory collapse	3	0.1	1	0.0
Coma	3	0.1	5	0.2
Hypoxia	3	0.1	1	0.0
Ileus	3	0.1	0	0.0
Lung cancer metastatic	3	0.1	2	0.1
Lung infection	3	0.1	0	0.0
Metastatic neoplasm	3	0.1	4	0.1
Respiratory arrest	3	0.1	0	0.0
Acute hepatic failure	2	0.1	2	0.1
Acute pulmonary oedema	2	0.1	2	0.1
Arrhythmia	2	0.1	0	0.0
Ascites	2	0.1	1	0.0
Atrial fibrillation	2	0.1	0	0.0
Cardiac failure congestive	2	0.1	2	0.1
Cerebral ischaemia	2	0.1	2	0.1
Chronic obstructive pulmonary disease	2	0.1	1	0.0

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Colon cancer metastatic	2	0.1	1	0.0
Haematemesis	2	0.1	1	0.0
Haemoptysis	2	0.1	1	0.0
Hepatic encephalopathy	2	0.1	5	0.2
Hepatorenal failure	2	0.1	0	0.0
Metastases to meninges	2	0.1	7	0.3
Neutropenic sepsis	2	0.1	0	0.0
Prostatic specific antigen increased	2	0.1	0	0.0
Pulmonary haemorrhage	2	0.1	1	0.0
Renal failure chronic	2	0.1	0	0.0
Subdural haemorrhage	2	0.1	0	0.0
Urinary retention	2	0.1	0	0.0
Urinary tract infection	2	0.1	1	0.0
Urosepsis	2	0.1	0	0.0

- Cases of hepatic failure were audited for each of the 3 trials. In each case, hepatic failure was due to liver metastasis or disease progression in the liver.
- Four cases of respiratory failure were audited for each of the 3 trials. In each case, the term accurately reflected the patient's history and was related to disease progression.
- The PT subdural hematoma was reviewed for each trial individually (see below).
- One incident of subarachnoid hemorrhage occurred 4 months after IP initiation and involved a patient with an elevated prothrombin time.
- All sudden deaths in the denosumab group were reviewed. Causes of death were unclear. Events occurred from 14 days to several months post IP initiation. In trial 103, one case occurred on the same day as Grade 4 hypocalcemia, after the patient's second dose of denosumab.
- Both cases of subdural hemorrhage were reviewed. In one case a patient in Trial 103 fell and had a supratherapeutic INR while on warfarin. In the second case a patient in Trial 136 experienced hemorrhage related to metastases and a supratherapeutic INR on warfarin.
- Three cases of circulatory collapse were reviewed. One case in Trial 103 involved an 84 year old patient with comorbidities such as AV block and a pacemaker. One case in Trial 244 was related to disease progression. Details of the second case in Trial 244 were unknown.
- One death caused by 'drug toxicity' was reported as opioid intoxication and involved renal failure occurring 2 days following the first and only dose of IP.

- One epistaxis report involved a patient with widely metastatic disease and thrombocytopenia.
- The report of extradural hematoma involved a patient with skull base metastases.
- The report of 'hemorrhage urinary tract' was presumed due to disease progression.
- One death due to hepatotoxicity was presumed related to metastatic disease.
- One death due to lower GI hemorrhage involved a patient with lower GI bleed related to radiation-induced proctitis.
- One death due to mesothelioma progression was reported as 'pericardial effusion'.

The following table shows the pooled analysis of fatal adverse events by HLT. Events occurring in more than one patient in either arm (and at least one patient in the denosumab group) are presented. In general causes of death (HLT analysis) were balanced between the treatment groups.

Table 39 Fatal Adverse Events by HLT (Trials 103, 136, and 244)

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Neoplasms malignant site unspecified NEC	96	3.4	88	3.1
Metastases to specified sites	91	3.2	89	3.1
General signs and symptoms NEC	88	3.1	104	3.7
Respiratory failures (excl neonatal)	69	2.4	62	2.2
Heart failures NEC	48	1.7	47	1.7
Hepatic failure and associated disorders	34	1.2	21	0.7
Breathing abnormalities	30	1.1	22	0.8
Ventricular arrhythmias and cardiac arrest	29	1.0	27	1.0
Prostatic neoplasms malignant	28	1.0	56	2.0
Death and sudden death	25	0.9	22	0.8
Lower respiratory tract and lung infections	22	0.8	15	0.5
Central nervous system haemorrhages and cerebrovascular accidents	18	0.6	16	0.6

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Sepsis, bacteraemia, viraemia and fungaemia NEC	17	0.6	17	0.6
Breast and nipple neoplasms malignant	16	0.6	24	0.9
General nutritional disorders NEC	15	0.5	22	0.8
Ischaemic coronary artery disorders	15	0.5	15	0.5
Renal failure and impairment	13	0.5	15	0.5
Metastases to unknown and unspecified sites	12	0.4	7	0.3
Pulmonary thrombotic and embolic conditions	10	0.4	9	0.3
Pulmonary oedemas	9	0.3	10	0.4
Non-site specific gastrointestinal haemorrhages	8	0.3	4	0.1
Cerebral injuries NEC	7	0.3	1	0.0
Neutropenias	6	0.2	0	0.0
Coma states	5	0.2	5	0.2
Hepatic enzymes and function abnormalities	5	0.2	5	0.2
Pneumothorax and pleural effusions NEC	5	0.2	9	0.3
Asthenic conditions	4	0.1	7	0.3
Circulatory collapse and shock	4	0.1	1	0.0
Gastrointestinal stenosis and obstruction NEC	4	0.1	3	0.1
Oncologic complications and emergencies	4	0.1	2	0.1
Anaemias NEC	3	0.1	5	0.2
Conditions associated with abnormal gas exchange	3	0.1	1	0.0
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	3	0.1	3	0.1
Bladder and urethral symptoms	2	0.1	0	0.0
Bronchospasm and obstruction	2	0.1	2	0.1
Cell marker procedures	2	0.1	0	0.0

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Colonic neoplasms malignant	2	0.1	1	0.0
Coughing and associated symptoms	2	0.1	1	0.0
Encephalopathies toxic and metabolic	2	0.1	5	0.2
Increased intracranial pressure disorders	2	0.1	1	0.0
Lower respiratory tract signs and symptoms	2	0.1	1	0.0
Parenchymal lung disorders NEC	2	0.1	1	0.0
Peritoneal and retroperitoneal disorders	2	0.1	2	0.1
Rate and rhythm disorders NEC	2	0.1	0	0.0
Supraventricular arrhythmias	2	0.1	1	0.0
Urinary tract infections	2	0.1	2	0.1
Coagulopathies	1	0.0	4	0.1
Encephalopathies NEC	1	0.0	2	0.1
Neoplasms unspecified malignancy and site unspecified NEC	1	0.0	3	0.1
Pain and discomfort NEC	1	0.0	3	0.1
Poisoning and toxicity	1	0.0	2	0.1
Respiratory tract disorders NEC	1	0.0	6	0.2
Total fluid volume decreased	1	0.0	2	0.1
Vascular hypotensive disorders	1	0.0	7	0.3

- The most common PT in the HLT 'Breathing abnormalities' was dyspnea. Most deaths due to dyspnea occurred in Trial 244. All cases audited occurred in lung cancer patients and were due to disease progression. Additional PTs comprising this HLT were evaluated at the PT level.
- The most common PTs in the HLT 'Non-site specific GI hemorrhages' were GI hemorrhage and hematemesis. GI hemorrhage was evaluated at the PT level. One case of the PT hematemesis occurred 9 months after IP initiation and was coded on the CRF as related to disease progression. The other case of the PT hematemesis occurred 4.5 months after initiation of IP and was also coded on the CRF as related to disease progression.

- The HLT 'Cerebral injuries' included the PTs 'subdural hematoma', 'extradural hematoma', and 'subdural hemorrhage', which were evaluated at the PT level.
- All cases in the HLT 'Neutropenias' were reviewed. All cases occurred in Trials 136 and 103 and were related to effects of chemotherapy.

Trial 103

The following table shows the analysis of fatal adverse events at the preferred term level for Trial 103. The difference between groups in per-patient incidence rate was less than 1% for all fatal events. Events occurring in more than one patient in the denosumab group are shown in the table.

Table 40 Fatal Adverse Events by PT (Trial 103)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Prostate cancer	21	2.2	43	4.6
Respiratory failure	18	1.9	10	1.1
Cardiac failure	17	1.8	18	1.9
Multi-organ failure	15	1.6	16	1.7
Cachexia	11	1.2	9	1.0
Death	11	1.2	10	1.1
General physical health deterioration	11	1.2	13	1.4
Hepatic failure	10	1.1	5	0.5
Metastases to bone	9	1.0	6	0.6
Metastases to central nervous system	8	0.9	2	0.2
Metastases to liver	8	0.9	2	0.2
Prostate cancer metastatic	7	0.7	13	1.4
Cardio-respiratory arrest	6	0.6	12	1.3
Cerebrovascular accident	6	0.6	3	0.3
Pulmonary embolism	6	0.6	2	0.2
Myocardial infarction	5	0.5	4	0.4
Renal failure acute	5	0.5	1	0.1
Cerebral haemorrhage	4	0.4	2	0.2
Performance status decreased	4	0.4	0	0.0
Pneumonia	4	0.4	5	0.5
Sepsis	4	0.4	2	0.2
Cardiac arrest	3	0.3	3	0.3
Sudden death	3	0.3	2	0.2
Acute myocardial infarction	2	0.2	3	0.3

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Acute pulmonary oedema	2	0.2	1	0.1
Anaemia	2	0.2	2	0.2
Asthenia	2	0.2	4	0.4
Bronchopneumonia	2	0.2	0	0.0
Cardiac failure congestive	2	0.2	2	0.2
Cardiogenic shock	2	0.2	0	0.0
Cardiopulmonary failure	2	0.2	6	0.6
Cerebral ischaemia	2	0.2	1	0.1
Lung infection	2	0.2	0	0.0
Malignant neoplasm progression	2	0.2	3	0.3
Metastases to bone marrow	2	0.2	0	0.0
Metastasis	2	0.2	1	0.1
Metastatic neoplasm	2	0.2	1	0.1
Neutropenic sepsis	2	0.2	0	0.0
Prostatic specific antigen increased	2	0.2	0	0.0
Renal failure chronic	2	0.2	0	0.0
Subdural haematoma	2	0.2	0	0.0
Urinary retention	2	0.2	0	0.0
Urinary tract infection	2	0.2	1	0.1

- Both cases of cardiogenic shock in the denosumab group were reviewed. One case was related to post-surgical bleeding complications (post radiation rectitis with anal bleed) and the other case appeared to be related to disease progression.
- The case of respiratory distress was reviewed. This event occurred 2 years post IP initiation and appeared related to disease progression.
- Both cases of subdural hematoma were reviewed. One case involved an 84 year old patient who was found after having suffered an ST elevation MI. The other case occurred 1 year post IP initiation and the patient was thrombocytopenic.
- The case of PT upper GI hemorrhage was reviewed. At the time of the event, the patient had a platelet count of 4 while on warfarin.

In general the results of the HLT analysis confirmed the results of the PT analysis for Trial 103.

Table 41 Fatal Adverse Events by HLT (Trial 103)

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
General signs and symptoms NEC	30	3.2	30	3.2
Metastases to specified sites	29	3.1	16	1.7
Prostatic neoplasms malignant	28	3.0	56	5.9
Heart failures NEC	24	2.6	27	2.9
Respiratory failures (excl neonatal)	18	1.9	14	1.5
Central nervous system haemorrhages and cerebrovascular accidents	14	1.5	8	0.9
Death and sudden death	14	1.5	12	1.3
General nutritional disorders NEC	11	1.2	9	1.0
Hepatic failure and associated disorders	10	1.1	5	0.5
Ventricular arrhythmias and cardiac arrest	9	1.0	16	1.7
Ischaemic coronary artery disorders	8	0.9	8	0.9
Lower respiratory tract and lung infections	8	0.9	5	0.5
Renal failure and impairment	8	0.9	9	1.0
Sepsis, bacteraemia, viraemia and fungaemia NEC	8	0.9	5	0.5
Pulmonary thrombotic and embolic conditions	6	0.6	3	0.3
Cerebral injuries NEC	4	0.4	0	0.0
Neoplasms malignant site unspecified NEC	4	0.4	4	0.4
Pulmonary oedemas	3	0.3	5	0.5
Anaemias NEC	2	0.2	2	0.2
Asthenic conditions	2	0.2	5	0.5
Bladder and urethral symptoms	2	0.2	0	0.0
Breathing abnormalities	2	0.2	3	0.3
Cell marker procedures	2	0.2	0	0.0
Circulatory collapse and shock	2	0.2	1	0.1

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Metastases to unknown and unspecified sites	2	0.2	1	0.1
Non-site specific gastrointestinal haemorrhages	2	0.2	2	0.2
Urinary tract infections	2	0.2	2	0.2

- The HLT 'CNS hemorrhages and cerebrovascular accidents' includes hemorrhagic and ischemic events. The most common PTs comprising this HLT were cerebral hemorrhage, CVA, cerebral ischemia, intracranial hemorrhage, and subarachnoid hemorrhage. The four cases of the PT 'cerebral hemorrhage' were reviewed. One case involved an 84 year old patient with a supratherapeutic INR. The second case involved a patient with DIC and occurred 4.5 months post IP initiation. The third case involved a patient with cerebral metastases who was receiving an oral anticoagulant. The fourth case involved an 81 year old patient with hypertension and occurred 4 months post IP initiation. Six cases of the PT CVA were reviewed. In general cases involved patients with hypertension, history of CVA, or hyperlipidemia, and occurred one to two years post IP initiation.
- All cases of the HLT 'Hepatic failure and associated disorders' were evaluated at the PT level. Five cases in Trial 103 were reviewed and all were related to disease progression in the liver.
- The HLT 'Cerebral injuries' includes the PTs extradural hematoma, subdural hematoma (2 cases), and subdural hemorrhage.
- The single event occurring in the HLT 'Bronchospasm and Obstruction' involved a patient with COPD.
- The single event occurring in the HLT 'Left ventricular failure' involved a patient with hypertension and chronic ischemic heart disease.
- The fatal HLT event 'Neurological signs and symptoms' consisted of a patient diagnosed with 'neurological decompensation'. Details of the case, which occurred 19 months post IP initiation, were unclear.

Trial 136

The following table shows the analysis of fatal events at the preferred term level for Trial 136. The difference between groups in per-patient incidence rate was less than 1% for all fatal events. Events occurring in more than one patient in the denosumab group are shown in the table.

Table 42 Fatal Adverse Events by PT (Trial 136)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Respiratory failure	19	1.9	16	1.6
Hepatic failure	18	1.8	12	1.2
Metastases to central nervous system	17	1.7	12	1.2
Metastases to liver	12	1.2	18	1.8
Breast cancer	11	1.1	14	1.4
General physical health deterioration	11	1.1	8	0.8
Dyspnoea	9	0.9	3	0.3
Metastasis	9	0.9	3	0.3
Disease progression	8	0.8	8	0.8
Multi-organ failure	8	0.8	9	0.9
Cardio-respiratory arrest	5	0.5	2	0.2
Hepatic function abnormal	5	0.5	5	0.5
Breast cancer metastatic	4	0.4	10	1.0
Malignant neoplasm progression	4	0.4	6	0.6
Malignant pleural effusion	4	0.4	0	0.0
Cachexia	3	0.3	6	0.6
Cardiac failure	3	0.3	3	0.3
Acute hepatic failure	2	0.2	2	0.2
Acute myocardial infarction	2	0.2	2	0.2
Acute respiratory distress syndrome	2	0.2	1	0.1
Ascites	2	0.2	1	0.1
Cardiopulmonary failure	2	0.2	4	0.4
Death	2	0.2	1	0.1
Febrile neutropenia	2	0.2	0	0.0
Gastrointestinal haemorrhage	2	0.2	0	0.0
Metastases to meninges	2	0.2	3	0.3
Pleural effusion	2	0.2	1	0.1
Respiratory distress	2	0.2	1	0.1
Subdural haematoma	2	0.2	0	0.0

- Both cases of GI hemorrhage were reviewed. One event occurred one year following the initiation of IP while the patient had a supratherapeutic INR. The

other occurred in a patient with GI metastases, coagulopathy, and disease progression in the liver.

- Both cases of respiratory distress were reviewed. One patient suffered disease progression in the lung and in the other patient, respiratory distress was due to pleural effusion (unclear if related to disease progression).
- Both cases of subdural hematoma were reviewed. One patient fell while thrombocytopenic due to chemotherapy. The other patient was thrombocytopenic due to chemotherapy and also suffered disease progression and cardiac arrest.

In general the results of the HLT analysis confirmed the results of the PT analysis for Trial 136. No HLT demonstrated a difference of more than 1% between the treatment groups. The following table shows the incidence rates by HLT for terms occurring in more than one patient in the denosumab group.

Table 43 Fatal Adverse Events by HLT (Trial 136)

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Metastases to specified sites	35	3.4	40	4.0
General signs and symptoms NEC	27	2.7	29	2.9
Hepatic failure and associated disorders	21	2.1	14	1.4
Respiratory failures (excl neonatal)	19	1.9	17	1.7
Breast and nipple neoplasms malignant	16	1.6	24	2.4
Breathing abnormalities	12	1.2	5	0.5
Metastases to unknown and unspecified sites	9	0.9	3	0.3
Heart failures NEC	6	0.6	7	0.7
Hepatic enzymes and function abnormalities	5	0.5	5	0.5
Ventricular arrhythmias and cardiac arrest	5	0.5	6	0.6
Neoplasms malignant site unspecified NEC	4	0.4	6	0.6
Oncologic complications and emergencies	4	0.4	1	0.1
Cerebral injuries NEC	3	0.3	0	0.0
Death and sudden death	3	0.3	2	0.2

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
General nutritional disorders NEC	3	0.3	6	0.6
Neutropenias	3	0.3	0	0.0
Non-site specific gastrointestinal haemorrhages	3	0.3	0	0.0
Pulmonary oedemas	3	0.3	1	0.1
Central nervous system haemorrhages and cerebrovascular accidents	2	0.2	3	0.3
Increased intracranial pressure disorders	2	0.2	1	0.1
Ischaemic coronary artery disorders	2	0.2	2	0.2
Peritoneal and retroperitoneal disorders	2	0.2	1	0.1
Pneumothorax and pleural effusions NEC	2	0.2	2	0.2

- The HLT 'Breathing abnormalities' included 9 cases of dyspnea, 2 cases of respiratory distress, and 1 case of respiratory arrest. The cases of dyspnea were audited and generally were related to disease progression, involving either pleural effusion or lung metastases.
- The 4 cases occurring in the HLT 'Oncologic complications and emergencies' were caused by malignant pleural effusion.
- The HLT Cerebral Injuries consisted of 2 cases of subdural hematoma and 1 case of subdural hemorrhage.
- The HLT 'Non-site specific GI hemorrhages' consisted of 2 cases of 'GI hemorrhage' and 1 case of hematemesis.
- The 'Bronchospasm and Obstruction' event involved a patient with COPD.

Trial 244

The following table shows the analysis of fatal events at the preferred term level for Trial 244. The difference between groups in per-patient incidence rate was less than 1% for all events except malignant neoplasm progression and cardiac arrest. Refer to Section 7.3.5 Submission Specific Primary Safety Concerns, subsection Cardiovascular Events, for a discussion of cardiac arrest events. Events occurring in more than one patient in the denosumab group are shown in the table.

Table 44 Fatal Adverse Events by PT (Trial 244)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Malignant neoplasm progression	87	9.9	75	8.5
Respiratory failure	29	3.3	29	3.3
General physical health deterioration	13	1.5	23	2.6
Metastases to central nervous system	13	1.5	17	1.9
Dyspnoea	12	1.4	12	1.4
Cardiac arrest	11	1.3	2	0.2
Pneumonia	11	1.3	7	0.8
Multi-organ failure	9	1.0	6	0.7
Cardiac failure	7	0.8	3	0.3
Cardiopulmonary failure	7	0.8	8	0.9
Metastases to liver	7	0.8	8	0.9
Death	6	0.7	8	0.9
Disease progression	6	0.7	12	1.4
Cardio-respiratory arrest	4	0.5	3	0.3
Renal failure	4	0.5	2	0.2
Septic shock	4	0.5	3	0.3
Acute respiratory failure	3	0.3	2	0.2
Febrile neutropenia	3	0.3	0	0.0
Lung cancer metastatic	3	0.3	2	0.2
Metastases to bone	3	0.3	1	0.1
Pulmonary embolism	3	0.3	3	0.3
Sepsis	3	0.3	5	0.6
Asthenia	2	0.2	0	0.0
Cardiac failure acute	2	0.2	1	0.1
Colon cancer metastatic	2	0.2	1	0.1

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Coma	2	0.2	5	0.6
Gastrointestinal haemorrhage	2	0.2	1	0.1
Haemoptysis	2	0.2	1	0.1
Hepatic failure	2	0.2	2	0.2
Hypoxia	2	0.2	1	0.1
Metastases to lung	2	0.2	2	0.2
Myocardial infarction	2	0.2	2	0.2
Performance status decreased	2	0.2	2	0.2
Pleural effusion	2	0.2	4	0.5
Pulmonary haemorrhage	2	0.2	1	0.1
Pulmonary oedema	2	0.2	2	0.2
Respiratory arrest	2	0.2	0	0.0
Respiratory distress	2	0.2	2	0.2

- Both cases of cardiac failure acute were reviewed. Both were related to disease progression.
- Both cases of pulmonary hemorrhage were reviewed. One case involved a patient with lung cancer and occurred approximately 7 months post IP initiation. The second case involved a patient with lung cancer, occurred 4 days post IP initiation, and was reported as due to erosion of a blood vessel and disease progression.

In general the results of the HLT analysis confirmed the results of the PT analysis for Trial 244. The HLT 'Ventricular arrhythmias and cardiac arrest' recapitulated the finding from the PT analysis.

Table 45 Fatal Adverse Events by HLT (Trial 244)

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Neoplasms malignant site unspecified NEC	88	10.0	78	8.9
Respiratory failures (excl neonatal)	32	3.6	31	3.5
General signs and symptoms NEC	31	3.5	45	5.1
Metastases to specified sites	27	3.1	33	3.8
Heart failures NEC	18	2.1	13	1.5
Breathing abnormalities	16	1.8	14	1.6

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Ventricular arrhythmias and cardiac arrest	15	1.7	5	0.6
Lower respiratory tract and lung infections	14	1.6	8	0.9
Death and sudden death	8	0.9	8	0.9
Sepsis, bacteraemia, viraemia and fungaemia NEC	8	0.9	8	0.9
Ischaemic coronary artery disorders	5	0.6	5	0.6
Renal failure and impairment	5	0.6	5	0.6
Coma states	3	0.3	5	0.6
Hepatic failure and associated disorders	3	0.3	2	0.2
Neutropenias	3	0.3	0	0.0
Non-site specific gastrointestinal haemorrhages	3	0.3	2	0.2
Pulmonary oedemas	3	0.3	4	0.5
Pulmonary thrombotic and embolic conditions	3	0.3	3	0.3
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	3	0.3	3	0.3
Asthenic conditions	2	0.2	0	0.0
Central nervous system haemorrhages and cerebrovascular accidents	2	0.2	5	0.6
Circulatory collapse and shock	2	0.2	0	0.0
Colonic neoplasms malignant	2	0.2	1	0.1
Conditions associated with abnormal gas exchange	2	0.2	1	0.1
Coughing and associated symptoms	2	0.2	1	0.1
Gastrointestinal stenosis and obstruction NEC	2	0.2	2	0.2
Lower respiratory tract signs and symptoms	2	0.2	1	0.1

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Pneumothorax and pleural effusions NEC	2	0.2	4	0.5

- The HLT 'Heart failures' included 7 cases of cardiac failure, 2 cases of acute cardiac failure, and 7 cases of cardiopulmonary failure. An audit of cases comprising each of the 3 PTs was conducted. In general cases were related to disease progression or cancer treatment complications.
- The HLT 'Ventricular arrhythmias and cardiac arrest' included 11 cases of cardiac arrest (see Section 7.3.5 Submission Specific Primary Safety Concerns, subsection Cardiovascular Events) and 4 cases of the PT cardiorespiratory arrest.

Overall Survival

Overall survival was balanced between treatment groups in each of the 3 trials. Refer to Section 6 Review of Efficacy for OS results. In a subgroup analysis of patients with multiple myeloma in Trial 244, mortality was higher with denosumab than with zoledronic acid. Refer to Section 9.2 regarding related labeling recommendations, including a limitation of use for the Indications and Usage Section regarding patients with multiple myeloma.

Table 46 Overall Survival in Patients with Multiple Myeloma

Multiple Myeloma	Denosumab	Zoledronic Acid
	N = 87	N = 93
Number of Events (%)	23 (26.6%)	13 (14.0%)
Median Survival (95% CI)	NE	NE (28.4, NE)
p-value (Superiority, log-rank)	0.021	
HR (95% CI)	2.26 (1.13, 4.50)	

* analysis performed by W. Yuan (Statistics Reviewer)

No detriment in OS was observed in patients with osteolytic lesions at baseline without multiple myeloma.

Table 47 Overall Survival in Patients with Osteolytic Lesions without Multiple Myeloma

Osteolytic Lesions at Baseline (multiple myeloma excluded)	Denosumab	Zoledronic Acid
	N = 342	N = 346
Number of Events (%)	151 (44.2%)	153 (44.2%)
Median Survival (95% CI)	22.2 (18.7, 29.0)	21.9 (16.5, NE)
HR (95% CI)	0.89 (0.71, 1.13)	

* analysis performed by W. Yuan (Statistics Reviewer)

7.3.2 Serious Adverse Events

A total of 3,219 patients experienced serious adverse events in Trials 103, 136, and 244. Serious adverse events (SAEs) were analyzed by MedDRA preferred term (PT) and high level term (HLT) for each trial and for the 3 trials pooled. For imbalances between treatment groups, case report forms or case narratives were reviewed.

Table 48 Serious Adverse Events (per patient incidence)

103		136		244		Overall	
Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
n=943	n=945	n=1020	n=1013	n=878	n=878	n=2841	n=2836
594	568	453	471	841	842	1599	1620

Trials 103, 136, and 244 pooled

The following table shows the pooled analysis of SAEs at the PT level for the three trials. The table presents events occurring in more than 10 patients in the denosumab group. In general, SAE terms occurred at similar frequencies between the treatment groups. Comments regarding highlighted terms follow the table.

Table 49 Serious Adverse Events by PT (Trials 103, 136, and 244)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Anaemia	160	5.6	163	5.8
Dyspnoea	144	5.1	120	4.2
Pneumonia	112	3.9	93	3.3
Malignant neoplasm progression	111	3.9	110	3.9

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Metastases to central nervous system	104	3.7	96	3.4
Respiratory failure	89	3.1	74	2.6
Dehydration	84	3	77	2.7
Vomiting	76	2.7	77	2.7
General physical health deterioration	75	2.6	81	2.9
Asthenia	70	2.5	59	2.1
Pyrexia	66	2.3	65	2.3
Pleural effusion	59	2.1	61	2.2
Spinal cord compression	57	2	67	2.4
Back pain	52	1.8	69	2.4
Pulmonary embolism	50	1.8	52	1.8
Metastases to liver	49	1.7	46	1.6
Fatigue	46	1.6	21	0.7
Febrile neutropenia	46	1.6	61	2.2
Bone pain	45	1.6	62	2.2
Diarrhoea	45	1.6	42	1.5
Urinary tract infection	44	1.6	48	1.7
Nausea	43	1.5	53	1.9
Abdominal pain	41	1.4	43	1.5
Hypocalcaemia	41	1.4	17	0.6
Neutropenia	40	1.4	29	1
Osteonecrosis	39	1.4	19	0.7
Thrombocytopenia	39	1.4	39	1.4
Cardiac failure	37	1.3	35	1.2
Multi-organ failure	37	1.3	35	1.2
Renal failure	37	1.3	50	1.8
Hepatic failure	36	1.3	26	0.9
Urinary retention	36	1.3	44	1.6
Prostate cancer	34	1.2	56	2
Pain	32	1.1	26	0.9
Haematuria	31	1.1	39	1.4
Decreased appetite	30	1.1	28	1
Sepsis	30	1.1	26	0.9
Chest pain	28	1	32	1.1
Renal failure acute	28	1	37	1.3
Deep vein thrombosis	27	1	29	1
Cachexia	24	0.8	29	1
Pain in extremity	23	0.8	30	1.1
Cerebrovascular accident	22	0.8	9	0.3
Hypotension	22	0.8	22	0.8
Oedema peripheral	22	0.8	20	0.7

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Hydronephrosis	21	0.7	14	0.5
Metastases to bone	21	0.7	19	0.7
Atrial fibrillation	20	0.7	20	0.7
Femur fracture	20	0.7	22	0.8
Confusional state	19	0.7	25	0.9
Death	19	0.7	19	0.7
Disease progression	19	0.7	27	1
Metastasis	19	0.7	7	0.3
Syncope	19	0.7	17	0.6
Arthralgia	18	0.6	25	0.9
Cardiac arrest	18	0.6	11	0.4
Cellulitis	18	0.6	12	0.4
Breast cancer	17	0.6	17	0.6
Cardio-respiratory arrest	17	0.6	19	0.7
Headache	17	0.6	16	0.6
Ascites	16	0.6	12	0.4
Cardiac failure congestive	14	0.5	15	0.5
Dizziness	14	0.5	10	0.4
Intestinal obstruction	13	0.5	11	0.4
Metastases to lung	13	0.5	14	0.5
Muscular weakness	13	0.5	13	0.5
Pancytopenia	13	0.5	16	0.6
Cardiopulmonary failure	12	0.4	19	0.7
Constipation	12	0.4	23	0.8
Dysphagia	12	0.4	10	0.4
Haemoptysis	12	0.4	9	0.3
Leukopenia	12	0.4	13	0.5
Myocardial infarction	12	0.4	19	0.7
Performance status decreased	12	0.4	12	0.4
Septic shock	12	0.4	10	0.4
Abdominal pain upper	11	0.4	8	0.3
Bronchitis	11	0.4	6	0.2
Convulsion	11	0.4	17	0.6
Hepatic function abnormal	11	0.4	8	0.3
Hypoxia	11	0.4	9	0.3

- The clinical relevance of the SAE fatigue was unclear. Audit of cases showed that underlying pathologies were generally manifestations of cancer progression.
- Refer to Section 7.3.5 Submission Specific Primary Safety Concerns for further detail regarding hypocalcemia, osteonecrosis, and cardiac events.

- The SAE cerebrovascular accident (CVA) included fatal adverse events reviewed in Section 7.3.1 (Fatal Adverse Events). In general, audit of cases showed that most involved patients with hypertension, history of CVA, or hyperlipidemia, and occurred 1-2 years post IP initiation. The difference in CVA events primarily occurred in Trial 103 and was not consistently observed between trials. When CVAs were analyzed at the HLT level, the apparent difference between treatment groups was less pronounced (1.5% versus 1.2%).

The following table shows the pooled analysis of SAEs at the HLT level for the three trials. Events occurring in more than 10 patients are presented in the table. In general SAE HLT terms were balanced between the treatment groups and results of the HLT analysis confirmed the results of the PT analysis. Comments regarding highlighted terms follow the table.

Table 50 Serious Adverse Events by HLT (Trials 103, 136, and 244)

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Metastases to specified sites	213	7.5	198	7
Anaemias NEC	162	5.7	163	5.8
Breathing abnormalities	155	5.5	129	4.6
Lower respiratory tract and lung infections	147	5.2	116	4.1
General signs and symptoms NEC	145	5.1	157	5.5
Neoplasms malignant site unspecified NEC	115	4.1	117	4.1
Asthenic conditions	112	3.9	83	2.9
Respiratory failures (excl neonatal)	96	3.4	82	2.9
Nausea and vomiting symptoms	89	3.1	95	3.4
Total fluid volume decreased	85	3	77	2.7
Musculoskeletal and connective tissue pain and discomfort	84	3	117	4.1
Neutropenias	83	2.9	86	3
Heart failures NEC	75	2.6	72	2.5
Renal failure and impairment	73	2.6	96	3.4
Febrile disorders	67	2.4	65	2.3
Pneumothorax and pleural effusions NEC	67	2.4	77	2.7
Pain and discomfort NEC	64	2.3	64	2.3

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Sepsis, bacteraemia, viraemia and fungaemia NEC	59	2.1	50	1.8
Spinal cord and nerve root disorders NEC	59	2.1	70	2.5
Gastrointestinal and abdominal pains (excl oral and throat)	53	1.9	50	1.8
Urinary tract infections	52	1.8	62	2.2
Pulmonary thrombotic and embolic conditions	51	1.8	53	1.9
Bone related signs and symptoms	49	1.7	63	2.2
Calcium metabolism disorders	46	1.6	28	1
Diarrhoea (excl infective)	46	1.6	43	1.5
Central nervous system haemorrhages and cerebrovascular accidents	43	1.5	35	1.2
Bladder and urethral symptoms	42	1.5	52	1.8
Prostatic neoplasms malignant	42	1.5	72	2.5
Hepatic failure and associated disorders	41	1.4	30	1.1
Bone disorders NEC	40	1.4	21	0.7
Thrombocytopenias	40	1.4	40	1.4
Ventricular arrhythmias and cardiac arrest	36	1.3	33	1.2
Ischaemic coronary artery disorders	34	1.2	48	1.7
Peripheral embolism and thrombosis	33	1.2	40	1.4
Appetite disorders	31	1.1	28	1
Disturbances in consciousness NEC	31	1.1	37	1.3
Urinary abnormalities	31	1.1	41	1.5
Gastrointestinal stenosis and obstruction NEC	30	1.1	18	0.6
General nutritional disorders NEC	30	1.1	36	1.3
Non-site specific gastrointestinal haemorrhages	29	1	28	1
Oedema NEC	28	1	30	1.1
Infections NEC	27	1	27	1

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Oncologic complications and emergencies	27	1	26	0.9
Supraventricular arrhythmias	26	0.9	29	1
Breast and nipple neoplasms malignant	25	0.9	28	1
Death and sudden death	25	0.9	22	0.8
Lower limb fractures and dislocations	24	0.8	24	0.9
Vascular hypotensive disorders	24	0.8	27	1
Bacterial infections NEC	23	0.8	21	0.7
Renal obstructive disorders	23	0.8	18	0.6
Abdominal and gastrointestinal infections	22	0.8	22	0.8
Confusion and disorientation	20	0.7	28	1
Joint related signs and symptoms	20	0.7	27	1
Peritoneal and retroperitoneal disorders	20	0.7	15	0.5
Metastases to unknown and unspecified sites	19	0.7	7	0.3
Neurological signs and symptoms NEC	18	0.6	13	0.5
Paralysis and paresis (excl cranial nerve)	18	0.6	33	1.2
Rate and rhythm disorders NEC	18	0.6	12	0.4
Headaches NEC	17	0.6	16	0.6
Coughing and associated symptoms	16	0.6	20	0.7
Marrow depression and hypoplastic anaemias	16	0.6	18	0.6
Cerebral injuries NEC	15	0.5	5	0.2
Pulmonary oedemas	15	0.5	19	0.7
Seizures and seizure disorders NEC	15	0.5	20	0.7
Muscle weakness conditions	14	0.5	13	0.5
Bronchospasm and obstruction	13	0.5	12	0.4
Cholestasis and jaundice	13	0.5	10	0.4
Conditions associated with abnormal gas exchange	13	0.5	9	0.3

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Gastrointestinal signs and symptoms NEC	13	0.5	15	0.5
Potassium imbalance	13	0.5	26	0.9
Gastrointestinal atonic and hypomotility disorders NEC	12	0.4	25	0.9
Leukopenias NEC	12	0.4	13	0.5
Hepatic enzymes and function abnormalities	11	0.4	8	0.3
Pericardial disorders NEC	11	0.4	7	0.3
Renal function analyses	11	0.4	6	0.2

- 'Calcium metabolism disorders' includes the PT hypocalcemia. Refer to Section 7.3.5 Submission Specific Primary Safety Concerns for further detail regarding hypocalcemia.
- 'Bone disorders NEC' includes osteonecrosis events. Refer to Section 7.3.5 Submission Specific Primary Safety Concerns for further detail regarding osteonecrosis.
- 'Cerebral injuries' included fatal adverse events reviewed in Section 7.3.1 Fatal Adverse Events. See Section 7.3.1 for analysis of the PTs 'subdural hematoma', 'extradural hematoma', and 'subdural hemorrhage'.
- Renal failure events occurred more frequently in the zoledronic acid group.

The following table shows SAEs at the HLGT level for the three trials pooled. Events occurring in more than 1% of denosumab-treated patients are presented in the table. Serious adverse event terms were balanced between the treatment groups.

Table 51 Serious Adverse Events by HLGT (Trials 103, 136, and 244)

HLGT	Denosumab		Zoledronic Acid	
	n	%	n	%
General system disorders NEC	311	11.0	317	11.2
Infections - pathogen unspecified	296	10.4	268	9.5
Respiratory disorders NEC	263	9.3	226	8.0
Metastases	229	8.1	204	7.2
Anaemias nonhaemolytic and marrow depression	178	6.3	180	6.4
Gastrointestinal signs and symptoms	139	4.9	149	5.3

HLGT	Denosumab		Zoledronic Acid	
	n	%	n	%
Miscellaneous and site unspecified neoplasms malignant and unspecified	116	4.1	120	4.2
Electrolyte and fluid balance conditions	102	3.6	107	3.8
White blood cell disorders	90	3.2	96	3.4
Renal disorders (excl nephropathies)	89	3.1	110	3.9
Bone disorders (excl congenital and fractures)	88	3.1	87	3.1
Musculoskeletal and connective tissue disorders NEC	87	3.1	121	4.3
Cardiac arrhythmias	81	2.9	72	2.5
Heart failures	79	2.8	74	2.6
Neurological disorders NEC	76	2.7	72	2.5
Pleural disorders	70	2.5	79	2.8
Urinary tract signs and symptoms	69	2.4	88	3.1
Body temperature conditions	67	2.4	65	2.3
Hepatic and hepatobiliary disorders	64	2.3	53	1.9
Spinal cord and nerve root disorders	62	2.2	72	2.5
Appetite and general nutritional disorders	58	2.0	62	2.2
Gastrointestinal motility and defaecation conditions	58	2.0	68	2.4
Pulmonary vascular disorders	52	1.8	54	1.9
Bone, calcium, magnesium and phosphorus metabolism disorders	49	1.7	31	1.1
Central nervous system vascular disorders	49	1.7	45	1.6
Bone and joint injuries	44	1.6	46	1.6
Reproductive neoplasms male malignant and unspecified	44	1.6	73	2.6
Embolism and thrombosis	40	1.4	56	2.0
Gastrointestinal stenosis and obstruction	40	1.4	24	0.9

HLGT	Denosumab		Zoledronic Acid	
	n	%	n	%
Platelet disorders	40	1.4	41	1.5
Bacterial infectious disorders	38	1.3	42	1.5
Gastrointestinal haemorrhages NEC	37	1.3	34	1.2
Coronary artery disorders	36	1.3	48	1.7
Decreased and nonspecific blood pressure disorders and shock	31	1.1	32	1.1

The following table shows SAEs at the SOC level for the three trials pooled. Events occurring in more than 1% of denosumab-treated patients are presented in the table. Serious adverse event terms were balanced between the treatment groups.

Table 52 Serious Adverse Events by SOC (Trials 103, 136, and 244)

SOC	Denosumab		Zoledronic Acid	
	n	%	n	%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	447	15.7	456	16.1
General disorders and administration site conditions	385	13.6	387	13.7
Respiratory, thoracic and mediastinal disorders	365	12.9	347	12.2
Infections and infestations	329	11.6	309	10.9
Gastrointestinal disorders	278	9.8	271	9.6
Blood and lymphatic system disorders	277	9.8	279	9.8
Nervous system disorders	234	8.2	247	8.7
Metabolism and nutrition disorders	201	7.1	188	6.6
Musculoskeletal and connective tissue disorders	201	7.1	231	8.2
Cardiac disorders	200	7.0	188	6.6
Renal and urinary disorders	163	5.7	187	6.6
Vascular disorders	95	3.3	115	4.1

SOC	Denosumab		Zoledronic Acid	
	n	%	n	%
Injury, poisoning and procedural complications	90	3.2	85	3.0
Hepatobiliary disorders	70	2.5	64	2.3
Investigations	44	1.6	35	1.2
Psychiatric disorders	42	1.5	50	1.8

Trial 103

The following table shows the analysis of SAEs at the PT level for Trial 103. Events occurring in more than 5 patients are presented in the table. In general SAE terms were balanced between the treatment groups. Comments regarding highlighted terms follow the table.

Table 53 Serious Adverse Events by PT (Trial 103)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Anaemia	108	11.5	82	8.7
Pneumonia	40	4.2	24	2.5
Asthenia	37	3.9	29	3.1
Dehydration	36	3.8	19	2.0
Dyspnoea	36	3.8	28	3.0
Prostate cancer	34	3.6	56	5.9
Urinary retention	32	3.4	35	3.7
Back pain	29	3.1	36	3.8
General physical health deterioration	29	3.1	28	3.0
Urinary tract infection	28	3.0	30	3.2
Renal failure	26	2.8	28	3.0
Bone pain	24	2.6	34	3.6
Hypocalcaemia	24	2.6	7	0.7
Respiratory failure	24	2.6	14	1.5
Spinal cord compression	24	2.6	33	3.5
Vomiting	24	2.6	22	2.3
Haematuria	23	2.4	37	3.9
Cardiac failure	21	2.2	23	2.4
Fatigue	20	2.1	10	1.1
Pulmonary embolism	20	2.1	16	1.7
Hydronephrosis	19	2.0	12	1.3
Pyrexia	19	2.0	18	1.9
Multi-organ failure	18	1.9	18	1.9
Renal failure acute	18	1.9	16	1.7
Pain	16	1.7	12	1.3

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Cerebrovascular accident	15	1.6	5	0.5
Cachexia	14	1.5	12	1.3
Metastases to central nervous system	14	1.5	6	0.6
Osteonecrosis	14	1.5	4	0.4
Decreased appetite	13	1.4	13	1.4
Metastases to liver	13	1.4	5	0.5
Oedema peripheral	13	1.4	8	0.9
Confusional state	12	1.3	10	1.1
Diarrhoea	12	1.3	13	1.4
Pleural effusion	12	1.3	9	1.0
Sepsis	12	1.3	11	1.2
Arthralgia	11	1.2	9	1.0
Death	11	1.2	10	1.1
Atrial fibrillation	10	1.1	8	0.9
Hepatic failure	10	1.1	6	0.6
Metastases to bone	10	1.1	9	1.0
Neutropenia	10	1.1	4	0.4
Pain in extremity	10	1.1	20	2.1
Syncope	10	1.1	6	0.6
Thrombocytopenia	10	1.1	5	0.5
Chest pain	9	1.0	13	1.4
Muscular weakness	9	1.0	4	0.4
Myocardial infarction	9	1.0	13	1.4
Performance status decreased	9	1.0	2	0.2
Abdominal pain	8	0.9	12	1.3
Cardiac failure congestive	8	0.9	7	0.7
Deep vein thrombosis	8	0.9	8	0.9
Febrile neutropenia	8	0.9	8	0.9
Hypotension	8	0.9	8	0.9
Nausea	8	0.9	14	1.5
Prostate cancer metastatic	8	0.9	17	1.8
Cardio-respiratory arrest	7	0.7	12	1.3
Subdural haematoma	7	0.7	2	0.2
Arrhythmia	6	0.6	2	0.2
Bronchitis	6	0.6	1	0.1
Cellulitis	6	0.6	4	0.4
Hyperkalaemia	6	0.6	5	0.5
Hypophosphataemia	6	0.6	0	0.0
Upper gastrointestinal haemorrhage	6	0.6	3	0.3

- The imbalance in pneumonia SAEs between treatment groups was not consistent across trials (no imbalance was observed in Trials 136 and 244).
- Refer to the SAE PT and HLT analyses for the 3 trials pooled regarding cerebrovascular accidents.
- Refer to Section 7.3.5 Submission Specific Primary Safety Concerns for further detail regarding hypocalcemia and osteonecrosis.
- Based on laboratory findings, this reviewer recommended the inclusion of hypophosphatemia in a 'Severe Mineral/Electrolyte Abnormalities' subsection of the Adverse Reactions Section of the product labeling. Refer to Section 9.2 Labeling Recommendations.

The following table shows the analysis of SAEs at the HLT level for Trial 103. Events occurring in more than 5 patients are presented in the table. In general SAE HLT terms were balanced between the treatment groups and results of the HLT analysis confirmed the results of the PT analysis. Comments regarding highlighted terms follow the table.

Table 54 Serious Adverse Events by HLT (Trial 103)

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Anaemias NEC	110	11.7	82	8.7
General signs and symptoms NEC	57	6.0	48	5.1
Asthenic conditions	56	5.9	41	4.3
Lower respiratory tract and lung infections	53	5.6	28	3.0
Renal failure and impairment	50	5.3	50	5.3
Metastases to specified sites	46	4.9	30	3.2
Prostatic neoplasms malignant	42	4.5	72	7.6
Musculoskeletal and connective tissue pain and discomfort	40	4.2	62	6.6
Bladder and urethral symptoms	37	3.9	38	4.0
Breathing abnormalities	37	3.9	30	3.2
Total fluid volume decreased	36	3.8	19	2.0
Heart failures NEC	35	3.7	37	3.9
Urinary tract infections	34	3.6	37	3.9
Central nervous system haemorrhages and cerebrovascular accidents	30	3.2	20	2.1
Nausea and vomiting symptoms	27	2.9	27	2.9

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Pain and discomfort NEC	26	2.8	27	2.9
Respiratory failures (excl neonatal)	26	2.8	18	1.9
Sepsis, bacteraemia, viraemia and fungaemia NEC	26	2.8	21	2.2
Spinal cord and nerve root disorders NEC	26	2.8	36	3.8
Bone related signs and symptoms	24	2.6	34	3.6
Calcium metabolism disorders	24	2.6	7	0.7
Urinary abnormalities	23	2.4	37	3.9
Ischaemic coronary artery disorders	21	2.2	32	3.4
Pulmonary thrombotic and embolic conditions	21	2.2	17	1.8
Renal obstructive disorders	21	2.2	16	1.7
Febrile disorders	19	2.0	18	1.9
Neutropenias	18	1.9	12	1.3
General nutritional disorders NEC	16	1.7	15	1.6
Bone disorders NEC	15	1.6	5	0.5
Oedema NEC	15	1.6	14	1.5
Death and sudden death	14	1.5	12	1.3
Disturbances in consciousness NEC	14	1.5	11	1.2
Appetite disorders	13	1.4	13	1.4
Confusion and disorientation	13	1.4	12	1.3
Joint related signs and symptoms	13	1.4	10	1.1
Non-site specific gastrointestinal haemorrhages	13	1.4	11	1.2
Supraventricular arrhythmias	13	1.4	12	1.3
Diarrhoea (excl infective)	12	1.3	13	1.4
Pneumothorax and pleural effusions NEC	12	1.3	13	1.4
Ventricular arrhythmias and cardiac arrest	12	1.3	17	1.8
Gastrointestinal and abdominal pains (excl oral and throat)	11	1.2	14	1.5
Hepatic failure and associated disorders	11	1.2	6	0.6
Thrombocytopenias	11	1.2	5	0.5

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Cerebral injuries NEC	10	1.1	3	0.3
Gastrointestinal stenosis and obstruction NEC	10	1.1	4	0.4
Muscle weakness conditions	10	1.1	4	0.4
Paralysis and paresis (excl cranial nerve)	10	1.1	12	1.3
Potassium imbalance	10	1.1	10	1.1
Vascular hypotensive disorders	10	1.1	11	1.2
Peripheral embolism and thrombosis	9	1.0	13	1.4
Rate and rhythm disorders NEC	9	1.0	4	0.4
Bacterial infections NEC	8	0.9	6	0.6
Genital and urinary tract disorders NEC	8	0.9	6	0.6
Abdominal and gastrointestinal infections	7	0.7	9	1.0
Pulmonary oedemas	7	0.7	9	1.0
Oncologic complications and emergencies	6	0.6	3	0.3
Phosphorus metabolism disorders	6	0.6	0	0.0
Renal function analyses	6	0.6	1	0.1

In general, the highlighted HLT differences were primarily driven by the occurrence of a single preferred term.

- 'Lower respiratory tract and lung infections' includes the PT pneumonia.
- 'Calcium metabolism disorders' includes the PT hypocalcemia.
- 'Bone disorders NEC' includes the PT osteonecrosis.
- 'Cerebral injuries' included fatal adverse events reviewed in Section 7.3.1 Fatal Adverse Events. See Section 7.3.1 for analysis of the PTs 'subdural hematoma', 'extradural hematoma', and 'subdural hemorrhage'.
- 'Phosphorus metabolism disorders' includes the PT hypophosphatemia.

Trial 136

The following table shows the analysis of SAEs at the PT level for Trial 136. Events occurring in more than 5 patients are presented in the table. In general SAE terms were balanced between the treatment groups.

Table 55 Serious Adverse Events by PT (Trial 136)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Dyspnoea	53	5.2	38	3.8
Metastases to central nervous system	47	4.6	46	4.5
Vomiting	31	3.0	31	3.1
Anaemia	27	2.7	32	3.2
Hepatic failure	24	2.4	16	1.6
Pleural effusion	24	2.4	25	2.5
Nausea	21	2.1	23	2.3
Pyrexia	21	2.1	26	2.6
General physical health deterioration	20	2.0	15	1.5
Metastases to liver	20	2.0	28	2.8
Pneumonia	20	2.0	25	2.5
Respiratory failure	20	2.0	20	2.0
Diarrhoea	19	1.9	16	1.6
Osteonecrosis	18	1.8	11	1.1
Breast cancer	17	1.7	17	1.7
Febrile neutropenia	17	1.7	22	2.2
Neutropenia	16	1.6	14	1.4
Abdominal pain	15	1.5	14	1.4
Fatigue	15	1.5	5	0.5
Dehydration	13	1.3	24	2.4
Headache	13	1.3	9	0.9
Asthenia	12	1.2	14	1.4
Thrombocytopenia	12	1.2	11	1.1
Disease progression	11	1.1	12	1.2
Femur fracture	11	1.1	12	1.2
Pulmonary embolism	11	1.1	18	1.8
Anorexia	10	1.0	7	0.7
Ascites	10	1.0	5	0.5
Bone pain	10	1.0	13	1.3
Hepatic function abnormal	10	1.0	7	0.7
Metastasis	9	0.9	3	0.3
Multi-organ failure	9	0.9	9	0.9
Back pain	8	0.8	14	1.4
Convulsion	8	0.8	10	1.0
Malignant pleural effusion	8	0.8	6	0.6
Pain in extremity	8	0.8	3	0.3
Breast cancer metastatic	7	0.7	11	1.1
Cellulitis	7	0.7	3	0.3
Dizziness	7	0.7	4	0.4

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Urinary tract infection	7	0.7	9	0.9
Cachexia	6	0.6	7	0.7
Cardiac failure	6	0.6	7	0.7
Cardio-respiratory arrest	6	0.6	4	0.4
Leukopenia	6	0.6	6	0.6
Malignant neoplasm progression	6	0.6	7	0.7
Metastases to lung	6	0.6	7	0.7
Spinal cord compression	6	0.6	8	0.8
Syncope	6	0.6	3	0.3

The following table shows the analysis of SAEs at the HLT level for Trial 136. Events occurring in more than 5 patients are presented in the table. In general SAE HLT terms were balanced between the treatment groups and results of the HLT analysis confirmed the results of the PT analysis.

Table 56 Serious Adverse Events by HLT (Trial 136)

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Metastases to specified sites	90	8.8	94	9.3
Breathing abnormalities	58	5.7	41	4.1
General signs and symptoms NEC	38	3.7	40	4.0
Nausea and vomiting symptoms	38	3.7	40	4.0
Neutropenias	30	2.9	36	3.6
Pneumothorax and pleural effusions NEC	28	2.8	33	3.3
Anaemias NEC	27	2.7	32	3.2
Hepatic failure and associated disorders	26	2.6	18	1.8
Asthenic conditions	25	2.5	20	2.0
Breast and nipple neoplasms malignant	25	2.5	28	2.8
Lower respiratory tract and lung infections	25	2.5	29	2.9
Febrile disorders	21	2.1	26	2.6
Respiratory failures (excl neonatal)	21	2.1	21	2.1
Diarrhoea (excl infective)	20	2.0	16	1.6
Bone disorders NEC	18	1.8	11	1.1
Gastrointestinal and abdominal pains (excl oral and throat)	18	1.8	17	1.7

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Musculoskeletal and connective tissue pain and discomfort	17	1.7	21	2.1
Heart failures NEC	14	1.4	16	1.6
Total fluid volume decreased	14	1.4	24	2.4
Headaches NEC	13	1.3	9	0.9
Lower limb fractures and dislocations	13	1.3	13	1.3
Bone related signs and symptoms	12	1.2	14	1.4
Oncologic complications and emergencies	12	1.2	12	1.2
Thrombocytopenias	12	1.2	12	1.2
Appetite disorders	11	1.1	8	0.8
Pain and discomfort NEC	11	1.1	18	1.8
Pulmonary thrombotic and embolic conditions	11	1.1	18	1.8
Bacterial infections NEC	10	1.0	5	0.5
Disturbances in consciousness NEC	10	1.0	12	1.2
Hepatic enzymes and function abnormalities	10	1.0	7	0.7
Infections NEC	10	1.0	9	0.9
Peritoneal and retroperitoneal disorders	10	1.0	6	0.6
Seizures and seizure disorders NEC	10	1.0	10	1.0
Metastases to unknown and unspecified sites	9	0.9	3	0.3
Urinary tract infections	9	0.9	13	1.3
Neurological signs and symptoms NEC	8	0.8	5	0.5
Calcium metabolism disorders	7	0.7	12	1.2
Cholestasis and jaundice	7	0.7	4	0.4
Non-site specific gastrointestinal haemorrhages	7	0.7	3	0.3
Oedema NEC	7	0.7	7	0.7
Peripheral embolism and thrombosis	7	0.7	11	1.1
Ventricular arrhythmias and cardiac arrest	7	0.7	8	0.8
Gastrointestinal stenosis and obstruction NEC	6	0.6	6	0.6
General nutritional disorders NEC	6	0.6	8	0.8

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Leukopenias NEC	6	0.6	6	0.6
Marrow depression and hypoplastic anaemias	6	0.6	2	0.2
Neoplasms malignant site unspecified NEC	6	0.6	7	0.7
Spinal cord and nerve root disorders NEC	6	0.6	8	0.8

Trial 244

The following table shows the analysis of SAEs at the PT level for Trial 244. Events occurring in more than 5 patients are presented in the table. In general SAE terms were balanced between the treatment groups. Comments regarding highlighted terms follow the table.

Table 57 Serious Adverse Events by PT (Trial 244)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Malignant neoplasm progression	103	11.7	100	11.4
Dyspnoea	55	6.3	54	6.2
Pneumonia	52	5.9	44	5.0
Respiratory failure	45	5.1	40	4.6
Metastases to central nervous system	43	4.9	44	5.0
Dehydration	35	4.0	34	3.9
Spinal cord compression	27	3.1	26	3.0
General physical health deterioration	26	3.0	38	4.3
Pyrexia	26	3.0	21	2.4
Anaemia	25	2.9	49	5.6
Pleural effusion	23	2.6	27	3.1
Asthenia	21	2.4	16	1.8
Febrile neutropenia	21	2.4	31	3.5
Vomiting	21	2.4	24	2.7
Pulmonary embolism	19	2.2	18	2.1
Abdominal pain	18	2.1	17	1.9
Thrombocytopenia	17	1.9	23	2.6
Metastases to liver	16	1.8	13	1.5
Sepsis	16	1.8	11	1.3
Back pain	15	1.7	19	2.2
Deep vein thrombosis	15	1.7	13	1.5
Chest pain	14	1.6	10	1.1
Diarrhoea	14	1.6	13	1.5

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Nausea	14	1.6	16	1.8
Neutropenia	14	1.6	11	1.3
Cardiac arrest	12	1.4	3	0.3
Hypocalcaemia	12	1.4	8	0.9
Pain	12	1.4	6	0.7
Bone pain	11	1.3	15	1.7
Fatigue	11	1.3	6	0.7
Haemoptysis	11	1.3	9	1.0
Cardiac failure	10	1.1	5	0.6
Multi-organ failure	10	1.1	8	0.9
Renal failure	10	1.1	13	1.5
Renal failure acute	10	1.1	15	1.7
Hypotension	9	1.0	6	0.7
Metastases to bone	9	1.0	8	0.9
Urinary tract infection	9	1.0	9	1.0
Cardiopulmonary failure	8	0.9	9	1.0
Disease progression	8	0.9	13	1.5
Haematuria	8	0.9	2	0.2
Intestinal obstruction	8	0.9	4	0.5
Atrial fibrillation	7	0.8	7	0.8
Dysphagia	7	0.8	5	0.6
Hypoxia	7	0.8	4	0.5
Metastasis	7	0.8	3	0.3
Osteonecrosis	7	0.8	4	0.5
Pancytopenia	7	0.8	11	1.3
Anorexia	6	0.7	7	0.8
Chronic obstructive pulmonary disease	6	0.7	7	0.8
Death	6	0.7	8	0.9
Lung cancer metastatic	6	0.7	3	0.3
Lung infection	6	0.7	1	0.1
Pericardial effusion	6	0.7	5	0.6
Septic shock	6	0.7	4	0.5

- Refer to Section 7.3.5 Submission Specific Primary Safety Concerns for further detail regarding cardiac events.

The following table shows the analysis of SAEs at the HLT level for Trial 244. Events occurring in more than 5 patients are presented in the table. In general SAE HLT terms were balanced between the treatment groups and results of the HLT analysis confirmed the results of the PT analysis. Comments regarding highlighted terms follow the table.

Table 58 Serious Adverse Events by HLT (Trial 244)

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Neoplasms malignant site unspecified NEC	104	11.9	106	12.1
Metastases to specified sites	77	8.8	74	8.4
Lower respiratory tract and lung infections	69	7.9	59	6.7
Breathing abnormalities	60	6.8	58	6.6
General signs and symptoms NEC	50	5.7	69	7.9
Respiratory failures (excl neonatal)	49	5.6	43	4.9
Neutropenias	35	4.0	38	4.3
Total fluid volume decreased	35	4.0	34	3.9
Asthenic conditions	31	3.5	22	2.5
Sepsis, bacteraemia, viraemia and fungaemia NEC	28	3.2	18	2.1
Febrile disorders	27	3.1	21	2.4
Musculoskeletal and connective tissue pain and discomfort	27	3.1	34	3.9
Pain and discomfort NEC	27	3.1	19	2.2
Pneumothorax and pleural effusions NEC	27	3.1	31	3.5
Spinal cord and nerve root disorders NEC	27	3.1	26	3.0
Heart failures NEC	26	3.0	19	2.2
Anaemias NEC	25	2.9	49	5.6
Gastrointestinal and abdominal pains (excl oral and throat)	24	2.7	19	2.2
Nausea and vomiting symptoms	24	2.7	28	3.2
Renal failure and impairment	22	2.5	31	3.5
Pulmonary thrombotic and embolic conditions	19	2.2	18	2.1
Peripheral embolism and thrombosis	17	1.9	16	1.8
Thrombocytopenias	17	1.9	23	2.6
Ventricular arrhythmias and cardiac arrest	17	1.9	8	0.9
Calcium metabolism disorders	15	1.7	9	1.0
Diarrhoea (excl infective)	14	1.6	14	1.6

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Gastrointestinal stenosis and obstruction NEC	14	1.6	8	0.9
Bone related signs and symptoms	13	1.5	15	1.7
Coughing and associated symptoms	12	1.4	18	2.1
Infections NEC	12	1.4	14	1.6
Ischaemic coronary artery disorders	11	1.3	9	1.0
Abdominal and gastrointestinal infections	10	1.1	8	0.9
Marrow depression and hypoplastic anaemias	9	1.0	12	1.4
Non-site specific gastrointestinal haemorrhages	9	1.0	14	1.6
Oncologic complications and emergencies	9	1.0	11	1.3
Urinary tract infections	9	1.0	12	1.4
Vascular hypotensive disorders	9	1.0	7	0.8
Bronchospasm and obstruction	8	0.9	9	1.0
Central nervous system haemorrhages and cerebrovascular accidents	8	0.9	7	0.8
Conditions associated with abnormal gas exchange	8	0.9	4	0.5
Death and sudden death	8	0.9	8	0.9
General nutritional disorders NEC	8	0.9	13	1.5
Rate and rhythm disorders NEC	8	0.9	4	0.5
Supraventricular arrhythmias	8	0.9	10	1.1
Urinary abnormalities	8	0.9	4	0.5
Appetite disorders	7	0.8	7	0.8
Bone disorders NEC	7	0.8	5	0.6
Disturbances in consciousness NEC	7	0.8	14	1.6
Gastrointestinal signs and symptoms NEC	7	0.8	7	0.8
Metastases to unknown and unspecified sites	7	0.8	3	0.3
Paralysis and paresis (excl cranial nerve)	7	0.8	13	1.5
Coma states	6	0.7	7	0.8
Lower limb fractures and dislocations	6	0.7	8	0.9

HLT	Denosumab		Zoledronic Acid	
	n	%	n	%
Oedema NEC	6	0.7	9	1.0
Parenchymal lung disorders NEC	6	0.7	6	0.7
Pericardial disorders NEC	6	0.7	5	0.6
Peritoneal and retroperitoneal disorders	6	0.7	8	0.9
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	6	0.7	4	0.5

- Refer to Section 7.3.5 Submission Specific Primary Safety Concerns for further detail regarding cardiac events.

7.3.3 Dropouts and/or Discontinuations

The numbers of patients who experienced adverse events (AEs) leading to IP or study discontinuation (derived from the AE datasets) are shown below. Overall numbers were balanced between treatment groups.

Table 59 Adverse Events Leading to IP Discontinuation (per-patient incidence)

103		136		244		Overall	
Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
n=943	n=945	n=1020	n=1013	n=878	n=878	n=2841	n=2836
164	138	98	125	91	109	353	372

Table 60 Adverse Events Leading to Study Discontinuation (per-patient incidence)

103		136		244		Overall	
Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
n=943	n=945	n=1020	n=1013	n=878	n=878	n=2841	n=2836
91	76	48	71	91	109	270	280

The numbers of patients in the ASLINFO datasets who discontinued IP or study due to an adverse event (presented in the Applicant's Summary of Clinical Efficacy) are lower than the numbers in the AE datasets (presented in the Applicant's Summary of Clinical Safety and in the tables above). The AE datasets were derived from the AE pages of the CRFs and the ASLINFO datasets were derived from the End of Study/End of Treatment pages of the CRFs.

Other reasons cited (derived from the ASLINFO datasets) for investigational product discontinuation included consent withdrawn (15% in the denosumab group; 14.5% in the zoledronic acid group), subject request (6.4% in the denosumab group; 7.3% in the zoledronic acid group), other (2.5% in the denosumab group; 2.5% in the zoledronic acid group), and administrative decision (0.7% in the denosumab group; 0.7% in the zoledronic acid group).

Other reasons cited (derived from the ASLINFO datasets) for study discontinuation included consent withdrawn (13.6% in the denosumab group; 14.8% in the zoledronic acid group), subject request (4.7% in the denosumab group; 5.7% in the zoledronic acid group), other (3.3% in the denosumab group; 3.5% in the zoledronic acid group), and administrative decision (0.6% in the denosumab group; 0.7% in the zoledronic acid group). An audit of datasets, CRFs, and narratives for cases in each category showed that very few involved adverse events occurring near the date of either IP or study discontinuation.

The following table shows adverse events by MedDRA preferred term (PT) leading to IP or study discontinuation in more than 0.2% of patients in Trials 103, 136, and 244. Highlighted are imbalances between treatment groups (osteonecrosis and hypocalcemia). This reviewer recommended the inclusion of osteonecrosis and hypocalcemia in the Warnings and Precautions Section of the product labeling. Refer to Sections 7.3.5 Submission Specific Primary Safety Concerns and 9.2 Labeling Recommendations.

Table 61 Adverse Events by PT Leading to Dropout or Discontinuation (per-patient incidence; Trials 103, 136, and 244)

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Malignant neoplasm progression	42	1.5	43	1.5
Osteonecrosis	32	1.1	20	0.7
General physical health deterioration	27	1.0	29	1.0
Hypocalcaemia	20	0.7	1	0.0
Fatigue	19	0.7	15	0.5
Metastases to central nervous system	19	0.7	24	0.9

PT	Denosumab		Zoledronic Acid	
	n	%	n	%
Asthenia	18	0.6	24	0.9
Dyspnoea	17	0.6	13	0.5
Renal failure	14	0.5	13	0.5
Metastases to liver	11	0.4	12	0.4
Respiratory failure	10	0.4	6	0.2
Spinal cord compression	10	0.4	10	0.4
Anaemia	9	0.3	9	0.3
Disease progression	9	0.3	7	0.3
Hepatic failure	9	0.3	6	0.2
Blood creatinine increased	7	0.3	12	0.4
Performance status decreased	7	0.3	5	0.2
Pneumonia	7	0.3	7	0.3
Decreased appetite	6	0.2	9	0.3
Dehydration	6	0.2	8	0.3
Multi-organ failure	6	0.2	6	0.2
Renal impairment	6	0.2	9	0.3

7.3.4 Significant Adverse Events

Following is an analysis of ≥ Grade 3 adverse events and a review of Trial 103, 136, and 244 databases and a pooled analysis using Standardized MedDRA queries (SMQs).

In addition to discussion in Section 7.4.1 Common Adverse Events, CTCAE Grade 3-5 adverse events were analyzed at each level of the MedDRA hierarchy in a pooled analysis of Trials 103, 136, and 244. At the PT level, other than hypocalcemia, hypophosphatemia, and ONJ, no terms occurred at 1% or greater increased incidence in the denosumab group compared to the zoledronic acid group. At the HLT level, for terms occurring at a per-patient incidence of at least 5% in either group, none occurred at 2% or greater increased incidence with denosumab. For HLT terms occurring at a per-patient incidence under 5% in either group, none occurred at 1% or greater increased incidence with denosumab with the exception of 'Calcium metabolism disorders' and 'Phosphorus metabolism disorders'. At the HLGT level, no terms occurred at 1% or greater increased incidence with denosumab other than 'Bone, calcium, magnesium, and phosphorus metabolism disorders'. No SOC terms occurred at 2% or greater increased incidence in the denosumab group.

SMQs (Standardized MedDRA Queries)

Narrow-scope MedDRA SMQs (NSMQs) were analyzed for each of Trials 103, 136, and 244, and for the 3 trials pooled. The following table shows results with an odds ratio

greater than 1 and a p-value less than 0.05, for the pooled analysis. P-values in this section are used for ranking purposes only and are not a measure of statistical significance.

NSMQ	Denosumab		Zoledronic Acid		Odds Ratio	p-value*
	n	%	n	%		
Tumour markers	40	1.4	20	0.7	2.0	0.013
Thyroid dysfunction	26	0.9	11	0.4	2.4	0.0197
Angioedema	95	3.3	67	2.4	1.4	0.0311

*for ranking purposes only; not a measure of statistical significance.

- Tumor markers: The NSMQ term 'tumour markers' is nonspecific and includes PSA (captured separately as a trial endpoint for Trial 103; refer to Section 6 Review of Efficacy) and other laboratory markers encompassing various tumor types. Disease progression was captured as a trial endpoint in each of Trials 103, 136, and 244, with no imbalance observed between treatment groups (refer to Section 6 Review of Efficacy).

- Thyroid dysfunction: Patients identified by the NSMQ in the denosumab group included 17 patients with hypothyroidism and 9 patients with hyperthyroidism. Patients in the zoledronic acid group included 7 patients with hypothyroidism and 4 patients with hyperthyroidism. Of cases in the denosumab group, none were of CTCAE Grade 2 or greater, none were fatal, none resulted in removal of a patient from study, and one was listed as a serious event. The case listed as a serious adverse event occurred on study day 567 and resulted in IP discontinuation. Review of datasets and CRFs showed that many cases in the denosumab group involved concomitant medications known to be associated with thyroid dysfunction and many involved patients with pre-existing thyroid disease.

- Angioedema: Most cases identified by the NSMQ in the denosumab group involved Grade 1 or 2 events and common PTs included urticaria, face oedema, and swelling face. None resulted in death, discontinuation of IP, or removal from study. Most were temporally unrelated to IP administration and were listed by investigators as not related to IP. Four cases were listed as serious events, all temporally unrelated to IP administration and listed by investigators as not related to IP: Grade 1 periorbital edema, Grade 3 angioedema, Grade 2 face oedema, and Grade 3 swelling face. There was no evidence of severe angioedema temporally related to IP administration.

For Trial 103, NSMQ results with an odds ratio greater than 1 and a p-value less than 0.05 included 'Accidents and injuries', 'Tumour markers', 'GI nonspecific inflammation and dysfunctional conditions', 'Thrombocytopenia', 'GI nonspecific symptoms and therapeutic procedures', and 'Hematopoietic cytopenias'. The 'Accidents and injuries'

SMQ contains disparate terms including fractures, which were captured separately as a trial endpoint (refer to Section 6 Review of Efficacy). Tumor markers included PSA which was also captured separately as a trial endpoint (refer to Section 6 Review of Efficacy). The two GI NSMQs are nonspecific and the two more common PTs in the SMQ, diarrhea and nausea, were recommended for inclusion in the product labeling. Cytopenias were analyzed elsewhere in the safety review (see Section 7.4.1 Common Adverse Events).

There were no NSMQ results for Trial 136 with an odds ratio greater than 1 and a p-value less than 0.05.

For Trial 244, 'Angioedema' was the only NSMQ result with an odds ratio greater than 1 and a p-value less than 0.05. Angioedema was described in the pooled analysis above.

7.3.5 Submission Specific Primary Safety Concerns

Hypocalcemia

Hypocalcemia is a known class effect of antiresorptive drugs and frequently occurred with denosumab in previously reported clinical trials. Adverse events of hypocalcemia in Trials 103, 136, and 244 are presented in the analyses below and included the MedDRA preferred terms hypocalcemia, blood calcium decreased, calcium deficiency, and calcium ionized decreased.

The protocols for Trials 103, 136, and 244 recommended but did not require supplementation with calcium and vitamin D. Eighty-eight percent of patients in the denosumab group and 86% of patients in the zoledronic acid group received oral calcium at some point during the trials. Analyses of calcium and vitamin D supplementation were limited by the manner in which this data were captured in the CRFs. The CRFs did not capture whether a patient received calcium as a preventive measure or whether it was administered as treatment for hypocalcemia. In addition, for patients who received calcium, the point of initiation of calcium on study and the duration of supplementation varied.

Hypocalcemia adverse events (AEs) occurred in 273 patients (9.6%) in the denosumab group, compared to 141 patients (5.0%) in the zoledronic acid group. Hypocalcemia AEs in the denosumab group included the preferred terms hypocalcemia (9.3%) and blood calcium decreased (0.5%). Hypocalcemia AEs in the zoledronic acid group included the preferred terms hypocalcemia (4.7%), blood calcium decreased (0.2%), calcium deficiency (< 0.1%), and ionized calcium decreased (< 0.1%). A higher incidence of hypocalcemia AEs in the denosumab group occurred in Trial 103 (12.8%, 5.8%) and Trial 244 (10.8%, 5.8%) compared to Trial 136 (5.6%, 3.5%). A total of 3.6%

of patients in the denosumab group and 1.7% in the zoledronic acid group experienced hypocalcemia AEs and received IV calcium. Overall, most patients experienced hypocalcemia AEs during the first 6 months on study (see table below). Forty-one patients (1.4%) in the denosumab group and 17 patients (0.6%) in the zoledronic acid group experienced a serious AE of hypocalcemia. Most of these patients required IV calcium, and no reported SAE cases of hypocalcemia were fatal. Hypocalcemia AEs ≥ Grade 3 occurred in 3.7% of patients in the denosumab group compared to 1.7% of patients in the zoledronic acid group.

Table 62 Hypocalcemia AEs by Trial

	103 (Prostate)		136 (Breast)		244 (Other)	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=943	n=945	n=1020	n=1013	n=878	n=878
Hypocalcemia AEs	12.8%	5.8%	5.6%	3.5%	10.8%	5.8%

Table 63 Per-patient Incidence of Hypocalcemia AEs by Trial Period

Study period	Denosumab	Zoledronic Acid
	n=2841	n=2836
	%	%
First 30 days	2.6	1.3
First 6 months	6.8	3.3
Months 6 - 12	2.5	1.2
> Month 12	1.7	1.3

Table 64 Summary of Hypocalcemia AEs (per-patient incidence)

Hypocalcemia AE	Denosumab	Zoledronic Acid
	n=2841	n=2836
	%	%
All	9.6	5
≥ Gr 2	7.1	3.3
≥ Gr 3	3.7	1.7
Serious	1.4	0.6

Table 65 Hypocalcemia AEs by MedDRA Preferred Term

Preferred Term	Denosumab	Zoledronic Acid
	n=2841	n=2836
Blood calcium decreased	13 (0.5%)	6 (0.2%)
Calcium deficiency	0 (0.0%)	2 (0.1%)
Calcium ionized decreased	0 (0.0%)	1 (0.0%)
Hypocalcemia	265 (9.3%)	134 (4.7%)
Overall	273 (9.6%)	141 (5.0%)
Number of events	550	234

This reviewer performed an analysis of hypocalcemia AEs by number of days since previous dose for the patients in the denosumab group. See the tables below. The increased incidence of events on Days 1 and 29 may have been an artifact of protocol mandated testing on these days. There appears to be an increased incidence of hypocalcemia AEs occurring on Day 8 following denosumab administration compared to other days in the treatment cycle.

Figure 16 Hypocalcemia AEs (all grades) by Days Since Previous Dose

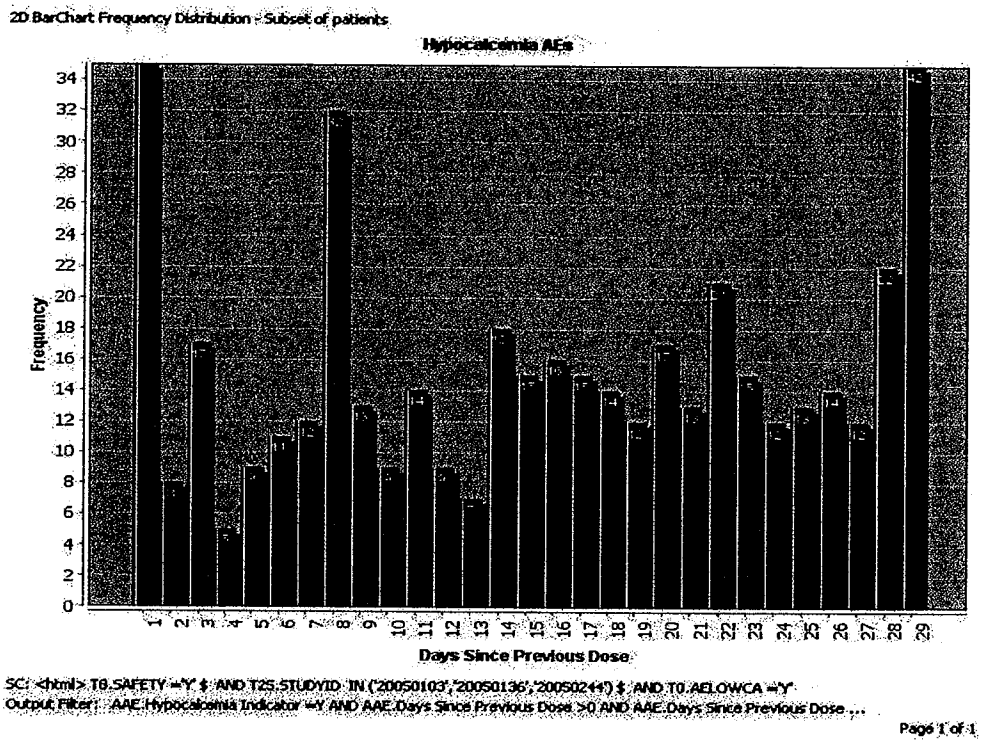
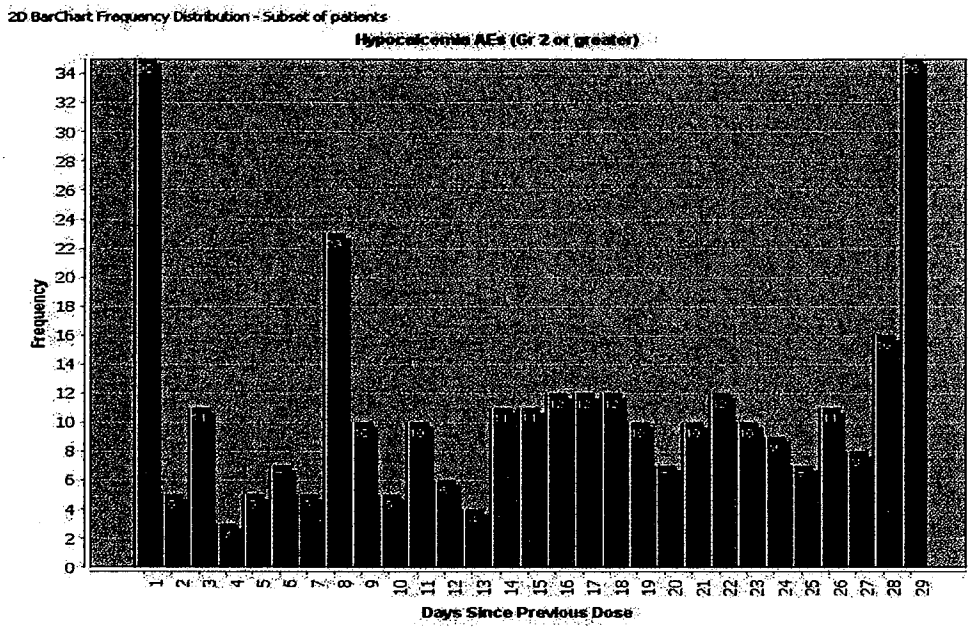


Figure 17 Hypocalcemia AEs (Grade 2 or higher) by Days Since Previous Dose



This reviewer agreed with the Applicant's inclusion of hypocalcemia in the Warnings and Precautions section of the product labeling. Refer to Section 9.2 Labeling Recommendations for further detail.

Patients with severe chronic kidney disease (CKD) and end-stage renal disease (ESRD) rely more heavily on bone resorption for maintenance of calcium homeostasis due to their impaired ability to absorb and resorb calcium through other routes. In addition, patients with severe CKD and ESRD can develop parathyroid hormone resistance, and overall can be more susceptible to hypocalcemia. Results of Trial 20040245 (refer to Section 5.3 Discussion of Individual Studies/Clinical Trials for a trial summary) showed that patients with a creatinine clearance less than 30 mL/min or receiving dialysis are at greater risk of severe hypocalcemia with denosumab compared to patients with normal renal function. In the trial, in 55 patients without cancer and with varying degrees of renal impairment who received a single dose of 60 mg denosumab, 8 of 17 patients with a creatinine clearance less than 30 mL/min or receiving dialysis experienced corrected serum calcium levels less than 8.0 mg/dL, as compared to 0 of 12 patients with normal renal function. In patients with a creatinine clearance less than 30 mL/min or receiving dialysis, the risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated. This reviewer

recommended inclusion of this information in the Warnings and Precautions section of the product labeling and recommended a postmarketing requirement for a clinical trial to estimate the incidence and severity of hypocalcemia with denosumab in this population (refer to Section 1.4 Postmarket Requirements and Commitments).

Refer to Section 7.4.2 Laboratory Findings for a discussion of serum calcium level abnormalities in Trials 103, 136, and 244.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) can occur in patients receiving bisphosphonates, primarily patients with cancer and bone metastases. In Trials 103, 136, and 244, all events reported as ONJ or corresponding to a prespecified list of MedDRA preferred terms (PTs) were reviewed by an external adjudication committee.

The Applicant's definition of ONJ (a lesion occurring in the oral cavity as an area of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found, associated with non-healing after appropriate care by a 8 weeks in a patient without prior history of radiation to the head, face, or mouth; the lesion can be asymptomatic, or oral or orofacial fistulas suspicious for underlying ONJ can be present) was accurate and consistent with current medical literature and the definitions developed by the American Dental Society and the American Society of Bone and Mineral Research. The PTs chosen by the Applicant (listed in the table below) appeared appropriate and reasonably comprehensive. The Adjudication Committee Manual of Procedures, meeting minutes, and adjudicator contact logs were reviewed. In the review of the contact logs, it was observed that one adjudicator voiced concerns that the adjudicators were being unblinded to treatment assignments of patients due to information contained in the adjudication packets, and that ONJ was being underdiagnosed because some adjudication packets contained insufficient information for adjudicators to make a diagnosis of ONJ. Despite this criticism, the conduct of the Adjudication Committee appeared appropriate. Case narratives for all positively adjudicated ONJ events were included in the sBLA and were reviewed. A listing of all adverse events sent to the Adjudication Committee was also included in the sBLA and reviewed, in addition to corresponding CRFs, narratives if available, AE dataset entries, and ONJ Final Adjudication Summary sheets. In total, 151 patients in the denosumab group and 125 patients in the zoledronic acid group experienced AEs that were sent to the Adjudication Committee for review. Ninety-nine events in the denosumab group and 88 events in the zoledronic acid group were negatively adjudicated.

Table 66 MedDRA Preferred Terms Used by the Applicant to Define Events for ONJ Adjudication Committee Review

MedDRA PT	MedDRA PT	MedDRA PT	MedDRA PT
Abscess jaw	Dental necrosis	Oral cavity fistula	Osteonecrosis
Abscess oral	Gingival abscess	Oral surgery	Pain in jaw
Alveolar osteitis	Gingival erosion	Oroantral fistula	Periodontal destruction
Bone debridement	Gingival ulceration	Ostectomy	Periodontal infection
Bone disorder	Jaw lesion excision	Osteitis	Periodontal operation
Bone erosion	Jaw operation	Osteomyelitis	Primary sequestrum
Bone fistula	Loose tooth	Osteomyelitis acute	Secondary sequestrum
Bone infarction	Maxillofacial operation	Osteomyelitis chronic	Sequestrectomy
Dental fistula	Necrosis	Osteomyelitis drainage	Tertiary sequestrum

The overall incidence of positively adjudicated ONJ in Trials 103, 136, and 244 was 1.8% (52 patients) in the denosumab group and 1.3% (37 patients) in the zoledronic acid group. Including the approximately 4-month treatment phase extension period in each trial (refer to Section 5.3 Discussion of Individual Studies/Clinical Trials), the incidence in the denosumab group was 2.2%. The overall incidence of the preferred term 'osteonecrosis' was 1.8% in the denosumab group and 1.2% in the zoledronic acid group. All cases were in the jaw, with the exception of 3 cases in the hip. All cases in the hip occurred in patients with bone metastases in the hip. Of patients with adverse events of the PT osteonecrosis, 41 patients in the denosumab group and 27 patients in the zoledronic acid group also had positively adjudicated ONJ. Other adverse event PTs positively adjudicated as ONJ were pain in jaw, osteomyelitis, jaw disorder, impaired healing, alveolar osteitis, bone erosion, tooth infection, toothache, periodontal infection, osteitis, oral disorder, gingival ulceration, gingival erosion, and bone disorder. There were no positively adjudicated ONJ events reported as fatal. The tables below summarize the positively adjudicated ONJ cases occurring in Trials 103, 136, and 244. The lower incidence of ONJ in Trial 244 compared to Trials 103 and 136 could be related to the lower exposures (number of doses of denosumab received) in Trial 244, which are consistent with the disease courses and prognoses of the underlying cancers.

Table 67 Summary of Positively Adjudicated ONJ Cases

	Denosumab	Zoledronic Acid
	n = 2841	n = 2836
Positively adjudicated	1.8%	1.3%
Fatal	0%	0%
Serious	0.8%	0.6%
Resulted in hospitalization	0.1%	0.1%
Resulted in IP discontinuation	1.2%	0.8%

Table 68 Incidence of ONJ by Trial

Trial	Denosumab	Zoledronic Acid
103 (Prostate)	22	12
136 (Breast)	20	14
244 (Other)	10	11
Total	52	37

Table 69 Time to ONJ

	Denosumab	Zoledronic Acid
ONJ events	52	37
Median time to ONJ (months)	14	14
Range	(4.4, 25.4)	(4.9, 30.0)

The Applicant states in the Summary of Clinical Safety that approximately half of patients with positively adjudicated ONJ in each treatment group underwent surgery for ONJ. Of these patients, 3 patients in the denosumab group and 1 patient in the zoledronic acid group required bone resection. Most subjects with ONJ in both treatment groups (81% in both groups) had a history ot tooth extraction, poor oral hygiene, or use of a dental appliance.

Of patients with positively adjudicated ONJ in Trials 103, 136, and 244, 23 (44%) patients in the denosumab group and 21 (57%) patients in the zoledronic acid group were over age 65 at enrollment. Twenty-four (46%) patients in the denosumab group and 17 (46%) patients in the zoledronic acid group were female.

Refer to Section 9.2 for relevant labeling recommendations.

Cardiac Events

For Trials 103, 136, and 244 pooled, the per-patient incidence rate of adverse events in the cardiac disorders SOC was 13.4% in the denosumab group and in the zoledronic acid group. The most common cardiac disorders were tachycardia (2.8% denosumab, 2.6% zoledronic acid), cardiac failure (1.7%, 1.8%), atrial fibrillation (1.5%, 1.3%), and palpitations (1.1%, 0.9%). No cardiac adverse event in the pooled analysis occurred with 0.5% or greater increased incidence in the denosumab group. By MedDRA HLT cardiac disorders were also similar between treatment groups. Serious adverse events in the cardiac disorders SOC occurred in 201 patients (7.1%) in the denosumab group and 192 patients (6.8%) in the zoledronic acid group. The most common serious cardiac events were cardiac failure (1.3% denosumab, 1.2% zoledronic acid), atrial fibrillation (0.7% in each group), cardiac arrest (0.6%, 0.4%), cardiorespiratory arrest (0.6%, 0.7%), congestive cardiac failure (0.5% in each group), and cardiopulmonary failure (0.4%, 0.7%).

A higher incidence of SAEs in the cardiac disorders SOC occurred in the denosumab group in Trial 244 (8.8% denosumab, 6.0% zoledronic acid), though the incidence was similar between treatment groups in Trials 103 and 136. The higher incidence of serious cardiac disorders in Trial 244 was driven by a higher incidence of cardiac arrest events (1.4% denosumab, 0.3% zoledronic acid). An external, blinded adjudication of the cardiac arrest events in Trial 244 showed that 10 of the 12 patients in the denosumab group and 2 of the 3 patients in the zoledronic acid group died of cancer progression, cancer-related complications, or unknown causes. Two of the patients in the denosumab group and one patient in the zoledronic acid group also experienced hypocalcemia adverse events. Relationship between the cardiac arrest events and hypocalcemia was not clear.

In pooled analysis of Trials 103, 136, and 244, fatal cardiac events occurred in 99 patients (3.5%) in the denosumab group and 96 patients (3.4%) in the zoledronic acid group. The most common fatal cardiac events were cardiac failure (1.0%, 0.8%), cardiorespiratory arrest (0.5%, 0.6%), cardiac arrest (0.5%, 0.3%), and cardiopulmonary failure (0.4%, 0.6%). The higher incidence of fatal cardiac events in the denosumab group in Trial 244 (4.7% denosumab, 2.8% zoledronic acid) was driven by the cardiac arrest events reviewed above and was not observed in Trials 103 or 136.

Injection-Related Reactions / Hypersensitivity

In clinical trials in women with osteoporosis, denosumab did not appear to be associated with injection-related reactions or hypersensitivity. For Trials 103, 136, and 244, the Applicant presented an analysis based on SMQs for angioedema, anaphylactic reactions, and severe cutaneous adverse reactions, and including the terms hypersensitivity and drug hypersensitivity. The table below lists the MedDRA preferred terms used by the Applicant to define these events. In addition, this reviewer performed analyses of AE datasets for Trials 103, 136, and 244 for other signs and symptoms of injection-related reactions (e.g., pyrexia, hypertension, hypotension, pain, and rash).

Table 70 MedDRA Preferred Terms Used by the Applicant to Define Events Potentially Associated with Hypersensitivity

MedDRA PT	MedDRA PT	MedDRA PT	MedDRA PT
Acute generalized exanthematous pustulosis	Drug hypersensitivity	Kounis syndrome	Swelling face
Allergic oedema	Epidermal necrosis	Laryngeal edema	Swollen tongue
Anaphylactic reaction	Epiglottic edema	Laryngotracheal edema	Tongue edema
Anaphylactic shock	Erythema multiforme	Lip edema	Toxic epidermal necrolysis
Anaphylactic transfusion reaction	Exfoliative rash	Lip swelling	Toxic skin eruption
Anaphylactoid reaction	Eye edema	Oculorespiratory syndrome	Tracheal edema
Anaphylactoid shock	Eye swelling	Oedema mouth	Type I hypersensitivity
Angioedema	Eyelid edema	Oropharyngeal swelling	Urticaria
Circulatory collapse	Face edema	Palatal edema	Urticaria cholinergic
Circumoral edema	First use syndrome	Periorbital edema	Urticaria chronic
Conjunctival edema	Gingival edema	Pharyngeal edema	Urticaria papular
Corneal edema	Ginigival swelling	Scleral edema	
Cutaneous vasculitis	Gleich's syndrome	Shock	
Dermatitis bullous	Hereditary angioedema	Skin necrosis	
Dermatitis exfoliative	Hypersensitivity	Small bowel angioedema	
Dermatitis exfoliative generalized	Idiopathic urticaria	Stevens-Johnson syndrome	

In Trials 103, 136, and 244, 152 patients (5.4%) in the denosumab group and 108 (3.8%) in the zoledronic acid group experienced adverse events potentially associated with hypersensitivity as defined in the table above. The most common events reported in either group were face edema (1.0% denosumab, 0.6% zoledonic acid), hypersensitivity (0.9%, 0.7%), drug hypersensitivity (0.9%, 0.4%), urticaria (0.6%, 0.5%), and face swelling (0.6%, 0.4%). Based on a review of verbatim terms, CRFs, and case narratives, events did not appear to be causally or temporally related to initiation of denosumab.

Drug hypersensivity (MedDRA preferred term) was reported for 0.9% of patients in the denosumab group and 0.4% of patients in the zoledronic acid group. All adverse event dataset entries, CRFs, and case narratives were reviewed. Most events were attributed to other medications known to be associated with hypersensitivity reactions. There was no evidence of severe drug hypersensitivity that appeared related to denosumab administration.

Serious adverse events potentially associated with hypersensitivity (as defined in the table above) occurred in 14 (0.5%) patients in the denosumab group and 8 (0.3%) patients in the zoledronic acid group. Three patients in the denosumab group and 2 patients in the zoledonic acid group had fatal events potentially associated with hypersensitivity. None were reported by investigators as related to investigational product. Of the 4 cases of circulatory collapse, 2 appeared to be related to etiologies other than denosumab administration and the remaining 2 cases were not temporally related to denosumab administration.

One patient in the denosumab group discontinued investigational product due to an event of Grade 4 anaphylactic reaction, which occurred after the patient's first dose of trastuzumab.

Overall, there was no evidence of severe injection-related reaction or hypersensitivity that appeared related to denosumab administration.

Renal Toxicity

Based on the mechanism of action and pharmacologic profile of denosumab, no adverse effects on renal function were expected. No renal effects were observed in nonclinical studies and there was no evidence of renal toxicity in the osteoporosis and hormone ablation therapy clinical development programs. However, renal toxicity can occur with zoledronic acid. In accordance with the zoledronic acid prescribing information, patients with a creatinine clearance of less than 30 mL/min were excluded from Trials 103, 136, and 244, the dose of IV investigational product was adjusted for baseline creatinine clearance, and IV doses were withheld if serum creatinine levels increased to above thresholds specified in the zoledronic acid prescribing information.

Two hundred seventy-seven (9.8%) patients in the zoledronic acid group had IV investigational product withheld due to elevations in serum creatinine, compared to 192 (6.8%) patients in the denosumab group. In the Summary of Clinical Safety, the Applicant presented a search of MedDRA preferred terms [PT (see the following table)] suggestive of renal toxicity. The incidence of adverse events potentially associated with renal toxicity as defined in the table below was 11.8% in the zoledronic acid group compared to 9.2% in the denosumab group. The most common renal adverse events were blood creatinine increased (3.7% denosumab, 4.7% zoledronic acid), renal failure (2.6%, 3.7%), acute renal failure (1.2%, 1.6%), and renal impairment (0.9%, 1.2%). The incidence of serious adverse events potentially associated with renal toxicity as defined in the table below was 2.9% in the denosumab group and 3.6% in the zoledronic acid group. Serious adverse events potentially associated with renal toxicity included renal failure (1.3%, 1.8%) and acute renal failure (1.0%, 1.3%). Fatal adverse events potentially associated with renal toxicity as defined in the table below occurred in 15 patients in the denosumab group and 16 patients in the zoledronic acid group. Adverse events potentially associated with renal toxicity led to withdrawal from investigational product for 31 patients (1.1%) in the denosumab group and 41 patients (1.4%) in the zoledronic acid group.

Table 71 MedDRA Preferred Terms Used by the Applicant to Define Events Potentially Associated with Renal Toxicity

MedDRA PT	MedDRA PT	MedDRA PT	MedDRA PT
Acute prerenal failure	Creatinine renal clearance decreased	Protein urine present	Renal tubular necrosis
Albuminuria	Dialysis	Proteinuria	Tubulointersitital nephritis
Anuria	Dialysis device complication	Pyelogram retrograde abnormal	Ultrasound kidney abnormal
Artifical kidney device user	Glomerular filtration rate abnormal	Renal amyloidosis	Urea renal clearance decreased
Azotemia	Glomerular filtration rate decreased	Renal failure	Ureteroscopy abnormal
Biopsy kidney abnormal	Hemodialysis	Renal failure acute	Urinary casts present
Blood creatinine abnormal	Hypercreatinemia	Renal failure chronic	Urinary system x-ray abnormal
Blood creatinine increased	Nephritis	Renal function test abnormal	Urine output decreased
Blood urea abnormal	Nephropathy toxic	Renal impairment	Urogram abnormal
Blood urea increased	Edema due to renal disease	Renal injury	Venogram renal abnormal
Blood urea nitrogen/creatinine ratio increased	Oliguria	Renal scan abnormal	

Complications of transplanted kidney	Peritoneal dialysis	Renal transplant	
Continuous hemodiafiltration	Postoperative renal failure	Renal tubular disorder	

Refer to Section 7.4.2 Laboratory Findings regarding serum creatinine laboratory values.

Infections

Due to the expression of RANKL on activated B and T cells in lymph nodes, the Applicant identified infections as adverse events of special interest. In addition, an analysis of skin infections was conducted due to an imbalance of serious adverse events of skin infection reported in a trial in patients with osteoporosis.

In Trials 103, 136, and 244, the pooled incidence of adverse events (AEs) in the infections and infestations system organ class (SOC)was 43% in the denosumab group and 43% in the zoledronic acid group. Additionally, the incidence of AEs was balanced between treatment groups within each trial. Common adverse events of infection occurring at 5% or greater incidence in either treatment group were urinary tract infection (7.7% denosumab, 9.2% zoledronic acid), nasopharyngitis (5.2%, 5.7%), and pneumonia (5.2%, 4.6%). The incidence of serious adverse events (SAEs) in the infections and infestations SOC was 11.6% in the denosumab group and 10.9% in the zoledronic acid group. The most common SAEs of infection by preferred term were pneumonia (3.9% denosumab, 3.3% zoledronic acid), urinary tract infection (1.5%, 1.7%), and sepsis (1.1%, 0.9%). Overall, the incidence of SAEs was balanced between treatment groups within each trial. Fatal AEs in the infections and infestations SOC were reported for 1.6% of patients in the denosumab group and 1.3% of patients in the zoledronic acid group. Pneumonia, sepsis, and septic shock were the most common fatal infections and were balanced between treatment groups. Adverse events of infection leading to withdrawal from investigational product occurred in 0.8% of patients in the denosumab group and 0.7% of patients in the zoledronic acid group. Adverse events of infection leading to withdrawal from study occurred in 0.5% of patients in the denosumab group and 0.4% of patients in the zoledronic acid group.

The pooled per patient incidence of skin infections was similar between treatment groups (3.0% denosumab, 2.7% zoledronic acid), as was the incidence of specific types of skin infections including cellulitis, erysipelas, skin infection, subcutaneous abscess, infected skin ulcer, impetigo, and necrotizing fasciitis. Additionally, incidence rates were similar between treatment groups within each trial. The per patient incidence of SAEs of skin infection was 0.9% in the denosumab group and 0.7% in the zoledronic acid group. SAEs by preferred term were cellulitis (0.6%, 0.4%), erysipelas (0.2%, <0.1%), skin infection (<0.1% in each group), subcutaneous abscess (<0.1% in each group),

infected skin ulcer (<0.1%, 0%), and necrotizing fasciitis (0%, <0.1%). Two fatal skin infections occurred, one case of cellulitis in a patient 3 weeks following the last dose of denosumab and 20 months after initiation of investigational product, and necrotizing fasciitis in a patient who received zoledronic acid, 1.5 months after IP initiation and one month after the last dose. Serious skin infections leading to IP withdrawal were cellulitis and infected skin ulcer, each occurring in one patient in the denosumab group.

Overall, there was no evidence of increased risk for infection, including serious skin infection, with denosumab compared to zoledronic acid.

Malignancies

Progression-free survival (PFS) was balanced between treatment groups in each of Trials 103, 136, and 244. Refer to Section 6 Review of Efficacy for PFS results.

This reviewer performed an analysis of new primary malignancies in Trials 103, 136, and 244 pooled, using a search strategy of malignancy preferred terms within the MedDRA neoplasm system organ class (SOC), then excluded terms for benign malignancies, recurrent malignancies, and disease progression (terms associated with the primary cancer or metastases). In total, new primary malignancies were reported for 25 (0.8%) patients in the denosumab group and 18 (0.6%) patients in the zoledronic acid group. In general, cases were single events across a range of tumor types, with no patterns observed in the types of new malignancies.

Table 72 Incidence of New Primary Malignancies (Trials 103, 136, and 244)

Preferred Term	Denosumab n=2841	Zoledronic Acid n=2836
Acute lymphocytic leukaemia	1	
Acute myeloid leukaemia		1
Bile duct cancer	1	1
Bladder cancer	2	2
Bladder transitional cell carcinoma	2	
Chronic myeloid leukaemia		1
Colon cancer	2	2
Endometrial cancer		1
Gastric cancer	3	1
Lung adenocarcinoma	1	
Lung neoplasm	1	
Lung neoplasm malignant	1	1
Lymphoma	1	

Preferred Term	Denosumab	Zoledronic Acid
	n=2841	n=2836
Malignant melanoma	1	1
Multiple myeloma	1	
Nasal sinus cancer	1	
Pancreatic carcinoma		1
Rectal cancer	3	1
Renal cell carcinoma	1	
Squamous cell carcinoma	2	4
Transitional cell carcinoma	1	
Uterine cancer		1

Acute Phase Reactions

Acute phase reactions are associated with zoledronic acid administration. The Applicant presented an analysis for Trials 103, 136, and 244 based on a search of MedDRA preferred terms suggestive of acute phase reaction, for the 3-day period following the first dose of investigational product (IP). The following table lists these preferred terms.

Table 73 MedDRA Preferred Terms Used by the Applicant to Define Events Potentially Associated with Acute Phase Reaction

MedDRA PT	MedDRA PT	MedDRA PT	MedDRA PT
Acute phase reaction	Fatigue	Influenza like illness	Myofascial pain syndrome
Arthralgia	Feeling cold	Lethargy	Non-cardiac chest pain
Asthenia	Feeling hot	Listless	Pain
Back pain	Feeling of body temperature change	Malaise	Pain in extremity
Bone pain	Flank pain	Muscle tightness	Pyrexia
Chest pain	Flushing	Musculoskeletal discomfort	Sluggishness
Chills	Headache	Musculoskeletal pain	Tenderness
Decreased activity	Hyperpyrexia	Musculoskeletal stiffness	
Decreased appetite	Hyperthermia	Myalgia	
Discomfort	Inflammatory pain	Myalgia intercostal	

The per patient incidence of adverse events potentially associated with acute phase reaction (as defined in the table above) during the first 3 days after IP initiation was higher in the zoledronic acid group (20.2%) than the denosumab group (8.7%). The imbalance was observed in each of Trials 103, 136, and 244. The most common event was pyrexia, which occurred in 7.2% of patients in the zoledronic acid group and 0.6% of patients in the denosumab group. The incidence for most individual preferred terms for acute phase reaction was higher in the zoledronic acid group compared to the denosumab group. The incidence of serious AEs potentially associated with acute phase reaction during the first 3 days after IP initiation was < 0.1% in the denosumab group and 0.6% in the zoledronic acid group.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Safety databases for Trials 103, 136, and 244 were analyzed at each level of the MedDRA hierarchy for common adverse events (AEs).

For the adverse reactions table in the product labeling, this reviewer recommended the inclusion of adverse reactions reported in at least 10% of denosumab-treated patients and occurring either with at least 1% greater incidence in the denosumab group, or with a between-group difference of less than 1% and more than 5% greater incidence in patients treated with zoledronic acid compared to placebo (per the US Prescribing Information for zoledronic acid). Adverse reactions meeting these criteria were nausea, diarrhea, fatigue/asthenia, hypocalcemia and hypophosphatemia (both laboratory-derived), headache, dyspnea, and cough.

Trials 103, 136, and 244 pooled

At the preferred term (PT) level, for AEs occurring at an incidence rate greater than 5% in the denosumab group (below), there were no AEs occurring at 1% or higher increased risk in the denosumab group compared to the zoledronic acid group with the exception of dyspnea and hypocalcemia. See the hypocalcemia subsection within Section 7.3.5 Submission Specific Primary Safety Concerns. This reviewer recommends that the adverse reactions table in the product labeling include laboratory dataset-derived incidence rates to more accurately characterize the incidence of hypocalcemia, rather than the AE rates below. Pyrexia occurred at a 6% lower incidence with denosumab than with zoledronic acid.

Table 74 AEs by PT in Trials 103, 136, and 244 (per patient incidence > 5%)

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=2841	n=2836	n=2841	n=2836
	%	%	%	%
Nausea	31	32	2	3
Anaemia	27	30	11	12
Fatigue	27	27	7	6
Back pain	25	26	5	7
Decreased appetite	23	25	3	3
Asthenia	21	22	6	6
Constipation	21	24	1	2
Dyspnoea	21	18	8	7
Diarrhoea	20	19	3	2
Arthralgia	20	22	3	3
Vomiting	20	20	3	3
Bone pain	20	23	6	6
Pain in extremity	18	19	3	4
Oedema peripheral	17	16	1	1
Cough	15	15	1	1
Pyrexia	14	20	1	1
Headache	13	13	1	1
Musculoskeletal pain	13	14	2	2
Weight decreased	12	12	1	1
Insomnia	11	11	0	0
Abdominal pain	10	10	2	2
Neutropenia	10	10	7	7
Alopecia	9	9	0	0
Hypocalcaemia	9	5	4	2
Chest pain	9	9	2	2
Dizziness	8	9	1	1
Pain	8	9	2	2
Urinary tract infection	8	9	1	2
Thrombocytopenia	8	7	4	4
Anxiety	7	6	1	0
Rash	7	7	0	0
Depression	7	6	0	1
Musculoskeletal chest pain	7	7	1	1
Dehydration	6	6	3	3
Paraesthesia	6	7	0	0
Abdominal pain upper	6	6	1	1
Leukopenia	6	6	3	3
Rib fracture	6	6	0	0
Pleural effusion	5	5	2	2

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=2841	n=2836	n=2841	n=2836
	%	%	%	%
Myalgia	5	7	0	0
Hypertension	5	5	1	1
Nasopharyngitis	5	6	0	0
Thoracic vertebral fracture	5	5	0	1
Neuropathy peripheral	5	5	0	0
Pneumonia	5	5	4	3
Stomatitis	5	4	0	0

At the high level term (HLT) level, for the adverse reactions table in the product labeling, this reviewer recommends a composite term to combine the PTs fatigue and asthenia, based on the HLT 'Asthenic conditions' consisting primarily of these 2 PTs. The HLT 'Breathing abnormalities', occurring at 2% higher incidence with denosumab than with zoledronic acid, occurred at a rate similar to that of the PT dyspnea. The incidence of the HLT 'Diarrhea (excluding infective)' was similar to that of the PT diarrhea. The incidence of the HLT 'Coughing and associated symptoms' was similar to that of the PT cough. The HLT 'GI and abdominal pains (excl. oral and throat)' consists of the disparate, nonspecific PTs abdominal pain, abdominal pain upper, and abdominal pain lower. The HLT 'Metastases to nonspecific sites' is not relevant as disease progression was a trial endpoint captured separately in the CRFs. The HLT 'Lower respiratory tract and lung infections' consists of the distinct PTs bronchitis (4.4%) and pneumonia (5.2%). The incidence of the HLT Calcium metabolism disorders is similar to that of the PT hypocalcemia.

Table 75 AEs by HLT in Trials 103, 136, and 244 (per patient incidence > 10%)

MedDRA HLT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=2841	n=2836	n=2841	n=2836
	%	%	%	%
Asthenic conditions	45	46	13	12
Musculoskeletal and connective tissue pain and discomfort	43	47	9	11
Nausea and vomiting symptoms	37	37	4	4
Anaemias NEC	27	30	11	12
Bone related signs and symptoms	23	25	6	7
Appetite disorders	23	25	3	3

MedDRA HLT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=2841	n=2836	n=2841	n=2836
	%	%	%	%
Gastrointestinal atonic and hypomotility disorders NEC	22	25	1	2
Breathing abnormalities	22	20	8	7
Joint related signs and symptoms	21	23	3	3
Diarrhoea (excl infective)	20	19	3	2
Oedema NEC	20	20	2	2
Pain and discomfort NEC	18	18	5	4
Coughing and associated symptoms	17	17	1	1
Gastrointestinal and abdominal pains (excl oral and throat)	16	15	3	3
Febrile disorders	14	20	1	1
Metastases to specified sites	14	13	8	8
Physical examination procedures	14	14	2	2
Upper respiratory tract infections	13	14	0	0
Headaches NEC	13	14	1	1
Neutropenias	11	12	8	9
Lower respiratory tract and lung infections	11	10	5	5
Calcium metabolism disorders	11	7	4	2
Bladder and urethral symptoms	11	12	2	2
General signs and symptoms NEC	10	12	6	7

At the high level group term (HLGT) level, for AEs with a per-patient incidence above 5%, there were no Grade 3 or higher AEs occurring at a 2% or greater increased incidence in the denosumab group. The HLGT GI signs and symptoms consists of disparate PTs including abdominal pain, nausea, and vomiting. The HLGT Infections consists of disparate PTs including urinary tract infection and various lower and upper respiratory tract infections, with an HLGT between-group difference in incidence of less than 1% for all grades and for Grade 3 and higher events. The HLGT Respiratory

Disorders includes disparate PTs such as cough and dyspnea, recommended for inclusion in the product labeling adverse reactions table at the PT level.

Table 76 AEs by HLGT in Trials 103, 136, and 244 (Grade 3 or higher per patient incidence > 5%)

MedDRA HLGT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=2841	n=2836	n=2841	n=2836
	%	%	%	%
General system disorders NEC	62	64	22	22
Gastrointestinal signs and symptoms	46	45	7	7
Musculoskeletal and connective tissue disorders NEC	44	48	9	12
Infections - pathogen unspecified	36	36	11	10
Respiratory disorders NEC	36	34	12	11
Anaemias nonhaemolytic and marrow depression	28	31	12	12
Bone disorders (excl congenital and fractures)	25	27	7	7
White blood cell disorders	15	15	10	10
Metastases	14	13	9	8
Electrolyte and fluid balance conditions	12	13	6	6

At the system organ class (SOC) level, there were no AEs occurring at greater than 2% increased incidence in the denosumab group for AEs of all grades or for AEs Grade 3 or higher.

Table 77 AEs by SOC in Trials 103, 136, and 244 (per patient incidence > 5%)

MedDRA SOC	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=2841	n=2836	n=2841	n=2836
	%	%	%	%
General disorders and administration site conditions	65	69	24	23
Musculoskeletal and connective tissue disorders	63	67	18	21
Gastrointestinal disorders	60	60	13	12
Infections and infestations	43	43	12	12
Nervous system disorders	43	46	12	13
Respiratory, thoracic and mediastinal disorders	42	40	16	14
Metabolism and nutrition disorders	40	40	14	13
Blood and lymphatic system disorders	37	40	21	21
Skin and subcutaneous tissue disorders	30	30	2	2
Investigations	26	29	8	7
Injury, poisoning and procedural complications	25	26	4	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	25	25	17	17
Psychiatric disorders	24	25	3	3
Vascular disorders	21	21	5	6
Renal and urinary disorders	19	22	7	7
Cardiac disorders	13	13	7	7
Eye disorders	12	11	1	1
Reproductive system and breast disorders	9	10	1	1
Hepatobiliary disorders	6	6	3	3

Trial 103

At the PT level, the incidence of hypocalcemia was higher with denosumab than in the pooled trials. There were no AEs occurring at 5% or greater increased incidence in the denosumab group with the exception of hypocalcemia. There were no AEs that occurred at a rate lower than 10% for all grades and with a rate above 5% for Grades 3 or higher.

Table 78 AEs by PT in Trial 103 (per patient incidence > 5%)

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=943	n=945	n=943	n=945
	%	%	%	%
Anaemia	36	36	18	15
Back pain	32	30	7	9
Nausea	29	26	2	3
Decreased appetite	28	29	5	4
Fatigue	27	23	7	5
Asthenia	25	25	9	8
Constipation	25	27	1	2
Bone pain	25	26	9	8
Pain in extremity	21	21	4	6
Arthralgia	21	21	3	3
Oedema peripheral	20	18	2	2
Diarrhoea	19	16	2	1
Vomiting	18	16	3	3
Weight decreased	16	14	2	1
Dyspnoea	15	12	5	4
Hypocalcaemia	12	5	5	2
Musculoskeletal pain	12	15	1	2
Urinary tract infection	11	13	2	3
Pyrexia	11	14	1	1
Cough	10	9	1	0
Pain	10	10	3	3
Insomnia	9	10	0	0
Haematuria	9	10	3	3
Urinary retention	9	8	5	3
Abdominal pain	8	7	2	2
Chest pain	8	7	2	1
Dehydration	7	6	4	3
Dysuria	7	6	0	0
Headache	7	8	1	1
Alopecia	6	7	0	0

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=943	n=945	n=943	n=945
	%	%	%	%
Muscular weakness	6	6	1	2
General physical health deterioration	6	5	4	4
Dizziness	6	7	1	1
Neutropenia	6	5	4	4
Paraesthesia	6	8	0	1
Depression	6	4	1	1
Renal failure	6	6	3	3
Thrombocytopenia	6	4	3	2
Muscle spasms	5	3	0	0
Musculoskeletal chest pain	5	6	1	0
Hypertension	5	5	1	1
Pneumonia	5	3	4	3

The per-patient incidence rate for HLTs 'Musculoskeletal and connective tissue pain and discomfort', 'anemias NEC', and 'Bladder and urethral symptoms' was 5% or higher with denosumab within Trial 103 compared to the trials pooled. In Trial 103, none of these 3 HLTs occurred at higher incidence compared to zoledronic acid. The only HLT occurring at more than 5% increased incidence with denosumab is 'Calcium metabolism disorders', with an incidence similar to that of the PT hypocalcemia. Other HLTs highlighted in the table below occurred at higher rates with denosumab than with zoledronic acid within Trial 103, though rates were similar to those with denosumab in the pooled trials.

Table 79 AEs by HLT in Trial 103 (per patient incidence > 10%)

MedDRA HLT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=943	n=945	n=943	n=945
	%	%	%	%
Asthenic conditions	50	46	16	13
Musculoskeletal and connective tissue pain and discomfort	49	50	11	15
Anaemias NEC	36	36	18	15
Nausea and vomiting symptoms	35	30	9	9
Appetite disorders	28	29	5	4
Bone related signs and symptoms	28	28	9	9

MedDRA HLT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=943	n=945	n=943	n=945
	%	%	%	%
Gastrointestinal atonic and hypomotility disorders NEC	26	27	0	0
Oedema NEC	23	22	2	3
Joint related signs and symptoms	22	22	3	3
Bladder and urethral symptoms	20	21	6	5
Diarrhoea (excl infective)	19	16	2	1
Pain and discomfort NEC	18	17	6	4
Physical examination procedures	17	15	2	2
Breathing abnormalities	17	15	6	5
Calcium metabolism disorders	13	6	5	2
Gastrointestinal and abdominal pains (excl oral and throat)	13	11	2	2
Urinary tract infections	13	15	3	3
General signs and symptoms NEC	12	12	7	7
Lower respiratory tract and lung infections	11	8	5	3
Coughing and associated symptoms	11	10	1	0
Febrile disorders	11	14	1	1
Renal failure and impairment	11	10	6	5
Metastases to specified sites	10	7	6	5

The per-patient incidence rate for the HLGT 'Bone disorders' was 8% higher in denosumab-treated patients compared to zoledronic acid in Trial 103 and included the PTs hypocalcemia (12.3%), hypophosphatemia (3%), and hypomagnesemia (1.4%). The most commonly occurring PTs in the HLGT 'General system disorders' included fatigue and asthenia. The HLGT contained other disparate PTs such as peripheral edema and pain. The HLGT 'Gastrointestinal signs and symptoms' occurred at 8% greater incidence with denosumab compared to zoledronic acid. The most commonly

occurring PTs within the HLGT were the disparate PTs nausea, vomiting, and abdominal pain. The most commonly occurring PTs within the Respiratory disorders HLGT were cough and dyspnea. The HLGT Metastases is not relevant as disease progression is a trial endpoint captured separately in the CRFs.

Table 80 AEs by HLGT in Trial 103 (Grade 3 or higher per patient incidence > 5%)

MedDRA HLGT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=943	n=945	n=943	n=945
	%	%	%	%
General system disorders NEC	65	63	26	23
Musculoskeletal and connective tissue disorders NEC	50	51	11	16
Gastrointestinal signs and symptoms	46	38	6	6
Anaemias nonhaemolytic and marrow depression	36	37	18	16
Infections - pathogen unspecified	35	34	12	10
Bone disorders (excl congenital and fractures)	30	30	10	9
Appetite and general nutritional disorders	30	31	7	6
Respiratory disorders NEC	28	25	9	7
Urinary tract signs and symptoms	27	29	8	7
Bone, calcium, magnesium and phosphorus metabolism disorders	15	7	6	2
Renal disorders (excl nephropathies)	14	14	7	7
Electrolyte and fluid balance conditions	13	12	6	5
Metastases	10	7	6	5
White blood cell disorders	10	8	6	5

The Gastrointestinal SOC includes the Gastrointestinal signs and symptoms HLGT. The Metabolism and nutrition disorders SOC includes the Bone, calcium, magnesium, and phosphorus metabolism disorders HLGT. The Respiratory, thoracic, and mediastinal SOC includes the Respiratory disorders HLGT.

Table 81 AEs by SOC in Trial 103 (per patient incidence > 5%)

MedDRA SOC	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=943	n=945	n=943	n=945
	%	%	%	%
Musculoskeletal and connective tissue disorders	70	72	23	26
General disorders and administration site conditions	69	67	28	24
Gastrointestinal disorders	61	55	13	11
Metabolism and nutrition disorders	46	42	18	13
Infections and infestations	43	40	14	12
Blood and lymphatic system disorders	42	41	24	21
Nervous system disorders	39	40	14	14
Renal and urinary disorders	36	37	15	13
Respiratory, thoracic and mediastinal disorders	34	29	12	10
Investigations	32	31	11	7
Injury, poisoning and procedural complications	26	21	4	4
Psychiatric disorders	22	22	3	3
Skin and subcutaneous tissue disorders	22	21	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22	21	13	13
Vascular disorders	19	20	5	5
Cardiac disorders	16	17	9	10
Reproductive system and breast disorders	12	12	2	2
Eye disorders	11	9	1	1

Trial 136

At the PT level there were no AEs occurring with a between-group difference greater than 5%, with the exception of pyrexia and bone pain which occurred at higher incidence in the zoledronic acid group. For AEs occurring at a per-patient incidence rate of less than 10%, there were no AEs occurring at a 3% or greater increased incidence in the denosumab group.

Table 82 AEs by PT in Trial 136 (per patient incidence > 5%)

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=1020	n=1013	n=1020	n=1013
	%	%	%	%
Nausea	35	38	2	3
Fatigue	30	32	6	6
Arthralgia	25	29	3	3
Back pain	24	26	4	4
Diarrhoea	23	20	3	2
Dyspnoea	22	19	8	6
Vomiting	21	23	3	3
Pain in extremity	20	22	2	2
Headache	19	21	2	2
Asthenia	19	20	4	4
Anaemia	19	23	7	7
Bone pain	18	24	3	4
Anorexia	18	18	2	1
Constipation	17	20	1	1
Oedema peripheral	17	15	1	1
Cough	17	18	0	0
Pyrexia	17	24	1	1
Alopecia	16	14	0	0
Musculoskeletal pain	15	15	1	1
Neutropenia	12	12	9	9
Insomnia	12	13	0	0
Abdominal pain	12	12	3	2
Dizziness	10	11	1	1
Rash	10	10	0	0
Chest pain	9	8	1	1
Palmar-plantar erythrodysaesthesia syndrome	9	9	1	1
Stomatitis	9	7	0	0
Nasopharyngitis	8	9	0	0
Rib fracture	8	9	0	0

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=1020	n=1013	n=1020	n=1013
	%	%	%	%
Musculoskeletal chest pain	8	8	1	1
Myalgia	8	10	1	0
Leukopenia	8	8	5	5
Weight decreased	8	9	1	1
Anxiety	7	7	0	0
Depression	7	8	0	0
Pain	7	10	1	2
Urinary tract infection	7	9	1	1
Abdominal pain upper	7	8	1	1
Neuropathy peripheral	7	7	0	0
Mucosal inflammation	7	6	0	0
Paraesthesia	7	7	0	0
Hypertension	7	6	1	1
Thrombocytopenia	7	6	3	4
Hot flush	7	7	0	0
Neck pain	6	7	1	0
Pleural effusion	6	6	3	2
Thoracic vertebral fracture	6	8	0	1
Metastases to central nervous system	6	6	4	4
Pruritus	6	7	0	0
Influenza	6	5	0	0
Toothache	6	4	0	0
Hypocalcaemia	5	3	2	1
Upper respiratory tract infection	5	6	0	0
Dyspepsia	5	7	0	0

At the HLT level, there were no AEs occurring at a 5% or higher increased incidence rate in the denosumab group.

Table 83 AEs by HLT in Trial 136 (per patient incidence > 10%)

MedDRA HLT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=1020	n=1013	n=1020	n=1013
	%	%	%	%
Asthenic conditions	45	49	10	10
Musculoskeletal and connective tissue pain and discomfort	45	49	7	7
Nausea and vomiting symptoms	40	43	3	4
Joint related signs and symptoms	26	29	3	3
Breathing abnormalities	23	21	9	6
Diarrhoea (excl infective)	23	20	3	2
Bone related signs and symptoms	23	27	3	5
Oedema NEC	20	19	1	1
Headaches NEC	20	21	2	2
Appetite disorders	19	19	2	2
Anaemias NEC	19	23	7	7
Gastrointestinal atonic and hypomotility disorders NEC	19	22	1	1
Gastrointestinal and abdominal pains (excl oral and throat)	18	19	3	3
Upper respiratory tract infections	18	21	0	0
Pain and discomfort NEC	18	18	3	3
Coughing and associated symptoms	17	18	0	1
Febrile disorders	17	24	1	1
Alopecias	16	14	0	0
Metastases to specified sites	15	16	9	10
Neutropenias	13	14	10	11
Peripheral neuropathies NEC	12	12	1	1
Neurological signs and symptoms NEC	11	12	1	1
Sensory abnormalities NEC	11	10	0	1

MedDRA HLT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=1020	n=1013	n=1020	n=1013
	%	%	%	%
Physical examination procedures	11	13	1	1
Stomatitis and ulceration	10	8	0	0

At the HLGT level, there were no AEs occurring at higher incidence rate in the denosumab group compared to zoledronic acid.

Table 84 AEs by HLGT in Trial 136 (Grade 3 or higher per patient incidence > 5%)

MedDRA HLGT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=1020	n=1013	n=1020	n=1013
	%	%	%	%
General system disorders NEC	63	66	16	17
Gastrointestinal signs and symptoms	48	53	6	7
Musculoskeletal and connective tissue disorders NEC	47	50	7	7
Infections - pathogen unspecified	38	41	6	8
Respiratory disorders NEC	36	37	11	8
Anaemias nonhaemolytic and marrow depression	19	23	7	7
White blood cell disorders	17	17	11	13
Metastases	16	17	10	10

At the SOC level, there were no AEs occurring at a greater than 2% increased incidence rate in the denosumab group compared to zoledronic acid.

Table 85 AEs by SOC in Trial 136 (per patient incidence > 5%)

MedDRA SOC	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=1020	n=1013	n=1020	n=1013
	%	%	%	%
General disorders and administration site conditions	67	72	17	18
Musculoskeletal and connective tissue disorders	65	70	13	15
Gastrointestinal disorders	62	65	12	10
Nervous system disorders	50	52	10	11
Infections and infestations	46	49	8	10
Respiratory, thoracic and mediastinal disorders	42	43	13	11
Skin and subcutaneous tissue disorders	41	40	4	3
Metabolism and nutrition disorders	34	35	8	10
Blood and lymphatic system disorders	31	35	17	19
Injury, poisoning and procedural complications	30	32	4	4
Psychiatric disorders	25	27	2	2
Vascular disorders	24	26	4	5
Investigations	23	29	6	8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23	24	13	15
Eye disorders	15	15	1	1
Hepatobiliary disorders	10	8	5	4
Cardiac disorders	10	11	4	4
Reproductive system and breast disorders	10	11	1	1
Renal and urinary disorders	8	11	1	2
Ear and labyrinth disorders	6	7	1	0

Trial 244

At the PT level, there were no AEs occurring at a more than 5% greater incidence rate in the denosumab group, with the exception of hypocalcemia.

Table 86 AEs by PT in Trial 244 (per patient incidence > 5%)

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=878	n=878	n=878	n=878
	%	%	%	%
Nausea	28	30	3	2
Anaemia	28	33	10	13
Dyspnoea	25	23	10	11
Fatigue	24	25	7	8
Constipation	22	24	1	3
Vomiting	21	21	3	3
Back pain	20	22	5	7
Cough	20	18	1	1
Asthenia	20	21	6	7
Diarrhoea	19	19	3	2
Anorexia	19	22	3	4
Bone pain	16	18	6	7
Pyrexia	16	21	1	1
Arthralgia	14	16	2	4
Pain in extremity	14	15	3	3
Malignant neoplasm progression	14	14	13	12
Oedema peripheral	12	16	1	1
Headache	12	11	1	1
Weight decreased	11	12	1	2
Neutropenia	11	12	8	8
Chest pain	11	11	4	3
Musculoskeletal pain	11	11	2	3
Abdominal pain	11	11	3	3
Thrombocytopenia	11	12	6	6
Hypocalcaemia	11	6	4	2
Insomnia	10	11	1	0
Anxiety	9	7	1	0
Dizziness	8	9	1	1
Dehydration	8	8	4	3
Pneumonia	8	6	6	5
Rash	8	9	0	1
Depression	7	6	0	1

MedDRA PT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=878	n=878	n=878	n=878
	%	%	%	%
Metastases to central nervous system	7	6	5	5
Pain	6	6	2	1
Hypokalaemia	6	7	3	3
Musculoskeletal chest pain	6	6	1	1
Pleural effusion	6	6	2	3
Abdominal pain upper	6	4	1	1
Leukopenia	6	8	3	4
Respiratory failure	6	5	5	5
Alopecia	5	7	0	1
Hypotension	5	4	1	1
Neuropathy peripheral	5	5	0	0
Paraesthesia	5	7	1	0
General physical health deterioration	5	6	5	5

At the HLT level, there were no AEs occurring at a more than 1% higher incidence rate in the denosumab group with the exception of the HLT 'Calcium metabolism disorders' and the HLT 'Breathing abnormalities'. The HLT 'Calcium metabolism disorders' occurred at a rate in the denosumab group similar to that of the PT 'hypocalcemia'. The HLT 'Breathing abnormalities' occurred at rate in the denosumab group similar to that of the PT 'dyspnea'.

Table 87 AEs by HLT in Trial 244 (per patient incidence > 10%)

MedDRA HLT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=878	n=878	n=878	n=878
	%	%	%	%
Asthenic conditions	40	42	13	14
Musculoskeletal and connective tissue pain and discomfort	35	41	11	12
Nausea and vomiting symptoms	35	37	4	4
Anaemias NEC	28	33	10	13
Breathing abnormalities	27	24	11	11

MedDRA HLT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=878	n=878	n=878	n=878
	%	%	%	%
Coughing and associated symptoms	23	22	2	2
Gastrointestinal atonic and hypomotility disorders NEC	23	25	2	3
Appetite disorders	23	26	4	4
Bone related signs and symptoms	19	20	7	7
Diarrhoea (excl infective)	19	20	3	2
Pain and discomfort NEC	18	17	6	5
Gastrointestinal and abdominal pains (excl oral and throat)	16	15	4	4
Metastases to specified sites	16	14	10	9
Febrile disorders	16	21	2	1
Joint related signs and symptoms	15	17	2	4
Oedema NEC	15	19	2	2
Neoplasms malignant site unspecified NEC	14	14	13	13
Lower respiratory tract and lung infections	14	14	8	8
Neutropenias	13	15	10	10
Physical examination procedures	13	13	1	2
Calcium metabolism disorders	12	7	5	2
Headaches NEC	12	11	1	1
Thrombocytopenias	11	12	6	6
Upper respiratory tract infections	11	10	1	1
General signs and symptoms NEC	10	12	8	9
Respiratory failures (excl neonatal)	6	5	6	5

At the HLGT level, there were no AEs occurring at greater than 1% increased incidence in the denosumab group with the exception of 'Respiratory disorders NEC', 'Bone, calcium, magnesium, and phosphorus metabolism disorders', and 'Metastases'. The

HLGT 'Respiratory disorders NEC' includes the HLT 'Breathing abnormalities'. The most common PTs in the HLGT were dyspnea (25%) and cough (19.7%). The most commonly occurring PT within the HLGT 'Bone, calcium, magnesium, and phosphorus metabolism disorders' was hypocalcemia.

Table 88 AEs by HLGT in Trial 244 (Grade 3 or higher per patient incidence > 5%)

MedDRA HLGT	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=878	n=878	n=878	n=878
	%	%	%	%
General system disorders NEC	56	62	24	26
Respiratory disorders NEC	44	41	18	17
Gastrointestinal signs and symptoms	44	45	9	8
Musculoskeletal and connective tissue disorders NEC	36	42	11	12
Infections - pathogen unspecified	34	33	15	14
Anaemias nonhaemolytic and marrow depression	29	33	11	14
Neurological disorders NEC	25	27	6	5
Bone disorders (excl congenital and fractures)	21	21	7	7
White blood cell disorders	17	21	12	12
Metastases	17	14	11	10
Electrolyte and fluid balance conditions	15	18	8	7
Bone, calcium, magnesium and phosphorus metabolism disorders	14	9	6	3
Miscellaneous and site unspecified neoplasms malignant and unspecified	14	14	13	13
Platelet disorders	11	12	6	6

At the SOC level, there were no AEs occurring at a 2% or greater increased incidence in the denosumab group.

Table 89 AEs by SOC in Trial 244 (per patient incidence > 5%)

MedDRA SOC	All Grades		≥ Grade 3	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
	n=878	n=878	n=878	n=878
	%	%	%	%
General disorders and administration site conditions	61	68	27	27
Gastrointestinal disorders	57	60	15	15
Musculoskeletal and connective tissue disorders	54	60	19	21
Respiratory, thoracic and mediastinal disorders	49	47	22	22
Metabolism and nutrition disorders	41	43	17	15
Infections and infestations	41	40	16	16
Nervous system disorders	41	45	12	14
Blood and lymphatic system disorders	39	45	21	25
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	32	30	24	23
Skin and subcutaneous tissue disorders	26	27	2	3
Psychiatric disorders	24	26	4	4
Investigations	23	26	5	6
Injury, poisoning and procedural complications	20	24	4	5
Vascular disorders	18	18	6	7
Cardiac disorders	15	13	9	7
Renal and urinary disorders	13	17	5	7
Eye disorders	9	8	1	1

7.4.2 Laboratory Findings

Serum chemistry and hematology parameters were measured once every 4 weeks and at the end of study visit. The X-axis tickmarks in the graphs below represent consecutive visits at which these parameters were measured [i.e. Week 4, Week 9, etc

(refer to the Schedule of Assessments in Section 5.3)]. Fewer patients were evaluated at later time points. Shift tables below show per-patient incidence rates of worsening laboratory values during the trials.

Hypocalcemia and hypophosphatemia (all grades) occurred at higher rates in the denosumab group compared to the zoledronic acid group. Differences in mean calcium and phosphorus values between the denosumab and zoledronic acid groups persisted over time. Severe (CTCAE Grade 3 or 4) hypocalcemia and hypophosphatemia also occurred at higher rates in the denosumab group compared to the zoledronic acid group (refer to the hypocalcemia subsection of Section 7.3.5 Submission Specific Primary Safety Concerns for further detail). This reviewer recommended that laboratory-derived incidence rates for both hypocalcemia and hypophosphatemia be included in the adverse reactions table in the product labeling. This reviewer further recommended that rates of severe calcium and phosphorus laboratory abnormalities be described in a 'Severe Mineral/Electrolyte Abnormalities' subsection of the Adverse Reactions Section of the product labeling.

A difference between treatment groups was observed for alkaline phosphatase, with lower mean values in the denosumab group compared to the zoledronic acid group that persisted over time. Elevations in creatinine levels occurred more frequently with zoledronic acid than with denosumab.

Though hepatotoxicity was not expected with denosumab, a review was conducted and no cases of Hy's Law were found in the datasets. Elevated ALT above 10x ULN occurred in 23 patients in the denosumab group and in 16 patients in the zoledronic acid group. Elevated ALT above 20x ULN occurred in 2 patients in the denosumab group and 1 patient in the zoledronic acid group. Elevated AST above 10x ULN occurred in 25 patients in the denosumab group and in 22 patients in the zoledronic acid group. Elevated AST above 20x ULN occurred in 6 patients in the denosumab group and 5 patients in the zoledronic acid group.

Calcium

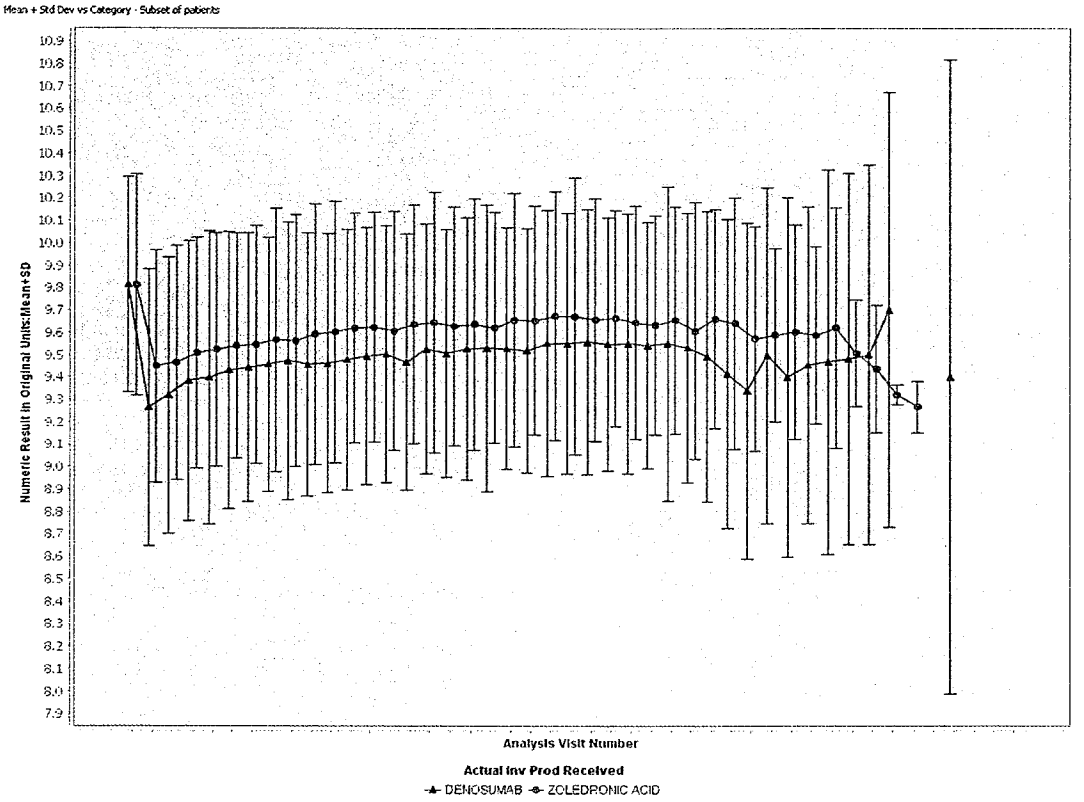
Table 90 Shift Table for Corrected Calcium (Decrease)

Baseline CTCAE Grade	Maximum Grade for Hypocalcemia				
	0	1	2	3	4
	Denosumab				
0	2214 (78%)	152 (5%)	264 (9%)	71 (2%)	16 (1%)
1	3 (0%)	0 (0%)	1 (0%)	1 (0%)	0 (0%)
	Zoledronic Acid				
0	2461 (87%)	108 (4%)	111 (4%)	33 (1%)	5 (0%)
1	3 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 91 Shift Table for Corrected Calcium (Increase)

Baseline CTCAE Grade	Maximum Grade for Hypercalcemia				
	0	1	2	3	4
	Denosumab				
0	2398 (84%)	188 (7%)	11 (0%)	4 (0%)	6 (0%)
1	67 (2%)	38 (1%)	6 (0%)	3 (0%)	0 (0%)
2	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid				
0	2339 (82%)	234 (8%)	18 (1%)	11 (0%)	12 (0%)
1	63 (2%)	30 (1%)	5 (0%)	2 (0%)	2 (0%)
2	2 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)
3	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)

Figure 18 Mean Calcium (corrected) by Visit Number

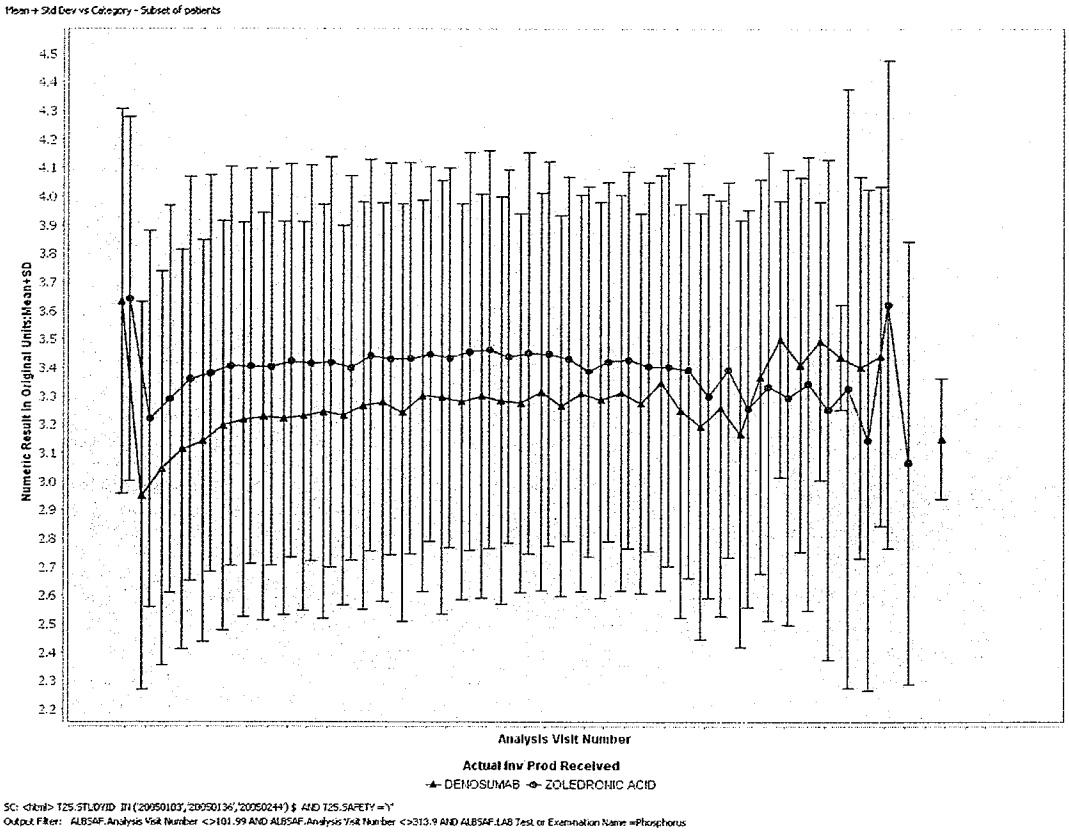


Phosphorus

Table 92 Shift Table for Phosphorus

Baseline CTCAE Grade	Maximum Grade for Hypophosphatemia				
	0	1	2	3	4
	Denosumab				
0	1803 (63%)	6 (0%)	455 (16%)	403 (14%)	16 (1%)
2	6 (0%)	0 (0%)	9 (0%)	10 (0%)	1 (0%)
3	5 (0%)	0 (0%)	2 (0%)	4 (0%)	1 (0%)
	Zoledronic Acid				
0	2155 (76%)	6 (0%)	333 (12%)	184 (6%)	3 (0%)
2	6 (0%)	0 (0%)	4 (0%)	13 (0%)	0 (0%)
3	3 (0%)	0 (0%)	2 (0%)	7 (0%)	1 (0%)

Figure 19 Mean Phosphorus by Visit Number



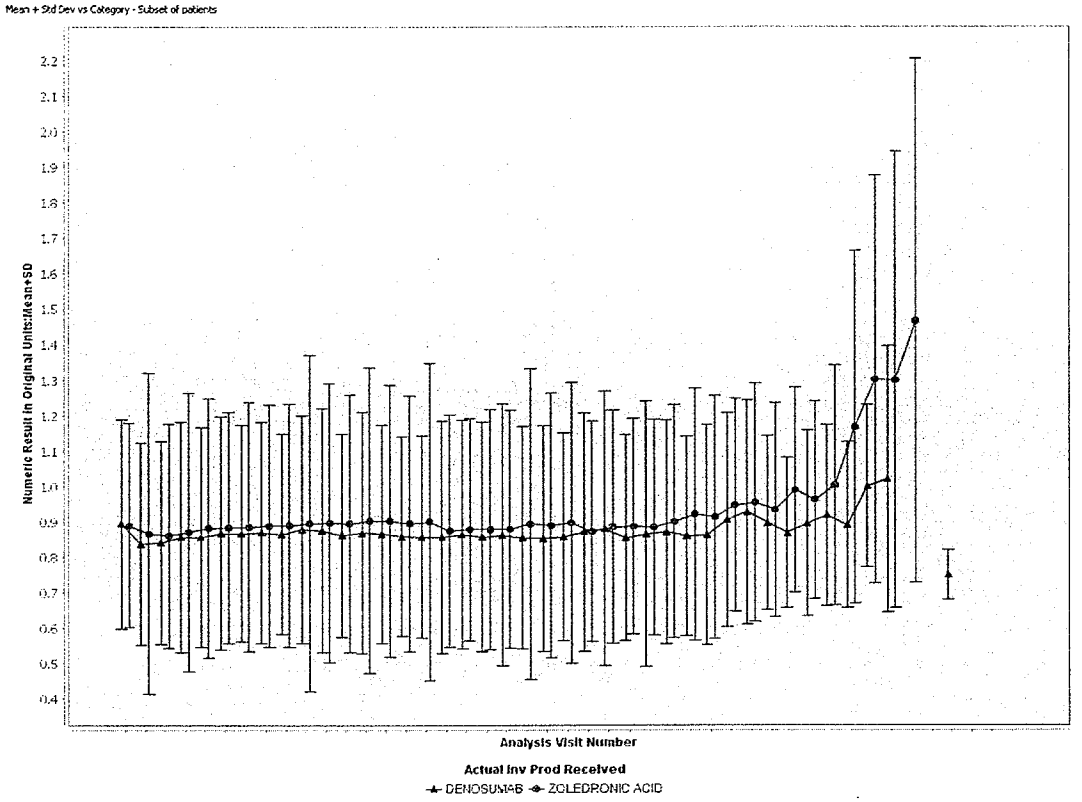
Creatinine

Table 93 Shift Table for Creatinine

Baseline CTCAE Grade	Maximum Grade for Increased Creatinine				
	0	1	2	3	4
	Denosumab				
0	2201 (77%)	288 (10%)	45 (2%)	18 (1%)	0 (0%)
1	38 (1%)	88 (3%)	28 (1%)	1 (0%)	0 (0%)
2	2 (0%)	5 (0%)	9 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid				
0	2093 (74%)	370 (13%)	77 (3%)	12 (0%)	8 (0%)
1	28 (1%)	61 (2%)	46 (2%)	5 (0%)	0 (0%)

2	1 (0%)	2 (0%)	7 (0%)	3 (0%)	1 (0%)

Figure 20 Mean Creatinine by Visit Number



SC: <html> T25.STLDYID IN ('20050103','20050136','20050244') $ AND T25.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name =Creatinine

Page 1 of 1

AST

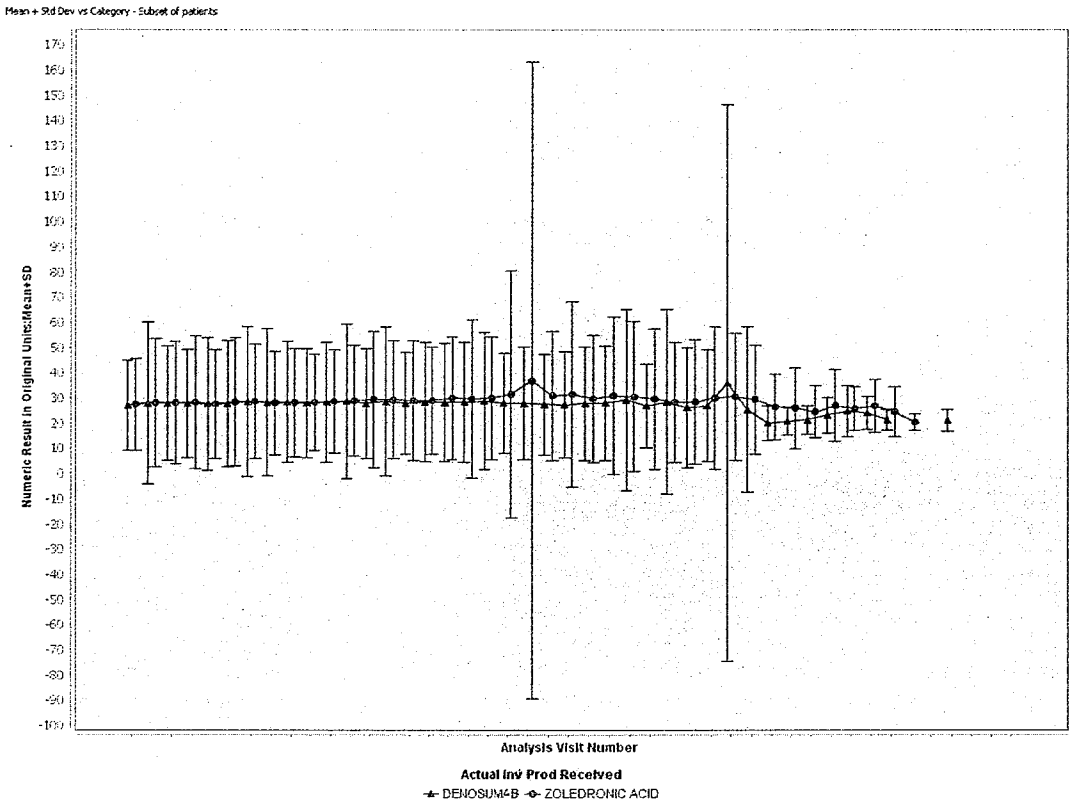
Table 94 Shift Table for AST

Baseline CTCAE Grade	Maximum Grade for Increased AST				
	0	1	2	3	4
	Denosumab				
0	1259 (44%)	823 (29%)	153 (5%)	73 (3%)	2 (0%)
1	55 (2%)	190 (7%)	77 (3%)	30 (1%)	1 (0%)
2	2 (0%)	7 (0%)	19 (1%)	6 (0%)	3 (0%)
3	0 (0%)	1 (0%)	1 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid				
0	1217 (43%)	834 (29%)	185 (7%)	57 (2%)	3 (0%)
1	68 (2%)	179 (6%)	84 (3%)	39 (1%)	2 (0%)
2	4 (0%)	6 (0%)	11 (0%)	8 (0%)	0 (0%)
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Formatted Table

Formatted Table

Figure 21 Mean AST by Visit Number



SC: <html> T25.STUDYID IN ('20050103','20050136','20050244') $ AND T25.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name ='Aspartate Amino Transferase

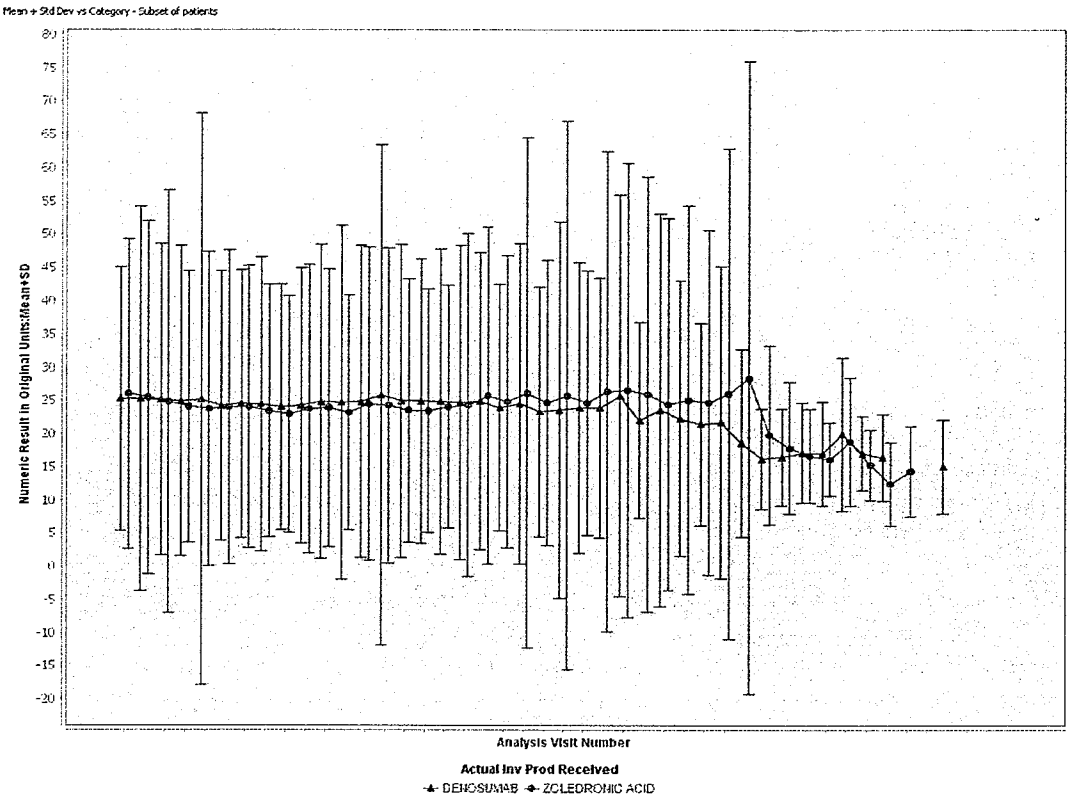
Page 1 of 1

ALT

Table 95 Shift Table for ALT

Baseline CTCAE Grade	Maximum Grade for Increased ALT				
	0	1	2	3	4
	Denosumab				
0	1378 (49%)	709 (25%)	175 (6%)	56 (2%)	2 (0%)
1	79 (3%)	193 (7%)	62 (2%)	19 (1%)	0 (0%)
2	4 (0%)	20 (1%)	19 (1%)	7 (0%)	0 (0%)
	Zoledronic Acid				
0	1411 (50%)	705 (25%)	154 (5%)	43 (2%)	1 (0%)
1	81 (3%)	157 (6%)	81 (3%)	24 (1%)	0 (0%)
2	11 (0%)	26 (1%)	14 (0%)	11 (0%)	0 (0%)

Figure 22 Mean ALT by Visit Number



SC: <html> T25.STUDYID IN ('20050103','20050136','20050244') $ AND T25.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name =Alanine Amino Transferase

Page 1 of 1

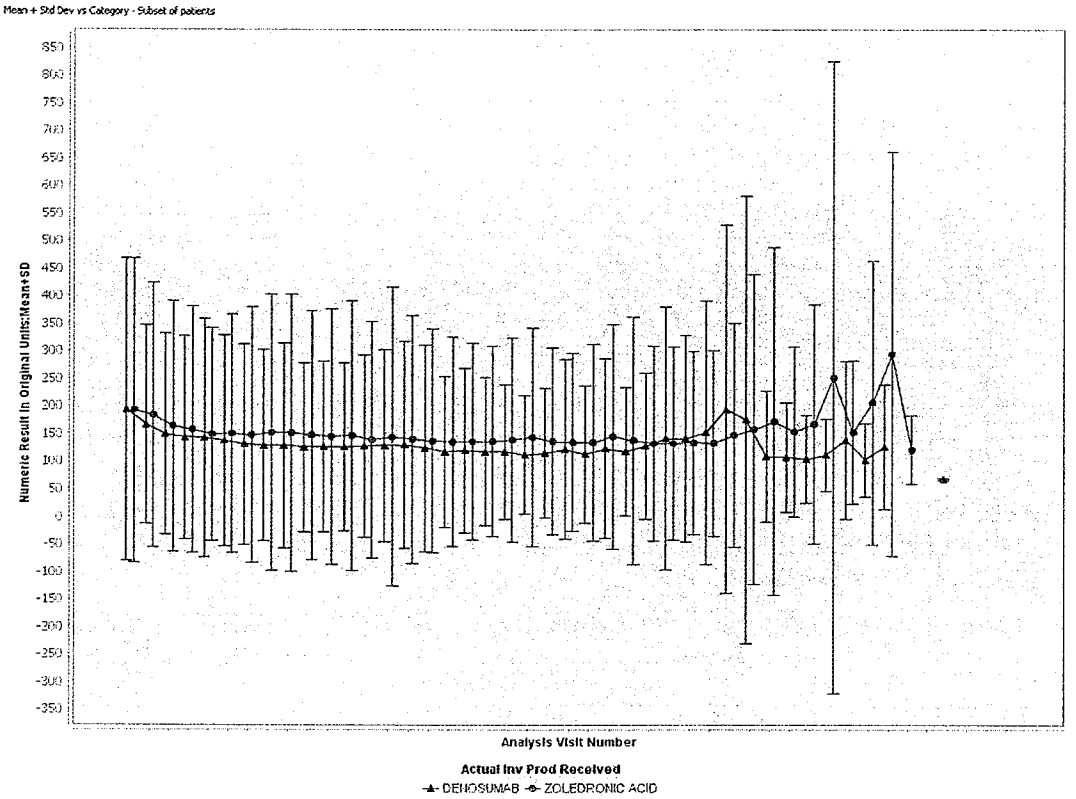
Alkaline Phosphatase

Table 96 Shift Table for Alkaline Phosphatase

Baseline CTCAE Grade	Maximum Grade for Increased Alkaline Phosphatase				
	0	1	2	3	4
	Denosumab				
0	983 (35%)	441 (16%)	105 (4%)	43 (2%)	2 (0%)
1	108 (4%)	467 (16%)	185 (7%)	83 (3%)	5 (0%)
2	3 (0%)	60 (2%)	82 (3%)	61 (2%)	1 (0%)
3	0 (0%)	1 (0%)	27 (1%)	62 (2%)	2 (0%)
4	0 (0%)	0 (0%)	0 (0%)	6 (0%)	0 (0%)
	Zoledronic Acid				

0	985 (35%)	420 (15%)	123 (4%)	63 (2%)	0 (0%)
1	84 (3%)	434 (15%)	221 (8%)	113 (4%)	5 (0%)
2	3 (0%)	21 (1%)	86 (3%)	63 (2%)	2 (0%)
3	0 (0%)	2 (0%)	17 (1%)	69 (2%)	6 (0%)
4	0 (0%)	0 (0%)	0 (0%)	5 (0%)	2 (0%)

Figure 23 Mean Alkaline Phosphatase by Visit Number



SC: <html> T2S.STUDYID IN ('20050103','20050136','20050244') $ AND T2S.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>312.9 AND ALBSAF.LAB Test or Examination Name =Alkaline Phosphatase

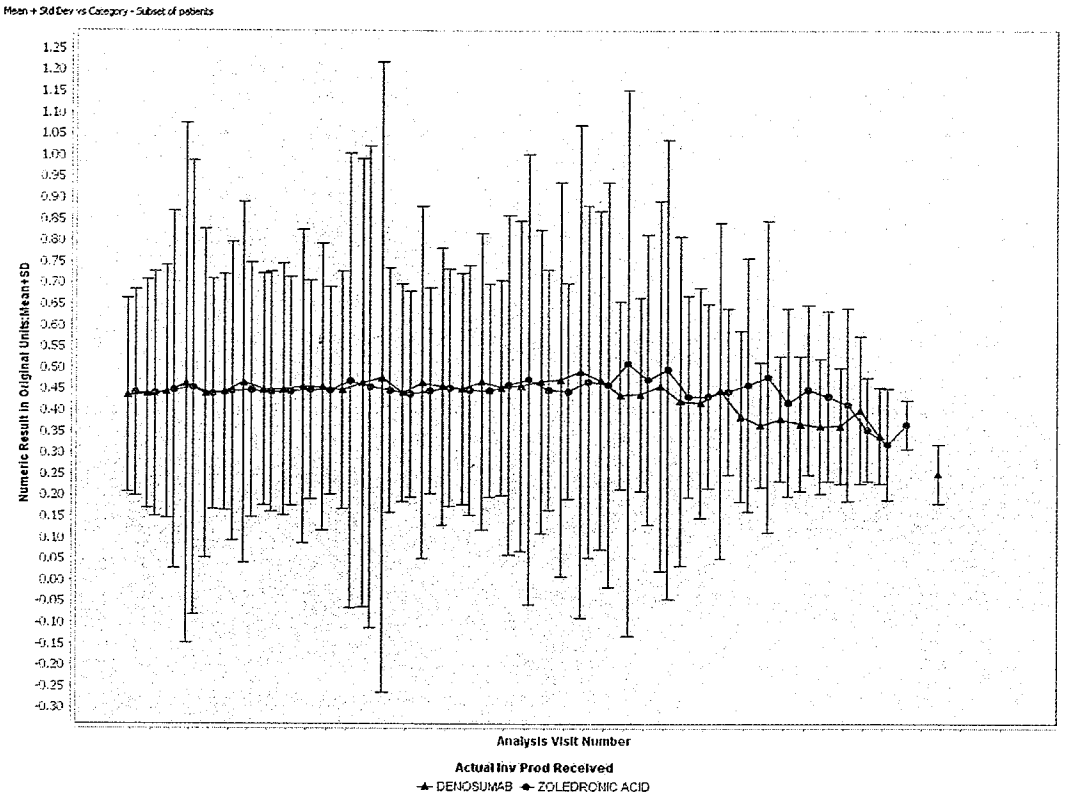
Page 1 of 1

Bilirubin

Table 97 Shift Table for Total Bilirubin

Baseline CTCAE Grade	Maximum Grade for Hyperbilirubinemia				
	0	1	2	3	4
	Denosumab				
0	2450 (86%)	138 (5%)	74 (3%)	29 (1%)	4 (0%)
1	14 (0%)	8 (0%)	5 (0%)	1 (0%)	0 (0%)
2	1 (0%)	2 (0%)	0 (0%)	0 (0%)	1 (0%)
	Zoledronic Acid				
0	2487 (88%)	106 (4%)	64 (2%)	28 (1%)	4 (0%)
1	12 (0%)	7 (0%)	8 (0%)	1 (0%)	0 (0%)
2	1 (0%)	0 (0%)	2 (0%)	1 (0%)	0 (0%)

Figure 24 Mean Total Bilirubin by Visit Number



SC: <html> TZS.STUDYID IN ('20050103','20050136','20050244') $ AND TZS.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name ='Total Bilirubin

Page 1 of 1

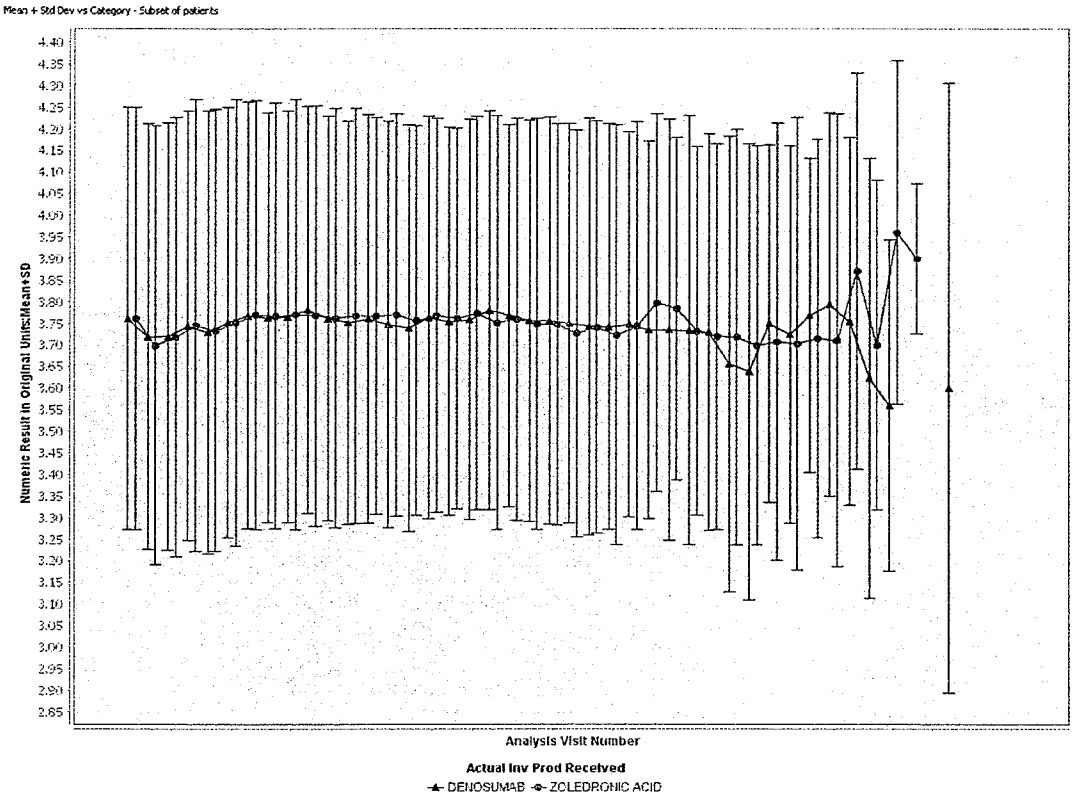
Albumin

Table 98 Shift Table for Albumin

Baseline CTCAE Grade	Maximum Grade for Hypoalbuminemia			
	0	1	2	3
	Denosumab			
0	1271 (45%)	438 (15%)	644 (23%)	43 (2%)
1	22 (1%)	38 (1%)	111 (4%)	10 (0%)
2	13 (0%)	24 (1%)	87 (3%)	21 (1%)
3	0 (0%)	0 (0%)	1 (0%)	3 (0%)
	Zoledronic Acid			
0	1256 (44%)	440 (16%)	629 (22%)	44 (2%)
1	33 (1%)	51 (2%)	108 (4%)	9 (0%)

2	24 (1%)	18 (1%)	85 (3%)	22 (1%)
3	0 (0%)	0 (0%)	1 (0%)	1 (0%)

Figure 25 Mean Albumin by Visit Number



SC: <html> T2S.STUDYID IN ('20050103','20050136','20050244') $ AND T2S.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name =Albumin

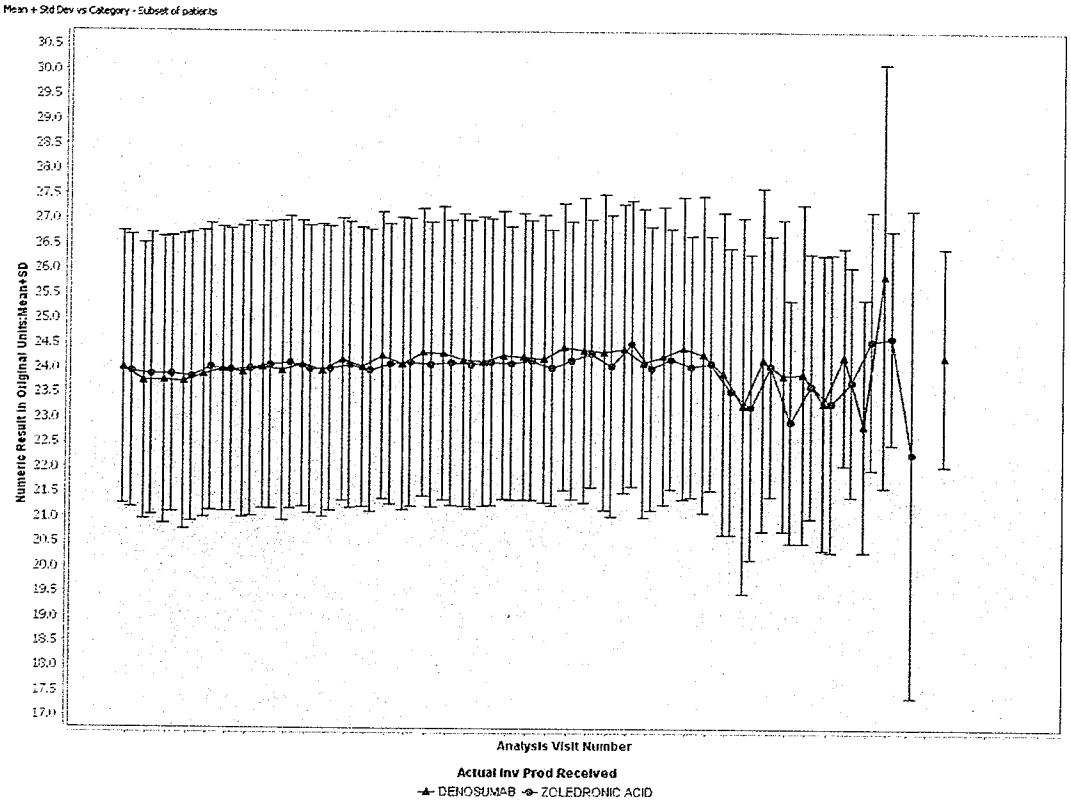
Page 1 of 1

Bicarbonate

Table 99 Shift Table for Bicarbonate

Baseline CTCAE Grade	Maximum Grade for Decreased Bicarbonate				
	0	1	2	3	4
	Denosumab				
0	2314 (81%)	155 (5%)	151 (5%)	4 (0%)	7 (0%)
1	11 (0%)	5 (0%)	2 (0%)	0 (0%)	0 (0%)
2	6 (0%)	0 (0%)	1 (0%)	1 (0%)	0 (0%)
	Zoledronic Acid				
0	2310 (81%)	168 (6%)	142 (5%)	4 (0%)	1 (0%)
1	10 (0%)	4 (0%)	4 (0%)	0 (0%)	0 (0%)
2	3 (0%)	0 (0%)	5 (0%)	0 (0%)	0 (0%)

Figure 26 Mean Bicarbonate by Visit Number



SC: <html> T2S.STUDYID IN ('20050103','20050136','20050244') $ AND T2S.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name =Bicarbonate

Page 1 of 1

Glucose

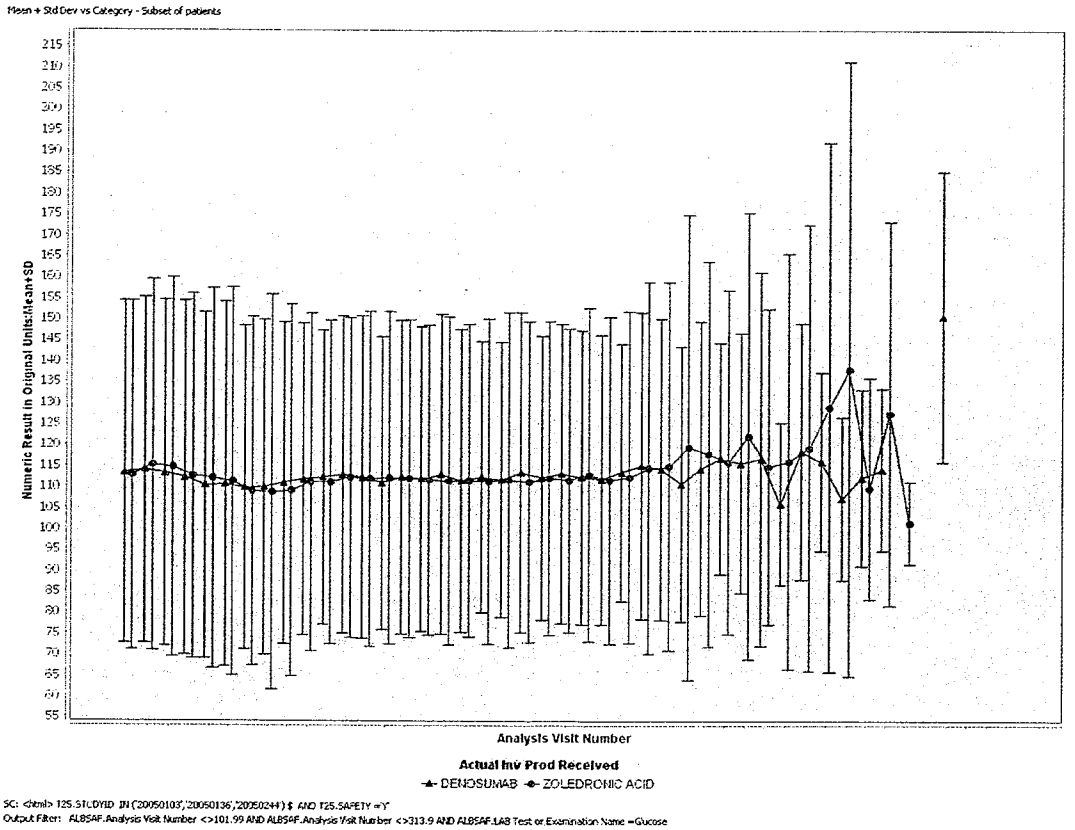
Table 100 Shift Table for Glucose (Decrease)

Baseline CTCAE Grade	Maximum Grade for Hypoglycemia			
	0	1	2	3
	Denosumab			
0	2458 (87%)	198 (7%)	42 (1%)	2 (0%)
1	7 (0%)	8 (0%)	2 (0%)	0 (0%)
2	1 (0%)	0 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid			
0	2440 (86%)	211 (7%)	44 (2%)	1 (0%)
1	11 (0%)	5 (0%)	0 (0%)	0 (0%)
2	0 (0%)	1 (0%)	0 (0%)	0 (0%)

Table 101 Shift Table for Glucose (Increase)

Baseline CTCAE Grade	Maximum Grade for Hyperglycemia				
	0	1	2	3	4
	Denosumab				
0	758 (27%)	911 (32%)	300 (11%)	47 (2%)	0 (0%)
1	48 (2%)	210 (7%)	158 (6%)	46 (2%)	3 (0%)
2	12 (0%)	36 (1%)	74 (3%)	70 (2%)	2 (0%)
3	3 (0%)	1 (0%)	9 (0%)	29 (1%)	0 (0%)
4	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid				
0	748 (26%)	904 (32%)	324 (11%)	43 (2%)	2 (0%)
1	59 (2%)	186 (7%)	170 (6%)	48 (2%)	6 (0%)
2	10 (0%)	29 (1%)	68 (2%)	74 (3%)	1 (0%)
3	2 (0%)	2 (0%)	9 (0%)	23 (1%)	4 (0%)
4	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)

Figure 27 Mean Glucose by Visit Number



SC: <html> T25.STUDYID IN ('20050103','20050136','20050244') $ AND T25.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name =Glucose

Page 1 of 1

Magnesium

Table 102 Shift Table for Magnesium (Decrease)

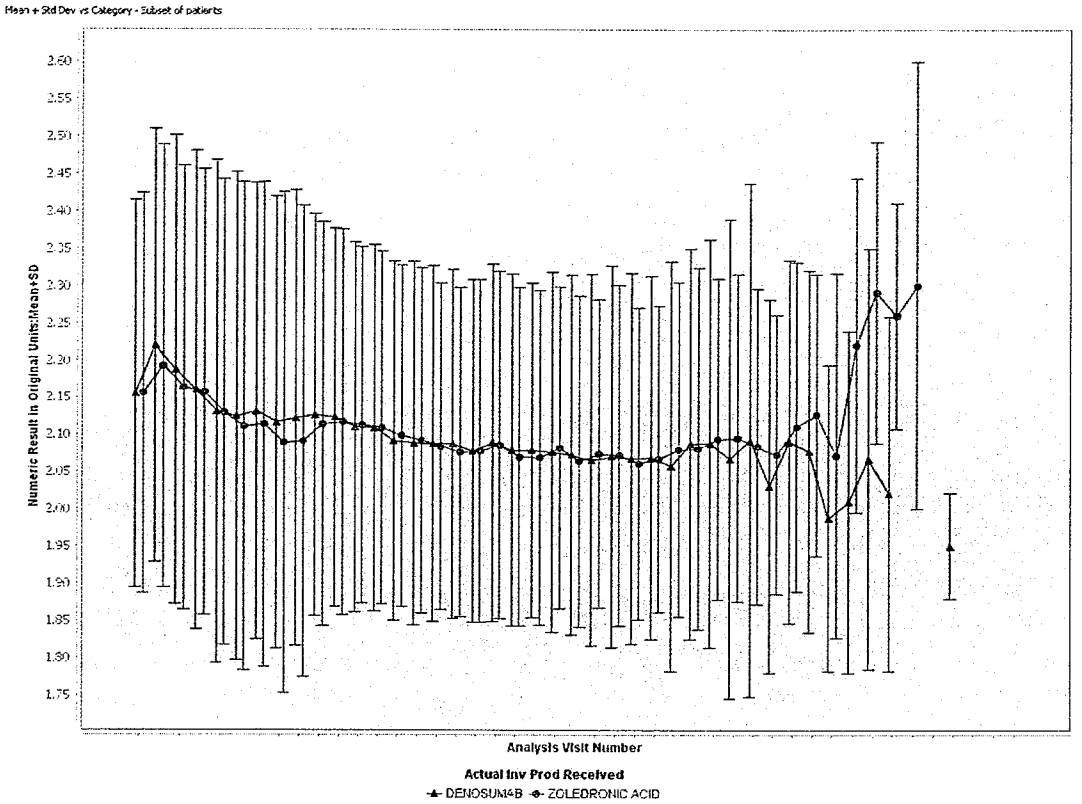
Baseline CTCAE Grade	Maximum Grade for Hypomagnesemia				
	0	1	2	3	4
	Denosumab				
0	2529 (89%)	111 (4%)	58 (2%)	10 (0%)	2 (0%)
1	5 (0%)	1 (0%)	3 (0%)	0 (0%)	0 (0%)
2	1 (0%)	3 (0%)	1 (0%)	1 (0%)	0 (0%)
3	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid				

0	2535 (89%)	110 (4%)	54 (2%)	6 (0%)	2 (0%)
1	5 (0%)	1 (0%)	3 (0%)	1 (0%)	0 (0%)
2	2 (0%)	2 (0%)	2 (0%)	0 (0%)	0 (0%)
3	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 103 Shift Table for Magnesium (Increase)

Baseline CTCAE Grade	**Maximum Grade for Hypermagnesemia**		
	0	**1**	**3**
	Denosumab		
0	2444 (86%)	104 (4%)	27 (1%)
1	2 (0%)	139 (5%)	8 (0%)
3	1 (0%)	0 (0%)	3 (0%)
	Zoledronic Acid		
0	2450 (86%)	103 (4%)	21 (1%)
1	4 (0%)	137 (5%)	7 (0%)
3	2 (0%)	0 (0%)	0 (0%)

Figure 28 Mean Magnesium by Visit Number



Potassium

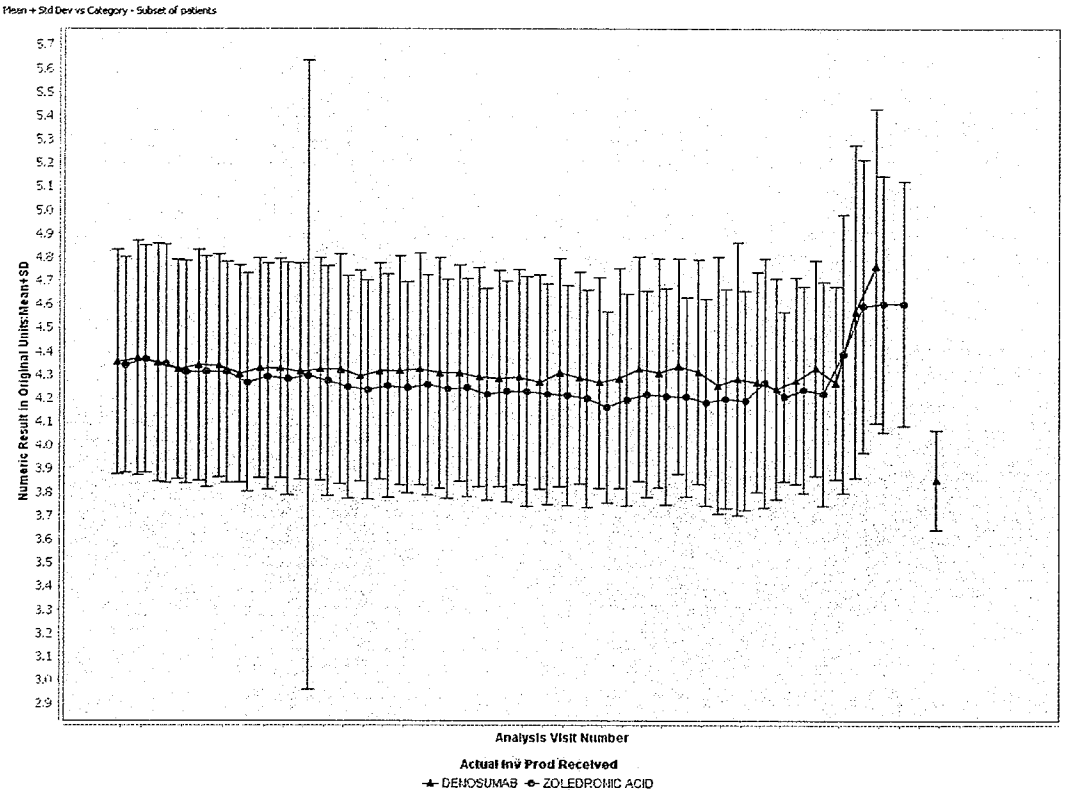
Table 104 Shift Table for Potassium (Decrease)

Baseline CTCAE Grade	Maximum Grade for Hypokalemia			
	0	1	3	4
	Denosumab			
0	2398 (84%)	207 (7%)	54 (2%)	12 (0%)
1	21 (1%)	15 (1%)	5 (0%)	0 (0%)
3	2 (0%)	1 (0%)	0 (0%)	0 (0%)
4	0 (0%)	1 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid			
0	2347 (83%)	255 (9%)	62 (2%)	17 (1%)
1	12 (0%)	9 (0%)	6 (0%)	0 (0%)
3	1 (0%)	1 (0%)	2 (0%)	0 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 105 Shift Table for Potassium (Increase)

Baseline CTCAE Grade	Maximum Grade for Hyperkalemia				
	0	1	2	3	4
	Denosumab				
0	2372 (83%)	83 (3%)	151 (5%)	49 (2%)	8 (0%)
1	11 (0%)	2 (0%)	3 (0%)	1 (0%)	0 (0%)
2	15 (1%)	3 (0%)	8 (0%)	3 (0%)	2 (0%)
3	0 (0%)	0 (0%)	4 (0%)	1 (0%)	0 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid				
0	2387 (84%)	72 (3%)	164 (6%)	32 (1%)	10 (0%)
1	7 (0%)	2 (0%)	3 (0%)	2 (0%)	0 (0%)
2	19 (1%)	3 (0%)	1 (0%)	5 (0%)	0 (0%)
3	0 (0%)	0 (0%)	2 (0%)	2 (0%)	0 (0%)
4	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Figure 29 Mean Potassium by Visit Number



SC: <html> T25.STUDYID IN ('20050103','20050136','20050214') $ AND T25.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name =Potassium

Page 1 of 1

Sodium

Table 106 Shift Table for Sodium (Decrease)

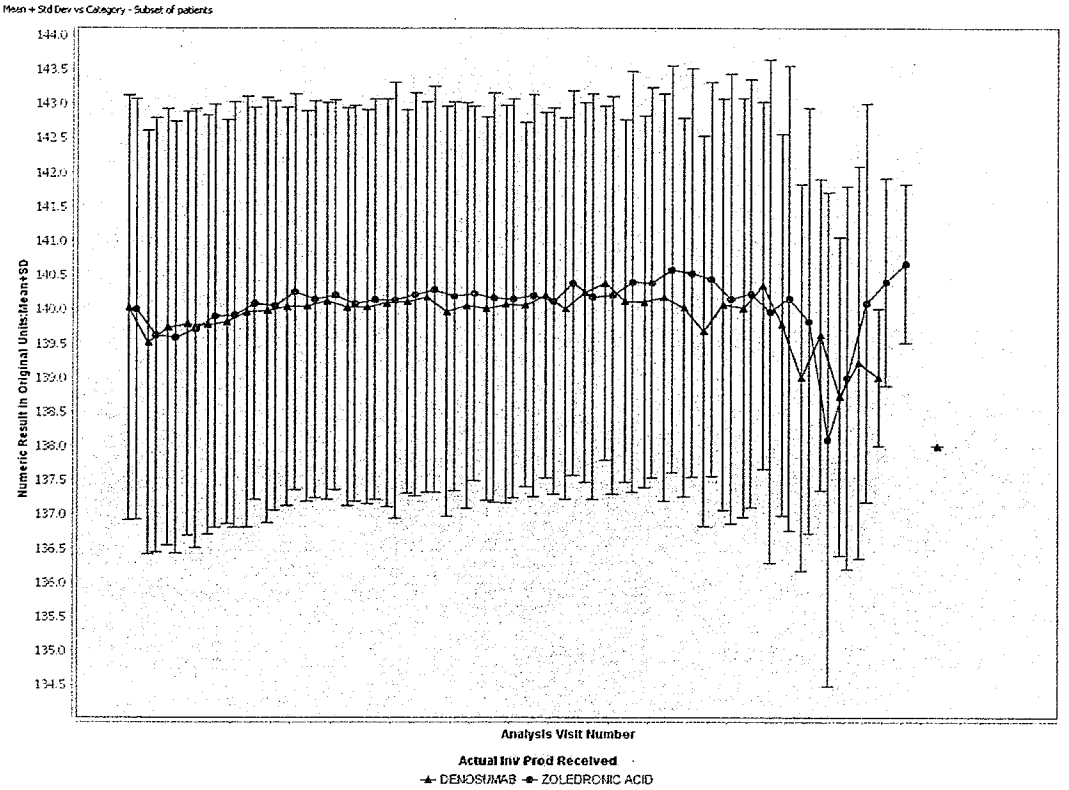
Baseline CTCAE Grade	Maximum Grade for Hyponatremia			
	0	1	3	4
	Denosumab			
0	2119 (75%)	407 (14%)	100 (4%)	8 (0%)
1	18 (1%)	44 (2%)	21 (1%)	0 (0%)
3	2 (0%)	0 (0%)	7 (0%)	1 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid			
0	2114 (75%)	403 (14%)	89 (3%)	4 (0%)
1	20 (1%)	57 (2%)	21 (1%)	1 (0%)

3	1 (0%)	5 (0%)	8 (0%)	0 (0%)
4	0 (0%)	0 (0%)	1 (0%)	0 (0%)

Table 107 Shift Table for Sodium (Increase)

Baseline CTCAE Grade	Maximum Grade for Hypernatremia				
	0	1	2	3	4
	Denosumab				
0	2430 (86%)	241 (8%)	9 (0%)	4 (0%)	3 (0%)
1	24 (1%)	12 (0%)	0 (0%)	0 (0%)	1 (0%)
2	1 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid				
0	2427 (86%)	238 (8%)	16 (1%)	3 (0%)	1 (0%)
1	20 (1%)	16 (1%)	2 (0%)	0 (0%)	0 (0%)
2	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)

Figure 30 Mean Sodium by Visit Number



SC: <html> TZ5.STUDYID IN ('20050103','20050136','20050244') $ AND TZ5.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name =Sodium

Page 1 of 1

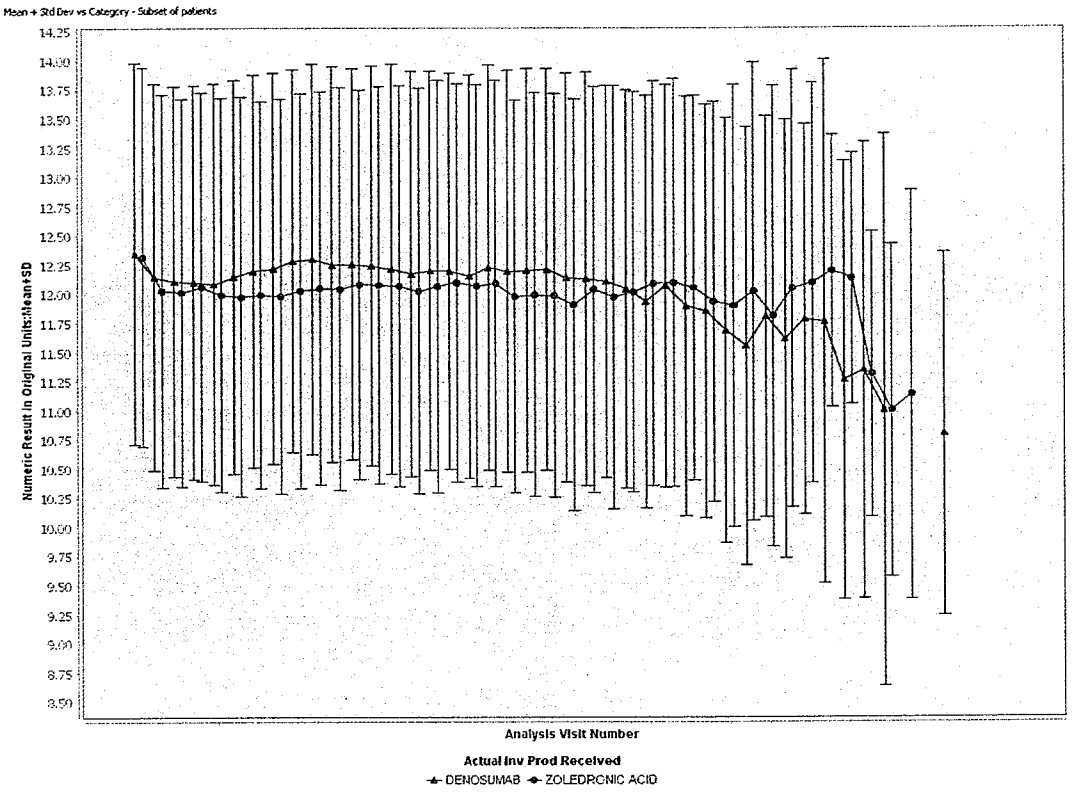
Hemoglobin

Table 108 Shift Table for Hemoglobin

Baseline CTCAE Grade	Maximum Grade for Anemia				
	0	1	2	3	4
	Denosumab				
0	590 (21%)	656 (23%)	315 (11%)	77 (3%)	21 (1%)
1	30 (1%)	314 (11%)	379 (13%)	83 (3%)	26 (1%)
2	6 (0%)	34 (1%)	89 (3%)	28 (1%)	10 (0%)
3	0 (0%)	2 (0%)	8 (0%)	10 (0%)	1 (0%)
4	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
	Zoledronic Acid				

0	490 (17%)	686 (24%)	357 (13%)	79 (3%)	19 (1%)
1	27 (1%)	313 (11%)	361 (13%)	110 (4%)	22 (1%)
2	1 (0%)	34 (1%)	88 (3%)	45 (2%)	12 (0%)
3	0 (0%)	1 (0%)	9 (0%)	8 (0%)	4 (0%)
4	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)

Figure 31 Mean Hemoglobin by Visit Number

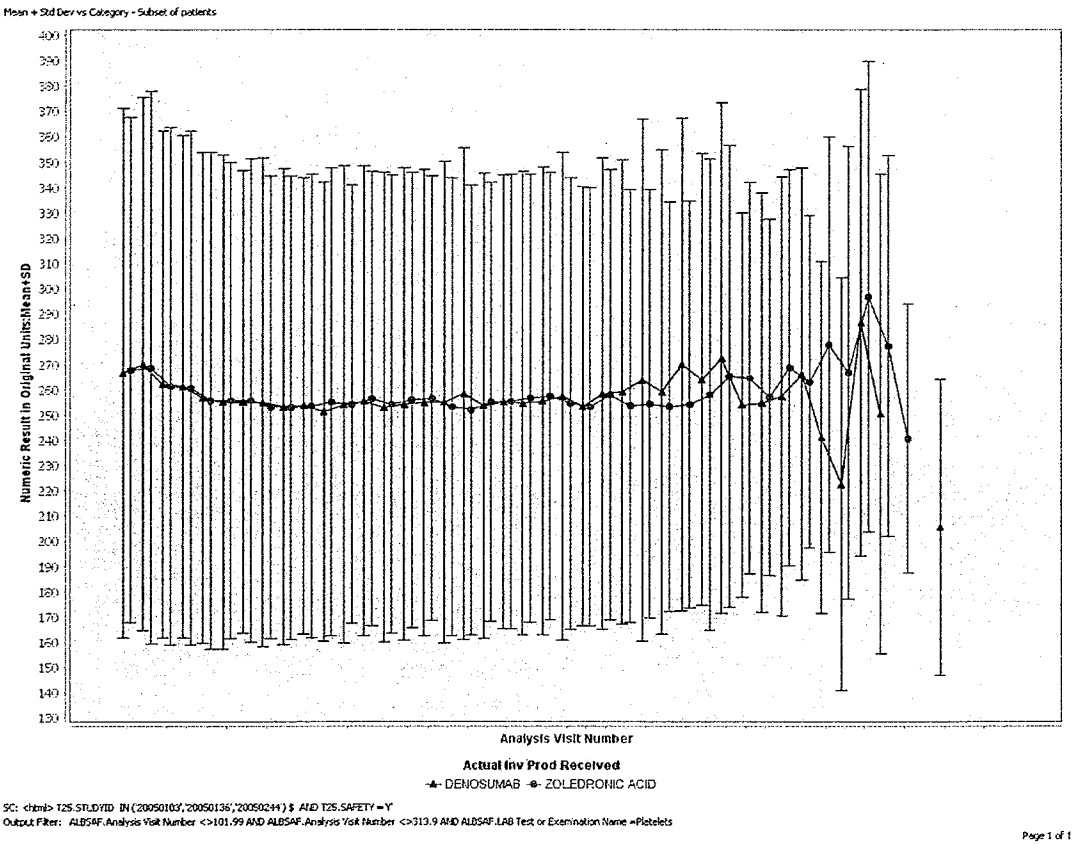


Platelets

Table 109 Shift Table for Platelets

Baseline CTCAE Grade	Maximum Grade for Thrombocytopenia				
	0	1	2	3	4
	Denosumab				
0	1941 (68%)	390 (14%)	76 (3%)	69 (2%)	21 (1%)
1	37 (1%)	40 (1%)	9 (0%)	8 (0%)	5 (0%)
2	3 (0%)	1 (0%)	3 (0%)	3 (0%)	0 (0%)
3	3 (0%)	1 (0%)	1 (0%)	3 (0%)	2 (0%)
4	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
	Zoledronic Acid				
0	1936 (68%)	384 (14%)	78 (3%)	58 (2%)	23 (1%)
1	15 (1%)	44 (2%)	13 (0%)	11 (0%)	6 (0%)
2	3 (0%)	2 (0%)	3 (0%)	2 (0%)	0 (0%)
3	0 (0%)	1 (0%)	0 (0%)	1 (0%)	2 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Figure 32 Mean Platelets by Visit Number



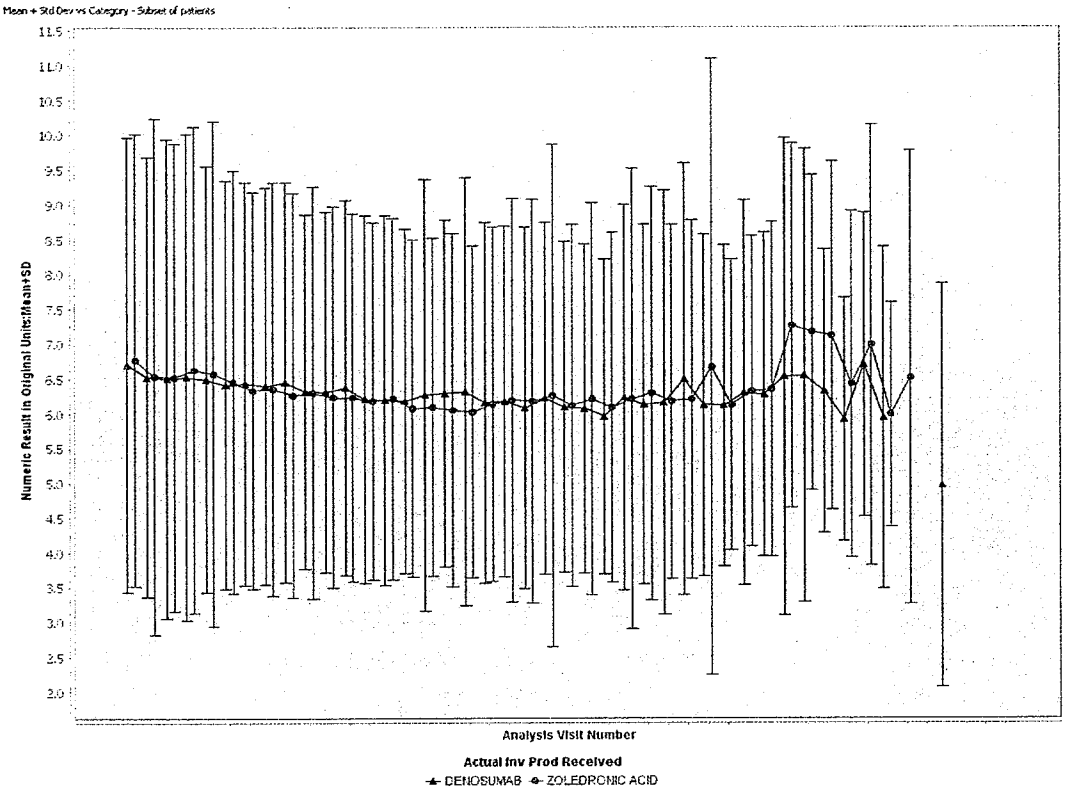
White Blood Cells

Table 110 Shift Table for White Blood Cells

Baseline CTCAE Grade	Maximum Grade for Leukopenia				
	0	1	2	3	4
	Denosumab				
0	1389 (49%)	407 (14%)	315 (11%)	202 (7%)	38 (1%)
1	41 (1%)	48 (2%)	61 (2%)	32 (1%)	5 (0%)
2	19 (1%)	13 (0%)	34 (1%)	22 (1%)	6 (0%)
3	14 (0%)	5 (0%)	8 (0%)	14 (0%)	4 (0%)
4	1 (0%)	0 (0%)	1 (0%)	1 (0%)	0 (0%)
	Zoledronic Acid				

0	1398 (49%)	367 (13%)	334 (12%)	196 (7%)	41 (1%)
1	43 (2%)	38 (1%)	63 (2%)	31 (1%)	7 (0%)
2	21 (1%)	19 (1%)	34 (1%)	25 (1%)	5 (0%)
3	5 (0%)	4 (0%)	12 (0%)	12 (0%)	4 (0%)
4	2 (0%)	1 (0%)	3 (0%)	2 (0%)	0 (0%)

Figure 33 Mean White Blood Cells by Visit Number



SC: <html> TZS.STUDYID IN ('20050103','20050136','20050244') $ AND TZS.SAFETY ='Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name ='White Blood Cells

Page 1 of 1

Segmented Neutrophils

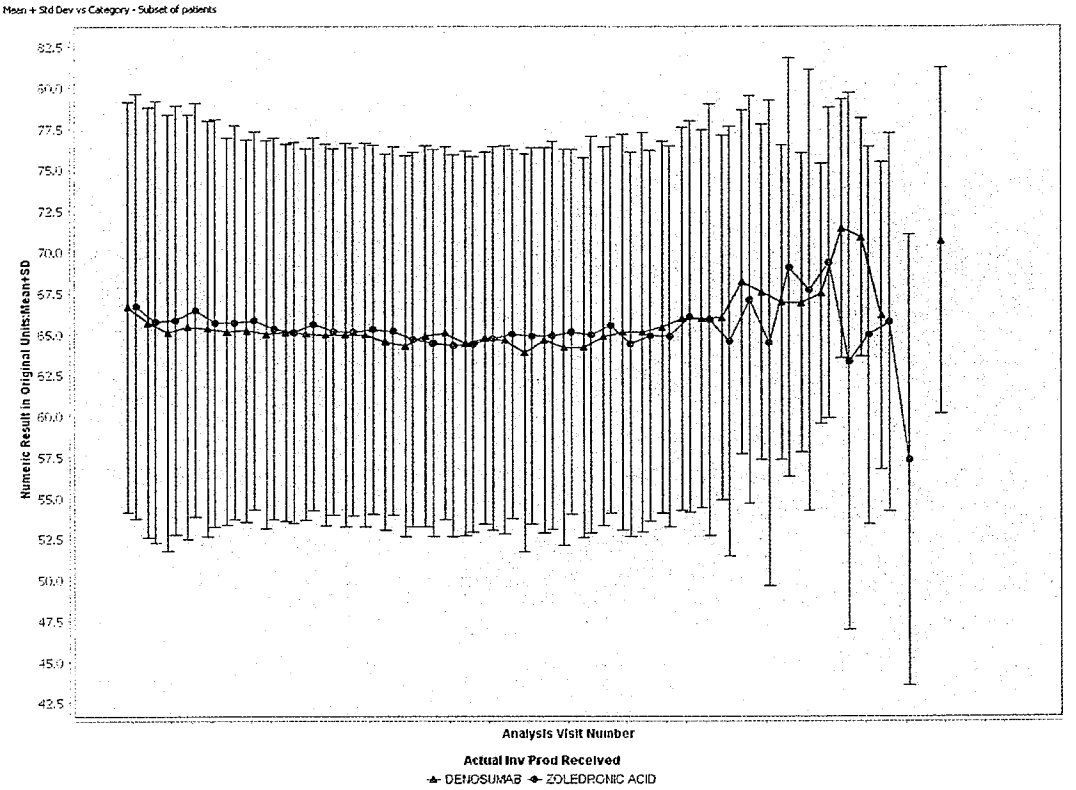
Table 111 Shift Table for Segmented Neutrophils

Baseline CTCAE Grade	Maximum Grade for Neutropenia				
	0	1	2	3	4
	Denosumab				
0	1552 (55%)	307 (11%)	260 (9%)	187 (7%)	127 (4%)
1	34 (1%)	28 (1%)	18 (1%)	23 (1%)	12 (0%)
2	23 (1%)	11 (0%)	12 (0%)	9 (0%)	10 (0%)
3	13 (0%)	4 (0%)	11 (0%)	7 (0%)	7 (0%)
4	4 (0%)	3 (0%)	2 (0%)	5 (0%)	6 (0%)

Formatted Table

	Zoledronic Acid				
0	1553 (55%)	299 (11%)	226 (8%)	217 (8%)	119 (4%)
1	28 (1%)	28 (1%)	28 (1%)	18 (1%)	8 (0%)
2	23 (1%)	10 (0%)	21 (1%)	12 (0%)	7 (0%)
3	10 (0%)	5 (0%)	9 (0%)	9 (0%)	6 (0%)
4	10 (0%)	3 (0%)	1 (0%)	7 (0%)	5 (0%)

Figure 34 Mean Segmented Neutrophils by Visit Number



SC: <html> T2S.STUDYID IN ('20050103','20050136','20050244') $ AND T2S.SAFETY = 'Y'
Output Filter: ALBSAF.Analysis Visit Number <>101.99 AND ALBSAF.Analysis Visit Number <>313.9 AND ALBSAF.LAB Test or Examination Name =Total Neutrophils

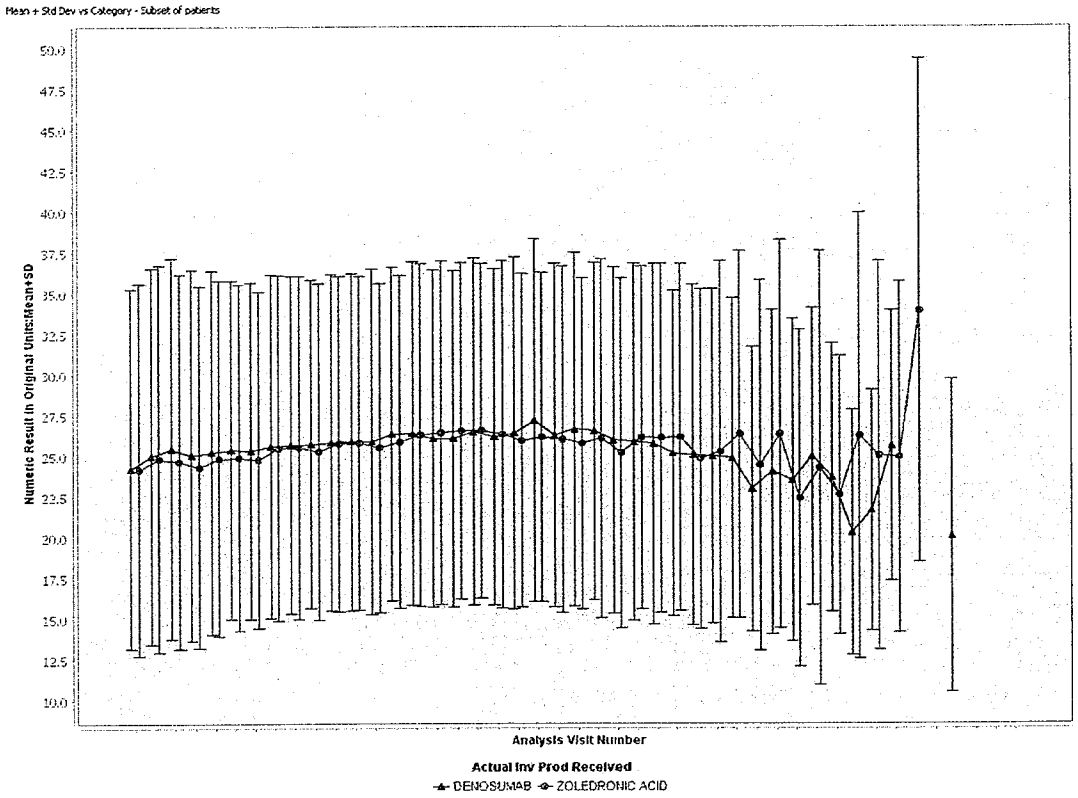
Page 1 of 1

Lymphocytes

Table 112 Shift Table for Lymphocytes

Baseline CTCAE Grade	Maximum Grade for Lymphopenia				
	0	1	2	3	4
	Denosumab				
0	1325 (47%)	75 (3%)	541 (19%)	218 (8%)	25 (1%)
1	21 (1%)	13 (0%)	28 (1%)	19 (1%)	1 (0%)
2	60 (2%)	15 (1%)	122 (4%)	110 (4%)	10 (0%)
3	7 (0%)	1 (0%)	21 (1%)	47 (2%)	8 (0%)
4	2 (0%)	0 (0%)	2 (0%)	3 (0%)	1 (0%)
	Zoledronic Acid				
0	1276 (45%)	74 (3%)	557 (20%)	263 (9%)	22 (1%)
1	8 (0%)	8 (0%)	26 (1%)	15 (1%)	1 (0%)
2	42 (1%)	10 (0%)	117 (4%)	116 (4%)	8 (0%)
3	13 (0%)	3 (0%)	35 (1%)	53 (2%)	8 (0%)
4	1 (0%)	0 (0%)	0 (0%)	4 (0%)	2 (0%)

Figure 35 Mean Lymphocytes by Visit Number

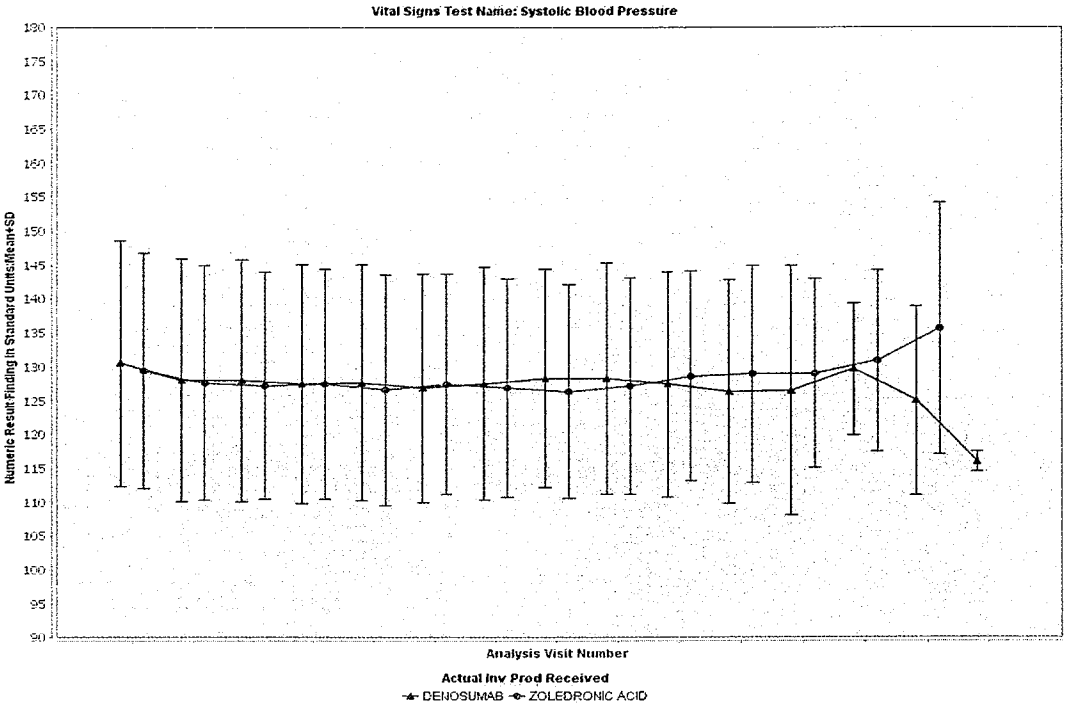


7.4.3 Vital Signs

Vital signs were measured once every 12 weeks and at the end of study visit. As shown below, there were no notable differences between treatment groups or notable upward or downward trends over time in mean systolic or diastolic blood pressure, heart rate, respiratory rate, temperature, or body weight. X-axis tickmarks in the graphs below represent consecutive visits at which vital signs were measured [i.e. Week 12, Week 24, Week 36, etc (refer to the Schedule of Assessments in Section 5.3)]. Fewer patients were evaluated at later time points.

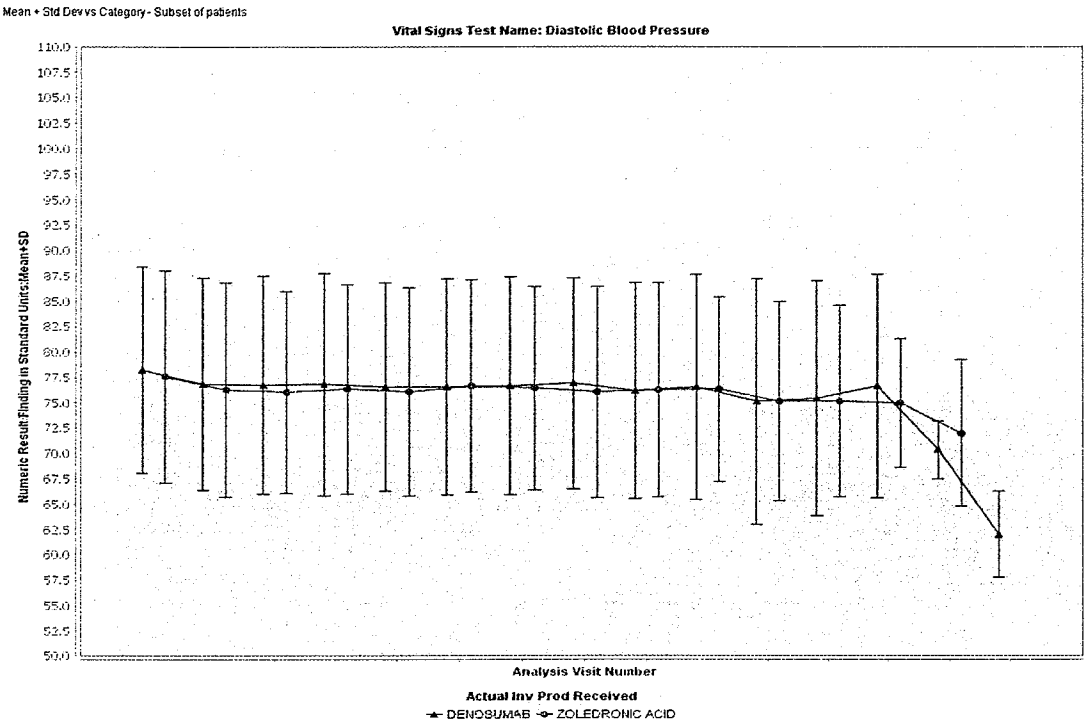
Figure 36 Systolic Blood Pressure

Mean + Std Dev vs Category - Subset of patients



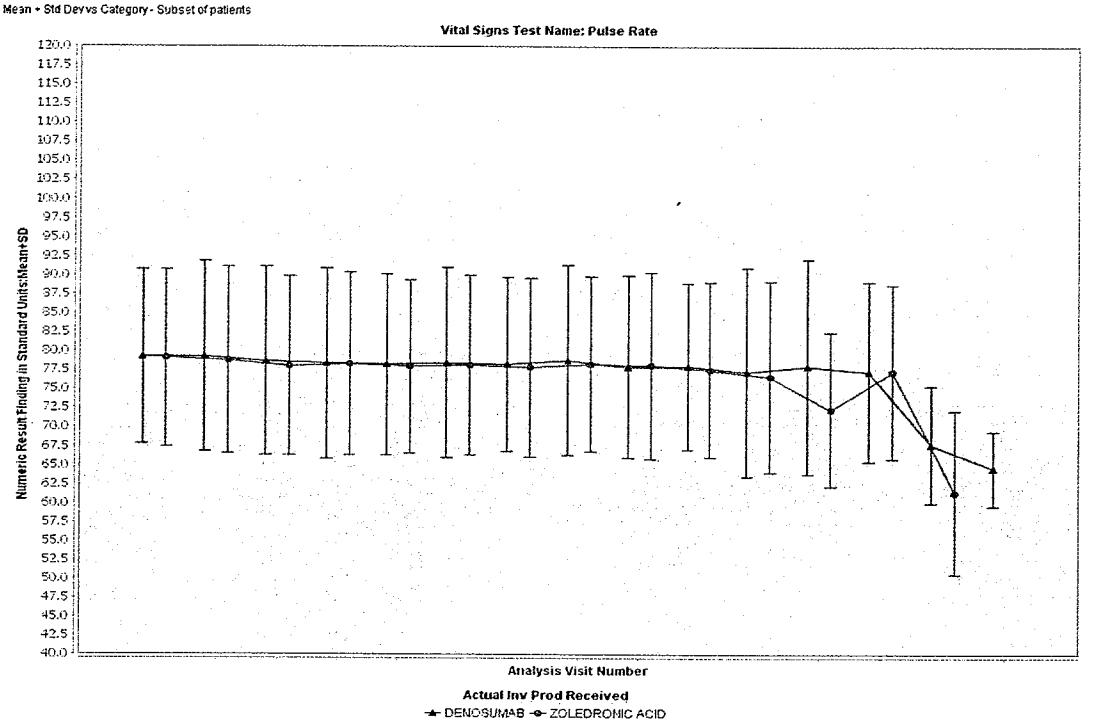
SC: <html> T25.STUDYID IN ('20050103','20050136','20050244') $ AND T25.SAFETY ='Y'
Output Filter: AVS.Analysis Visit Number >. AND AVS.Analysis Visit Number is not missing

Figure 37 Diastolic Blood Pressure



SC: <html> T25.STUDYID IN ('20050103','20050136','20050244') $ AND T25.SAFETY='Y'
Output Filter: AVS.Analysis Visit Number >. AND AVS.Analysis Visit Number is not missing

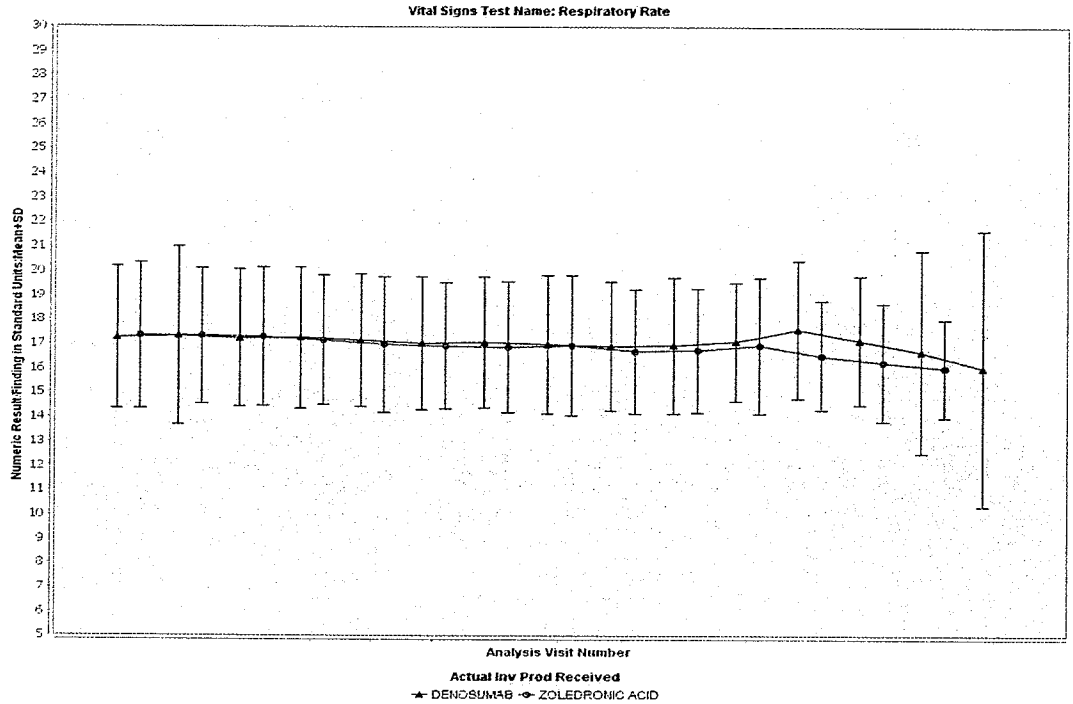
Figure 38 Pulse Rate



SC: <html> T25.STUDYID IN ('20050103','20050136','20050244') $ AND T25.SAFETY='Y'
Output Filter: AVS.Analysis Visit Number >. AND AVS.Analysis Visit Number is not missing

Figure 39 Respiratory Rate

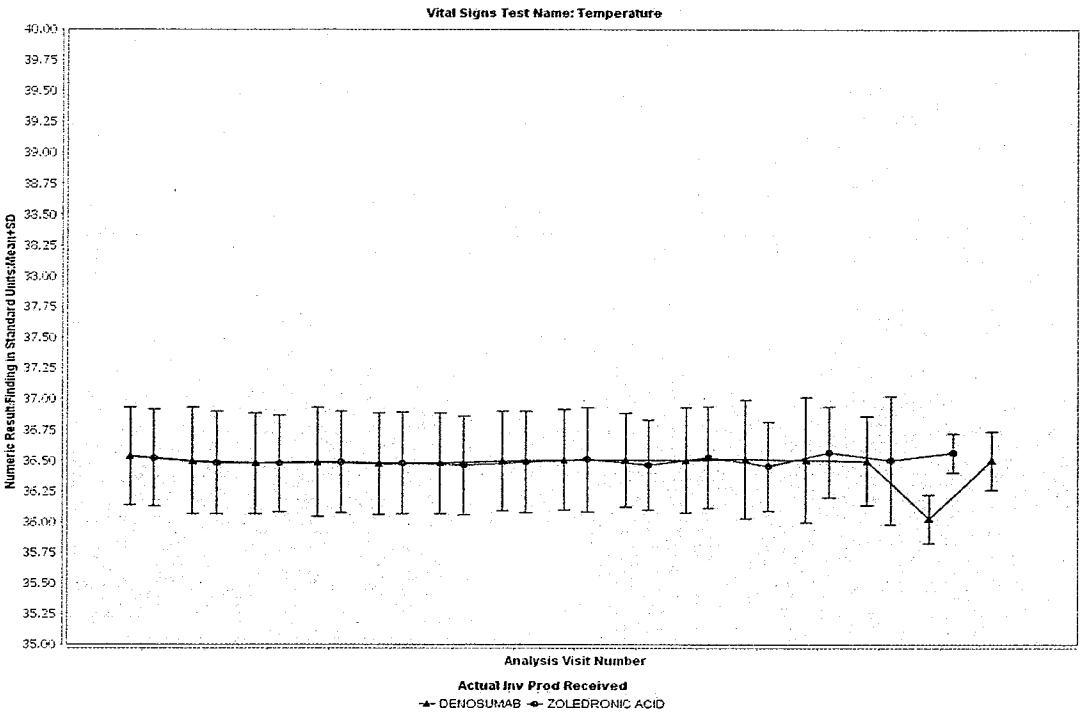
Mean + Std Dev vs Category - Subset of patients



SC: <html> T25.STUDYID IN ('20050103','20050136','20050244') $ AND T25.SAFETY='Y'
Output Filter: AVS.Analysis Visit Number >. AND AVS.Analysis Visit Number is not missing

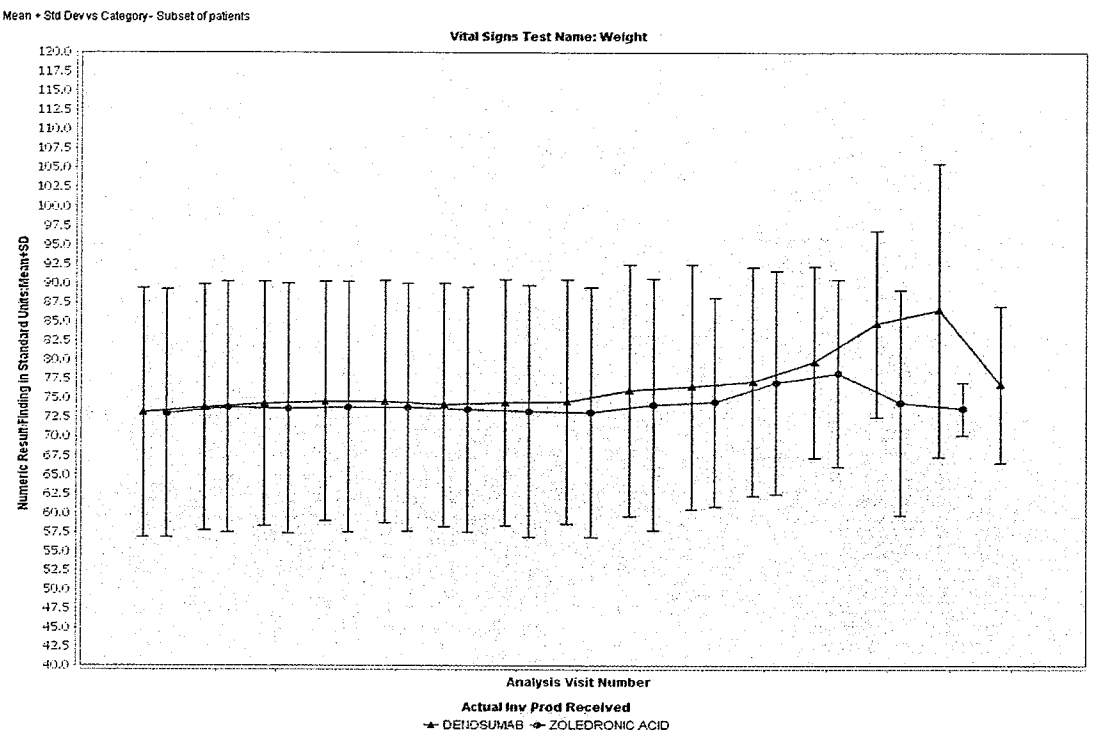
Figure 40 Body Temperature

Mean + Std Dev vs Category - Subset of patients



SC: <html> T25.STUDYID IN ('20050103','20050136','20050244') $ AND T25.SAFETY='Y'
Output Filter: AVS.Analysis Visit Number >. AND AVS.Analysis Visit Number is not missing

Figure 41 Body Weight



7.4.4 Electrocardiograms (ECGs)

At the time of the original BLA submission a thorough QT trial was not required, though a QT consult was requested from the IRQT team to evaluate any effect of denosumab on the QT interval. The consultant's opinion was that the Applicant's ECG evaluations appeared adequate and there were no large effects on the QTc interval due to denosumab.

ECGs were not required in Trials 103, 136, and 244.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted.

7.4.6 Immunogenicity

In trials included in this sBLA, 3,508 patients were tested for anti-denosumab antibodies. Samples were screened for binding antibodies and if positive, were tested for neutralizing antibodies.

Of patients tested, 0.4% were positive for binding antibodies. Ten patients developed binding antibodies after receiving at least one dose of denosumab and in five patients binding antibodies were pre-existing. No neutralizing antibodies have been observed with denosumab to date.

Overall safety profiles including individual adverse events were reviewed for the 4 patients in Trials 103, 136, and 244 who tested positive for binding antibodies. In these patients, denosumab immunogenicity did not appear to be associated with clinical sequelae.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Patients in Trials 103, 136, and 244 were treated with a uniform dose level of denosumab.

7.5.2 Time Dependency for Adverse Events

See Section 7.3.5 for time dependency explorations of hypocalcemia and ONJ.

7.5.3 Drug-Demographic Interactions

This reviewer conducted analyses of all adverse events and of ≥ Grade 3 adverse events by age, sex, and race.

The overall incidence and pattern of adverse events were similar between men and women. Differences in adverse events profiles by sex were likely related to underlying disease and demographic differences between Trials 103 and 136 (prostate and breast cancer, respectively).

Analyses by age were conducted at each level of the MedDRA hierarchy, using < 65 years of age vs ≥ 65 years of age subgroups. There were no differences in overall incidence or pattern of adverse events by age group or across treatment groups.

Analyses by race were limited by the small number of patients in some non-White subgroups. Numeric differences observed in the overall incidence and pattern of adverse events were generally inconsistent across subgroups and likely attributable to small numbers of patients.

7.5.4 Drug-Disease Interactions

Refer to Section 7.3.5 for discussion regarding differences in rates of hypocalcemia and ONJ in denosumab-treated patients among Trials 103, 136, and 244.

Refer to Section 7.3.5 for discussion regarding greater risk of hypocalcemia with denosumab in patients with a creatinine clearance less than 30 mL/min or receiving dialysis, compared to patients with normal renal function.

Refer to Section 7.4.1 for comparisons of common adverse events, analyzed at each level of the MedDRA hierarchy, among the three trials.

7.5.5 Drug-Drug Interactions

Ability to evaluate the effect of prior bisphosphonate therapy on the incidence rates and severity of adverse events including ONJ was limited in Trials 103, 136, and 244 by exclusion from the trials of patients who received prior IV bisphosphonate and by the small number of patients who received prior oral bisphosphonate (5% of patients enrolled in Trial 136).

An analysis was conducted to evaluate the incidence rates of hypocalcemia in patients who received concomitant medications that can lower serum calcium levels. In Trials 103, 136, and 244, a total of 604 denosumab-treated patients and 642 zoledronic acid-treated patients received concomitant treatment with a loop diuretic (furosemide, bumetanide, or torsemide; derived from the ACM datasets). Of these patients, 114 (19%) in the denosumab group and 61 (10%) in the zoledronic acid group experienced hypocalcemia adverse events (derived from the AE datasets), compared to 9% of all denosumab-treated patients and 5% of all zoledronic acid-treated patients. Of patients who received concomitant treatment with a loop diuretic, 47 (8%) in the denosumab group and 27 (4%) in the zoledronic acid group experienced Grade 3 or 4 hypocalcemia adverse events, compared to 4% of all denosumab-treated patients and 2% of all zoledronic acid-treated patients. This reviewer recommended the inclusion of a statement in the Hypocalcemia subsection of the Warnings and Precautions Section of

the product labeling that calcium levels should be monitored more frequently when denosumab is administered with other drugs that can also lower serum calcium levels.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant stated in the submission that because denosumab is considered to be nongenotoxic, any carcinogenic potential would be unrelated to direct DNA damage. The carcinogenic potential has not been evaluated in long term nonclinical studies.

Refer to Section 7.3.5 Submission Specific Primary Safety Concerns, subsection Malignancies, regarding the incidence of new primary malignancies in Trials 103, 136, and 244. Additionally, based on the analyses of progression free survival (refer to Section 6 Review of Efficacy), there was no evidence of tumor promotion in pre-existing cancers.

7.6.2 Human Reproduction and Pregnancy Data

No formal studies of denosumab have been conducted in pregnant or breastfeeding women. Four patients became pregnant during denosumab clinical trials. Two healthy volunteers became pregnant in a bioequivalence study within 6 months of receiving a single 60 mg dose of denosumab. A third pregnancy was confirmed in another bioequivalence study in which a healthy woman and her healthy male partner each received a single dose of denosumab (60 mg and 78 mg, respectively). The patient was confirmed to be pregnant within 3 months of receiving denosumab and gave birth to an apparently healthy infant. The fourth pregnancy occurred in a healthy volunteer who had participated in a bioequivalence study. The pregnancy was confirmed within 2 months of administration of a single 60 mg dose of denosumab and the patient gave birth to an apparently healthy infant.

7.6.3 Pediatrics and Assessment of Effects on Growth

No clinical studies have been conducted with denosumab in skeletally immature pediatric patients and the sBLA included a request for deferral of pediatric studies. Data from studies in skeletally immature animals suggest that the use of denosumab in children with open growth plates may impair bone growth and eruption of dentition. The application was presented before the FDA Pediatric Review Committee (PeRC) and a deferral will be granted for studies required under PREA (Pediatric Research Equity

Act). Refer to Section 1.4 (Postmarket Requirements and Commitments) for postmarketing studies required under PREA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no experience with overdose of denosumab. Amgen studied doses up to 180 mg every 4 weeks in cancer patients with no acute harm observed. No data suggest that denosumab can lead to dependence.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120-day safety update on September 10, 2010. The amendment consisted of materials previously agreed upon by FDA including new and updated case narratives and CRFs through April 1, 2010. Also included were updated integrated results regarding adverse events of interest. Datasets were not included. Overall, the results from the safety update were consistent with the findings presented in the sBLA. Updated integrated results included positively adjudicated ONJ in 2.2% of patients in the denosumab group and 1.6% in the zoledronic acid group, and hypocalcemia AEs in 10% of patients in the denosumab group and 5.1% in the zoledronic acid group.

8 Postmarket Experience (S. Pradhan)

There is no postmarketing experience with denosumab at the proposed dosing schedule.

9 Appendices

9.1 Literature Review/References

Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R *et al.*, 1996, Efficacy of Pamidronate in Reducing Skeletal Events in Patients with Advanced Multiple Myeloma, NEJM, 334: 488-493.

Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, *et al.*, 1998, Long-Term Pamidronate Treatment of Advanced Multiple Myeloma Patients Reduces Skeletal Events. Myeloma Aredia Study Group, JCO, 16:593–602.

Body JJ, Diel IJ, Bell R, Percherstorfer M, Lichinitser MR, et al., 2004, Oral Ibandronate Improves Bone Pain and Preserves Quality of Life in Patients with Skeletal Metastases Due to Breast Cancer, Pain, 111:306–312.

Cox, DR, 1972, Regression Models and Life-Tables (with discussion). J Royal Stat Soc, Series B., 34:187-220.

Domchek, SM, Younger J, Finkelstein DM, and Selden MV, 2000, Predictors of Skeletal Complications in Patients with Metastatic Breast Carcinoma, Cancer, 89: 363-8.

Gralow JR, Biermann, JS, Farooki A, Fornier MN, Gagel RF *et al.*,2003, NCCN Task Force Report: Bone Health in Cancer Care, JNCCN, 7 (supplement 3): s1-s32.

Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A *et al.*, 1996, Efficacy of Pamidronate in Reducing Skeletal Complications in Patients with Breast Cancer and Lytic Bone Metastases, NEJM, 335:1785-1791.

Hung HM, Wang S, Tsong Y, Lawrence J, O'Neil RT, 2003, Some Fundamental Issues with Non-Inferiority Testing in Active Controlled Trials. Statistics in Medicine, 22:213-225.

Kaplan EL, Meier P, 1958, Nonparametric Estimation from Incomplete Observation. JASA, 1958;53:457-481.

Kohno N, Aogi K, Minami H, Nakamura S, Asaga T, *et al.*, 2005, Zoledronic Acid Significantly Reduces Skeletal Complications Compared with Placebo in Japanese Woman with Bone Metastases from Breast Cancer: A Randomized Placebo-Controlled Trial, JCO, 23:3314-3321.

Lipton A, Theriault RL, Hortobagyi GN, Simeone J, Knight RD, *et al.*, 2000, Pamidronate Prevents Skeletal Complications and Is Effective Palliative Treatment in Women with Breast Carcinoma and Osteolytic Bone Metastases: Long Term Follow-up of Two Randomized, Placebo Controlled Trials, Cancer, 88:1082–1090.

Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, *et al.*, 2001, Zoledronic Acid versus Pamidronate in the Treatment of Skeletal Metastases in Patients with Breast Cancer or Osteolytic Lesions of Multiple Myeloma: A Phase III, Double-Blind, Comparative Trial, Cancer, 7:377-387.

Rosen LS, Gordon D, Tchekmedyian S, Yanagihara R, Hirsh V, *et al.*, 2003, Zoledronic Acid versus Placebo in the Treatment of Skeletal Metastases in Patients with Lung Cancer and Other Solid Tumors: A Phase III, Double-Blind, Randomized Trial - The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. JCO, 21: 3150-3157.

Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, *et al.*, 2003, Long-Term Efficacy and Safety of Zoledronic Acid Compared with Pamidronate Disodium in the Treatment of Skeletal Complications in Patients with Advanced Multiple Myeloma or Breast Carcinoma, Cancer, 98: 1735-1744.

Rosen LS, Gordon DH, Dugan W, Major, P, Eisenberg D *et al.*, 2004, Zoledronic Acid is Superior to Pamidronate for the Treatment of Bone Metastases in Breast Carcinoma Patients with at Least One Osteolytic Lesion, Cancer, 100:36-43.

Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, *et al.*, 2004, Long-Term Efficacy and Safety of Zoledronic Acid in the Treatment of Skeletal Metastases in Patients with Non-Small Cell Lung Carcinoma and Other Solid Tumors: A Randomized, Phase III, Double-Blind, Placebo-Controlled Trial, Cancer, 100:2613–2621.

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, *et al.*, 2002, A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients with Hormone-Refractory Metastatic Prostate Cancer, JNCI, 94: 1458-1468.

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, *et al.*, 2004, Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Carcinoma, JNCI, 96: 879-882.

Theriault RL, Lipton A, Hortobagyi GN Leff R, Glück S, *et al.*, 1999, Pamidronate Reduces Skeletal morbidity in Women with Advanced Breast Cancer and Lytic Bone Lesions: A Randomized, Placebo-Controlled Trial, JCO, 17:846-854.

9.2 Labeling Recommendations (S. Pradhan)

This reviewer recommended the following key labeling changes. Further, the Division deemed that a Medication Guide is not necessary to ensure the safe use of denosumab in medical oncology practice in the intended patient population.

Indications and Usage

- Change the indication from (b) (4) to prevention of SREs in patients with bone metastases from solid tumors
- Inclusion of an 'Important Limitation of Use' stating that denosumab is not indicated for the prevention of SREs in patients with multiple myeloma

Warnings and Precautions

- Removal of the (b) (4) (b) (4)
- Revision of the Hypocalcemia warning, including
  - Inclusion of information regarding the risk of hypocalcemia with denosumab (at a dose lower than that proposed in this sBLA) in patients with a creatinine clearance of less than 30 mL/min or receiving dialysis
  - Inclusion of information regarding monitoring of calcium levels, administration of calcium and vitamin D as necessary, and more frequent monitoring when denosumab is administered with other drugs that can also lower calcium levels
- Revision of the ONJ warning to include further detail regarding the signs and symptoms and incidence of ONJ
- (b) (4)

Adverse Reactions

- Replacement of the adverse event table with a table showing selected adverse reactions and including laboratory-derived incidence rates for hypocalcemia and hypophosphatemia
- Replacement of the Hypocalcemia Section with a Section regarding severe (NCI CTCAE Grade 3 or 4) mineral/electrolyte abnormalities
- Revision of the ONJ Section to include data from an extended treatment phase
- Removal of the Section titled (b) (4)

- Removal of the Section titled [redacted] (b) (4)

Use in Specific Populations

- Renal Impairment
  - Removal of the statement that [redacted] (b) (4)
  - Inclusion of information regarding the risk of hypocalcemia with denosumab (at a dose lower than that proposed in this sBLA) in patients with a creatinine clearance of less than 30 mL/min or receiving dialysis
- Removal of the Hepatic Impairment Section (monoclonal antibody; no study was conducted in this patient population)

Clinical Trials

- Inclusion of information regarding increased mortality in the subgroup of patients with multiple myeloma in Trial 244
- Inclusion of demographic information for the study populations
- Removal of results from [redacted] (b) (4)
- Inclusion of information regarding the individual components of the composite SRE endpoint

Patient Counseling Information

- [redacted] (b) (4)
- Revision of information regarding ONJ and hypocalcemia (for clarity)
- [redacted] (b) (4)

9.3 Advisory Committee Meeting (S. Pradhan)

Due to the robustness of the results demonstrating superiority over zoledronic acid in Trials 103 and 136 for the established, clinically relevant endpoint of delaying time-to-SRE; the demonstration of non-inferiority over zoledronic acid for the same endpoint in Trial 244; and the overall favorable risk-benefit assessment in the intended population of patients with bone metastases from solid tumors, an Advisory Committee Meeting was not deemed necessary.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 23, 2010
To:	Patricia Keegan, M.D. Director, Division of Biologic Oncologic Products
Through:	Judy Staffa, Ph.D, R.Ph. Acting Director, Division of Epidemiology
	Rita Ouellet-Hellstrom, Ph.D., M.P.H Team Leader, Division of Epidemiology
From:	Fatmatta Kuyateh, M.D., M.S. Medical Officer, Division of Epidemiology
Subject:	Review of ONJ Case Registry
Drug Name(s):	Denosumab
Application Type/Number:	BLA 125320/7/5
Applicant/sponsor:	Amgen Incorporated
OSE RCM #:	2010-1884

CONTENTS

EXECUTIVE SUMMARY

This document describes a review of a protocol for an Osteonecrosis of the Jaw (ONJ) Registry proposed by Amgen Inc. This review was requested by the Division of Biologic Oncology Products as part of the review for the overall pharmacovigilance plan of BLA supplement 125320/7 for denosumab. Denosumab is a human monoclonal IgG2 antibody that targets receptor activator of nuclear factor kappa B ligand (RANKL) thus suppressing bone turnover. Previously conducted clinical trials showed that ONJ occurred with similar frequency during treatment with denosumab as during treatment with zoledronic acid (a bisphosphonate) in patients with cancer. Consequently, the sponsor has proposed an ONJ case registry of cancer patients as part of the denosumab post-marketing pharmacovigilance program. (b) (4), (b) (5)

(b) (4), (b) (5)

7 Page(s) has been Withheld in Full as b4 (CCI/TS) and b5 immediately following this page

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125320/7 **Applicant: Amgen, Inc.** **Stamp Date: May 19, 2010**

Drug Name: Denosumab **NDA/BLA Type: BLA**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			(eCTD)
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			On initial review, the label appears to be in acceptable PLR format.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	Biologic agent.
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: 20040113 Study Title: A Randomized, Active-controlled Study of AMG 162 in Breast Cancer Subjects with Bone Metastasis Who Have Not Previously Been Treated With Bisphosphonate Therapy. Sample Size: 255 Arms: 6; refer to submission Location in submission: CSR 20040113 (5.3.4.2)	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1: 20050103 (b) (4) [redacted] Pivotal Study #2: 20050136 (b) (4) [redacted] Pivotal Study #3: 20050244 (b) (4) [redacted]				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		On initial inspection. Studies 20050103, 20050136, and 20050244 were each conducted in the US and abroad.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			On initial review.
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			On initial inspection. The application contains a summary of ECG data from denosumab clinical studies (the Bone Loss BLA ECG Summary, with an Advanced Cancer addendum, is included in this application).
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			On initial inspection.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			All verbatim and preferred terms are included in .xpt files.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			On initial review.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			On initial inspection of studies 20050103, 20050136, and 20050244.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			On initial review.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			A request for pediatric deferral was submitted with the BLA. Additional information has been requested by the Agency.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		On initial inspection. Studies 20050103, 20050136, and 20050244 were each conducted in the US and abroad.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			

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

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			Appears acceptable during initial safety review
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			On initial review.
34.	Are all datasets to support the critical safety analyses available and complete?	X			On initial review.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			On initial review.
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Source lab data were not included.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			On initial inspection
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			A statement that "clinical trials were conducted under GCP as described in ICH E6, under the principles of the Declaration of Helsinki, and in accordance with local and regional regulations" was identified in 1.3 of section 2.5 ("Clinical Overview").

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

- Please provide financial disclosure information for AE adjudicators/adjudication committee members (cardiovascular events and ONJ adjudication).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 30, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Product Quality Team Leader Review: Denosumab: BL STN 125320/7

Team leader sign-off is located in the Product Quality review.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Monoclonal Antibodies
Bethesda, MD 20892
Tel. 301-827-0850

Memorandum of Review

Date: September 29, 2010

To: File for STN: 125320/7

From: Sarah Kennett, Ph.D.

Through: Chana Fuchs, Ph.D., Team Leader

Through: Patrick Swann, Ph.D., Deputy Division Director

Subject: 70 mg/ml 1.7 ml vial presentation

Applicant: Amgen
Contact: Bradley J. Glasscock, Director, Regulatory Affairs (805) 447-1000

Product: Denosumab

Filing Action Date: July 18, 2010 **Status:** Filed

Action Due Date: November 18, 2010

Review Recommendation: The data submitted in this supplement to the Biologics License Application support the conclusion that the manufacture of 70 mg/ml denosumab is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that 70mg/ml denosumab in a 1.7 ml vial fill be approved for human use (under conditions specified in the package insert).

3. QUALITY
3.2.S Drug Substance
3.2.S.1 General Information
3.2.S.1.1 Nomenclature

Product Name:	Under review (Xgeva)
INN Name:	Denosumab
Compendial Name:	Not Applicable
Chemical Name:	Immunoglobulin G2 human monoclonal antibody to RANK ligand
Company or Laboratory Code:	AMG 162
USAN/BAN/JAN Name:	Denosumab
CAS Registry Number:	615258-40-7

3.2.S.1.2 Structure

Denosumab is a full-length human monoclonal IgG2. (b) (4)

(b) (4)

Figure 1. Schematic of Denosumab Structure

(b) (4)

3.2.S.1.3 General Properties

Molecular mass: (b) (4) 147, (b) (4)

(b) (4)

Denosumab binds specifically to the D-E loop of human receptor activator of nuclear factor kappa B ligand (RANKL; epitope: DLATE; cross-reacts with non-human primate). The apparent K_d is $3x10^{-12}$M, as determined by KinExA assay, and $1x10^{-12}$M, as determined by BIAcore assay. The binding interaction prevents the binding of RANKL to RANK on the surface of osteoclasts and their precursors, inhibiting the formation, function, and survival of osteoclasts, which are responsible for bone resorption.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

"ACO"	"BIP"
Amgen Inc.	Boehringer Ingelheim Pharma GmbH &Co. Kg
LakeCentre Facility (Bldg AC-7)	Birkendorfer Strasse 65
5550 Airport Boulevard	88397 Biberach an der Riss
Boulder, CO 80301	Germany

3.2.S.2.2 Description of Manufacturing Process

Denosumab drug substance manufacture was described in detail in the original denosumab BLA submission (STN 125320). There have been no manufacturing changes for drug substance.

The sections discussing future drug substance manufacture at AML have been removed; Amgen states that a post-approval filing will be submitted to add AML as a commercial drug substance site.

3.2.S.2.3 Control of Materials

There have been no changes in the raw materials used for denosumab manufacture.

3.2.S.2.4 Controls of Critical Steps and Intermediates

There have been no significant changes in the controls of critical steps with the exception of the bioburden test method used at BIP. As was indicated in the original BLA submission (125320), the contamination control test that had been used for the (b) (4) (b) (4) (b) (4) No changes have been made to the test methods.

3.2.S.2.5 Process Validation and/or Evaluation

There have been no changes to the validation of cell culture and harvest. A statement regarding the commitment to place the (b) (4) (b) (4) this was agreed to during the review of the original BLA submission.

(b) (4)

3.2.S.2.6 Manufacturing Process Development

There have been no additions to the drug substance manufacturing process development other than (b) (4)

3.2.S.3 Characterization

There have been no additions to drug substance characterization.

3.2.S.4 Control of Drug Substance

There have been no changes to the control of drug substance.

3.2.S.4.1 Specification

The specification for lot release and stability are unchanged from the original BLA.

Table 1: Denosumab 70 mg/mL Drug Substance Specification

(b) (4)

[redacted]

3.2.S.4.3 Validation of Analytical Procedures

Analytical procedures were validated in accordance with (b) (4)

(b) (4)

[redacted]

3.2.S.6 Container Closure System

The only significant change in the DS container closure system is an update to the [redacted] Testing with 12 containers each (10 media fills and 2 positive controls) has been performed on the 10 L and 20 L containers (an earlier test with only the 20L containers was provided in the original BLA). The results are acceptable. In addition, the supplier name changed from [redacted].

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The stability data were updated in the current submission. There are no significant differences in the new data. The recommended storage condition for 70 mg/ml denosumab is -30°C, and the proposed shelf life is 36 months; this proposal was found to be acceptable during review of the original BLA submission.

3.2.P.1 Description and Composition of the Drug Product

The denosumab drug product (DP) currently submitted for licensure is supplied at 70 mg/ml as a 1.7 ml fill in a 3 ml vial. The presentations included in the original license are a 60 mg/ml (1 ml) vial and 60 mg/ml (1 ml) prefilled syringe (PFS). [redacted] Data from the 60 mg/ml presentation is included as supporting information; the 60 mg/ml DP presentation is prepared by dilution of the 70 mg/ml DS in 10 mM acetate, 5% sorbitol, pH 5.2 [redacted]

Reviewer Comment: Amgen recently recalled certain lots of Epogen and Procrit vials due to formation of lamellae (glass flakes). The lamellae result from an interaction of the formulation with the glass vials. While denosumab is formulated in an acetate [redacted] both Epogen and Procrit are formulated in sodium chloride/ citrate or sodium

chloride/citrate/phosphate buffer (from prescribing information). As the formulations are different, there is no cause to request additional information regarding lamellae formation in denosumab vials.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

DS at a concentration of 70 mg/ml denosumab contains an average of 18 mM acetate and 4.6% sorbitol at a pH of 5.2.

3.2.P.2.1.2 Excipients

Excipients that are constituents of the denosumab DS include glacial acetic acid and sodium hydroxide to provide buffer at pH 5.2 and sorbitol [redacted] (b) (4)

(b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

DP developed for phase 1 clinical studies was formulated as 30 mg/ml vials and stored at -30°C. For phase 2/3 clinical studies and commercial use, DP has been formulated as 60 mg/ml vials and PFS with 1 ml deliverable volumes and as a 70 mg/ml vial at a 1.7 ml deliverable volume; each presentation is stored at 5°C. All denosumab presentations contain denosumab formulated using the same acetate and sorbitol pH 5.2 [redacted] (b) (4). Formulation studies were described and reviewed for the original BLA submission.

3.2.P.2.2.2 Overages

The 70 mg/ml presentation is filled to ensure a deliverable volume of 1.7 ml; the volume is controlled through fill weight checks conducted during the fill process.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physiochemical and biological properties of denosumab DP are the same as the DS properties.

3.2.P.2.3 Manufacturing Process Development

[redacted] (b) (4)

(b) (4)

[redacted]

60 mg/ml (1.0 ml) vial to 70 mg/ml (1.7 ml) vial (COMP-000012; RPTC-000015)

Analytical comparability and bioequivalence (study 20060446) were assessed, and these studies were presented in the original BLA submission as 70 mg/ml vial data were used to support the application. Product quality attributes most likely to be affected by these differences include size and visible and subvisible particle formation. These characteristics were assessed through analyses of lot release testing and stability data and forced degradation studies. The 60 mg/ml vial and 70 mg/ml vial were found to be comparable during the review of the original BLA.

70 mg/ml vial ATO to 70 mg/ml vial AML (COMP-000016; RPTC-000033)

Reviewer Comment: During the review of the original BLA submission, the 60 mg/ml ATO vial and the 60 mg/ml AML vial were determined to be comparable. The current submission contains the finalized comparability report.

(b) (4)

[redacted]

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

(b) (4)

Reviewer Comment: The comparability acceptance criteria appear to be appropriate for this study. The 70 mg/ml 1.7 ml fill vials manufactured at ATO are sufficiently comparable to those manufactured at AML to provide data in support of the commercial use of AML-manufactured DP.

3.2.P.2.4 Container Closure System

DMF cross-references are provided for the vial and stopper. There is no change from the clinical or commercial 60 mg/ml vial container closure. For details on container closure system, see section 3.2.P.7.

3.2.P.2.5 Microbiological Attributes

Testing is unchanged from the original BLA submission. (b) (4)

(b) (4)

3.2.P.2.6 Compatibility

(b) (4)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Formulation, fill/finish, and packaging of DP and DP storage occur at:
Amgen Manufacturing Limited (AML)
State Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777

DP storage and distribution occur at:

Amgen Inc. (LDC)	Amgen Inc. (ATO)
12000 Plantside Dr., Louisville, KY 40299	1 Amgen Center Dr., Thousand Oaks, CA 91320

DP lot release and stability testing occur at AML and ACO (4000 Nelson Rd., Longmont, CO 80503).

Container closure testing for stability occurs at AFR (6701 Kaiser Dr., Fremont, CA 94555).

3.2.P.3.2 Batch Formula

The DS and DP have the same formulation and denosumab concentration; no formulation is required at this stage.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

(b) (4)

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The proposed shelf-life is 36 months. The approved shelf-life for the 60 mg/ml vial and 60 mg/ml PFS presentations is 30 months. The primary stability lots were manufactured at ATO from ATO or ACO DS, the commercial lots were manufactured at AML from BIP DS, and the supporting lots were manufactured at ATO from BIP DS. Long term stability testing is performed on vials stored in both upright and inverted positions; up to 36 months of data are available for the primary lots, 18 months of data are available for the commercial lots, and up to 18 months of data are available for the additional supporting lots.

For long term studies, DP is stored at the recommended storage condition of 5°C (2-8°C), with testing scheduled to 48 months. A subset of the lot release tests are performed, and acceptance criteria are the same as those used for release. Testing is performed to assess strength, potency, purity, sterility, visual appearance, subvisible particulates, and pH. Container closure integrity is assessed (b) (4) as part of the commercial program. Analyses of samples subjected to stress indicate that SE-HPLC, rCE-SDS, CE-HPLC, and the HTRF potency assay are stability indicating assays.

The stability profiles of the DP held at accelerated (29°C) or stressed (37°C) storage conditions for up to 12 and 6 months, respectively, are comparable between the primary, commercial, and supporting lots.

Studies were also performed to demonstrate stability at elevated temperatures (25°C and 29°C) after long term storage under recommended storage conditions.

Stability of the DP subjected to light exposure and temperature cycling has also been evaluated. The DP is stable under conditions that may be encountered during clinical use.

A statistical analysis was performed per ICH Q1B to support the proposed shelf life for DP held at 5°C. A regression line was fit to potency and purity data. Upper and lower 95% confidence intervals on the mean response were computed and these confidence intervals were evaluated against the stability specification limits. The projected upper and lower 95% confidence limits on the mean remain within the proposed acceptance criteria through the proposed shelf life of 36 months.

Table 4. Confidence Limits for 36 Month Shelf Life

Test Methods (Parameter)	Proposed Acceptance Criteria	Lower Confidence Limit of Mean	Upper Confidence Limit of Mean
HTRF potency assay (% relative potency)	(b) (4)	95	102
SE-HPLC (% main peak)		98.8	98.9
SE-HPLC (% HMWS)		1.0	1.2
CE-HPLC (% main peak)		75	77
rCE-SDS (% main peak)		98	98

Reviewer Comment: The real-time stability data provided (see below) indicate that the 70 mg/ml DP is stable through 36 months when stored under recommended storage conditions (2-8°C); therefore, the proposed expiration period is acceptable. The data also provide for limited storage of the DP at RT, see comments below.

(b) (4)

Table 1. Drug Product Stability Assays and Acceptance Criteria

Assay Number	Parameter	Test Method	Method Number	Acceptance Criteria
1	Appearance	Appearance		(b) (4)
2	Purity	SE-HPLC		
3	Purity	rCE-SDS		
4	Purity	CE-HPLC		
5	Potency	HTRF potency		
6	Quantity	Protein concentration		
7	General tests	pH		
8	General tests	Subvisible particles		
9	General tests	Container closure integrity		
10	Adventitious agents	Sterility		

Table 2. Drug Product Stability Test Schedule

Time Point (Months)	Storage Condition: 5°C
0	Assays 1 to 8; 10
3	Assays 1 to 5
6	Assays 1 to 7
9	Assays 1 to 5
12	Assays 1 to 9
18	Assays 1 to 5
24	Assays 1 to 9
30	Assays 1 to 9
36	Assays 1 to 9
48	Assays 1 to 9

3.2.P.8.3 Stability Data

Reviewer Comment: In addition to full data tables, numerous primary data (chromatograms, electropherograms) were provided; all forms of data were included in the assessment of denosumab DP stability.

HTRF potency results remain within specification with no significant change outside the inherent assay variability for samples stored under recommended, accelerated, stressed storage conditions.

Reviewer Comments: (1) For 1 of 4 lots tested through 36 months, the final data point shows a significant decrease; however, as there are similar one-time decreases at other time points for other lots, it appears that this is due to assay variability and is not indicative of a true decrease in potency. (2) Data submitted in the original BLA show that samples stored under 60°C stressed conditions did have reduced potency that correlated with the formation of (b) (4) (b) (4) ; therefore, this is a stability-indicating assay.

SE-HPLC results remain within specification for samples stored under recommended conditions for up to 36 months. There is a decrease of up to 0.6% main peak, with a corresponding increase in (b) (4) over time. When stored at elevated temperatures, the loss in main peak and increase in HMW species becomes more evident (up to 1.5% at 12 months under accelerated conditions and 1.9% at 6 months under stressed conditions). No change is seen in (b) (4) under recommended conditions; a small increase is seen under elevated temperature conditions. Chromatograms reveal no new peaks.

CE-HPLC results reveal no significant change in main peak for samples stored under recommended conditions through 36 months. Under conditions of elevated temperature, there is a loss of main peak and post-main peaks with an increase in pre-peak that is mostly due to an increase in deamidated species. Loss of main peak can reach up to 45% by the end of the testing program (12 months for accelerated and 6 months for stressed) and generally begins at month 6-9 under accelerated conditions and at month 2-3 under stressed conditions. Chromatograms reveal the formation of no new species.

Reviewer Comment: Data were provided to the original BLA to demonstrate that the deamidated species retain full potency as measured using the HTRF assay.

rCE-SDS results reveal no significant change in main peak for samples stored under recommended conditions. A loss in main peak (up to 5%) with increases in non-main and post heavy chain peaks is observed in samples stored at elevated temperature. Electropherograms reveal no new peaks under recommended conditions. There appear to be no new peaks under elevated temperatures; however, it is difficult to thoroughly assess all minor species due to the limiting amounts in RS.

No significant changes in protein concentration or pH are observed. Subvisible particulate levels show no trend over time. Color, clarity, and particulates assessed by the visual inspection remain within the acceptance criteria for all lots. All container closure integrity tests to date have met acceptance criteria, and sterility is maintained for up to 36 months.

SDS-PAGE, used as a stability assay during development, reveals no significant formation of (b) (4) and no apparent new bands relative to RS under recommended storage conditions through 18 months. Under accelerated or stressed conditions some degradation is observed, similar to the CE-SDS results; no new bands are apparent.

A photostability study was conducted per ICH Q1B using primary stability lot 049A074424. Unlabeled vials and vials packaged into cartons representative of the dispensing packs were subjected to an illumination of approximately 1.2 million lux hours, consisting of both cool white fluorescent light and at least 200 watt hours/square meter of UV irradiance. Untreated control samples were tested to provide baseline data. There were no changes in packaged samples. For exposed samples, there were no significant changes in protein concentration, visual appearance, or pH. Potency was 124% for untreated control, 95% for the packaged control, and 97% for exposed vial; these differences are likely within the inherent assay variability. SE-HPLC revealed a loss in main peak and an increase from 0.6% to 2.4% HMW species. CE-HPLC showed an approximate 3% loss in main peak and an increase in pre-peak formation. rCE-SDS also showed an approximate 1% loss in main peak. No new peaks were identified using any of these methods.

A photostability study was also conducted under conditions intended to simulate clinical use. Vials were subjected to conditions representing up to 14 consecutive days of light exposure at 2000 lux at room temperature. Samples were pulled at designated time points. There were no significant changes in protein concentration, visual appearance, pH, rCE-SDS or potency (range of 92-113%). SE-HPLC showed an increase in HMW species throughout the time course with an approximate increase of 1.2% at 14 days. CE-HPLC showed a very slight decrease in main peak. No new peaks were identified using any of these methods.

A temperature cycling study was performed to assess the effects of excursions outside of recommended storage. Each cycle consisted of storage at -20°C for 48 hours followed by storage at 29°C for 48 hours. Samples were cycled up to a total of 5 times prior to placement at the recommended storage temperature for long term monitoring. No significant differences between the cycled vials and untreated controls were observed through the 24 month time point.

To support end-user storage and handling, Amgen performed stability studies for DP held at elevated temperature at the end of shelf life. DP lot 049A086143 was stored under the recommended storage condition for 24 months (proposed expiry period is 36 months) and then stored at 25°C and 29°C for 4 months. All stability acceptance criteria were met through 3 months at both 25°C and 29°C. Through this time period, there was an increase in SEC HMWS, and decrease in monomer, of 0.1%, a decrease in rCE-SDS monomer of 1%, and there were no significant changes in CEX. At the 4 month time point, there was a decrease in CEX main peak to levels below the acceptance criterion (61.6% at 25°C and 58.4% at 29°C); all other parameters remained within the acceptance criteria (1% decrease in CE-SDS main peak and 0.2% increase in SEC HMWS). Chromatograms reveal no new peaks in SEC, CEX, or CE-SDS analyses.

Reviewer Comment: The sudden significant decrease in CEX main peak is consistent with all other stability data for denosumab.

The storage and handling information of the approved Prolia PI includes "Once removed from the refrigerator, Prolia must not be exposed to temperatures above 25°C/77°F and must be used within 14 days. If not used within the 14 days, [TRADENAME] should be discarded." (b) (4)

(b) (4)

The combined data for the 70 mg/ml DP stability through the end of shelf life under recommended conditions; through 3 months at 25°C or 29°C at the end of shelf life; through 1 month at 37°C at t=0 indicate that the material should remain stable at RT for the 14 days approved for the 60 mg/ml presentations, even if the storage site "RT" is greater than the 25°C specified. However, the data that would demonstrate unequivocally that the denosumab DP is stable for 30 days at the end of shelf life at temperatures representative of worst case for actual RT conditions (i.e. those found in a doctors office or during transport by a patient from a pharmacy versus the 25°C CRT found in a stability testing chamber) have not yet been provided. (b) (4) t

(b) (4)

[redacted]

3.2.A Appendices

3.2.A.1 Facilities and Equipment

For the original denosumab BLA submission, Facilities and Equipment information was predominantly reviewed by DMPQ and was additionally reviewed by DMA and DMPQ during the pre-approval inspections of the drug substance manufacturing facilities and the biennial inspection of the drug product manufacturing facility. There are no significant changes reported in this submission; updated drawings have been provided.

3.2.A.2 Adventitious Agents Safety Evaluation

The adventitious agents safety evaluation did not change from the original submission with the exception of minor corrections and updates to the certificates of suitability.

3.2.A.3 Novel Excipients

No novel excipients are used in the manufacture of denosumab.

3.2.R Regional Information (U.S.A.)

3 .2.R.1 Executed Batch Records (U.S.A.)

Executed batch records were provided for DS lot 049C048023 (ACO; reviewed as part of the original BLA submission) and 76002 (BIP; reviewed as part of the original BLA submission) and for DP lot 0010006190.

The batch records are acceptable.

3.2.R.2 Method Validation Package (U.S.A.)

Validation of the updated [redacted] (b) (4) ***was included; see section 3.2.P.5.3.***

3.2.R.3 Comparability Protocols (U.S.A.)

Comparability protocols for AML DS and DP manufactured from AML DS were submitted in and reviewed as part of the original BLA. It was noted in the IR sent to Amgen on August 20, 2009 that if there are any statistically significant differences, comprehensive assessment by FDA would be required prior to release of the AML-produced materials and may require submission of the data under a PAS; Amgen agreed.

Immunogenicity

5.3.5.3. Immunogenicity Overview

Amgen has developed immunoassays to detect binding antibodies to denosumab and cell based bioassays to determine the neutralizing potential of anti-drug antibodies (ADA). Pre-existing antibodies were detected in 0.2% (6 of 3649) of subjects, and 0.3% (10 of 3508) subjects developed binding assays; 5 subjects were transiently positive, and the other 5 were positive only at the last time point tested. No subjects tested positive for neutralizing antibodies. The higher dose given for the cancer indications does not correlate with an increased incidence of immunogenicity.

Binding antibodies are detected with a validated ECL bridging immunoassay. The earliest version of the assay, used for studies 20010123 and 20010124, was performed with an Igen M8 reader. Drug tolerance was optimized for the second version, which was used for the next 3 clinical studies (20030148, 20030164, and 20010180). Drug tolerance and reliability were further improved by switching to the Meso Scale Discovery Sector Imager RP 100 system; this method was used in all pivotal and ancillary studies starting with 20040113. Samples that are positive for binding antibodies are tested for neutralizing activity using a validated cell-based chemiluminescent mRNA expression bioassay that monitors induction of TRAP mRNA.

The immunogenicity assays used for the studies included in this submission are the same as those found to be acceptable during the review of the original BLA. As was reviewed for the original submission, the threshold value (cut point) determined for the current version of the assay (used for the majority of the subjects) is similar to the threshold value obtained using samples from breast and prostate cancer study subjects. The binding antibody assay was tolerant of up to 5 µg/ml soluble denosumab when assaying the 15 ng/ml QL and was tolerant of up to 50 µg/ml denosumab when assaying 250 ng/ml of ADA. The neutralizing assay is more sensitive to the presence of denosumab; in the presence of 1.1 µg/ml denosumab, the LOD decreases to 2.56 µg/ml ADA. For a 120 mg dose, the average maximum denosumab serum concentration was 11.8 µg/ml. By the 1 month time point, this value falls to approximately 8 µg/ml.

Mapping Table for Analytical Methods and Method Validation Reports Referenced in the Department of Clinical Immunology Integrated Immunogenicity Report

Previous Number	Current Number	Document Title
2260.5028	MET-002074	Bioassay to detect neutralizing antibodies to AMG 162/Denosomab in 5% human serum by measuring tartrate resistant acid phosphatase (TRAP) mRNA induction in RAW 264.7 Cells
2260.5079	MET-001897	Bioassay for the Detection of Neutralizing Antibodies to AMG 162 in 1% Human Serum
2260.6085	MET-001880	Analytical Procedure for an Immunoassay to Detect Antibodies to AMG 162 in Human Serum Using the IGEN M8
2260.6114	MET-002025	Analytical Procedure for an Immunoassay to Detect Antibodies to AMG 162 in Human Serum Using the MSD Sector PR
2260.6119	MET-001914	Analytical Procedure for a Confirmatory Immunoassay for AMG 162 in Human Serum using the MSD Sector PR
2260.7056	MVR-000036	Validation of a Bioassay Method to Detect Neutralizing Antibodies to AMG 162 in Human Serum Using RAW 264.7 Cells
2260.7139	MVR-000046	Validation Report for an Immunoassay to Detect Antibodies to AMG 162 in Human Serum Using the IGEN M8
2260.7185	MVR-000192	Validation of a Screening Immunoassay to Detect Antibodies to AMG 162 in Human Serum using the MSD Sector PR
2260.7190	MVR-000188	Partial Validation of a Confirmatory Immunoassay to Detect Antibodies to AMG 162 in Human Serum using the MSD Sector PR
2260.7208	MVR-000057	Validation of Analytical Procedure 2260.5079: A Bioassay for the Detection of Neutralizing Antibodies to AMG 162 in Human Serum

1.12.14 Environmental Analysis

Amgen claims categorical exclusion under 21 CFR 25.15(d) and 21 CFR 25.31(c). No extraordinary circumstances exist that modify this exclusion.

Reviewer Comment: The claim of categorical exclusion is appropriate.

SUMMARY OF POST-MARKETING COMMITMENTS:

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70: None

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR BLA/NDA Supplements (OBP & DMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
125320/7	Amgen	May 19, 2010
Established/Proper Name: denosumab	**BLA/NDA Type:** PAS – Priority 6 month	

Brief description of the change:	A 70 mg/ml 1.7 ml fill vial presentation has been added.
Reviewer:	Sarah Kennett
Office/Division:	OBP/DMA

On **initial** overview of the BLA/NDA **supplement** for filing:

The following was submitted in support of the change (check all that apply):

X	A detailed description of the proposed change
X	Identification of the product(s) involved
X	A description of the manufacturing site(s) or area(s) affected
X	A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product
X	The data derived from such studies
X	Relevant validation protocols and data
	A reference list of relevant standard operating procedures (SOP's)

The following deficiencies were identified (identify those that are potential filing issues): None

IS THE PRODUCT QUALITY SECTION OF THE SUPPLEMENT FILEABLE? (Yes) No

If the supplement is not fileable from the product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
See page 2.

Product Quality Reviewer — Date: 7/9/2010

Branch Chief/Team Leader/Supervisor — Date: 7/12/10

1. Validation of the updated subvisible particulates method MET-001340 was performed at ACO; however, lot release and stability testing are performed at both ACO and AML.
   a. Clarify if this method is intended for use at AML.
   b. If this method is intended for use at AML, submit the method transfer report.

2. The proposed PI for the 70 mg/ml presentation includes a 25°C/77°F storage period of up to (b) (4). Discussions regarding data necessary to support storage of drug product under these conditions occurred during the labeling meetings for the 60 mg/ml denosumab presentations under STN 125320. Our concern was that in most cases the end users do not have controlled temperature conditions to assure product storage is maintained at or below 25°C when out of refrigeration. Temperatures may reach above 40°C in some areas of the United States, and drug product may be exposed to such extreme temperatures either at the physician's office or when transported by the patient after product is picked up from the pharmacy. Supporting stability data should be provided to the BLA for the 70 mg/ml presentation to allow for the inclusion of an extended storage period outside of refrigeration.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	BLA 125320
Supporting document/s:	007
Document location:	E-BLA Submission
	EDR Location:
	\\CDSESUB1\EVSPROD\IND009838\009838.enx
Applicant's letter date:	May 14, 2010
CDER stamp date:	May 19, 2010
Product:	Denosumab
Indication:	(b) (4)
	(b) (4)
Applicant:	Amgen Inc.
	One Amgen Center Drive
	Thousand Oaks, CA 91320-1799
Review Division:	Division Biologic Oncology Products (HFD-170)
Reviewer:	Dr. Michael S. Orr, Ph.D., D.A.B.T.
Supervisor/Team Leader:	Dr. Anne M. Pilaro, Ph.D.
Division Director:	Dr. Patricia Keegan, M.D.
Project Manager:	Melanie Pierce

Template Version: December 7, 2009

Disclaimer: Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125320/7 are owned by Amgen Inc. or are data for which [name of applicant] has obtained a written right of reference.
Any information or data necessary for approval of BLA 125320/7 that Amgen Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Amgen Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of BLA 125320/7.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

The nonclinical data provided in the present supplement (STN BLA #125320/7), and those cross-referenced to the original submission (STN BLA#125320/0) support the approval of denosumab at a dose of 120 mg administered once monthly by subcutaneous injection, for the (b) (4)

1.1.2 Additional Non Clinical Recommendations

No additional nonclinical studies are required.

1.1.3 Labeling

Please see Appendix A for the "Revised Label as of October 18, 2010," on page 58 of this review.

Please see Appendix B for the "Original Label as of May 2010," on page 82 of this review.

1.2 Brief Discussion of Nonclinical Findings

Primary Pharmacology Findings

Comment: The nonclinical studies were designed to evaluate the effects of inhibition RANKL, leading to modulations in the RANK/RANKL pathway. RANKL-induced RANK signaling is essential for the formation, function, and survival of mature osteoclasts, which are responsible for bone resorption. RANKL is produced by osteoblastic lineage cells and activated T-cells, and its expression is regulated by various cytokines, glucocorticoids, and PTH. Since denosumab does not recognize mouse or rat RANKL, OPG-Fc was used as a surrogate for denosumab in the mice models. However, these data do not address if denosumab itself is capable of reducing tumor growth and osteolysis in monkeys and humans. Furthermore, it is unclear how to extrapolate the dose levels of OPG-Fc used in the mouse tumor models relative to the dose levels of denosumab being utilized in monkeys and humans. No comparisons between species were made based upon modulation of pharmacodynamic (PD) biomarkers such as TRAP5b by OPG-Fc (rodents) and denosumab (monkey and human) that would facilitate this comparison.

***In Vivo* Breast Tumor Models**

The nonclinical findings provide evidence that inhibition of RANKL by OPG-Fc in female athymic nude mice injected with syngeneic breast (MDA-MB-231[estrogen receptor negative] and MCF-7 [estrogen receptor positive]) tumors leads to reduction in tumor cell growth and subsequent tumor burden, reduction in the area of osteolytic lesions resulting from metastases, and sustained reductions in TRAP5b, a biomarker of osteoclastogenesis. The combination of OPG-Fc-mediated inhibition of RANKL and reduction of tumor cell growth via inhibition of the estrogen receptor by tamoxifen did not appear to provide additional reductions in tumor cell growth or reductions in osteolytic lesions as compared to either agent alone in this *in vivo* cancer model.

***In Vivo* Prostate Tumor Model**

In male athymic nude male mice injected with PC-3 cells, the combination of OPG-Fc and docetaxel significantly reduced the tumor burden (whole body, hind limb, and head region) and osteolytic lesion area to a greater extent, as compared to the inhibition of body tumor burden by either agent alone.

***In Vivo* Lung Tumor Models**

In athymic nu/nu female mice injected with H1975 non-small lung cancer cells, OPG-Fc reduced tumor growth (whole body, hind limb, and head region), and reduced the osteolytic lesion area. In a second lung cancer in vivo tumor model in which H1299 cells were injected in TAC NCR nu/nu female mice, significant tumor growth inhibition (whole body, hind limb, and head region) and significant reductions in skeletal tumor burden based on histological measurements were reported after OPG-Fc treatment. In an additional study investigating the effects of the combination OPG-Fc and docetaxel, OPG-Fc did not significantly reduce the whole body tumor burden while docetaxel alone significantly reduced whole body tumor burden. All treatments resulted in significant reductions in skeletal tumor hind limb tumor burden and reductions in hind limb osteolytic lesions. These data evidence that treatment of H1299 human NSCLC tumor-bearing mice with the combination of OPG-Fc and docetaxel induced greater reductions in whole body tumor burden, hind limb tumor burden, hind limb osteolytic lesions, and hind limb tumor area as compared taxotere alone.

Secondary Pharmacology Findings

OPG-Fc and Rat Angiogenesis

In a rat model of angiogenesis, OPG-Fc in combination with VEGF induced a statistically significant increase in VEGF-induced angiogenesis in the rat corneal disk implant model. However, a second independent study failed to replicate the initial findings in the VEGF-induced angiogenesis in the rat corneal disk implant model. Therefore, the findings in the two independent VEGF-induced angiogenesis in the rat corneal disk implant studies were considered equivocal and it is unclear what the toxicological significance of these findings. Additionally, OPG-Fc had no effect on the βFGF-induced angiogenesis.

2 Drug Information

2.1 Drug

Denosumab

2.1.1 CAS Registry Number (Optional)

615258-40-7

2.1.2 Generic Name

Denosumab

2.1.3 Code Name

AMG 162

2.1.4 Chemical Name

Not applicable

Table 1: Physical and Chemical Properties of Denosumab (abstracted from the Amgen's CMC section in the original BLA submission)

Table 1. Physical and Chemical Properties of Denosumab

Expression System	CHO cells and encoded by cDNAs
Immunoglobulin subclass	IgG2
Sequence	Fully Human Sequence
Binding site	Specific Binding to human RANKL at the D-E Loop (epitope:DLATE)
Molecular weight	144, (b) (4)
	147, (b) (4)
Cysteines	(b) (4)
Number of disulfide bonds	
Glycosylation	
Theoretical extinction coefficient	
Isoelectric point	
T_m (melting points)	

[a] For peptide portion; accounting for C-terminal Lysine processing at the heavy chain
[b] Glycosylated mass includes 2 copies of the most abundant G0 glycan

2.1.5 Molecular Formula/Molecular Weight

(b) (4)

2.1.6 Structure

(b) (4)

(b) (4)

2.1.7 Pharmacologic class

RANK ligand inhibitor

2.2 Relevant IND/s, NDA/s, BLA/s and DMF/s

BB-IND 9837 – initial IND – DRUP – treatment of postmenopausal osteoporosis
BB-IND 9838 – DBOP – treatment of bone disease associated with cancer
BB-IND 11709 – DBOP – treatment of sex hormone ablation bone loss associated with aromatase inhibitors in patients with breast or prostate cancer
BB-IND 11707 – DAARP – treatment of bony erosions, osteoporosis, and osteopenia associated rheumatoid arthritis

(b) (4)

STN BL 125320/0 Preserved: "Original Application" as described under section of the Public Health Service Act: Treatment of postmenopausal osteoporosis in women.

STN BL 125331/0-Converted to STN BL 125330/4:
"Prior Approval Supplement-Efficacy" as described under 21 CFR 601.12(b) for the prevention of osteoporosis in postmenopausal women.

STN BL 125332/0-Converted to STN BL 125330/5:
"Prior Approval Supplement-Efficacy" as described under 21 CFR 601.12(b) for the treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer.

STN BL 125333/0-Converted to STN BL 125330/6:
"Prior Approval Supplement-Efficacy" as described under 21 CFR 601.12(b) for the treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer.

BL 125355/0-Converted to 125320/7: "Prior Approval Supplement-Efficacy" as described under 21 CFR 60 1.12(b) for the (b) (4)

2.3 Clinical Formulation

Single-use 3.0 ml glass vials containing 1.7 ml of 70 mg denosumab per ml of 18 mM sodium acetate, 5% sorbitol, with a pH of 5.2.

2.3.1 Drug Formulation

70 mg/ml denosumab, 18 mM sodium acetate (1 mg/ml), 4.6% (w/v) sorbitol (46 mg/ml), at a pH of 5.2

2.3.2 Comments on Novel Excipients

No new excipients were used in the drug product

Table 2: Drug Product Formulation Excipients (abstracted from the Amgen's CMC section in the original BLA submission)

Table 9. Drug Product Formulation Excipients

Excipient	Grade
Water for injection	USP, (b) (4)
Sorbitol	(b) (4)
Glacial acetic acid	
Sodium hydroxide[a]	

[a] (b) (4)

2.3.3 Comments on Impurities/Degradants of Concern

None

2.4 Proposed Clinical Population and Dosing Regimen

Proposed Clinical Population: (b) (4)

Dosing Regimen: 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh or abdomen.

2.5 Regulatory Background

Amgen, Inc. submitted four original biologic licensing applications (BLA) on December 19, 2008 for four separate indications. Three of these BLAs were later converted to post-approval efficacy supplements, after approval of the initial BLA for denosumab in the treatment of postmenopausal osteoporosis. The original indications and the associated BLA numbers are provided under Section 2.2 (Relevant INDs, NDAs and BLAs), above:

The two postmenopausal indications were reviewed by the DRUP (Division of Reproductive and Urologic Products) and the two indications for bone loss in cancer patients were reviewed by DBOP (Division of Biologic Oncology Products). The four original BLAs (12530 to 125332) were jointly reviewed by DRUP and DBOP and a Complete Response Action Letter was sent on October 16, 2009.

Amgen submitted a complete response to the October 16, 2009 Action Letter on January 25, 2010, and STN BL 125320/0 was subsequently approved on June 1, 2010. The STN BL 125320/0 became the "original application". The applications for all other indications were converted to post-approval supplements, under the original BLA. A list of the applications is provided under Section 2.2, above.

STN BL 125320/7 was submitted on May 19, 2010 to the Division of Biologic Oncology Drugs for the indication: (b) (4)
The PDUFA Goal Date for this submission is November 18, 2010.

3 Studies Submitted

3.1 New Nonclinical Studies Submitted to /Reviewed for the Present sBLA:

Pharmacology-Primary Pharmacodynamics (b) (4) sBLA on 19 May 2010)	
Study #	**Title**
R2006160	Effects of OPG-Fc on Tumor Burden and Osteolysis in MDA231-F11Luc Bone Metastasis Model in Female Athymic Nude Mice, Prevention Setting
R2006161	Effects of OPG-Fc on Tumor Burden and Osteolysis in MDA231-F11Luc Bone Metastasis Model in Female Athymic Nude Mice, Therapeutic Setting
R20080162	The Effect of Tamoxifen and the RANKL Inhibitor Osteoprotegerin (OPG-Fc) on the Growth of MCF-7 Cells in an Established Bone Metastasis Model in Female Athymic Nude Mice
R20070953	The Effect of Pretreatment of OPG-Fc on Prevention of Bone Mets in MDA-MB-231(F11)Luc Bone Metastasis Model in Female Athymic Nude Mice
R20080161	The Effect of Tamoxifen and the RANKL Inhibitor Osteoprotegerin (OPG-Fc) on the Growth of MCF-7 Cells in an Established Bone Metastasis Model in Female Athymic Nude Mice
R20080162	The Effect of Tamoxifen and the RANKL Inhibitor Osteoprotegerin (OPG-Fc), Alone and in Combination, on the Growth of MCF-7 Cells in an Established Bone Metastasis Model in Female Athymic nude mice
R20070963	The Effect of Human OPG-Fc Treatment on Tumor Burden and Osteolysis in a Murine Model of Bone Metastasis of Human Non-Small Cell Lung Cell Line H1975 Luc in Athymic Nude Female Mice
R20080310	The Effect of the RANK Ligand Inhibitor OPG-Fc on Tumor Burden and Osteolysis in a Murine Model of Bone Metastasis of Human Non-Small-Cell Lung Cell Line H1299 in Female Athymic Nude Mice
R20080331	Effect of OPG-Fc (in Combination with Docetaxel) Treatment on Tumor Burden and Osteoclast Remodeling in a Murine Model of Bone Metastasis of Human Non-Small-Cell Lung Cell Line H1299 in Female Athymic Nude Mice
R20080332	Effect of OPG-Fc (Alone and in Combination with Docetaxel) Treatment on Tumor Burden and Osteolysis in a Murine Model of Bone Metastasis of Human Non-Small-Cell Lung Cell Line H1299 in Athymic Nude Female Mice
Pharmacology-Secondary Pharmacodynamics (Bone metastases from solid tumors indications sBLA on 19 May 2010)	
Study #	**Title**
R20090211	Effect of the RANKL Inhibitor RANK-Fc versus Vehicle on Tumor Development in a Hormone and Carcinogen Induced Model of Mammary Tumorgenesis
R2002266	Effects of OPG-Fc on Neovascularization in the Rat Corneal Disk Implant Model of Angiogenesis
R2002204	The Effect of OPG-Fc on Neovascularization in the Rat Corneal Disk Implant Model of Angiogenesis
R2002267	The Effect of OPG-Fc on Neovascularization in the Rat Corneal Disk Implant Model of Angiogenesis

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Data reviewed for the original BLA submission by Dr. Michael Orr or Kim Hatfield can be found in the non-clinical reviews for STN BL 125320/0.

4 Pharmacology

For the full review of the complete pharmacology information for denosumab submitted to STN BLA 125320/0, please see the original reviews by Dr. Michael Orr and Kim Hatfield. Below is a brief summary of those findings, with the inclusion of additional information pertinent to the present cancer indication, i.e. (b) (4)

Denosumab is a fully human monoclonal IgG2 antibody that binds to and inactivates RANKL (receptor activator of nuclear factor kappa B ligand). The mechanism of action of this antibody involves blocking the binding of RANKL with its receptor RANK, thereby preventing receptor activation and downstream signaling. RANKL-induced RANK signaling is essential for the formation, function, and survival of mature osteoclasts, which are responsible for bone resorption. RANKL is produced by osteoblastic lineage cells and activated T-cells, and its expression is regulated by various cytokines, glucocorticoids, and PTH.

Surrogate models used to evaluate the pharmacodynamic role of RANKL in rodents included a mouse knock-in (KI) model expressing human RANKL, a rat transgenic model overexpressing osteoprotegerin (OPG) and a surrogate fusion protein construct of osteoprotegerin bound to antibody Fc region (OPG-Fc). OPG is the natural endogenous inhibitor of RANKL that is active in both rodents and humans.

Denosumab inhibits RANKL in monkeys and humans, while OPG-Fc inhibits RANKL in mice and rats. Since denosumab does not recognize mouse or rat RANKL, OPG-Fc was used as a surrogate inhibitor of RANKL instead of denosumab in the rodent models.

The OPG/RANK/RANKL axis is abnormally regulated in several malignancies that metastasize to bone, including breast cancer, prostate cancer and multiple myeloma. In malignancies that metastasize to bone, the result is often tumor-induced osteolysis, which can cause fracture, hypercalcemia, and severe morbidity. Osteolysis, in turn, releases growth factors from the bone matrix that can further support the growth of tumor cells in the bone microenvironment. Inhibition of RANKL by OPG-Fc treatment

has been shown to decrease tumor-induced osteolysis, as measured by histological staining at terminal endpoints.[1]

4.1 Primary Pharmacology

Study Title: Effect of OPG-Fc on Tumor Burden and Osteolysis in MDA231-F11Luc Bone Metastasis Model in Female Athymic Nude Mice, Prevention Setting, Study Number R2006160

Key Findings:

- Treatment of female athymic nude mice with the vehicle (PBS), 0.3, or 3 mg/kg of OPG-Fc did not significantly change animal body weights during this study.

- When MDA-MB-231(F11)luc (luc = Luciferase) gene-modified tumor cells were injected in female athymic nude mice, OPG-Fc at 3 mg/kg induced a 72% inhibition of tumor growth on day 25 compared to controls, based on whole body bioluminescence. However, in mice treated with 0.3 mg/kg OPG-Fc, there was no effect on tumor growth inhibition relative to the vehicle control.

- OPG-Fc (0.3 and 3 mg/kg dose groups) induced a dose-dependent decrease in osteolysis, based on X-ray evaluation of the bone lesion area (histomorphometric analysis).

Methods: Female athymic nude mice were injected intra-cardiac into the left ventricle with $1x10^5$ MDA-MB-231(F11)luc tumor cells expressing luciferase. Treatment with OPG-Fc started on day 0 and continued until day 21. OPG-Fc at 0.3 and 3.0 mg/kg was administered subcutaneously (SC) twice per week from day 0 to day 21. Bioluminescence and body weight of each animal were measured twice per week. Degree of osteolysis was determined by X-ray histomorphometry.

In vivo bioluminescence (BLI) was measured twice weekly and was performed with an IVIS200 (Xenogen Corp.) imaging system. Images and measurements of bioluminescent signals were analyzed using Living Image software (Xenogen Corp.). Prior to OPG-Fc treatment and tumor imaging, mice were injected with 150mg/kg luciferin intra-peritoneal (IP) on day 0 after tumor cell injection, then were evaluated with the IVIX200 system to confirm accurate intra-cardiac (IC) injection of the tumor cells. Mice with successful injections as determined by whole body bioluminescence were randomized into groups (10 mice/group). For measurements of BLI, three regions of interest (ROI) were selected on dorsal-side-up images, as follows: Individual legs BLI = one ROI around the proximal tibia and distal femur of each leg, then summed. Hind limb BLI = one rectangular ROI over the entire hind limb region of the animal. Whole Body BLI = one rectangular ROI around the entire animal. Analysis of osteolysis: mice were

1 Morony S, Capparelli C, Sarosi I, Lacey DL, Dunstan C, Kostenuik P. Osteoprotegerin inhibits osteolysis and decreases skeletal tumor burden in syngeneic and nude mouse models of experimental bone metastasis. *Cancer Research* 2001, 61:4432-4436.

scanned on day 25 using a Faxitron MX-20 digital XRay, and bone lesion area was measured by tracing and quantifying images using MetaMorph image analysis software. Units are in mm^2. Images were blinded for histomorphometric analysis. For histological analysis, femurs and tibias were harvested, fixed, decalcified, sectioned and stained with H&E. Quantification of tumor area was performed on one section per leg (femur/tibia) in a blinded fashion, using BioQuant software.

Statistical Analyses:

The objective of the studies was to compare the imaging and osteolysis (X-ray morphometry) findings in the control (vehicle) to the OPG-Fc treatment groups. This was accomplished by computing the slopes of the measurements over time (rate of change) and comparing them, and by comparing the mean BLI between groups at each time point. Bioluminescence analysis was done using SAS V9.1 on a Windows 2000 Professional operating system. Each area of the body was analyzed separately. During the course of the analysis, it was found that the standard errors of the group means increased with the size of the means, so that a log transformation was used on the BLI measurements to stabilize the variances. Treatment groups were compared using SAS proc mixed. The slopes were compared using Bonferroni corrected linear contrasts to compare treatment groups with the control. The control and treatment means were compared at each time point using Dunnett's test. For the osteolysis analysis, Bonferroni/Dunn analysis was conducted on the lesion areas using Statview software. For statistical analysis for the tumor volume measurements by histology, and Dunnet's multiple comparison tests were performed.

Results:

Figure 2: Effect of OPG-Fc on Body Weight of Athymic Nude Mice

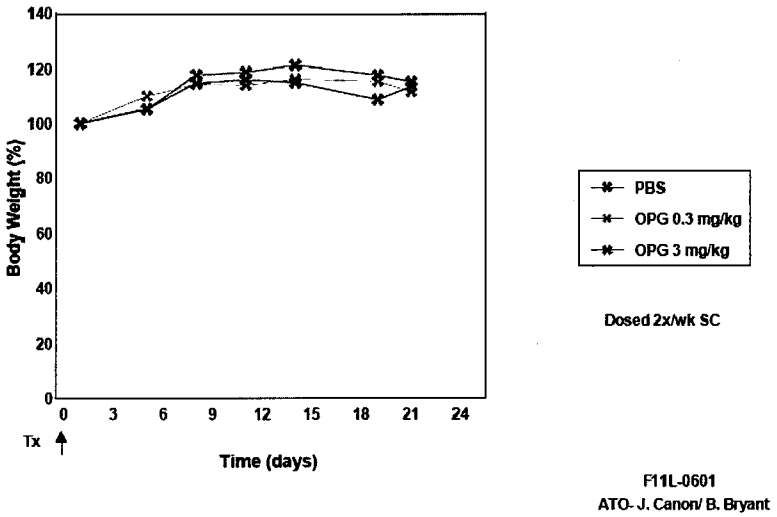


Figure 4. Mice (n=10 per group) were injected with 100,000 cells into the cardiac left ventricle on day 0. Treatment began on day 0. Body weight was measured twice weekly. Data represent percent body weight, with 100% representing the mean body weight on day 1. Error bars represent ± standard error of the mean.

Figure 3: Effect of OPG-Fc on Whole Body Bioluminescence

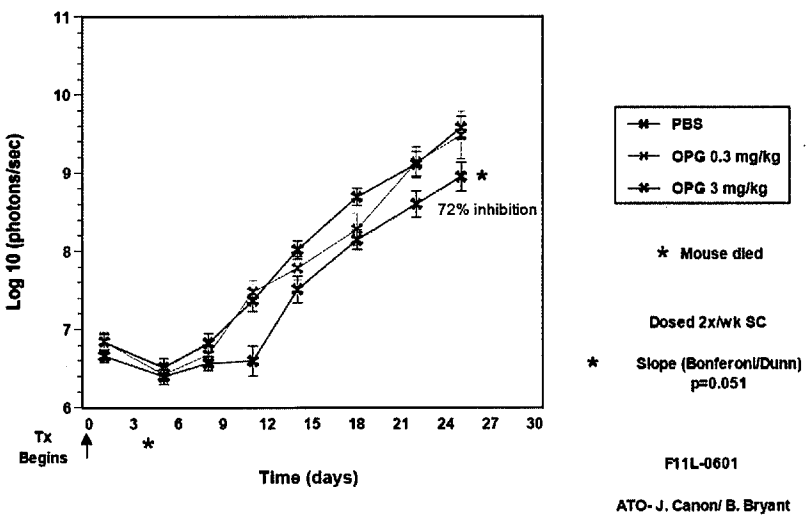


Figure 2. Mice (n=10 per group) were injected with 100,000 cells into the cardiac left ventricle on day 0. Treatment began on day 0. Data is the log of the bioluminescence value (photons/sec) from the Whole Body, and represent the mean ± standard error of the mean. Percent of inhibition was calculated using untransformed results.

Figure 4: Radiographical Analysis of Effect of OPG-Fc on Osteolysis

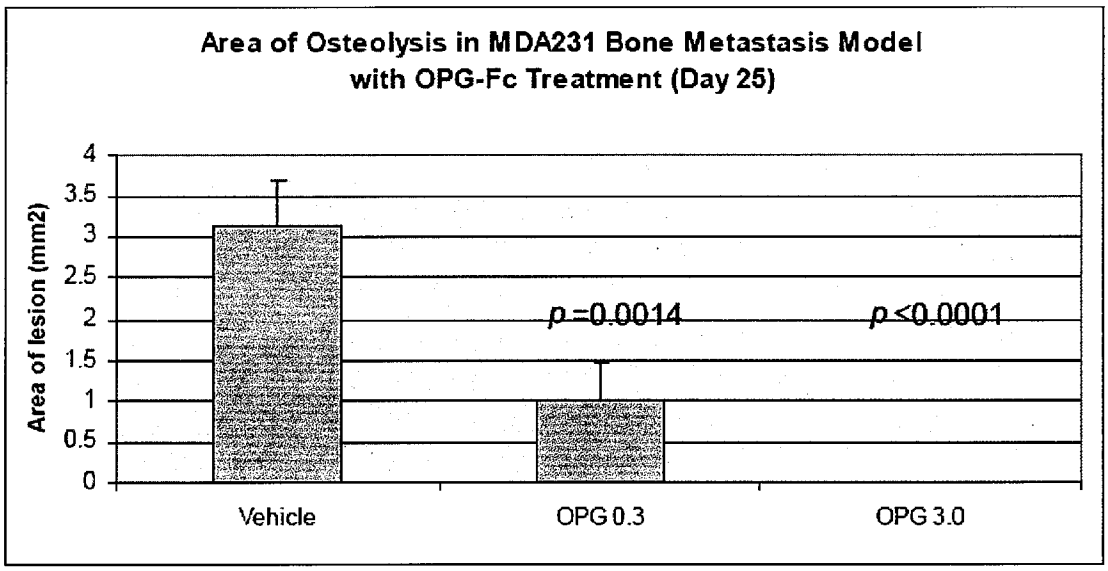
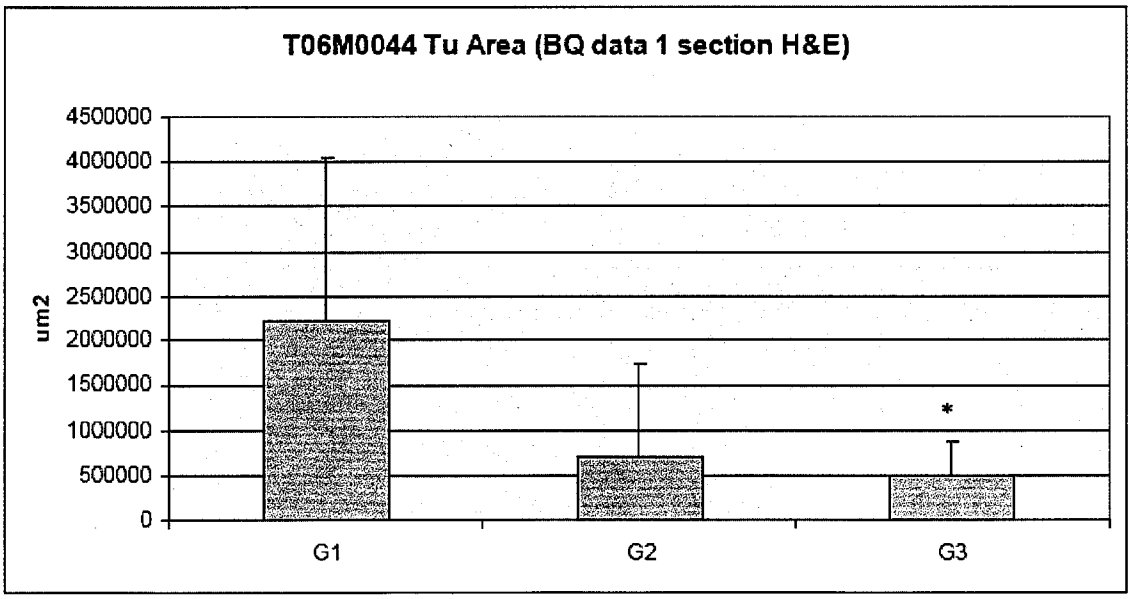


Figure 5. Area of osteolytic lesions in each group were averaged. Statistical analysis was performed using a Bonferoni/Dunn test in Statview.

Figure 5: Tumor Area in Femur/Tibia by Histology



Dunnett's Multiple Comparison Test	Mean Diff.	q	P value	95% CI of diff
G1 vs G3	1272000	2.345	P < 0.05	215.3

* 78% inhibition compared to vehicle (G1)

Discussion of Results:

OPF-Fc at 3 mg/kg induced a significant reduction in MDA-MB-231(BB)luc tumor cell growth, based on the whole body bioluminescence evaluation in female athymic nude mice (see Figure 3) OPG-Fc (0.3 and 3 mg/kg) caused significant dose-dependent reductions in osteolysis based on X-ray evaluation of the bone lesion area (see Figure 4). The tumor area was reduced in the Femur/Tibia area by 78% relative to the vehicle control based on histology evaluation (see Figure 5). No significant changes in body weight were observed between the different treatment groups (see Figure 2).

Reviewer Comments: The use of OPG-Fc to inhibit tumor growth provides evidence that inhibition of the RANK pathway reduces tumor growth and osteolysis in mice. However, these data do not address if denosumab is capable of reducing tumor growth and osteolysis in monkeys or humans. Furthermore, it is unclear how to extrapolate the dose levels of OPG-Fc used in the mouse tumor models, relative to the dose levels of denosumab being utilized in monkeys and humans. No comparisons between species were made based upon modulation of pharmacodynamic (PD) biomarkers such as TRAP5b, which could potentially have provided data that would facilitate this comparison.

Study Title: Effect of OPG-Fc on Tumor Burden, Osteolysis, and Survival in MDA231-F11Luc Bone Metastasis Model in Therapeutic Setting, Study Number R2006161

Key Findings:

- Administration of OPG-Fc at 0.3 and 3 mg/kg inhibited osteolysis in a dose-dependent manner in the hind limb of female athymic nude mice injected with MDA231-F11 cells.
- OPG-Fc at 0.3 and 3 mg/kg dose group inhibited growth of MDA-MB-231(F11)luc cells in athymic nude mice.
- The body weight did not significantly change in the vehicle (PBS), 0.3, and 3 mg/kg dose groups.

Methods:

Athymic nude mice were injected intra-cardiac into the left ventricle with $1x10^5$ MDA-MB-231(F11)luc tumorcells expressing luciferase. Dosing with OPG-Fc started on day 7 and continued until the end of study. OPG-Fc at 0.3 and 3.0 mg/kg was administered SC twice per week for 25 days. Bioluminescence and body weight of each animal were measured twice per week from Day 5 to Day 21. Degree of osteolysis was determined by X-Ray histomorphometry.

Results:

Figure 6: Effect of OPG-Fc on Hind limb Bioluminescence

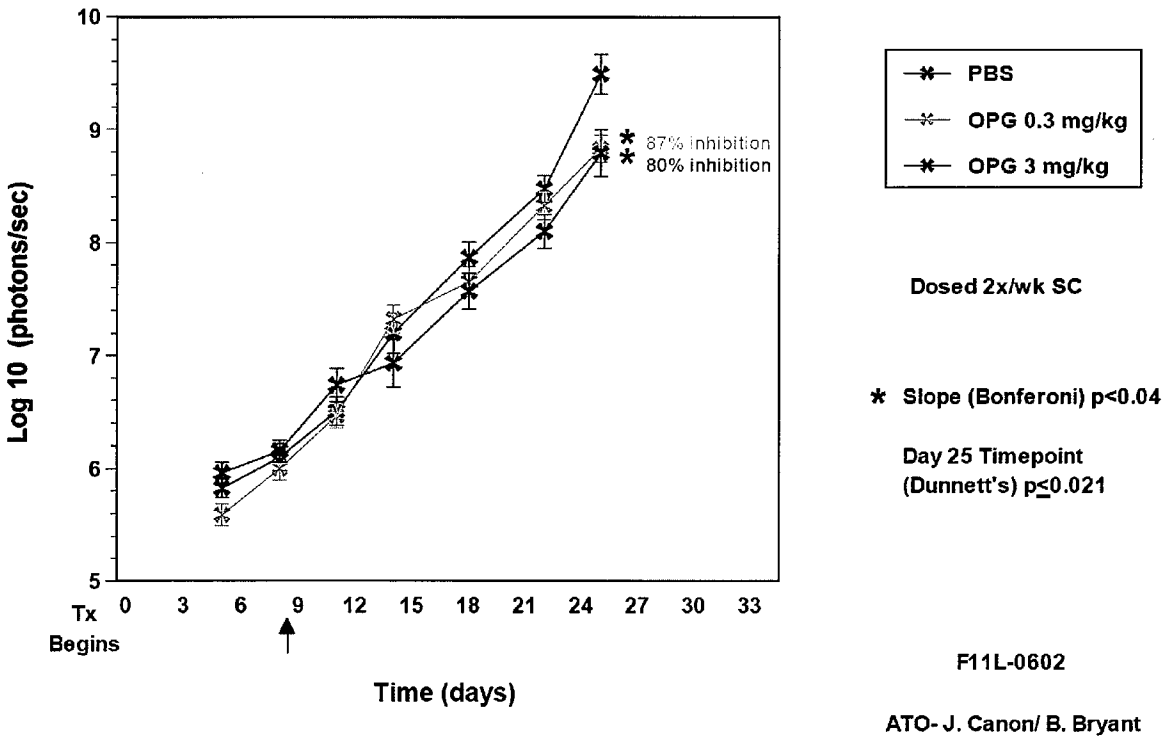


Figure 3. Mice (n=10 per group) were injected with 100,000 cells into the cardiac left ventricle on day 0. Treatment began on day 7. Data is the log of the bioluminescence value (photons/sec) from the Hindlimb ROI, and represent the mean ± standard error of the mean. Percent of inhibition was calculated using untransformed results.

Reviewer Comment:

Clear differences in tumor growth inhibition in the OPG-Fc treated animals were only observed on days 21 and 24 relative to the vehicle control (PBS). While both the 0.3 and 3 mg/kg doses of OPG-Fc were capable inducing growth inhibition, a clear dose-response effect was not observed in this model.

Figure 7: Radiographical Analysis of Effect of OPG-Fc on Osteolysis

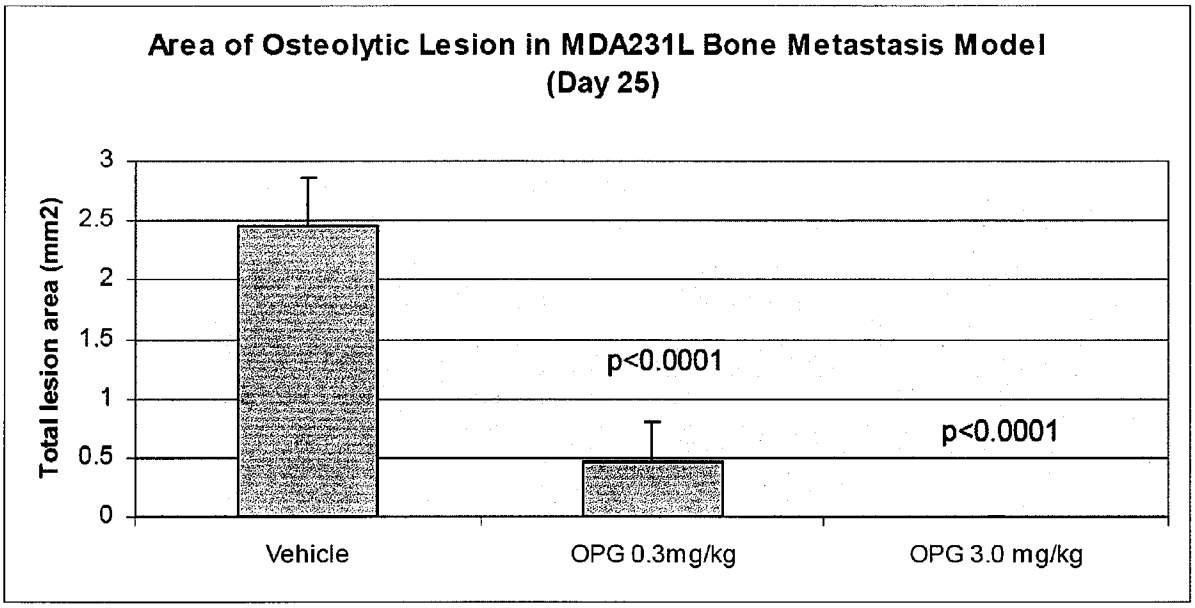


Figure 5. Mice (n=10 per group) were injected with 100,000 cells into the cardiac left ventricle on day 0. Treatment began on day 7. X-ray histomorphometric analysis was conducted, and data is the mean area of osteolytic lesion ± standard error of the mean. Statistical analysis performed with Statview using Bonferoni/Dunn test.

Reviewer Comment:
Dose-dependent reductions in the area of osteolytic lesions were observed following administration of 0.3 or 3 mg/kg of OPG-Fc.

Study Results:

OPG-Fc inhibited the growth of MDA-MB-231(F11) cells expressing luciferase in the hind limbs of female athymic nude mice (See Figure 6). The body weight did not significantly change between the vehicle (PBS), and the 0.3 and 3 mg/kg OPG-Fc dose groups (data not shown). Significant dose-dependent reductions in osteolysis following treatment with OPG-Fc were observed based on histomorphometric analysis (see Figure 7).

Study Title: The Effect of Pretreatment of OPG-Fc on Prevention of Bone Mets in MDA-MB-231(F11)Luc Bone Metastasis, Study Number R20070953

Key Findings:

- Pretreatment with OPG-Fc reduced TRAP5b levels in a dose-dependent manner in tumor-bearing, female athymic nude mice.
- Administration of OPG-Fc at 0.3 and 3 mg/kg dose levels inhibited osteolysis in a dose-dependent manner in female athymic nude mice.
- OPG-Fc pretreatment reduced the percent of hind limb metastases in a dose-dependent manner in the MDA-MB-231(F11)Luc athymic nude mice model.

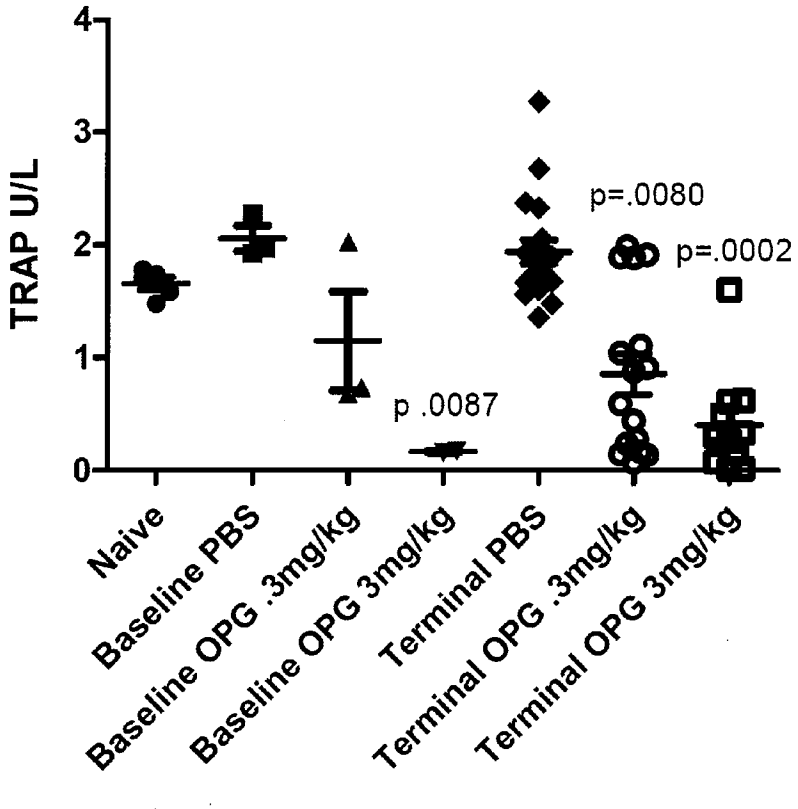
Methods:

This study uses luciferase-labeled MDA-MB-231(F11)Luc breast carcinoma cancer cells that have the capacity to form bone metastasis in athymic nude mice. The cell location was determined by the use of bioluminescence imaging of the MDA-MB-231(F11)Luc cells. Eighty female athymic nude mice (n = 20/group) were injected intra-cardiac into the left ventricle with $1x10^4$ MDA-MB-231(F11)Luc cells expressing luciferase. Mice were randomized into 3 groups (n = 20/group). Dosing with OPG-Fc or the vehicle, PBS (3x/wk), started on day -7, and continued until day 21. OPG-Fc at 0.3 mg/kg and 3.0 mg/kg was administered SC three times per week from day -7 to day 21.

Determination of hind limb bone metastases was conducted on blinded In vivo bioluminescence (BLI) images. Bioluminescence was measured three times per week. Degree of osteolysis in hind limbs was determined by X-Ray histomorphometry. On day 0 and day 24, serum was taken for TRAP5b measurement, to determine level of osteoclastogenesis.

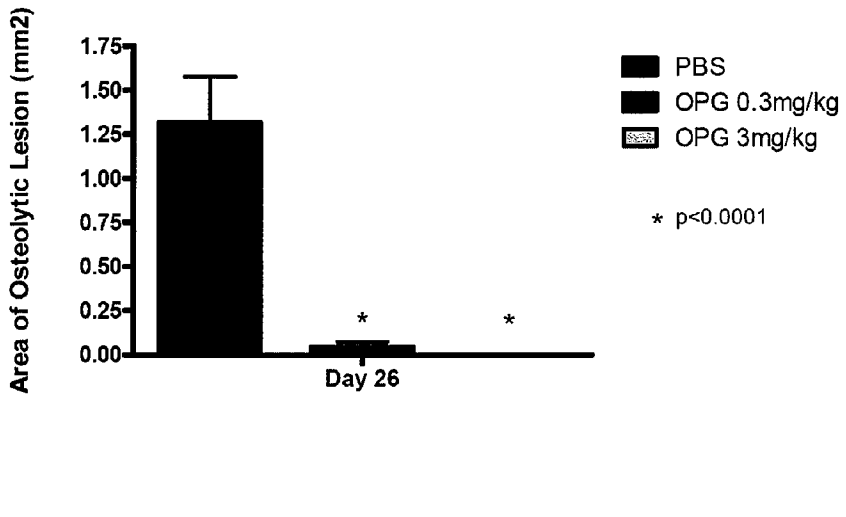
Results:

Figure 8: Serum TRAP5b Levels



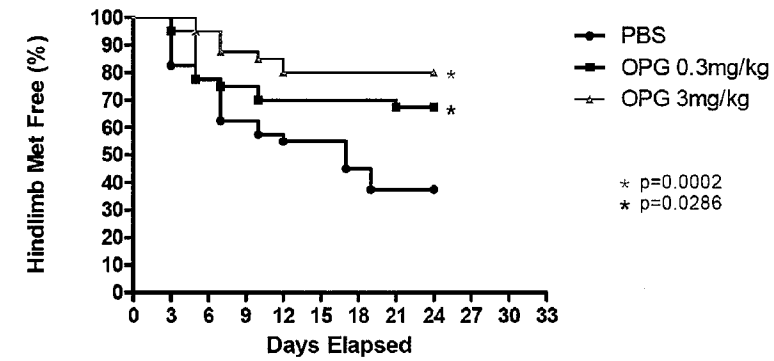
Pretreatment of OPG-Fc at 3mg/kg resulted in a significant decrease in serum TRAP5b on Day 0. Osteoclast activity was determined on day 0 (baseline) before tumor inoculation and at study termination (day 24) by analyzing for the osteoclast marker Trap-5b. Values reported on this figure are mean ± standard deviation with individual data points representing the individual values.

Figure 9: Average Area of Osteolytic Lesion in MDA-MB-231(F11)Luc Bone Met Model



N = 10/group. Area of osteolytic lesions in each group were averaged. Values represent the mean ± standard error of the mean. Statistical analysis was performed using a Bonferroni/Dunn test in Statview. Both treatment groups were statistically different than the Vehicle group.

Figure 10: Pretreatment of OPG Blocks Hind limb Tumor Formation in an MDA-MB-231(F11)Luc Bone Metastasis Model



RANKL inhibition by OPG-Fc treatment delays de novo metastasis formation by MDA-231 tumor cells. Mice (n = 20 per group) were injected with 10,000 MDA-231Luc cells into the cardiac left ventricle on day 0. Treatment began on day -7 and continued until Day 21 for all groups. BLI scans were analyzed for evidence of signal in the hind limbs in a blinded fashion. Hind limbs with a BLI signal were determined to be positive for metastases and no longer considered met free. There was a statistically significant difference between both OPG-Fc groups when compared to the vehicle group (Gehan-Breslow-Wilcoxon Test).

Study Results and Conclusion:

Pretreatment of tumor-bearing mice with OPG-Fc reduced osteolysis in a dose dependent manner (see Figure 9). Pretreatment of MDA-MB-231(F11)Luc cells with OPG-Fc at 3 mg/kg significantly reduced serum TRAP5b on day 0 (see Figure 8).

Similar to other experiments using MDA-MB-231(F11)Luc cells that are estrogen receptor negative, dose-dependent reductions in osteolytic lesions were observed following treatment with 0.3 and 3 mg/kg of OPG-Fc. OPG-Fc pretreatment reduced the percent of hind limb metastases in a dose-dependent manner in this experimental *in vivo* cancer model (see Figure 10).

Study Title: The Effect of Tamoxifen and the RANKL Inhibitor Osteoprotegerin (OPG-Fc), Alone and in Combination, on the Growth of MCF-7 Cells in an Established Bone Metastasis Model in Female Athymic Nude Mice; Study Number R20080162

Key Findings:

- Administration of the combination of tamoxifen at 0.1 mg and OPG-Fc at 3 mg/kg induced a reduction in hind limb tumor burden in the MCF-7-Luc cancer model that was similar to the reduction in tumor burden on day 41 after exposure to tamoxifen alone.

- Tamoxifen alone, OPG alone, and the combination of tamoxifen and OPG significantly reduced the area of osteolytic lesions relative to the vehicle control.

- Tamoxifen alone was capable of significantly reducing serum TRAP5b levels. Serum TRAP5b levels were reduced to a greater degree following administration of OPG-Fc, as compared to tamoxifen treatment alone.

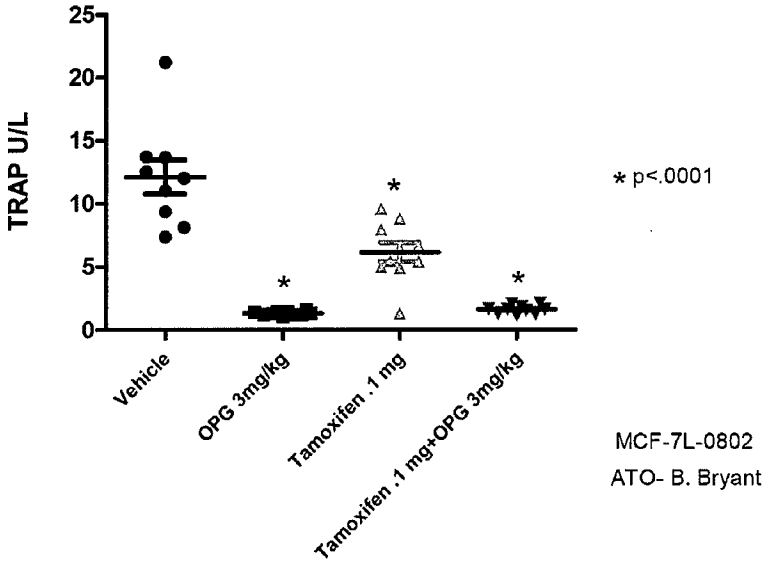
- No effects on body weight in the MCF-7Luc bone metastasis model were observed for any of the dose groups tested (data not shown).

Methods:

Athymic nude mice were injected intra-cardiac into the left ventricle with $5x10^5$ MCF-7 cells expressing luciferase. Treatment with OPG-Fc and Tamoxifen started on day 7 and continued until day 39. Tamoxifen at 0.1 mg was administered IP five times per week and OPG-Fc at 3 mg/kg was dosed 3 times per week SC. The In Vivo Imaging System (IVIS) was used to measure tumor burden by bioluminescence. Bioluminescence and body weight of each animal were measured twice per week (except for weeks 1, 2, 3, and 5, where BLI was measured once weekly). On day 41 (Day 36 for vehicle animals), serum was obtained for measurement of the osteoclast marker TRAP5b to determine level of osteoclastogenesis. The degree of osteolysis was determined by X-Ray histomorphometry.

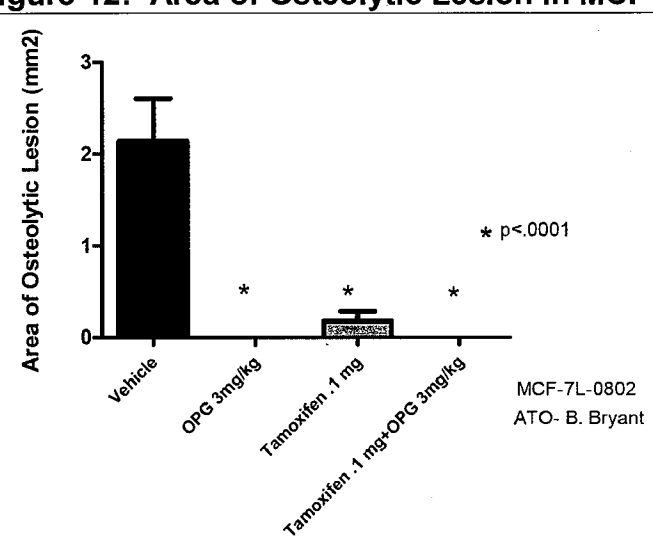
Results:

Figure 11: Serum TRAP5b



Serum was collected from the vehicle group on Day 36 and the treatment groups at study termination (day 41) and analyzed for the osteoclast marker Trap-5b. All treatment groups demonstrated a statistically- significant reduced serum TRAP5b level compared to the control group.

Figure 12: Area of Osteolytic Lesion in MCF-7 Luc Bone Met Model (Day 36)

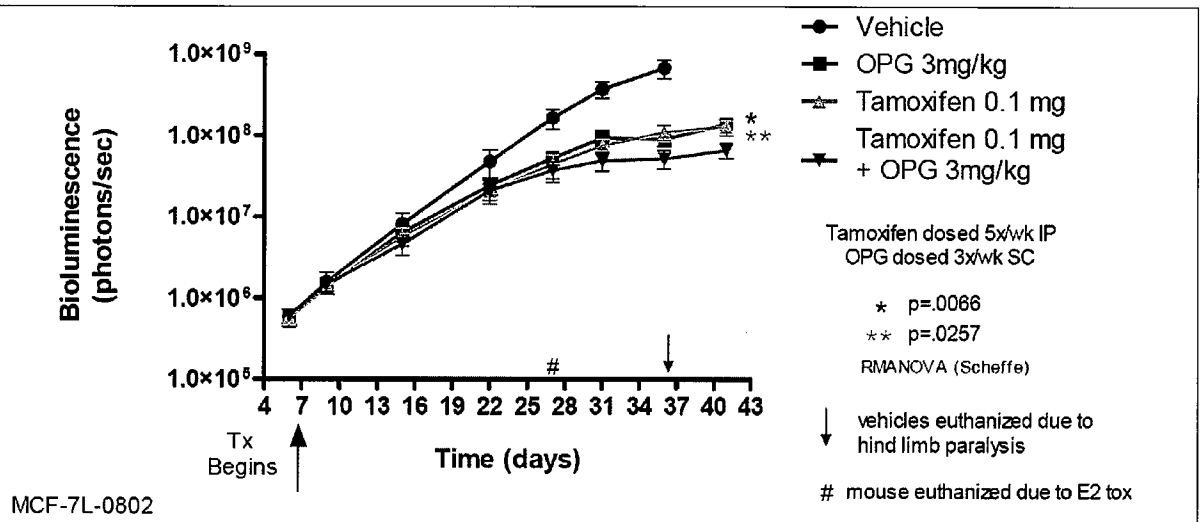


Area of osteolytic lesions in each group were averaged. Statistical analysis was performed using a Bonferroni/Dunn test in Statview. All treatment groups were statistically different than the control group.

Reviewer Comment:

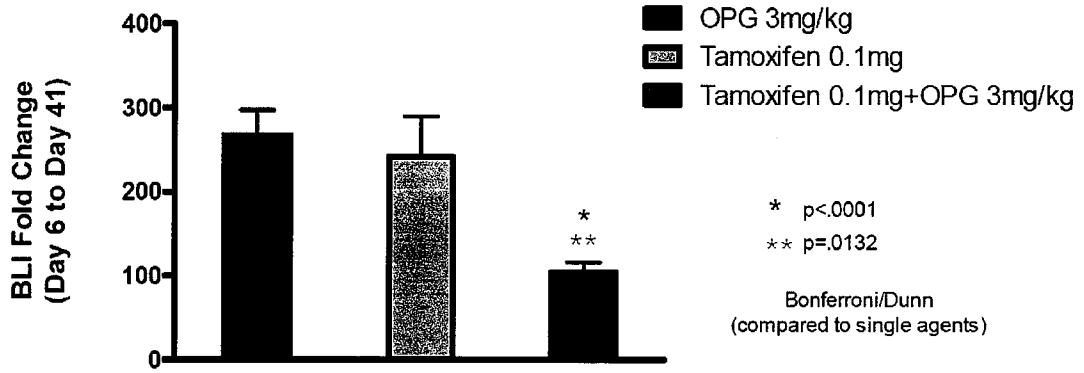
There were reductions in TRAP-5b in the tamoxifen alone treatment group. Tamoxifen alone significantly reduced the area of osteolytic lesions. The combination of treatment with OPG-Fc and tamoxifen did not induce a statistically significant reduction in osteolytic lesions, as compared to either agent alone. The data suggests that there is no added benefit from treatment with the combination of tamoxifen and OPG-Fc, as compared to the use of each respective agent alone.

Figure 13: Effect of Tamoxifen, Alone and in Combination with OPG-Fc, on Hind limb Tumor Burdon in a MCF-7Luc Bone Metastasis Model



Mice (n = 10 per group) were injected with 500,000 cells into the cardiac left ventricle on day 0. Treatment began on day 7 with OPG-FC at 3 mg/kg and Tamoxifen at .1 mg, alone or in combination, plus vehicle treatment. Dosing continued until Day 39. Data is the sum of the bioluminescence value (photons/sec) from the individual leg ROI, and represent the mean ± standard error of the mean. The combination group was statistically significant compared to the single agents.

Figure 14: Hind limb BLI Fold Change (Day 6 to Day 41)



Fold change from Day 6 to Day 41 was calculated for the treatment groups. Statistical analysis was performed using a Bonferroni/Dunn test in Statview. The combination group was statistically different from the single agents. Values reported are mean ± standard error or BLI fold change.

Study Results and Conclusion:

There were significant reductions in TRAP-5b levels in all treatment groups, providing evidence for reductions in bone resorption (see Figure 11). Administration of the combination of tamoxifen at 0.1 mg and OPG-Fc at 3 mg/kg induced a reduction in hind limb tumor burden in the MCF-7-Luc cancer model that was similar to exposure of tamoxifen alone on day 41 (see Figure 13). The addition of OPG-Fc did not provide any additional reduction in tumor growth in this cancer model relative to tamoxifen alone, based upon the data plotted in Figure 13. However, Figure 14 shows that based on BLI fold change, there is a statistically significant reduction in the combination of the OPG-Fc and tamoxifen relative to OPG-Fc alone or tamoxifen alone. Overall, the addition of OPG-Fc to tamoxifen did not provide a statistically significant reduction in hind limb tumor burden and osteolytic lesion area relative to either OPG-Fc alone or tamoxifen alone. All treatments were capable of reducing hind limb tumor burden and osteolytic lesion area. Additive or synergistic effects were not observed following the administration of the combination of tamoxifen and OPG-Fc. At least in the MCF-7-Luc tumor xenograft model, there does not appear to be any added benefit from combination treatment with tamoxifen and OPG-Fc as compared to effect induced by OPG-Fc alone or tamoxifen alone.

Reviewer Comment:

It is unclear how significant differences in the hind limb tumor burden were determined for Figure 14. Based upon the raw data for bioluminescence shown in Figure 13, the results indicate no remarkable differences between OPG alone, tamoxifen alone, and the combination of OPG and tamoxifen.

Study Title: The Effect of the RANK Ligand Inhibitor OPG-Fc and Docetaxel, Alone or in Combination, on Tumor Burden and Osteolysis in a PC-3 Prostate Cancer Bone Metastasis Model in Male Athymic Nude Mice, Study Number R20080083

Key Findings:

- In the PC-3 (prostate tumor cell line) Luc Bone Metastasis Model, the combination of OPG-Fc and docetaxel reduced whole body tumor burden, hind limb tumor burden, and head region tumor burden to a significantly greater degree as compared to the inhibition of body burden for either agent alone.

- The combination of docetaxel and OPG-Fc (3 mg/kg) reduced the osteolytic lesion area to a greater degree as compared to docetaxel alone (either 5 or 10 mg/kg dose groups).

- OPG-Fc treated mice maintained significantly reduced levels of TRAP5b during this study.

Methods:

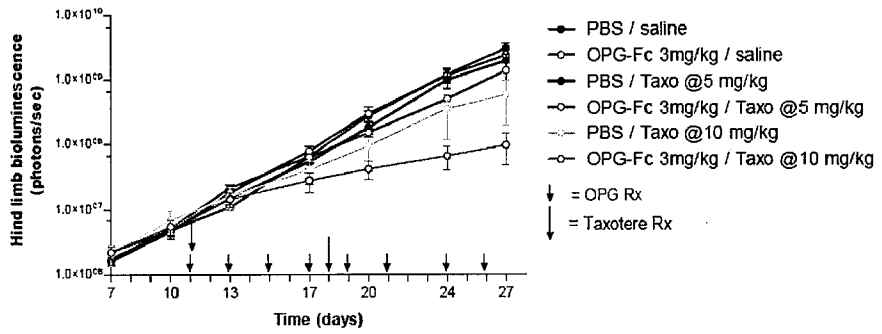
Athymic nude male mice were challenged with $1x10^6$ PC-3 cells expressing luciferase (PC-3 Luc) into the left cardiac ventricle on day 0, and 48 animals with successful tumor injection were utilized for treatment. At day 1 post-tumor challenge, mice were separated into six treatment groups as follows: Group 1 PBS, Group 2 OPG-Fc (3 mg/kg, 3x/week, throughout study), Group 3 OPG-Fc (3 mg/kg, 3x/week) plus docetaxel (5 mg/kg, 1x/wk x 2 treatments), Group 4 docetaxel (10 mg/kg 1x/wk x 2 treatments), Group 5 docetaxel (5 mg/kg, 1x/wk x 2 treatments) Group 6 OPG-Fc (3 mg/kg, 3x/week) plus docetaxel (10 mg/kg, 1x/wk x 2 treatments). Bioluminescence was measured twice weekly beginning on Day 7 through Day 27. Animals were sacrificed at day 28 for histologic evaluation of tumor burden. Osteolytic lesions were measured from x-ray radiographic images on days 13, 20, and 27.

Experimental Design

Primary Rx	Frequency	Route	Secondary Rx	Frequency	Route	N	Pathology #
PBS	3x/week (d11 on)	SC	Saline	1x/week (x2) (d11 & d18	IP	8	1
Hu OPG Fc 3 mg/kg	3x/week (d11 on)	SC	Saline	1x/week (x2) (d11 & d18	IP	8	2
PBS	3x/week (d11 on)	SC	Docetaxel 5 mg/kg	1x/week (x2) (d11 & d18)	IP	8	5
Hu OPG Fc 3 mg/kg	3x/week (d11 on)	SC	Docetaxel 10 mg/kg	1x/week (x2) (d11 & d18)	IP	8	6
PBS	3x/week (d11 on)	SC	Docetaxel 10 mg/kg	1x/week (x2) (d11 & d18	IP	8	4
Hu OPG Fc 3 mg/kg	3x/week (d11 on)	SC	Docetaxel 5 mg/kg	1x/week (x2) (d11 & d18	IP	8	3

Results:

Figure 15: Effect of Docetaxel, Alone and in Combination with OPG-Fc on Whole Body Tumor Burden in a PC-3 Luc Bone metastasis Model

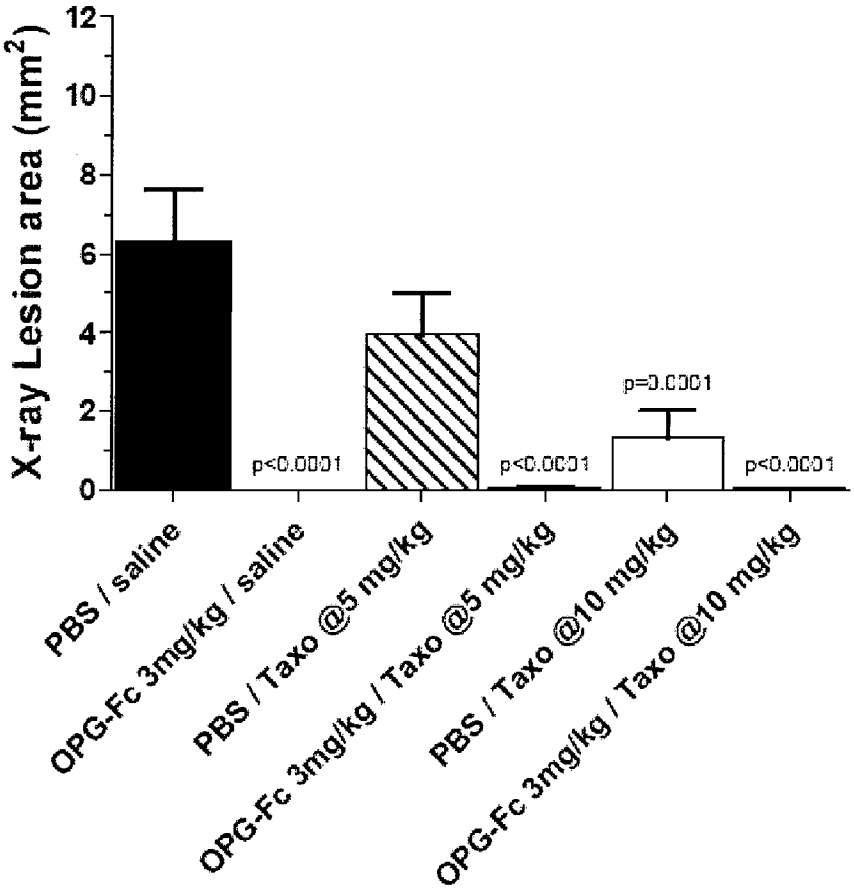


Statistical anaylysis using Dunnett's test for multiple comparisons

Compare	To	Day 13	Day 17	Day 20	Day 24	Day 27
OPG-Fc Taxo 10m	PBS Saline		0.0040	<0.0001	<0.0001	<0.0001
OPG-Fc Taxo 5m	PBS Saline	0.0260	N.S.	N.S.	N.S.	0.0072
OPG-Fc Saline	PBS Saline	N.S.	N.S.	N.S.	N.S.	N.S.
PBS Taxo 10m	PBS Saline	N.S.	0.0434	0.0005	<0.0001	<0.0001
PBS Taxo 5m	PBS Saline	N.S.	N.S.	N.S.	N.S.	N.S.
OPG-Fc Taxo 10m	PBS Taxo 10m	N.S.	N.S.	N.S.	0.0493	0.0008
OPG-Fc Taxo 5m	PBS Taxo 5m	0.0417	N.S.	N.S.	0.0247	0.0083

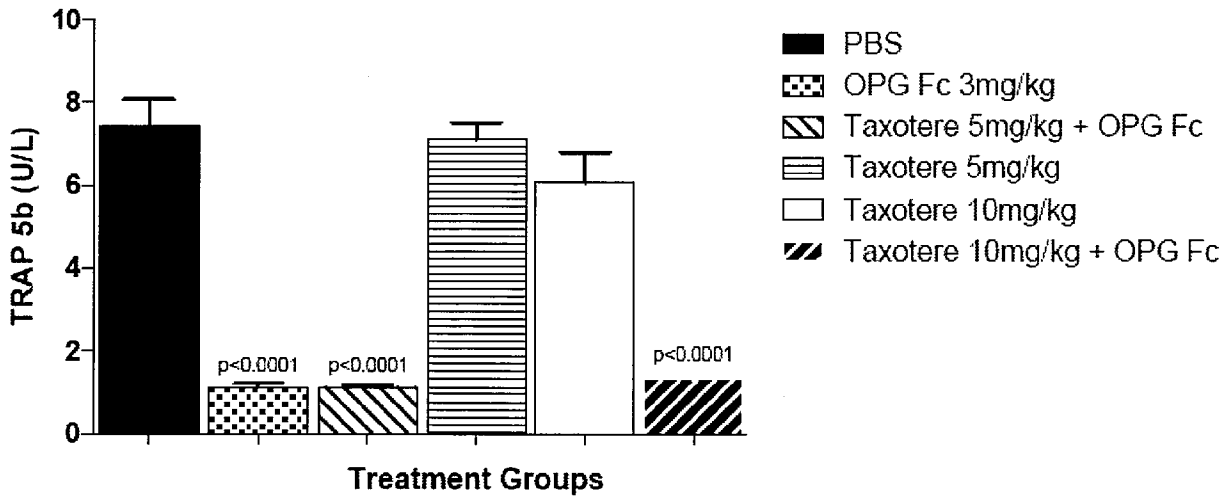
Mice (n = 8 per group) were injected with 1,000,000 PC-3 luc human prostate cancer cells into the cardiac left ventricle on day 0. Treatments began on day 11, Taxotere was given as 2 weekly injections and OPG-Fc was given 3x/week until the end of study. Data is the sum of the bioluminescence value (photons/sec) from the individual leg Hind limb ROI's combined from both dorsal and ventral imaging and represent the mean ± standard error of the mean.

Figure 16: Effect of Docetaxel, Alone and in Combination with OPG-Fc on Osteolytic Lesion Area



X-ray lesion area was determined from femurs and tibia at Day 27 post-tumor challenge. The data represent the mean lesion area/mouse + SEM (n = 8/group). Statistical analysis performed with JMP7 using Dunnett test.

Figure 17: Effect of Docetaxel, Alone and in Combination with OPG-Fc on Serum Trap5b



Serum samples were collected at the time of necropsy and frozen at –80°C. Serum TRAP5b levels were measured by ELISA using MouseTRAP™ Assay (Immunodiagnostic Systems Limited, Bolton UK). The data represent the mean concentration + SEM (n = 8/group). Statistical analysis performed with JMP7 using Dunnett test.

Study Results and Conclusion:

Studies in the PC-3 Luc tumor model provided evidence that the combination of docetaxel at 10 mg/kg and OPG-Fc at 3 mg/kg induced a significant reduction in tumor burden (whole body, head [see Figure 15], and limb regions [data not shown]) based on the bioluminescence signals in the athymic mice. The combination of docetaxel and OPG-Fc (3 mg/kg) reduced the osteolytic lesion area to a greater degree as compared to the single treatment with docetaxel at 5 mg/kg or 10 mg/kg dose groups (see Figure 16). As shown in Figure 17, any OPG-Fc treated dose group maintained remarkable reductions in TRAP5b serum levels in this study. Overall, these data provide evidence that the combination of docetaxel and OPG-Fc inhibits tumor growth and osteolytic lesions in an additive manner in the PC-3 athymic mouse model.

Study Title: The Effect of Human OPG-Fc Treatment on Tumor Burden and Osteolysis in a Murine Model of Bone Metastasis of Human Non-Small Cell Lung Cell Line H1975 Luc in Athymic Nude Female Mice, Study Number R20070963

Key Findings:

- OPG-Fc (3 mg/kg) treatment beginning on Day 1 or Day 7 significantly reduced the skeletal tumor burden (tumor growth inhibition of 70 to 75%, respectively) in the non small cell lung cancer model, based on histological analysis.

- OPG-Fc significantly reduced the osteolytic lesion area in the non-small cell lung cancer model, based on X-ray measurements.

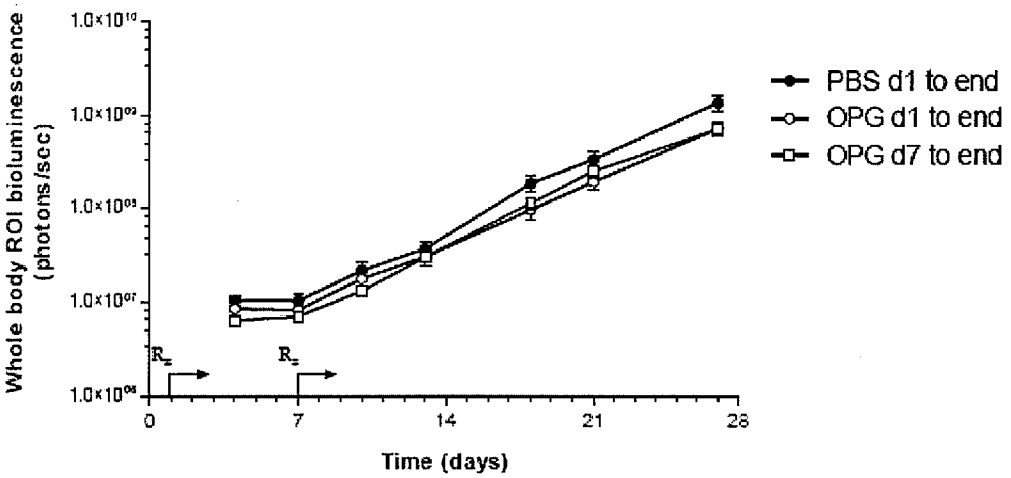
- OPG-Fc reduced serum Trap5b levels from day 1 to the end of the study (data not shown, but provided in Study R20070963).

Methods:

Four to 6 week old Athymic nu/nu female mice were challenged with luciferase-labeled H1975 non-small cell lung cancer cells into the left cardiac ventricle on day 0. Mice were pretreated with enoxoparin IV to prevent tumor induced thrombosis prior to intra-cardiac injection. Successful injections were verified by bioluminescent imaging (BLI). Mice were treated with either PBS or OPG-Fc. OPG-Fc treatment was given at an early time point (day 1 after tumor cell inoculation) or a late time point (day 7 post-tumor cell inoculation). Tumor progression was then monitored by bioluminescence and histological measures. The effect of OPG-Fc on osteolytic bone disease was analyzed by radiographic progression. Treatments groups were PBS (3x/week), beginning day 1, OPG-Fc (3 mg/kg, 3x/week), beginning day 1, or OPG-Fc (3 mg/kg, 3x/week), beginning day 7. Bioluminescence was measured twice weekly and animals were sacrificed at day 27 for histologic evaluation of tumor burden. Osteolytic lesions were measured by X-ray on day 27.

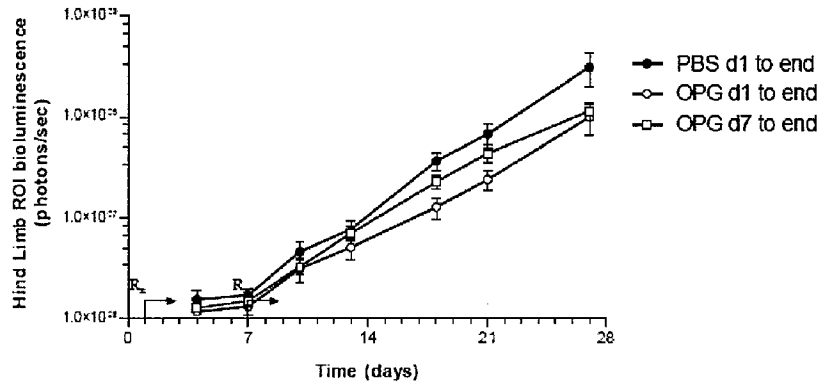
Results:

Figure 18: Effect of OPG-Fc on Whole Body Tumor Burden in a Non-Small Cell Lung Cancer Model



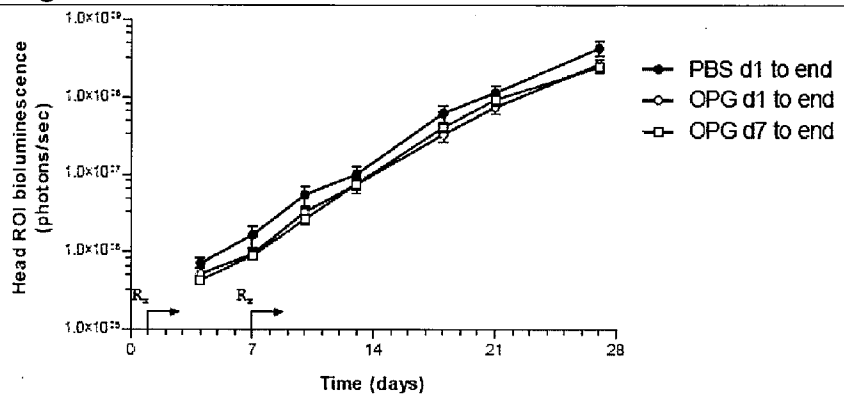
Mice (n = 9 to10 per group) were injected with 1e6 H1975 cells into the cardiac left ventricle on day 0. PBS as a vehicle control was given 3x/week beginning one day 1 after tumor challenge until the end of study. OPG-Fc was given 3x/week beginning on day 1 or day 7 post tumor challenge and continued until the end of study. Data is the bioluminescence value (photons/sec) from combined dorsal and ventral whole body ROI and represent the mean ± SEM.

Figure 19: Effect of OPG-Fc on Hind Limb Tumor Burden in a Non-Small Cell Lung Cancer Model



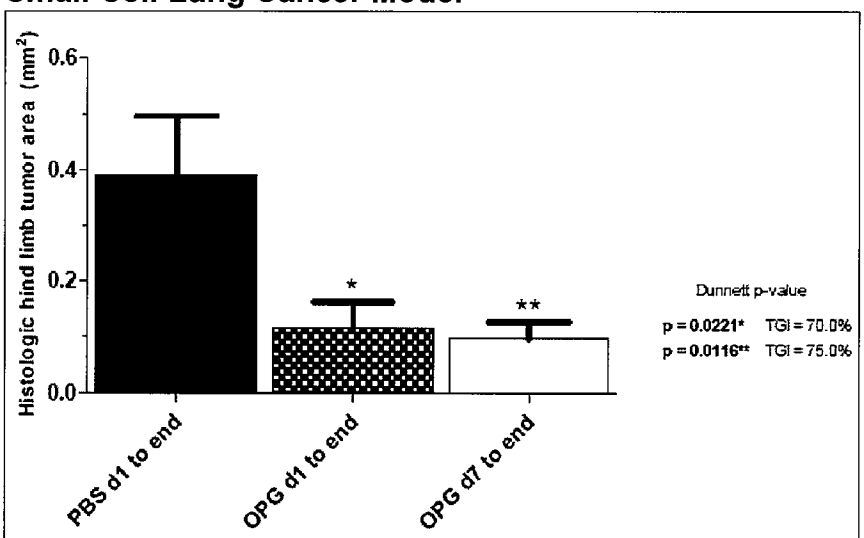
Mice (n = 9 to10 per group) were injected with 1e6 H1975 cells into the cardiac left ventricle on day 0. Treatment began on day 1 or day 7. PBS as a vehicle control was given 3x/week beginning one day 1 after tumor challenge until the end of study. OPG-Fc was given 3x/week beginning on day 1 or day 7 post tumor challenge and continued until the end of study. Data is the sum of the bioluminescence value (photons/sec) from the individual leg hind limb ROI combined from both dorsal and ventral imaging and represent the mean ± SEM.

Figure 20: Effect of OPG-Fc on Head Region Tumor Burden in a Non-Small Cell Lung Cancer Model



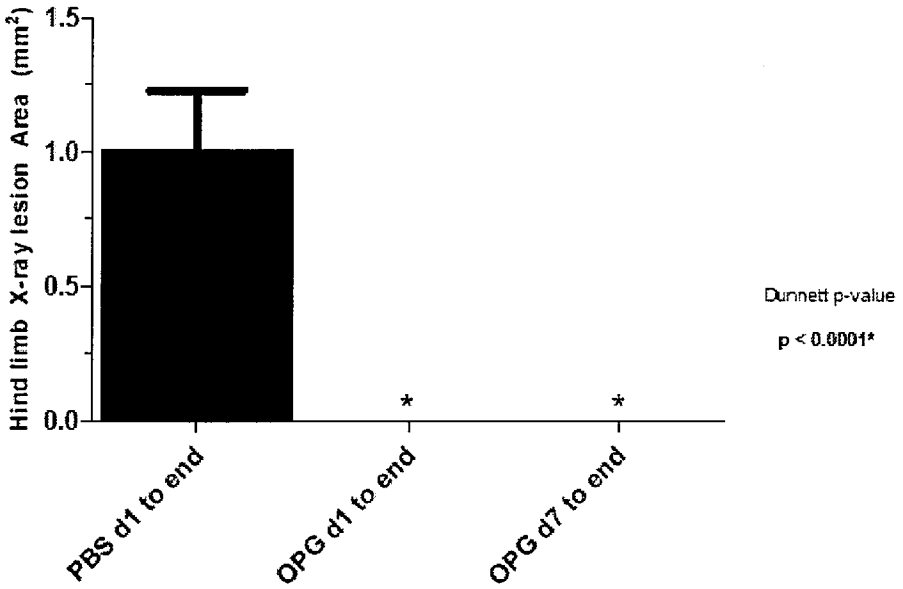
Mice (n = 9 to10 per group) were injected with 1e6 H1975 cells into the cardiac left ventricle on day 0. Treatment began on day 1 or day 7. PBS as a vehicle control was given 3x/week beginning one day 1 after tumor challenge until the end of study. OPG-Fc was given 3x/week beginning on day 1 or day 7 post tumor challenge and continued until the end of study. Data is the sum of the bioluminescence value (photons/sec) from the head ROI ventral imaging and represent the mean ± SEM.

Figure 21: Effects of OPG-Fc on Histological Skeletal Tumor Burden in a Non-Small Cell Lung Cancer Model



Mice (n = 9 to10 per group) were injected with 1e6 H1975 cells into the cardiac left ventricle on day 0. Treatment began on day 1 or day 7. PBS as a vehicle control was given 3x/week beginning one day 1 after tumor challenge until the end of study. OPG-Fc was given 3x/week beginning on day 1 or day 7 post tumor challenge and continued until the end of study. Data represent the mean histological skeletal tumor burden in the hind limbs and d27 harvest ± SEM. Statistical analysis performed with JMP7 using Dunnett's test.

Figure 22: Effects on OPG-Fc on Osteolytic Lesion Area in a Non-Small Cell Lung Cancer Model



Mice (n = 9 to10 per group) were injected with 1e6 H1975 cells into the cardiac left ventricle on day 0. Treatment began on day 1 or day 7. PBS as a vehicle control was given 3x/week beginning one day 1 after tumor challenge until the end of study. OPG-Fc was given 3x/week beginning on day 1 or day 7 post tumor challenge and continued until the end of study. X-ray lesion area was determined from femurs and tibia at Day 27 post-tumor challenge. The data represent the mean lesion area/mouse ± SEM. Statistical analysis performed with JMP7 using Dunnett's test.

Study Results and Conclusion:

OPG-Fc induced slight reductions in whole body tumor burden and hind limb tumor burden in the H1975 non-small cell lung cancer model on day 27 (see Figure 18 and 19). OPG-Fc did not induce reductions in the head region tumor burden in the H1975 non-small cell lung cancer model (see Figure 20). OPG-Fc reduced the skeletal tumor burden based on histological analysis (see Figure 21). OPG-Fc treatment beginning on Day 1 or Day 7 reduced the osteolytic lesion area based on X-ray measurements (see Figure 22). OPG-Fc reduced serum Trap5b levels from day 1 to the end of the study (data not shown, but provided in Study R20070963).

Study Title: The Effect of RANK Ligand Inhibitor of OPG-Fc on Tumor Burden and Osteolysis in a Murine Model of Bone Metastasis of Human Non-Small Cell Lung Cell Line H1299 in Female Athymic Nude Mice, Study Number R20080310

Key Findings:

- Administration of OPG-Fc (3 mg/kg) on day 1 or at 1 week post tumor challenge showed a significant tumor growth inhibition in all regions (whole body, hind limb, and head region) as measured by bioluminescence, for either the high tumor burden or low tumor burden challenged mice.

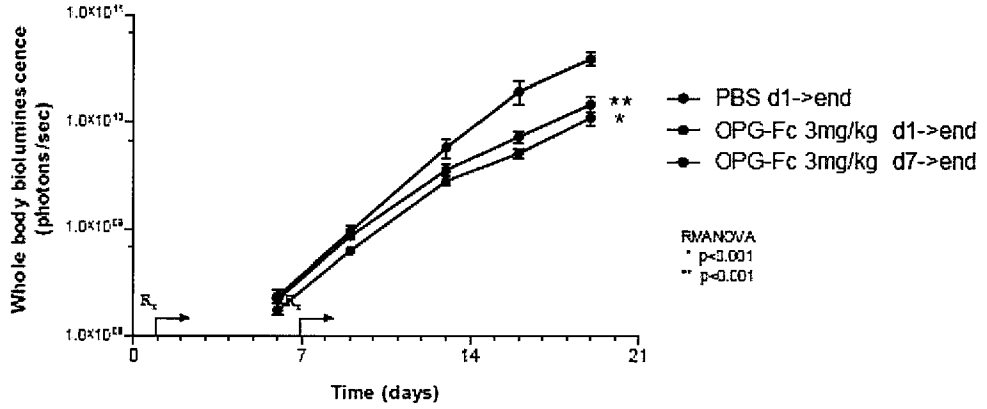
- Administration of OPG-Fc (3 mg/kg) on day 1 or at 1 week post tumor challenge caused significant reductions in skeletal tumor burden based on histological measurements in NCR nu/nu female mice injected with H1299 non-small cell lung cancer cells.

Methods:
Six week old TAC NCR nu/nu female mice were challenged with luciferase-labeled H1299 non-small cell lung cancer cells into the left cardiac ventricle on day 0. High tumor burden challenge consisted of injecting 1x 10^6 cells while the low tumor burden challenge consisted of injecting 1x 10^5 cells. Successful injections were verified by bioluminescent imaging (BLI). Mice were treated with either PBS or OPG-Fc. OPG-Fc treatment was given at an early time point (day 1 after tumor cell inoculation) or a late time point (day 7 or 8 post-tumor cell inoculation). Tumor progression was then monitored by bioluminescence and radiographic progression. Treatments for each tumor challenge dose were: PBS (3x/week) day 1, OPG-Fc (3 mg/kg 3x/week) day 1, OPG-Fc (3 mg/kg 3x/week) day 7 or 8.

Treatment Groups

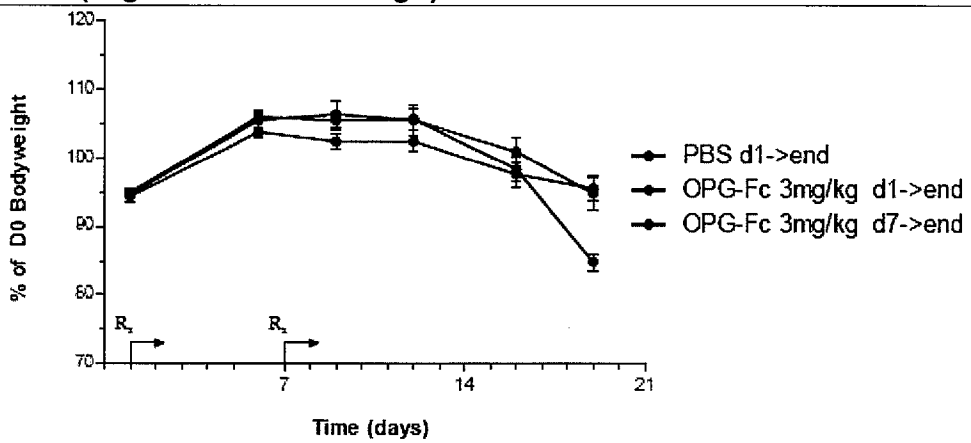
Group 1	PBS starting day 1	1e6 H1299 IC challenge d=0	N=9
Group 2	OPG-Fc (3 mg/kg 3x/week) starting day 1	1e6 H1299 IC challenge d=0	N=9
Group 3	OPG-Fc (3 mg/kg 3x/week) starting day 7	1e6 H1299 IC challenge d=0	N=9
Group 4	PBS starting day 1	1e5 H1299 IC challenge d=0	N=10
Group 5	OPG-Fc (3 mg/kg 3x/week) starting day 1	1e5 H1299 IC challenge d=0	N=10
Group 6	OPG-Fc (3 mg/kg 3x/week) starting day 8	1e5 H1299 IC challenge d=0	N=10

Figure 23: Effect of OPG-Fc on Whole Body Tumor Burden in a Non-Small Cell Lung Cancer Model (High Tumor Challenge)



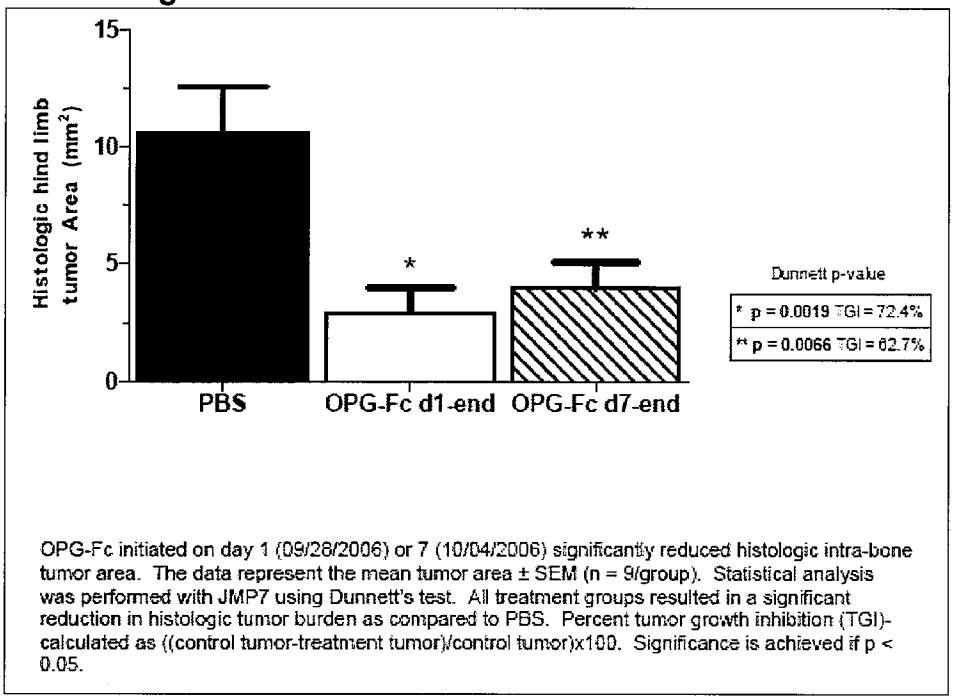
Mice (n = 9 per group) were injected with 1e6 cells into the cardiac left ventricle on day 0 (09/27/2006). PBS as a vehicle control was given 3x/week beginning on day 1 after tumor challenge (09/28/2006) until the end of study. OPG-Fc was given 3x/week beginning on day 1 or day 7 (10/04/2006) post tumor challenge and continued until the end of study. Data is the sum of the bioluminescence value (photons/sec) from the whole body ROI combined from both dorsal and ventral imaging and represent the mean ± SEM. There was a statistically significant difference between both early (d1) and late (d7) OPG-Fc treatment. Significance is achieved if $p < 0.05$.

Figure 24: Effect of OPG-Fc on Body Weight in a Non-Small Cell Lung Cancer Model (High Tumor Challenge)



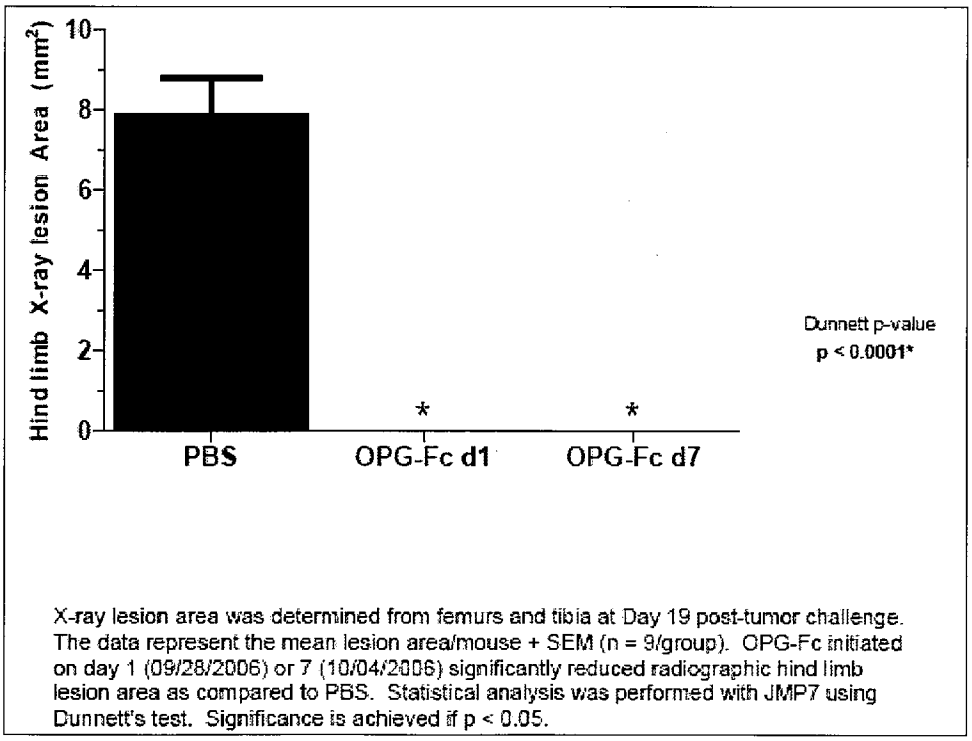
Mice (n = 9 per group) were injected with 1e6 cells into the cardiac left ventricle on day 0 (09/27/2006). PBS as a vehicle control was given 3x/week beginning on day 1 after tumor challenge (09/28/2006) until the end of study. OPG-Fc was given 3x/week beginning on day 1 or day 7 (10/04/2007) post tumor challenge and continued until the end of study. Data represent percent body weight, with 100% representing the mean body weight on day 0. Error bars represent ± SEM. No statistical analysis performed.

Figure 25: Effect of OPG-Fc on Histological Skeletal Tumor Burden in a Non-Small Lung Cancer Model



OPG-Fc initiated on day 1 (09/28/2006) or 7 (10/04/2006) significantly reduced histologic intra-bone tumor area. The data represent the mean tumor area ± SEM (n = 9/group). Statistical analysis was performed with JMP7 using Dunnett's test. All treatment groups resulted in a significant reduction in histologic tumor burden as compared to PBS. Percent tumor growth inhibition (TGI)-calculated as ((control tumor-treatment tumor)/control tumor)x100. Significance is achieved if $p < 0.05$.

Figure 26: Effect of OPG-Fc on Osteolytic Lesion Area in a Non-Small Cell Lung Cancer Model



X-ray lesion area was determined from femurs and tibia at Day 19 post-tumor challenge. The data represent the mean lesion area/mouse + SEM (n = 9/group). OPG-Fc initiated on day 1 (09/28/2006) or 7 (10/04/2006) significantly reduced radiographic hind limb lesion area as compared to PBS. Statistical analysis was performed with JMP7 using Dunnett's test. Significance is achieved if $p < 0.05$.

Study Results and Conclusions:

Administration of OPG-Fc on day 1 or at 1 week post tumor challenge showed a significant tumor growth inhibition in all regions (whole body [see Figure 23], hind limb [data not shown], and head region [data not shown]), as measured by bioluminescence for either the high tumor or low tumor burden challenged mice. The two different treatment schemes (start on day 1 post challenge or day 7 or 8 post challenge) caused significant reductions in histologic skeletal tumor burden, with growth inhibitions of between 63 to 72% for the high tumor challenge and 84 to 85% growth inhibition for the low tumor challenged mice (see Figure 25). A reduction in body weights was observed in the PBS treated group (high tumor challenge) of approximately 10% on day 19 relative to the percent body weight on day 0 (see Figure 24). The OPG-Fc treated groups mean body weights were similar between day 0 and day 19.

Study Title: Effect of OPG-Fc (in Combination with Docetaxel) Treatment on Tumor Burden and Osteoclast Remodeling in a Murine Model of Bone Metastasis of Human Non-Small-Cell Lung Cell Line H1299 in Female Athymic Nude Mice, Study Number R20080311

Key Findings:

- OPG-Fc (3 mg/kg) alone did not significantly reduce the tumor burden as assessed by whole body bioluminescence in the female H1299 tumor model.
- Treatment with docetaxel alone significantly reduced the tumor burden based on the whole body bioluminescence assessment in female mouse H1299 tumor model.
- All treatments resulted in significant decreases in histologic skeletal tumor burden based on evaluation of the hind limb tumor area and reductions in osteolytic lesions based on hind limb X-ray lesion area.
- It could not be determined if the inhibition of RANKL signaling via OPG-Fc in combination with taxotere provided additional benefit in female mouse H1299 tumor model.

Methods:

Six-week old athymic nu/nu female mice were challenged with 1 x 10^6 H1299 Luc cells into the left cardiac ventricle on day 0. Successful injections were verified by bioluminescent imaging (BLI) in 64 surviving animals and at day 5 post-tumor challenge, 60 mice were separated into treatment groups. Mice were distributed into 6 groups of 10 based on the day 5 bioluminescence. Bioluminescence was measured twice weekly beginning on day 2, through Day 21. Animals were sacrificed at day 22 for histologic

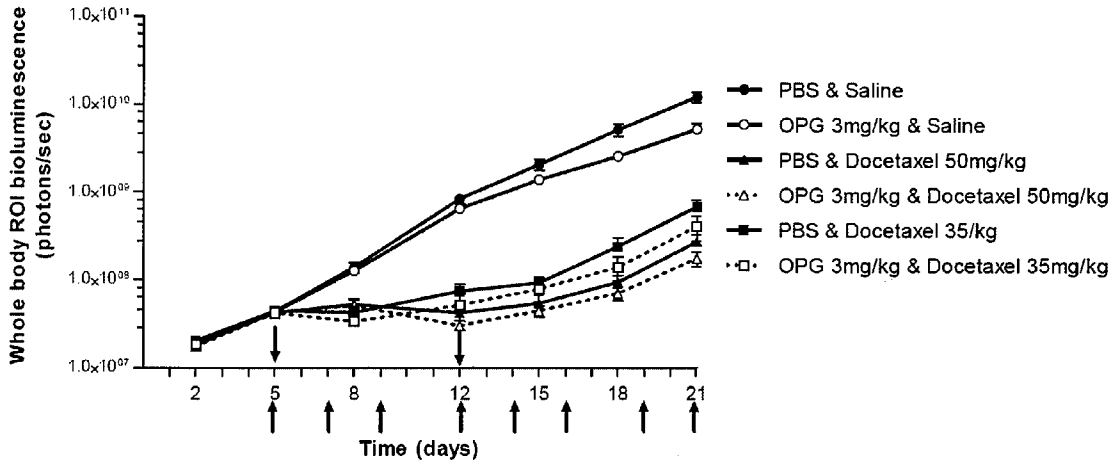
evaluation of tumor burden. X-ray radiography of hind limbs (femurs and tibiae) occurred on days 8, 15, 18 and 21 and osteolytic lesions were calculated from day 21 images.

Overview of Treatment Groups

Treatments:	
Group 1	OPG-Fc (3 mg/kg 3x/week) plus docetaxel (50 mg/kg 1x/wk x 2 treatments)
Group 2	PBS (3x/week) plus Saline (1x/wk x 2 treatments)
Group 3	OPG-Fc (3 mg/kg 3x/week) plus docetaxel (35 mg/kg 1x/wk x 2 treatments)
Group 4	OPG-Fc (3 mg/kg 3x/week) plus saline (1x/wk x 2 treatments)
Group 5	PBS (3x/week) plus docetaxel (35 mg/kg 1x/wk x 2 treatments)
Group 6	PBS (3x/week) plus docetaxel (50 mg/kg 1x/wk x 2 treatments)

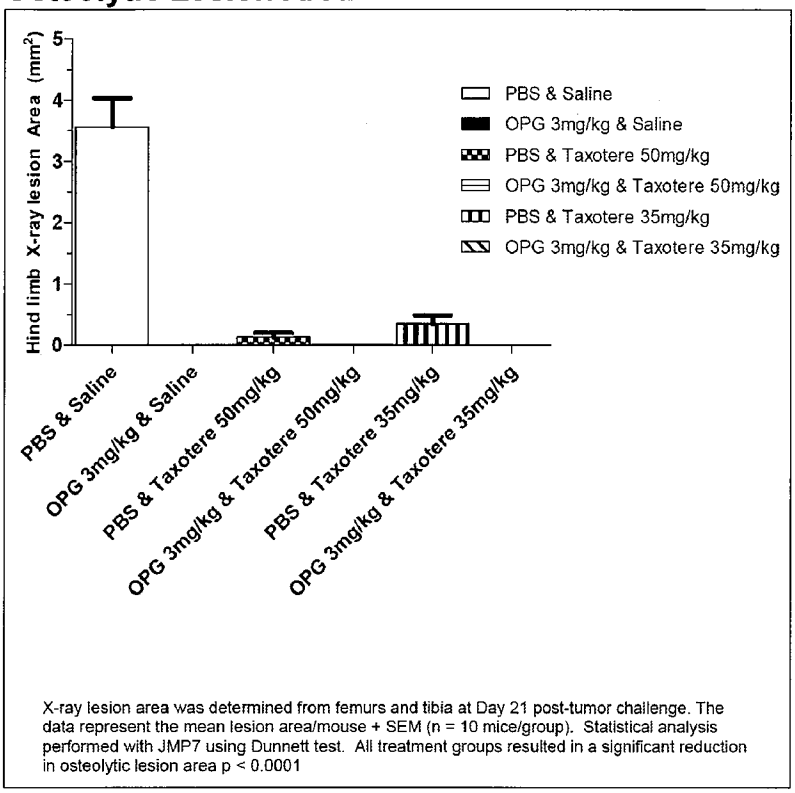
Results:

Figure 27: Effect of Docetaxel, Alone and in Combination with OPG-Fc on Whole Body Tumor Burden in a H1299 Luc Bone Metastasis Model



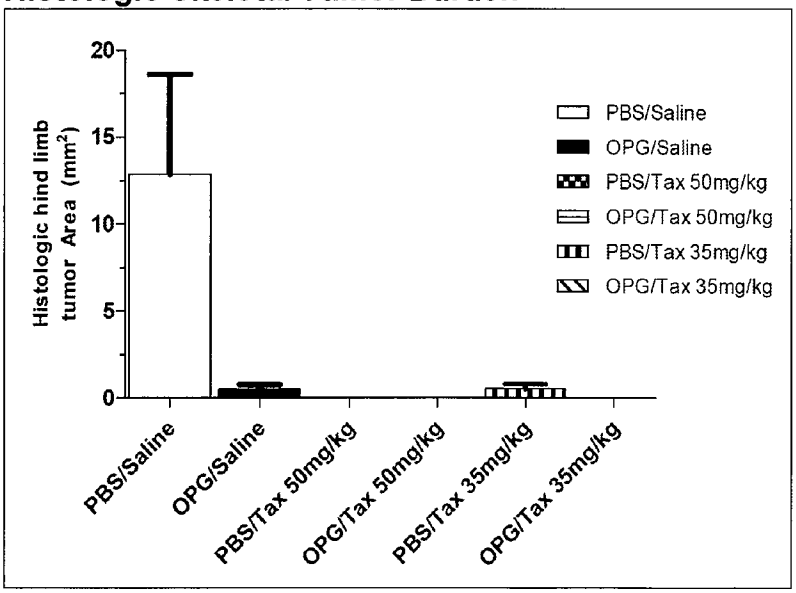
One hundred athymic nude female mice were injected with 1e6 H1299 cells into the cardiac left ventricle on day 0. Day 5 hind limb bioluminescence was used to distribute 60 mice into normalized groups (n = 10 per group) for treatment. Treatment began on day 5. Data is the bioluminescence value (photons/sec) from combined dorsal and ventral whole body ROI and represent the mean ± standard error of the mean. Red arrows indicate docetaxel or saline dosing. Blue arrows indicate OPG-Fc or PBS dosing.

Figure 28: Effect of Docetaxel, Alone and in Combination with OPG-Fc on Osteolytic Lesion Area



X-ray lesion area was determined from femurs and tibia at Day 21 post-tumor challenge. The data represent the mean lesion area/mouse + SEM (n = 10 mice/group). Statistical analysis performed with JMP7 using Dunnett test. All treatment groups resulted in a significant reduction in osteolytic lesion area $p < 0.0001$

Figure 29: Effect of Docetaxel, Alone and in Combination with OPG-Fc on Histologic Skeletal Tumor Burden



Reviewer Comments:

Since Taxotere (docetaxel) induced such robust reductions in the hind limb tumor area based on x-ray or histologic analysis, it was unclear if the OPG-Fc in combination with docetaxel provided any added effect in this cancer model. All treatment groups induced a robust response in the hind limb; however, at least in the H1299 tumor model, taxotere alone provided more anti-tumor effect. Based on the whole body tumor burden results, taxotere caused a significant reduction in tumor burden, while OPG-Fc did not reduce the whole body tumor burden. Since OPG-Fc alone did not reduce the whole body tumor burden, it appears that the pharmacological response for the combination of docetaxel and OPG-Fc in the H1299 mouse tumor model was being driven by the docetaxel effect. Utilization of a lower dose of docetaxel in future studies may reveal the combination effects of OPG-Fc and docetaxel in this model system.

Study Results and Conclusion:

OPG-Fc (3 mg/kg) alone did not significantly reduce the tumor burden in the mouse H1299 tumor model, as assessed by whole body bioluminescence (see Figure 27). However, treatment of tumor-bearing mice with docetaxel significantly reduced the tumor burden in this model (see Figure 27). All treatments resulted in significant decreases in histologic skeletal tumor burden based on evaluation of the hind limb tumor area, and reductions in osteolytic lesions based on hind limb X-ray lesion area (see Figures 28 and 29).

Study Title: Effect of OPG-Fc (Alone and in Combination with Docetaxel) Treatment on Tumor Burden and Osteolysis in a Murine Model of Bone Metastasis of Human Non-Small-Cell Lung Cell Line H1299 in Athymic Nude Female Mice, Study Number R20080332

Key Findings:

- The combination of OPG-Fc (3 mg/kg) and docetaxel (15 mg/kg) treatment significantly reduced whole body tumor burden and hind limb tumor burden relative to docetaxel (15 mg/kg) treatment alone in the H1299 athymic nude female mice.

- The combination of OPG-Fc and docetaxel treatment significantly reduced osteolytic hind limb lesion area and hind limb tumor area relative to docetaxel treatment alone in the athymic nude femal mice.

- All OPG-Fc treatment groups had significantly reduced serum TRAP5b levels.

Methods:

Seven week old athymic nu/nu female mice were challenged with 1 x 10^6 H1299 Luc cells into the left cardiac ventricle. Successful injections were verified by bioluminescent imaging (BLI). At day 6 post-tumor challenge, mice were separated into 4 treatment groups, based on the day 6 bioluminescence results. Groups were randomly assigned to receive either vehicle controls, OPG-Fc (3 mg/kg), docetaxel (15 mg/kg) or the combination or OPG-Fc (3 mg/kg) and docetaxel (15 mg/kg). Treatments were initiated on day 7 post tumor challenge. Bioluminescence was measured twice weekly, and animals were sacrificed at day 23 for histologic evaluation of tumor burden. Osteolytic lesions were measured by X-ray on day 23.

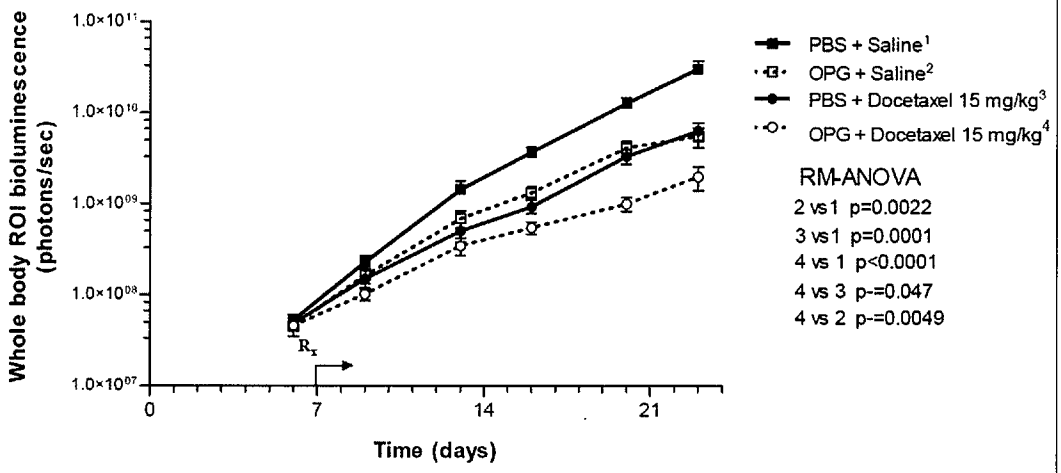
Overview of Treatment Groups

Experimental Design

Random Grp Assignment	Primary Rx	Frequency	Route	Secondary Rx	Frequency	Rte	N
4	PBS	3x/week (d7 on)	SC	Saline	1x/week (x2) d7 & d14	IP	7
2	Hu OPG Fc 3 mg/kg	3x/week (d7 on)	SC	Saline	1x/week (x2) d7 & d14	IP	8
3	PBS	3x/week (d7 on)	SC	Docetaxel 15 mg/kg	1x/week (x2) d7 & d14	IP	8
1	Hu OPG Fc 3 mg/kg	3x/week (d7 on)	SC	Docetaxel 15 mg/kg	1x/week (x2) d7 & d17	IP	7

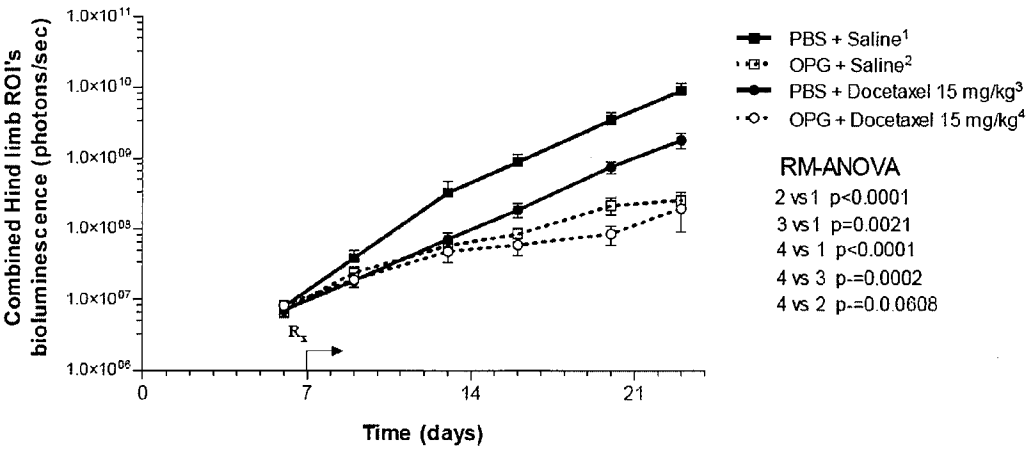
Results:

Figure 30: Effect of OPG-Fc, Alone and in Combination with Docetaxel on Whole Body Tumor Burden in a H1299 Luc Bone Metastasis Model



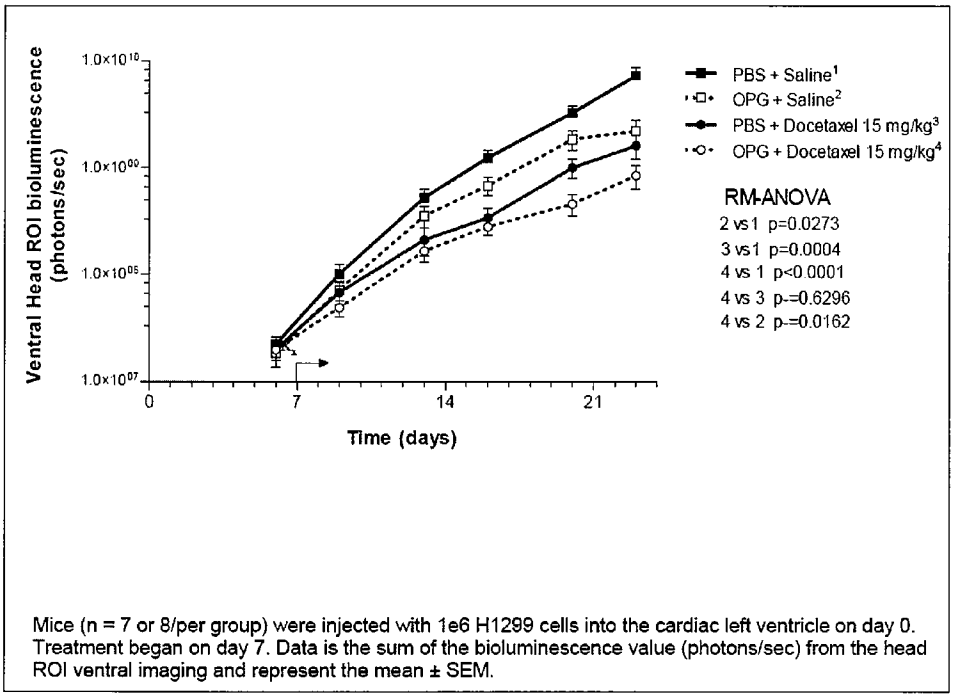
Mice (n = 7 or 8/per group) were injected with 1e6 H1299 cells into the cardiac left ventricle on day 0. Treatment began on day 7. Data is the bioluminescence value (photons/sec) from combined dorsal and ventral whole body ROI and represent the mean ± SEM.

Figure 31: Effect of OPG-Fc, Alone and in Combination with Docetaxel on Hind Limb Tumor Burden in a H1299 Lu Bone Metastasis Model



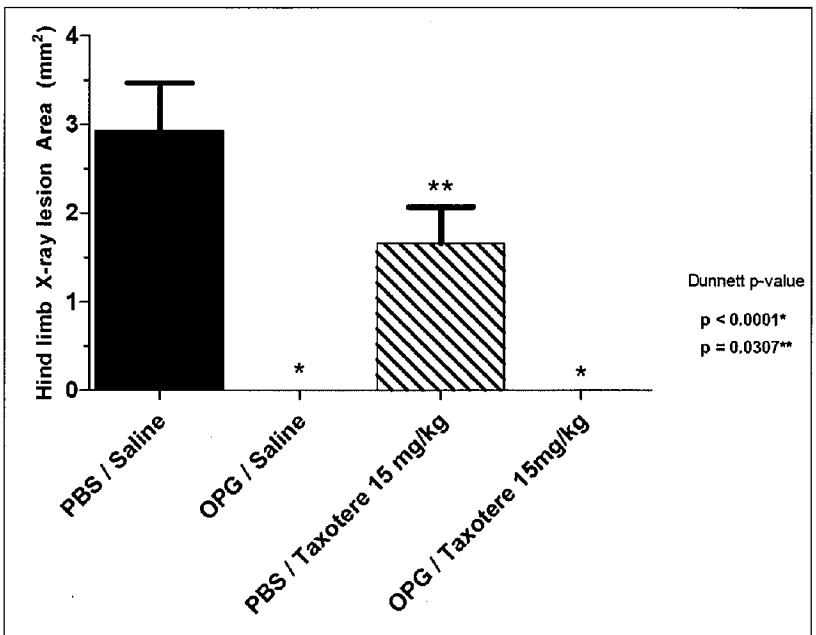
Mice (n = 7 or 8/per group) were injected with 1e6 H1299 cells into the cardiac left ventricle on day 0. Treatment began on day 7. Data is the bioluminescence value (photons/sec) from combined dorsal and ventral images of the Hind limb ROI's and represent the mean ± SEM.

Figure 32: Effect of OPG-Fc, Alone and in Combination with Docetaxel on Head Region Tumor Burden in a H1299 Luc Bone Metastasis Model



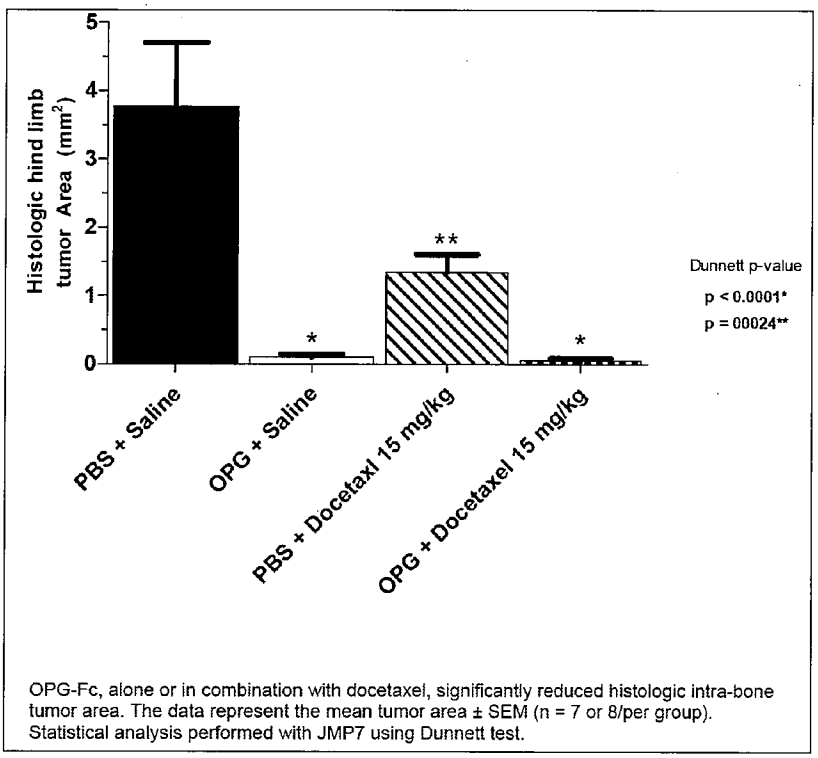
Mice (n = 7 or 8/per group) were injected with 1e6 H1299 cells into the cardiac left ventricle on day 0. Treatment began on day 7. Data is the sum of the bioluminescence value (photons/sec) from the head ROI ventral imaging and represent the mean ± SEM.

Figure 33: Effect of OPG-Fc, Alone and in Combination with Docetaxel on Osteolytic Lesion Area



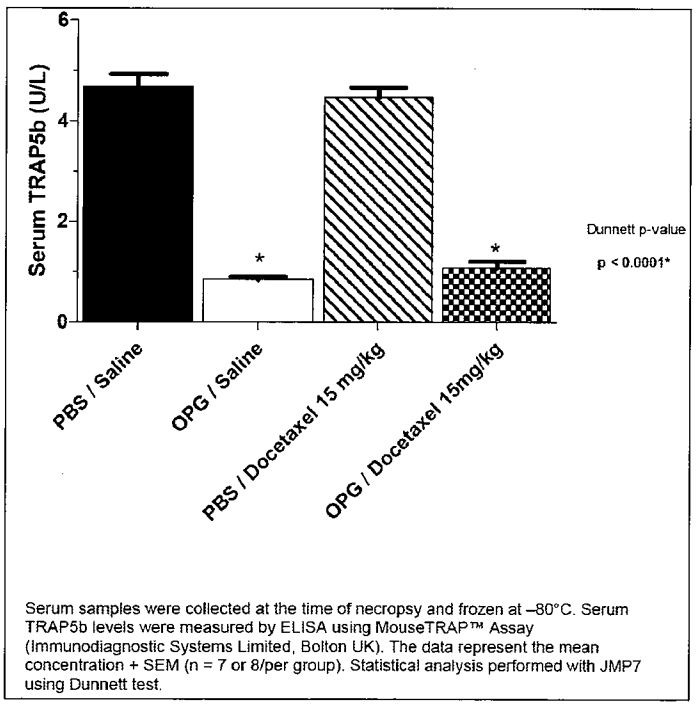
X-ray lesion area was determined from femurs and tibia at Day 23 post-tumor challenge. The data represent the mean lesion area/mouse + SEM (n = 7 or 8/per group). Statistical analysis performed with JMP7 using Dunnett test.

Figure 34: Effect of OPG-Fc, Alone and in Combination with Docetaxel on Histologic Skeletal Tumor Burden



OPG-Fc, alone or in combination with docetaxel, significantly reduced histologic intra-bone tumor area. The data represent the mean tumor area ± SEM (n = 7 or 8/per group). Statistical analysis performed with JMP7 using Dunnett test.

Figure 35: Effect of OPG-Fc, Alone and in Combination with Docetaxel on Serum TRAP5b



Serum samples were collected at the time of necropsy and frozen at –80°C. Serum TRAP5b levels were measured by ELISA using MouseTRAP™ Assay (Immunodiagnostic Systems Limited, Bolton UK). The data represent the mean concentration + SEM (n = 7 or 8/per group). Statistical analysis performed with JMP7 using Dunnett test.

Study Results and Conclusions:

Based on measurement of tumor bioluminescence, the combination of 3 mg/kg/dose OPG-Fc and docetaxel (15 mg/kg) caused a significant reduction in whole body tumor burden and hind limb tumor burden. The reduction in tumor burden (whole body and hind limb) was significantly greater for the combination of OPG-Fc and docetaxel, as compared to either agent alone (see Figures 30 and 31). However, a significant reduction on head region tumor burden was not observed following treatment of tumor-bearing mice with OPG-Fc and docetaxel at 15 mg/kg (See Figure 32). Significant reductions in hind limb osteolytic lesion area and hind limb tumor area were observed in all treatment groups (see Figure 33 and 34). The combination of OPG-Fc and docetaxel induced a statistically significant greater reduction in hind limb lesion area as compared to docetaxel alone. In addition, significant reductions in TRAP5b levels were observed in the OPG-Fc treated mice providing evidence for reductions in osteoclastogenesis (see Figure 35).

This study provides evidence that treatment of H1299 human NSCLC tumor-bearing mice with the combination of OPG-Fc and docetaxel induced greater reductions in whole body tumor burden, hind limb tumor burden, hind limb osteolytic lesions, and hind limb tumor area as compared taxotere alone.

4.2 Secondary Pharmacology

Study Title: Effect of OPG-Fc on Neovascularization in the Rat Corneal Disk Implant Model of Angiogenesis, Study Number R2002266

Key Findings:

- In the rat corneal model of angiogenesis, subcutaneous administration of OPG-Fc for 7 days in combination with rHu-VEGF induced significantly greater number of blood vessels in the cornea as compared to the number of blood vessels induced by rHu-VEGF alone.

Pertinent Background:

Osteoprotegerin (OPG) acts as a non-signaling decoy receptor, which can bind OPGL (also known as TRANCE, ODF and RANKL) and prevent activation of the osteoclast receptor, RANK (for review see Kostenuik and Shalhoub 2001)[2]. A role for OPG in angiogenesis has not been clearly defined; however, OPG has been shown to influence the survival of endothelial cells in vitro. Serum deprivation combined with the inactivation of NF-KB signaling led to endothelial cell apoptosis, and this apoptosis

2 Kostenuik PJ. Shalhoub V. Osteoprotegerin: a physiological and pharmacological inhibitor of bone resorption. Current Pharmaceutical Design. 7(8):613-35, 2001

could be blocked with high doses of OPG (Malyankar et al, 2000)3. More recently, it has been reported that OPGL can induce angiogenesis in human endothelial cells in vitro and in a matrigel plug assay in vivo (Kim et al, 2002)4. In this study, the sponsor evaluated the effect of systemic treatment of OPG-Fc on VEGF-induced corneal angiogenesis. Treatment with OPG-Fc (4 mg/kg/day s.c., lot # 43001-B) began on the day of surgery and was continued for seven days. Treatment with OPG-Fc induced a statistically significant increase in the angiogenic response when compared to the PBS treated group. There was no evidence of overt toxicity based on the body weights of the treated animals.

Methods:

Disk preparation: The tip of a 20-gauge needle was cut off square and beveled with emery paper to create a punch. This tip was then used to cut out ~0.6 mm diameter disks from a Nylaflo filter paper sheet (Gelman Sciences, cat #66600). Prepared disks were then placed into eppendorf microfuge tubes containing solutions of either 0.1% BSA in PBS (vehicle), or 10 µM rHu-VEGF (R&D Systems, lot # 131061 and 31121) in vehicle, and allowed to soak for 45 - 60 minutes at 4°C before use. Each filter disk absorbs ~0.1 µL of solution based on our unpublished observations.

Female Sprague Dawley rats weighing approximately 250 grams (8-12 weeks of age) were randomized into one of four treatment groups. On the day of surgery, the rats were temporarily anesthetized in an isofluorane gas chamber (delivering 2.5 liters/min oxygen + 5% Isofluorane). An orthoscope was then placed inside the mouth of the animal to visualize the vocal cords. A tip-blunted wire was advanced in between the vocal cords and used as a guide for the placement of an endotracheal Teflon tube (Small Parts, TFE-standard Wall R-SWTT-18). A volume-controlled ventilator (Harvard Apparatus, Model 683) was connected to the endotracheal tube to deliver a mixture of oxygen and 3% Isofluorane. Upon achieving deep anesthesia, the whiskers were cut short and the area around the eye gently washed with Betadine soap and rinsed with sterile saline. The cornea was irrigated with one drop of Proparacaine Hydrochloride (0.5%) ophthalmic topical anesthetic solution (Bausch and Lomb Pharmaceuticals). The rat was then positioned under the dissecting microscope and the corneal surface brought into focus. A vertical incision was made on the midline of the cornea using a diamond blade knife. A pocket was created by using fine scissors to separate the connective tissue layers of the stroma, tunneling towards the limbus of the eye. The distance between the apex of the pocket and the limbus was approximately 1.8 mm. After the pocket had been made, the presoaked nylon filter disk was inserted under the lip of the pocket. The disk was pushed into position at the required distance from the limbal

---

3 Malyankar Uriel M; Scatena Marta; Suchland Katherine L; Yun Theodore J; Clark Edward A; Giachelli Cecilia M [a]. Osteoprotegerin is an alphavbeta3-induced, NF-kappaB-dependent survival factor for endothelial cells. Journal of Biological Chemistry. 275(28). July 14, 2000. 20959-20962.

4 Young-Mi Kim; Young-Myoung Kim, You Mie Lee, Hae-Sun Kim, Jong Dai Kim, Yongwon Choi, Kyu-Won Kim, Soo-Young Lee, and Young-Guen Kwon, TNF-related Activation-induced Cytokine (TRANCE) induces Angiogenesis through the Activation of Src and Phospholipase C (PLC) in Human Endothelial Cells. The Journal of Biological Chemistry 277(9) March 1, 2002 6799-6805.

vessels. Vetropolycin ophthalmic antibiotic ointment (Pharmaderm) was applied to the eye to prevent drying and infection, and the rat was returned to its cage to recover. Study Termination: After seven days, the rats were euthanized by CO2 asphyxiation, and the implanted corneas photographed at 25X using a Nikon SV-3 Ophthalmic Slit Lamp (Nikon Ophthalmic) equipped with a Nikon D-1 digital camera back. A reference stage micrometer was photographed for calibration. The images were transferred to a desktop PC, optimized for image analysis, and transferred to a Metamorph IA system for computerized analysis.

Image analysis: Numerical data were generated from the D-1 digital images using the Metamorph image analysis system (Universal Imaging). Three endpoints were analyzed on each corneal image: (1) disk placement distance (mm) from the limbus, (2) number of vessels intersecting a 2.0 mm perpendicular line at the midpoint of the disk placement distance, and (3) blood vessel area (mm^2), as determined by thresholding and automated pixel counting.

Statistical Analysis: Results were analyzed with the Stat View statistical program using one-way ANOVA, followed by Fisher's least significant difference test. Data are presented as mean ±SE and $P<0.05$ was considered significant.

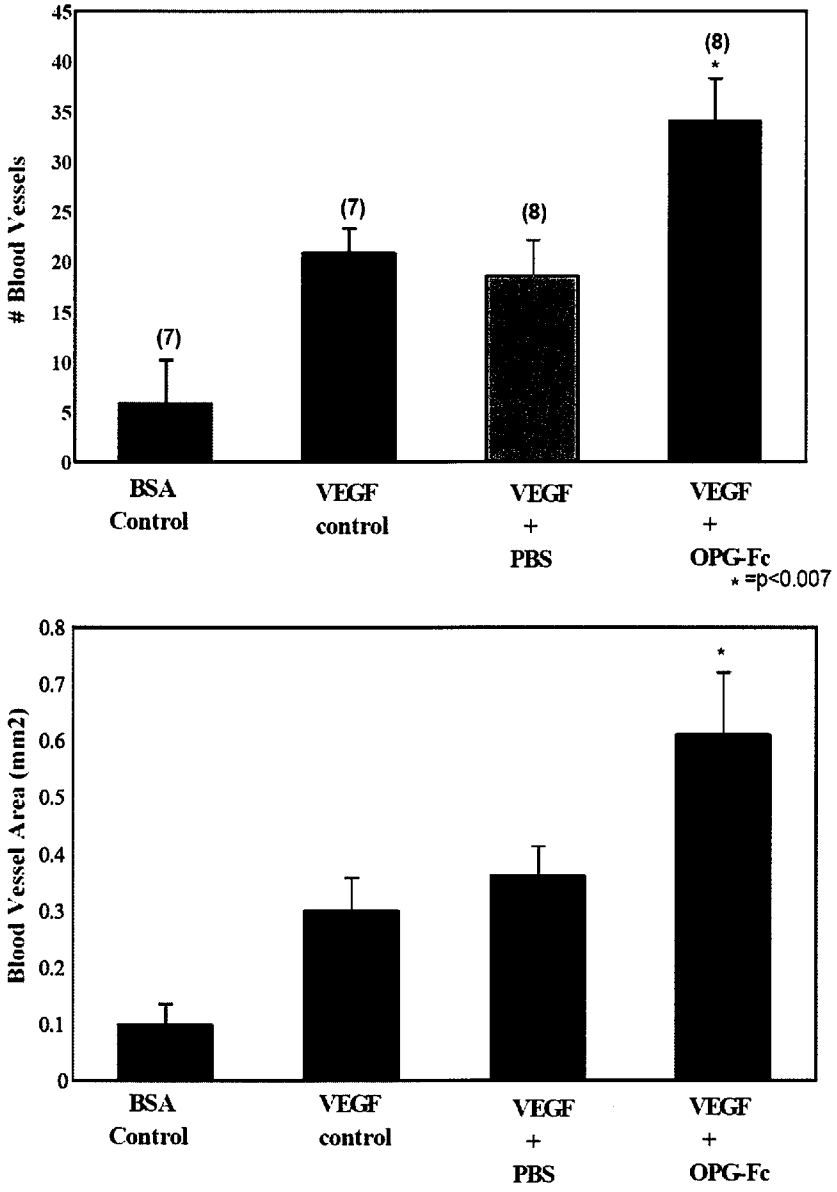
Experimental Design:

Gp #	Ani #	Route	Treatment	
			DISK	DOSING
1*	01-08	Disk/sc	0.1% BSA in PBS	N/A
2**	09-16	Disk/sc	10 µM rHu-VEGF and 0.1% BSA in PBS	N/A
3	17-24	Disk/sc	10 µM rHu-VEGF and 0.1% BSA in PBS	PBS 100 µL/rat/day subcutaneously
4	25-32	Disk/sc	10 µM rHu-VEGF and 0.1% BSA in PBS	OPG-Fc 4 mg/kg/day subcutaneously

*negative control group; **positive control group; N/A = not applicable

Results:

Figure 36: The Effect of OPG-Fc on VEGF-induced Corneal Angiogenesis



Data represent mean +/- s.e. for each group. Numbers in parenthesis refer to the number of animals included in the final analysis. Statistical analysis performed by ANOVA with Fisher's post-Hoc test. * = $p < 0.001$ compared with VEGF control treated with PBS. OPG-Fc was evaluated in the rat corneal model of angiogenesis. rhu-VEGF was used as a neovascular stimulus and rats were treated with 4 mg/kg/day subcutaneously of OPG-Fc. Treatment began on the day of surgery and was continued for 7 days. Treatment with OPG-Fc induced a statistically significant increase in the angiogenic response when compared to the PBS treated group.

Study Conclusion:

OPG-Fc (4 mg/kg/day) administered for seven days induced a statistically significant increase in the angiogenic response, as the number of blood vessels and the blood vessel area had statistically significant increases as compared to VEGF treatment alone (see Figure 36).

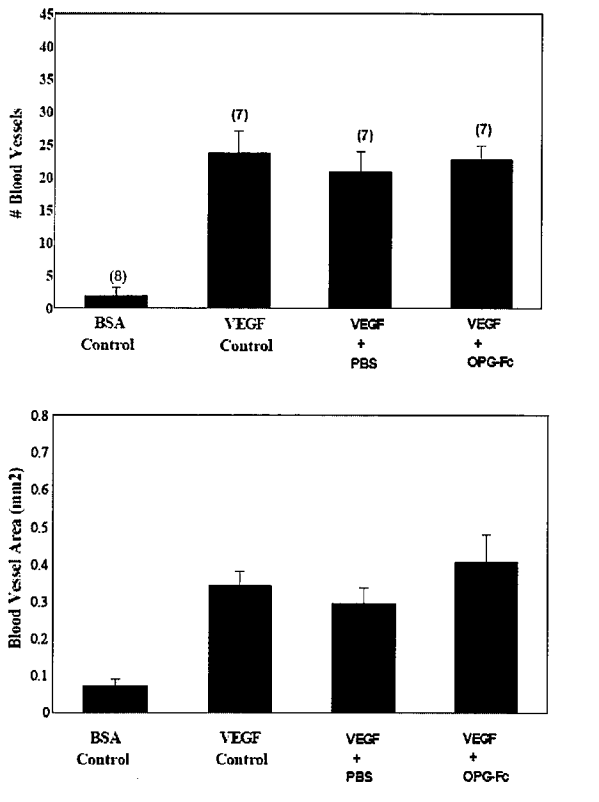
Study Title: Effect of OPG-Fc on VEGF Induced Corneal Angiogenesis, Study Number R2002204

Key Findings:

- OPG-Fc administered subcutaneously at 4 mg/kg/day had no effect on VEGF induced angiogenesis in the rat corneal disk implant model of angiogenesis, there were no significantly different effects on number of blood vessels and blood vessel area between the treatment groups.

Results:

Figure 37: The Effect of OPG-Fc on VEGF-induced Corneal Angiogenesis



Data represent mean ± s.e. for each group. Numbers in parenthesis refer to the number of animals included in the final analysis. Statistical analysis performed by ANOVA with Fisher's post-Hoc test. OPG-Fc was evaluated in the rat corneal model of angiogenesis. rHu-VEGF was used as a neovascular stimulus and rats were treated with 4mg/kg/day/subcutaneously of OPG-Fc. Treatment began on the day of surgery and was continued for 7 days. Treatment with OPG-Fc had no effect on the VEGF-induced angiogenic response when compared to the PBS treated group. Treatment with OPG-Fc had no effect on body weight.

Study Conclusion:

The subcutaneous administration of 4 mg/kg OPG-Fc daily for 7 days did not increase or decrease the VEGF induced angiogenesis in this rat model (see Figure 37).

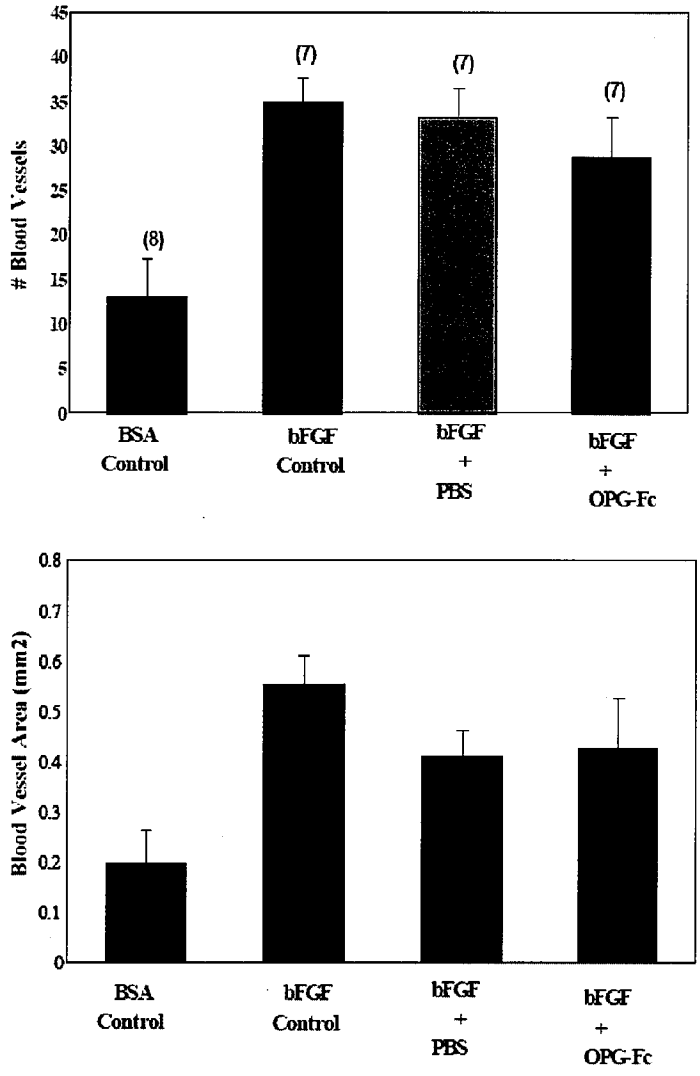
Study Title: Effect of OPG-Fc on bFGF Induced Corneal Angiogenesis, Study Number R2002267

Key Findings:

- OPG-Fc administered subcutaneously at 4 mg/kg/day did not significantly modulate bFGF induced angiogenesis in the rat corneal disk implant model of angiogenesis (see Figure 38).

Results:

Figure 38: The Effect of OPG-Fc on βFGF-induced Corneal Angiogenesis



Data represent mean ± s.e. for each group. Numbers in parenthesis refer to the number of animals included in the final analysis. Statistical analysis performed by ANOVA with Fisher's post-Hoc test. OPG-Fc was evaluated in the rat corneal model of angiogenesis. rHu-bFGF was used as a neovascular stimulus and rats were treated with 4 mg/kg/day subcutaneously of OPG-Fc. Treatment began on the day of surgery and was continued for 7 days. Treatment with OPG-Fc had no effect on the bFGF-induced agiogenic response.

4.3 Safety Pharmacology

The data was reviewed by both Dr. Michael Orr and Kim Hatfield for STN BL 125320/0. Please see the original reviews for details.

5 Pharmacokinetics/ADME/Toxicokinetics

The data was reviewed by both Dr. Michael Orr and Kim Hatfield for STN BL 125320/0. Please see the original reviews for details.

6 General Toxicology

The data was reviewed by both Dr. Michael Orr and Kim Hatfield for STN BL 125320/0. Please see the original reviews for details.

7 Genetic Toxicology

No genetic toxicology studies were conducted by the sponsor.

8 Carcinogenicity

Carcinogenicity risk has not been evaluated. Denosumab is pharmacologically active only in humans and non-human primates, which are not an appropriate model in which to evaluate the tumorigenic potential of denosumab over a lifetime of exposure.

9 Reproductive and Developmental Toxicology

The data was reviewed by both Dr. Michael Orr and Kim Hatfield for STN BL 125320/0. Please see the original reviews for details.

10 Special Toxicology Studies

The data was reviewed by both Dr. Michael Orr and Kim Hatfield for STN BL 125320/0. Please see the original reviews for details.

11 Integrated Summary and Safety Evaluation

Since denosumab does not recognize mouse or rat RANKL, OPG-Fc was used as a surrogate for denosumab in the mouse models. However, these data do not address if denosumab itself is capable of reducing tumor growth and osteolysis in monkeys and humans. Furthermore, it is unclear how to extrapolate the dose levels of OPG-Fc used in the mouse tumor models relative to the dose levels of denosumab being utilized in monkeys and humans. However, the sponsor did provide evidence that the inhibition of RANKL by OPG-Fc in female athymic nude mice injected with syngeneic breast (MDA-MB-231[estrogen receptor negative] and MCF-7 [estrogen receptor positive]) tumors

leads to reduction in tumor cell growth and subsequent tumor burden, reduction in the area of osteolytic lesions resulting from metastases to the bone. The combination of OPG-Fc-mediated inhibition of RANKL and tamoxifen did not appear to provide additional reductions in tumor cell growth or reductions in osteolytic lesions as compared to either agent alone in the MCF-7 *in vivo* cancer model tested.

In male athymic nude male mice injected with PC-3 prostate cancer cells, the combination of OPG-Fc and docetaxel significantly reduced the tumor burden (whole body, hind limb, and head region) and osteolytic lesion area to a greater extent, as compared to the inhibition by either agent alone.

In athymic nu/nu female mice injected with H1975 non-small lung cancer cells, OPG-Fc reduced tumor growth (whole body, hind limb, and head region), and reduced the osteolytic lesion area. In a second lung cancer *in vivo* tumor model in which H1299 cells were injected in TAC NCR nu/nu female mice, significant tumor growth inhibition (whole body, hind limb, and head region) and significant reductions in skeletal tumor burden based on histological measurements were reported after OPG-Fc treatment. In an additional study investigating the effects of the combination OPG-Fc and docetaxel, OPG-Fc did not significantly reduce the whole body tumor burden while docetaxel alone significantly reduced whole body tumor burden. All treatments resulted in significant reductions in skeletal tumor hind limb tumor burden and reductions in hind limb osteolytic lesions. Treatment of H1299 human NSCLC tumor-bearing mice with the combination of OPG-Fc and docetaxel induced greater reductions in whole body tumor burden, hind limb tumor burden, hind limb osteolytic lesions, and hind limb tumor area as compared taxotere alone

The nonclinical data provided evidence that the inhibition of RANKL in mice by OPG-Fc can induce significant reductions in osteolytic lesions. Furthermore, the sponsor provides evidence that the inhibition of RANKL can lead to significant reductions in tumor growth in the *in vivo* mouse cancer models tested. At least in the human H1299 lung cancer model and human PC-3 prostate cancer model, there is evidence indicating that the combination of docetaxel and inhibition of the RANKL by OPG-Fc can induce greater reductions in hind limb osteolysis and tumor growth inhibition as compared to either agent alone.

The secondary pharmacodynamic studies were designed to assess the role of RANKL/RANK pathway in angiogenesis in rats provided equivocal results when the VEGF was utilized to induce the angiogenic response (See studies R2002266 and R2002204). However, blocking RANK signaling by OPG-FC in the presence of a second angiogenic-inducing agent (bFGF) (Fibroblast Growth Factor basic) did not induce an increase in the angiogenic response above the levels induced by bFGF alone (see review of study # R2002267 below). Based on the three independent studies provided, there is a lack of clear evidence for the role of RANKL inhibition in the rat angiogenesis. However, the positive findings in one of the VEGF-induced angiogenesis in rats can not be ignored either. There is some limited evidence to support that denosumab and/or radiolabeled protein fragments of denosumab may be able to

distribute to the cornea in cynomolgus monkeys (Study # 104105; reviewed for the original BLA application STN BLA 125320/0). However, the tissue cross-reactivity studies did not provide evidence that denosumab binds to the eye in the cynomolgus monkey or human tissue samples that were evaluated (data reviewed by Dr. Michael Orr in STN BL 125320/0, Please see the original review for details). In addition, the repeat dose 1 month and 6/12 month toxicology studies in cynomolgus monkeys administered denosumab at doses 25 times greater than the proposed human doses in cancer patients lacked any noteworthy ocular toxicities based on opthalmic examinations. Based on the totality of the toxicology data thus far, inhibition of the RANKL pathway by denosumab has not induced remarkable ocular toxicity in cynomolgus monkeys.

Denosumab was previously approved for the treatment of postmenopausal osteoporosis in women on June 1, 2010. Denosumab dosing in this patient population is 60 mg, once every six months. In oncology, the proposed clinical dose is 120 mg dosed once a month. NOAELs for the pivotal toxicology and pharmacology studies (102090, 103981 and 102842) were determined based on the toxicology data previously reviewed in the original BLA 125302/0 and are presented in the Table 3 below. Dose multiples were calculated based on body weight (mg/kg), and provide an appropriate safety margin for clinical use. The proposed clinical dose of denosumab is a single subcutaneous injection of 120 mg every month, which for a 60 kg patient equates to a 2 mg/kg dose every month.

Table 3 Evaluation of human dose multiples

Study	Species	NOAEL (mg/kg) M/F	Dose Multiple (based on mg/kg)
12 month Study # 102090	Cynomolgus Monkey	50 mg/kg (monthly dosing)	25
16-month Study # 103981	Cynomolgus Monkey	50 mg/kg (monthly dosing)	25
Embryo/fetal Study	Cynomolgus Monkey	12.5 mg/kg (weekly)	6.5
PK in human Study 20010223	Human	2 mg/kg (Q4W)	

*Based on data reviewed by Dr. Michael Orr and Kim Hatfield in STN BL 125320/0

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	BLA 125320
Supporting document/s:	007
Applicant's letter date:	May 14, 2010
CDER stamp date:	May 19, 2010
Product:	Denosumab
Indication:	(b) (4)
Applicant:	Amgen, Inc. 11000 Thousand Oaks Blvd Thousand Oaks, CA 07677
Review Division:	Division of Biologic Oncology Products
Reviewer:	Michael S. Orr, Ph.D., D.A.B.T.
Supervisor/Team Leader:	**Anne M. Pilaro, Ph.D.**
Division Director:	Patricia Keegan, M.D.
Project Manager:	Melanie Pierce

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of BLA #125,320/007 are owned by Amgen, Inc. or are data for which Amgen, Inc. has obtained a written right of reference. Any information or data necessary for approval of BLA #125,320/007 that Amgen, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Amgen, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of BLA #125,320/007.

MEMORANDUM

TO: The file
CC: Patricia Keegan, M.D., Director, Division of Biologic Oncology Products, Office of Oncology Drug Products (OODP), Center for Drug Evaluation and Research (CDER)
John Leighton, Ph.D., D.A.B.T., Associate Director for Pharmacology and Toxicology, OODP
FROM: Anne M Pilaro, Ph.D., Supervisory Toxicologist, Pharmacology/Toxicology Branch, Division of Biologic Oncology Products, OODP, CDER
STN BLA #: 125320/007
SPONSOR: Amgen, Inc.
PRODUCT: Xgeva™ (denosumab)
SUBMISSION TYPE: efficacy supplement; **new indication**
DATE: November 10, 2010

SYNOPSIS:
Amgen, Inc. has submitted efficacy supplement STN BLA #125320/007 to support approval of denosumab (proposed trade name, Xgeva™) for the treatment of (b) (4) (b) (4) Denosumab is a fully human IgG2 monoclonal antibody, directed against an epitope present on the receptor activator of nuclear factor-KB (RANK) ligand (RANK-L). RANK-L binds to RANK on osteoclast precursors and mature osteoclasts, stimulates osteoclasts to resorb bone, and promotes differentiation of the precursor cells into osteoblasts. Binding of denosumab to RANK-L inhibits interaction of the ligand with target receptors such as RANK, thereby neutralizing the effects of RANK-L. Since RANK-L binding to RANK is involved with the formation, function, and survival of cells that resorb bone such as osteoclasts, the inhibition of RANK-L binding to RANK by denosumab leads to the suppression in osteoclast-mediated bone turnover. In patients with solid tumors that have metastasized to bone, treatment with denosumab and subsequent suppression of the RANK-L pathway is expected to inhibit both tumor- and osteoclast-mediated osteolytic lesions.

This memorandum summarizes the principle nonclinical issues related to the approval of denosumab (proposed trade name, Xgeva™) for the present indication of (b) (4) my conclusions regarding the findings as presented in the primary reviewer's review, and the appropriateness of the proposed labeling.

Since denosumab binding is restricted to human and non-human primate RANK-L, nonclinical studies evaluating the effects of inhibition of the RANK-L pathway in support of the present supplemental BLA were conducted using the rodent fusion protein osteoprotegerin-Fc (OPG-Fc), as a surrogate for denosumab. A summary of the mechanism by which osteoprotegerin acts to inhibit RANK-L, and supporting data for its use as a surrogate for denosumab can be found in Section 4.2, *Secondary Pharmacology* of Dr. Orr's current review for STN BLA 125320/007, and in Section 4.1, *Primary Pharmacology* of Dr. Orr's review of the original STN BLA #125320/000

application. I concur that the data presented in both the present supplemental and original BLA submissions support the use of OPG-Fc in rodents as an appropriate surrogate for identification of the effects of inhibition of the RANK-L pathway by denosumab in humans and non-human primates.

There are no new nonclinical toxicology, safety pharmacology, or other safety data included in the supplemental BLA submission. Nonclinical studies using OPG-Fc alone or in combination with chemotherapy agents in human tumor xenograft models, and investigative studies evaluating the effects of combined OPG-Fc and vascular endothelial cell growth factor-b (bVEGF) in a rat neovascularization model were included in the present supplemental BLA submission, and reviewed by the primary non-clinical reviewer, Michael Orr, Ph.D., D.A.B.T Nonclinical safety data to support the labeling of Xgeva™ were incorporated by cross-reference to the original BLA submission STN BLA #125320/000, and were previously jointly reviewed by Dr. Orr and Dr. Kimberly Hatfield in the Division of Reproductive and Urologic Products (DRUP), to support the initial approval of denosumab (trade name Prolia™) for the treatment of post-menopausal osteoporosis.

My conclusions from the results presented in Dr. Orr's present review for STN BLA #125320/007 are that OPG-Fc dosing of non-small cell lung cancer, estrogen-positive or estrogen-negative breast carcinoma, or prostate tumor-bearing mice did not result in any appreciable anti-tumor effect by itself, and in these models, suppression of the RANK-L pathway by OPG-Fc did not either augment or inhibit the anti-tumor effects of docetaxel or tamoxifen. However, inhibition of the RANK-L pathway by OPG-Fc did significantly decrease the osteolytic lesion area from metastases to bone in these models, supporting the proposed rationale for the initial use of denosumab in patients with metastatic breast or prostate cancer. The pivotal clinical studies in these patient populations demonstrated similar effects on osteolytic lesions to those observed in the animal studies, and are the basis for this supplemental application and new indication for denosumab.

Tissue cross-reactivity data using denosumab with a panel of human and cynomolgus monkey tissues were reviewed by Dr. Orr in support of the original BLA approval, and demonstrated equivocal staining in the cornea from monkey, but not human tissues and limited distribution of radiolabeled denosumab to monkey cornea in a follow-on, investigative study (Study #104192; reviewed by Dr. Orr for the original BLA application STN BLA 125320/0). In the present BLA submission, data were reviewed by Dr. Orr from three separate, investigative studies, in which a rat corneal model was used to investigate whether suppression of the RANK-L pathway by OPG-Fc could affect bVEGF-induced neovascularization in the eye. In one study, OPG-Fc treatment of rats implanted in the cornea with a filter-paper disc containing bVEGF statistically significantly increased corneal blood vessel number and blood vessel area, while two additional studies demonstrated no effect of OPG-Fc treatment on new blood vessel formation as compared to the control animals. These equivocal findings do not confirm or refute the sponsor's previous finding in cynomolgus monkey cornea, nor suggest that inhibition of the RANK-L pathway by OPG-Fc in the rodent, or by denosumab in humans will result in ocular changes that could adversely affect patient safety.

The labeling for Xgeva™ was derived from the initial labeling for the approved denosumab product, Prolia™ for the treatment of post-menopausal osteoporosis. Sections that included nonclinical data were modified only for presentation style, and there are no differences in the data included in either Sections 8.1 (Use in Specific Populations: Pregnancy), 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility), or 13.2 (Animal Toxicology and Pharmacology) from those in the original label with the exception of modifications to the location of the nonclinical data in each section, which were made solely for clarity of presentation. In the labeling, comparison of the doses used in the animal testing with the recommended human dose for the present indication were based on body weight (i.e. mg/kg), rather than exposure (i.e. area under the concentration-time curve [AUC]) for both the initial approval of denosumab, and for the present supplemental indication because development of anti-denosumab antibodies in the animal toxicology studies precluded the ability to accurately estimate exposure using AUC. For proteins such as denosumab with high molecular weight that are administered systemically, dose comparisons on a body weight basis are appropriate, as distribution of these proteins tends to be confined to the vascular space, and plasma volume across species also scales by body weight.

Recommendation: Based on the nonclinical data provided in the present supplemental BLA submission, there are no new safety issues identified (i.e. loss of anti-tumor activity of effective chemotherapy, or increased/decreased neovascularization in the cornea) in rodent models following inhibition of the RANK-L pathway by the surrogate molecule, OPG-Fc. No new nonclinical safety issues are therefore identified that would impact the safety of denosumab treatment for the present indication (b) (4) (b) (4)

I concur with Dr. Orr's current recommendation that the supplemental licensing application for Xgeva™ as treatment (b) (4) , and his recommendations regarding the nonclinical language for the prescribing information. A copy of Dr. Orr's review, with supervisory sign-off, has been conveyed to the regulatory project manager for inclusion in the final action package, and to be uploaded into the RMS-BLA database.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA OR SUPPLEMENT

NDA/BLA Number: 125320/7 **Applicant:** Amgen **Stamp Date:** 5-19-2010

Drug Name: denosumab **NDA/BLA Type:** Supplement

On initial overview of the BLA application for filing:

	Content Parameter	Yes	No	Comment
1.	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	Y		
2.	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Y		
3.	Is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	Y		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	Y		Tissue cross reactivity studies are provided with human and animal tissues; pivotal studies are in appropriate species (monkey); transgenic models used for pharmacodynamics; antibody formation addressed in studies 101447, 102090, 103948, 103981; CV and respiratory safety pharmacology with single dose study incorporated; PK and PD studies; repeat dose studies over appropriate duration; local tolerance incorporated into repeat dose studies. No carcinogenicity or genotoxicity studies are required since this is a therapeutic protein product with restricted species-specificity to humans and non-human primates.
5.	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	Y		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	Y		The subcutaneous route for clinical trials was used in all pivotal nonclinical studies.
7.	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	Y		Located on page 5 of the nonclinical overview.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Y		See comments below for information requested via meetings and submission comments.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA OR SUPPLEMENT

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	Y		
10	Have any impurity - etc. issues been addressed? (New toxicity studies may not be needed.)	Y		
11	Has the applicant addressed any abuse potential issues in the submission?	Y		No indication that drug interacts with receptors associated with drug dependence or neurotropic activity (p 29 of nonclinical overview). Label indicates "no experience with overdosage".
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Y

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

Additional notes:

New Nonclinical studies submitted to the sBLA:

Pharmacology-Primary Pharmacodynamics (Bone metastases from solid tumors indications sBLA on 19 May 2010)	
Study #	**Title**
R2006160	Effects of OPG-Fc on Tumor Burden and Osteolysis in MDA231-F11Luc Bone Metastasis Model in Female Athymic Nude Mice, Prevention Setting
R2006161	Effects of OPG-Fc on Tumor Burden and Osteolysis in MDA231-F11Luc Bone Metastasis Model in Female Athymic Nude Mice, Therapeutic Setting
R20080162	The Effect of Tamoxifen and the RANKL Inhibitor Osteoprotegerin (OPG-Fc) on the Growth of MCF-7 Cells in an Established Bone Metastasis Model in Female Athymic Nude Mice
R20070953	The Effect of Pretreatment of OPG-Fc on Prevention of Bone Mets in MDA-MB-231(F11)Luc Bone Metastasis Model in Female Athymic Nude Mice
R20080161	The Effect of Tamoxifen and the RANKL Inhibitor Osteoprotegerin (OPG-Fc) on the Growth of MCF-7 Cells in an Established Bone Metastasis Model in Female Athymic Nude Mice
R20080162	The Effect of Tamoxifen and the RANKL Inhibitor Osteoprotegerin (OPG-Fc), Alone and in Combination, on the Growth of MCF-7 Cells in an Established Bone Metastasis Model in Female Athymic nude mice
R20070963	The Effect of Human OPG-Fc Treatment on Tumor Burden and Osteolysis in a Murine Model of Bone Metastasis of Human Non-Small Cell Lung Cell Line H1975 Luc in Athymic Nude Female Mice
R20080310	The Effect of the RANK Ligand Inhibitor OPG-Fc on Tumor Burden and Osteolysis in a Murine Model of Bone Metastasis of Human Non-Small-Cell Lung Cell Line H1299 in Female Athymic Nude Mice

R20080331	Effect of OPG-Fc (in Combination with Docetaxel) Treatment on Tumor Burden and Osteoclast Remodeling in a Murine Model of Bone Metastasis of Human Non-Small-Cell Lung Cell Line H1299 in Female Athymic Nude Mice
R20080332	Effect of OPG-Fc (Alone and in Combination with Docetaxel) Treatment on Tumor Burden and Osteolysis in a Murine Model of Bone Metastasis of Human Non-Small-Cell Lung Cell Line H1299 in Athymic Nude Female Mice
Pharmacology-Secondary Pharmacodynamics (Bone metastases from solid tumors indications sBLA on 19 May 2010)	
Study #	**Title**
R20090211	Effect of the RANKL Inhibitor RANK-Fc versus Vehicle on Tumor Development in a Hormone and Carcinogen Induced Model of Mammary Tumorgenesis
R2002266	Effects of OPG-Fc on Neovascularization in the Rat Corneal Disk Implant Model of Angiogenesis
R2002204	The Effect of OPG-Fc on Neovascularization in the Rat Corneal Disk Implant Model of Angiogenesis
R2002267	The Effect of OPG-Fc on Neovascularization in the Rat Corneal Disk Implant Model of Angiogenesis
R20090070	The Effects of OPG-Fc or Alendronate on Tooth Eruption and on Bone Density, Geometry and Strength in Neonatal Rats: A Recovery Study
R20090069	A Study of Long Bone Geometry in 1- and 2-month Old Transgenic Rats Overexpressing the Soluble RANKL Inhibitor OPG during Growth and Development
R20090282	Dose-Dependent Effects of OPG-Fc on Tooth Eruption, Bone Growth and Bone Strength in Neonatal Rats

Additional comments:

Reviewing Toxicologist – Michael S. Orr, Ph.D., DABT — Date: July 12, 2010

Team Leader/Supervisor – Anne M. Pilaro, Ph.D. — Date: July 12, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 30, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Statistical Team Leader Review: Denosumab: BL STN 125320/7

Team leader sign-off is located in the statistical reviews.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125320/7
Drug Name:	Denosumab
Indication(s):	Bone metastases from solid tumors
Applicant:	Amgen Inc.
Receipt Date:	May 19, 2010
PDAFA Goal Date:	November 18, 2010
Review Priority:	Priority
Biometrics Division:	V (HFD-715)
Statistical Reviewer:	Weishi (Vivian) Yuan
Concurring Reviewers:	Kun He, Ph. D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Biologic Oncology Products
Clinical Team:	Shan Pradhan, MD, Clinical Reviewer
	Michael Axelson, MD, Clinical Reviewer
	Steven Lemery, MD, Team Leader
Project Manager:	Ms. Melanie Pierce

Keywords: Non-inferiority, synthetic method, Andersen and Gill method, WLW homogeneity test, sekeletal related events.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant submitted data and final study reports of three pivotal studies to support a new drug approval for denosumab indicated for (b) (4) (b) (4)

This application was based on three pivotal phase III, international, randomized, double-blind, active-controlled studies comparing denosumab with zoledronic acid among patients with bone metastasis and prostate cancer (Study 20050103 [103]), breast cancer (Study 20050136 [136]), and solid tumors excluding prostate and breast cancer or multiple myeloma (Study 20050244 [244]).

In all three studies, the primary and secondary endpoints evaluated the occurrence of one or more skeletal related events (SREs) defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression, compared with zoledronic acid (Zometa®). The primary objective was non-inferiority (NI) in time to first on-study SRE, tested using a synthesis method. The secondary objectives were superiority in time to first on-study SRE, and superiority in time to first and subsequent on-study SRE, tested using the Hochberg procedure.

In this review, Study 244 will be discussed. Please refer to Dr. Jenny Zhang's review for data and analyses results of Studies 103 and 136.

For Study 244, the data and analyses from current submission showed that denosumab was non-inferior to zoledronic acid. The median time to first on-study SRE was 20.5 months in the denosumab arm compared with 16.3 months in the zoledronic acid arm. The estimated hazard ratio (HR) was 0.84 with 95% CI = (0.71, 0.98). The p-value for the protocol defined non-inferiority test was <0.001. However, denosumab failed to demonstrate superiority to zoledronic acid based on the planned statistical testing procedure for superiority.

Based on the data and analyses perprotocol, the study results demonstrated that denosumab was non-inferior to zoledronic acid in the primary endpoint. Whether the size of the treatment effect is adequate for approval depends on the risk-benefit assessment and clinical decision.

1.2 Brief Overview of Clinical Studies

Study 244 was a randomized, double-blind, multicenter study of denosumab compared with zoledronic acid (Zometa®) in the treatment of bone metastases in subjects with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.

Patients were randomized in a 1:1 ratio to receive either 120 mg denosumab subcutaneously (SC) and zoledronic acid placebo intravenously (IV) every 4 weeks (Q4W), or denosumab placebo SC and zoledronic acid IV at a dose of 4 mg Q4W. Randomization was stratified by tumor type (non-small cell lung cancer or multiple myeloma or other), previous SRE (yes or no), and systemic anticancer therapy (e.g., chemotherapy, biologic therapy or hormonal therapy, yes or no).

The primary study objective was to test for non-inferiority in time to first on-study SRE of patients treated with denosumab versus zoledronic acid. Secondary objectives were to test superiority in time to first SRE and superiority in time to first and subsequent SRE.

The primary and secondary efficacy endpoints were analyzed based on the ITT population. Time to first on-study SRE was analyzed using a Cox model, with treatment arms as the independent variable and stratified by randomization stratification factors. A synthesis approach was used for the non-inferiority test for the primary endpoint.

Testing for superiority would be performed if denosumab was shown to be non-inferior to zoledronic acid. To control the overall type I error for multiple comparisons at a significance level of 0.05, the two secondary efficacy endpoints were tested simultaneously using the Hochberg procedure. A stratified log-rank test was used to test whether or not denosumab was superior to zoledronic acid with respect to time to first on-study SRE. For time to first-and-subsequent on-study SRE (multiple-event analysis), the Andersen and Gill approach was used.

1.3 Statistical Issues and Findings

A total of 1776 patients were randomized to the two arms, with 886 in the denosumab arm, and 890 in the zoledronic acid arm. There were 278 patients in the denosumab arm and 323 patients in the zoledronic acid arm experienced at least one on-study SRE. The median time to first on-study SRE was 20.6 months for the denosumab arm and 16.3 months for the zoledronic acid arm. The hazard ratio (HR) based upon a Cox model including the randomization stratification factors as strata was 0.84 with 95% CI = (0.71, 0.98). The results from the study demonstrated non-inferiority of denosumab to zoledronic acid with p-value <0.001, but failed to prove superiority with an adjusted p-value of 0.060. For the time to first-and-subsequent on-study SRE, the estimated HR was 0.90 with 95% CI = (0.77, 1.04) with an adjusted p-value of 0.145, which was also not statistically significant.

The following table summarized the major efficacy analysis results.

Table 1.3.1 Summary of Efficacy Results

Endpoints (Time to…)	Median (95% CI)		p-value (Note)	HR (95% CI)
	D	Z		
1st SRE (NI)	20.5 (15.0, NE)	16.3 (12.2, 19.4)	0.0007 (Synthesis)	0.84 (0.71, 0.98)
1st SRE (Sup)	20.5 (15.0, NE)	16.3 (12.2, 19.4)	0.06 (Log-rank, Adj.)	0.84 (0.71, 0.98)
1st-and Subseq. SRE (Sup)	NA	NA	0.145 (AG Model, Adj.)	0.90 (0.77, 1.04)

Subgroup analysis revealed that denosumab increased the risk of death compared with zoledronic acid among multiple myeloma patients. There were 23 (26.6%) deaths among the 87 patients in the denosumab arm and 13 (14.0%) deaths among the 93 patients in the zoledronic acid arm. The estimated HR for overall survival (OS) was 2.26 with 95% CI = (1.13, 4.50). However, due to small sample size and lack of randomization, one should be cautious in interpreting this result.

2. INTRODUCTION

2.1 Overview

The applicant submitted data and final study reports of three pivotal studies to support a new drug approval for denosumab indicated for (b) (4) (b) (4)

This application was based on three phase III, international, randomized, double-blind, active-controlled studies comparing denosumab with zoledronic acid: Studies 20050103 (103) in prostate cancer, 20050136 (136) in breast cancer, and 20050244 (244). Study 244 was in adults with other solid tumors (including NSCLC, renal cell cancer, colorectal cancer, small cell lung cancer, bladder cancer, head and neck cancer, GI/genitourinary cancer, and others, excluding breast and prostate cancer) and bone metastasis or multiple myeloma. It was conducted in a total of 321 centers in 33 countries (159 centers in Europe, 86 in North America, 54 in Latin America, and 22 in other regions). The enrollment period was from June 2006 to May 2008. The primary analysis data cut-off date was April 30, 2009.

In this review, Study 244 will be discussed. Please refer to Dr. Jenny Zhang's review for data and analyses results of Studies 103 and 136.

2.2 Data Sources

Data used for review is from the electronic submission received on May 19, 2010. The network path is \\cbsap58\m\eCTD_Submissions\STN125355\0000.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy for Study 244

3.1.1 Study Objectives

The primary objective of Study 244 was to determine if denosumab was non-inferior to zoledronic acid with respect to time to first on-study SRE in patients with advanced cancer and bone metastases. The secondary objectives of the study were to determine if denosumab was superior to zoledronic acid with respect to time to first on-study SRE and time to first-and-subsequent on-study SRE, and to assess the safety and tolerability of denosumab compared with zoledronic acid.

3.1.2 Study Design

Study 244 was an international, phase III, randomized, double-blind, active-controlled study comparing denosumab in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Patients enrolled were adults with histologically or cytologically confirmed advanced cancers including solid tumors, multiple myeloma, and lymphoma, and current or prior radiographic evidence of ≥ 1 bone metastasis (or lytic bone lesion from multiple myeloma).

Patients were randomized 1:1 to receive either 120 mg denosumab subcutaneous every 4 weeks or 4 mg zoledronic acid (dose-adjusted for reduced renal function) IV every 4 weeks, up to primary analysis data cut-of date. Randomization was stratified by tumor type (non-small cell lung cancer or multiple myeloma or other), previous SRE (yes or no), and systemic anticancer therapy (e.g., chemotherapy, biologic therapy or hormonal therapy, yes or no).

3.1.3 Efficacy Endpoints

The protocol-specified primary efficacy endpoint was time to first on-study SRE. Secondary endpoints included time to first-and-subsequent on-study SRE.

SRE was a composite endpoint defined as one or more of the following local, irreversible events: pathologic fracture (vertebral or nonvertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression (SCC). A central imaging vender, RadPharm, and the Skeletal Related Event Review Committee (SRERC) reviewed and confirmed scans of fractures and SCCs.

The secondary endpoint, time to first-and-subsequent on-study SRE accounted for both the absolute number of SREs and the timing between two consecutive events. A subsequent SRE must have occurred at least 21 days after the previous SRE.

3.1.4 Sample Size Consideration

Since Study 244 was designed to assess non-inferiority with respect to time to first on-study SRE, historical data from the literature were used to estimate the hazard ratio of placebo versus the active control, zoledronic acid.

In the final Study 244 protocol, the sample size consideration was based on the following estimates and assumptions:

- 1:1 randomization scheme.
- The median time to first SRE for subjects treated with zoledronic acid was 250 days. This was based on published data for the solid tumor (non-small cell lung cancer (NSCLC) - approximately 171 days; other solid tumors -

approximately 314 days) (Rosen et al, 2003a) and multiple myeloma (approximately 380 days) (Rosen et al, 2003b) subject populations.

- Denosumab was non-inferior to zoledronic acid with respect to time to first on-study SRE with a hazard ratio of 0.9, based on a synthesis approach (Hung et al, 2003) designed to demonstrate that denosumab preserves at least 50% of the effect of zoledronic acid compared with placebo (97% power).
- Denosumab was superior to zoledronic acid for at least one of the two secondary endpoints (time to first on-study SRE and time to first-and-subsequent SRE) with a hazard ratio of 0.8 and a correlation coefficient of 0.6 between these two endpoints (90% power).

The sample size was calculated using a simulation procedure. The planned sample size was 1690 subjects with 745 subjects experiencing at least one SRE following randomization. With an enrollment period of 23 months and a combined lost-to-follow-up and death rate of 55% per year, the study was anticipated to reach the primary analysis data cut-off date in approximately 30 months.

Reviewer's Comments:

There were limited historical data available for the estimation of the hazard ratio of placebo versus zoledronic acid. The key parameters, hazard ratio of placebo versus zoledronic acid, and its standard error, were estimated based on three historical studies via a three-step procedure.

Step	Trial	Relative Effect	Relative HR (95% CI)
1	Novartis solid tumor trial 011	Placebo/Zoledronic	1.36 (1.04, 1.80)
2	Novartis multiple myeloma trial 12	Placebo/pamidronate	1.45 (1.07, 2.0)
	Novartis trial 10	Zoledronic/pamidronate	0.97 (0.71, 1.31)
	Combined 10 &12	Placebo/Zoledronic	1.50 (0.97, 2.32)
3	Combined steps 1 & 2	Placebo/Zoledronic	1.40 (1.11, 1.77)

The estimate of hazard ratio might not be accurate.

- The meta-analysis was only based on two key historical trials, Novartis Trials 011 and 010. Trial 011 was a double-blind Phase III study testing for superiority of zoledronic acid versus placebo with 773 patients. Trial 010 was a double-blind Phase III study testing for non-inferiority of zoledronic acid versus pamidronate with 1648 patients.
- The fact that Trial 010 itself was a non-inferiority design might introduce bias into the estimation procedure.
- Since the control arm in Trial 010 was not placebo, result from Trial 012, which compared placebo with pamidronate, was borrowed to estimate the HR of placebo versus zoledronic acid. This step might also introduce bias to the estimation procedure.

3.1.5 Efficacy Analysis Methods

A proportional hazards model stratified by the randomization stratification factors was used to analyze time to first on-study SRE based on the ITT population. A synthesis approach was to test whether denosumab preserved at least 50% of the effect of zoledronic acid on time to first on-study SRE. The test statistic was given as

$$Z_{PV} = \frac{\log(HR_{DZ}) - 0.5 \times \log(HR_{PZ})}{\sqrt{\{\sigma_{DZ}^2 + 0.25 \times \sigma_{PZ}^2\}}},$$

where HR_{DZ} was the estimated hazard ratio of denosumab compared to zoledronic acid adjusted by stratification factors in time to first on-study SRE in current study; and HR_{PZ} was the historical estimate of the hazard ratio of placebo compared with zoledronic acid in time to first SRE. The 50% effect would be considered preserved if $Z_{PV} < -1.96$ at $\alpha=0.05$.

The statistical inferences of the treatment effect on secondary efficacy endpoints would be carried out only when denosumab was shown to be non-inferior to zoledronic acid. To control the overall type I error for multiple comparisons at a significance level of 0.05, the two secondary objectives were tested using the Hochberg procedure. The superiority test for time to first on-study SRE was carried out by a stratified log-rank test. The Andersen and Gill (AG) model (Andersen and Gill, 1982; Lin, Wei, Yang and Ying, 2000) stratified by the randomization stratification factors was used for the superiority test of time to first-and-subsequent on-study SRE.

As a supportive analysis, Wei, Lin & Weissfeld (WLW) approach (Wei, Lin & Weissfeld, 1989) was used to evaluate the homogeneity of the treatment effects on time to first on-study SRE (superiority) for each individual component of SRE.

3.1.6 Applicant's Results and Statistical Reviewer's Findings/Comments

3.1.6.1 Study Population

Patients enrolled should have Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; adequate organ function, life expectancy ≥ 6 months; and no current or prior exposure to any IV bisphosphonates or oral bisphosphonates (for treatment of bone metastases/osteolytic lesions).

A total of 1776 patients were randomized to the two study arms, of which 886 were randomized to the denosumab arm, and 890 to the zoledronic acid arm. The patient disposition is summarized in Table 3.1.6.1.1.

The percentages of patients who discontinued treatment were 79.7% (706/886) in the denosumab arm and 80% (712/890) in the zoledronic acid arm. Majority of the

patients received at least one dose of investigational product (878 denosumab, 878 zoledronic acid; per randomization).

Table 3.1.6.1.1 Patient Disposition (ITT)

	Denosumab N (%)	Zoledronic acid N (%)
Randomized	886 (100%)	890 (100%)
On Study through Data Cut-Off	180 (20.3%)	178 (20.0%)
Discont. before Data Cut-Off	706 (79.7%)	712 (80.0%)
Received Treatment	878 (99.1%)	878 (98.7%)
Treat through Data Cut-Off	169 (19.1%)	168 (18.9%)
Discont. before Data Cut-Off	709 (80.0%)	710 (79.8%)
Never Received Treatment	8 (0.9%)	12 (1.3%)

3.1.6.2 Demographic and Other Baseline Characteristics

Demographic characteristics at baseline for the ITT population are summarized in Table 3.1.6.2.1.

Table 3.1.6.2.1 Demographics at Baseline (ITT)

	Denosumab N (%)	Zoledronic Acid N (%)
Randomized	886 (100%)	890 (100%)
Gender		
Male	588 (66.4%)	552 (62.0%)
Female	298 (33.6%)	338 (38.0%)
Race		
Caucasian	770 (86.9%)	770 (86.5%)
Non-Caucasian	116 (13.1%)	120 (13.5%)
Age		
< 65	587 (66.3%)	554 (62.2%)
≥ 65	299 (33.7%)	336 (37.8 %)
Stratum: Tumor Type (assigned)		
Multiple Myeloma	86 (9.7%)	93 (10.4%)
Non-Small Cell Lung Cancer	343 (38.7%)	345 (38.8%)
Other	457 (51.6%)	452 (50.8%)
Stratum: Previous SRE		
Yes	440 (49.7%)	446 (50.1%)
No	446 (50.3%)	444 (49.9%)
Stratum: Systemic Anti-Cancer Tx		
Yes	746 (84.2%)	747 (83.9%)
No	140 (15.8%)	143 (16.1%)

Disease characteristics at baseline for the ITT population are summarized in Table 3.1.6.2.2.

Table 3.1.6.2.2 Disease Characteristic at Baseline (ITT)

	Denosumab N (%)	Zoledronic Acid N (%)
Randomized	886 (100%)	890 (100%)
Tumor Type (Verified)		
Multiple Myeloma	87 (9.8%)	93 (10.4%)
Non-Small Cell Lung Cancer	350 (39.5%)	352 (39.6%)
Other	449 (50.7%)	445 (50.0%)
ECOG Status at Baseline		
0	240 (27.1%)	236 (26.5%)
1	508 (57.3%)	492 (55.3%)
2	136 (15.3%)	157 (17.6%)
Missing	2 (0.2%)	5 (0.6%)
Tumor Stage at Initial Diagnosis		
I	59 (6.7%)	54 (6.1%)
II	98 (11.1%)	101 (11.3%)
III	183 (20.7%)	214 (24.0%)
IV	520 (58.7%)	483 (54.3%)
Other	17 (1.9%)	27 (3.0%)
Missing	9 (1.0%)	11 (1.2%)
No. of Metastatic Bone Lesions		
≤ 2	749 (84.5%)	746 (83.8%)
> 2	137 (15.5%)	144 (16.2%)
Time from Cancer Diagnosis to 1st Bone Mets (Months)		
n	884	885
Mean (St. Dev.)	13.3 (28.7)	14.3 (32.0)
Median (Q1, Q3)	2.1 (0.0, 15.0)	2.9 (0.0, 14.5)
Time from Diagnosis of Bone Mets to Randomization (Months)		
n	884	886
Mean (St. Dev.)	4.4 (10.7)	4.7 (10.4)
Median (Q1, Q3)	1.7 (0.9, 3.8)	1.8 (0.9, 4.1)

Reviewer's comments:

The demographic and baseline characteristics of the ITT population are generally balanced over the two arms, except the percentages of male patients and younger patients (<65 years) were slightly higher in the denosumab arm.

3.1.6.3 Efficacy Analysis

Primary Endpoint Analysis: Time to First On-Study SRE (Non-Inferiority)

There were a total of 601 patients experienced at least one SRE following randomization, of which 278 (31.4%) were in the denosumab arm and 323 (36.3%) were in the zoledronic acid arm.

Table 3.1.6.3.1 summarizes the main efficacy analysis results for the protocol specified non-inferiority testing of the primary endpoint. Denosumab was shown non-inferior to zoledronic acid with p-value = 0.0007. The median time to first on-study SRE was 20.5 months for denosumab and 16.3 months for zoledronic acid. The estimated HR was 0.84 with 95% CI = (0.71, 0.98).

Table 3.1.6.3.1 Results of Primary Analysis

	Denosumab N = 886	Zoledronic Acid N = 890
Number of Events (%)	278 (31.4%)	323 (36.3%)
Median Time to 1st SRE (95% CI)	20.5 (15.0, NE)	16.3 (12.2, 19.4)
p-value (Non-Inferiority)	0.0007	
HR (95%CI)	0.84 (0.71, 0.98)	

Figure 3.1.6.3.1 shows the estimated Kaplan-Meier curve for the distribution of time to first on-study SRE.

Figure 3.1.6.3.1 K-M Curve of Time to First On-Study SRE

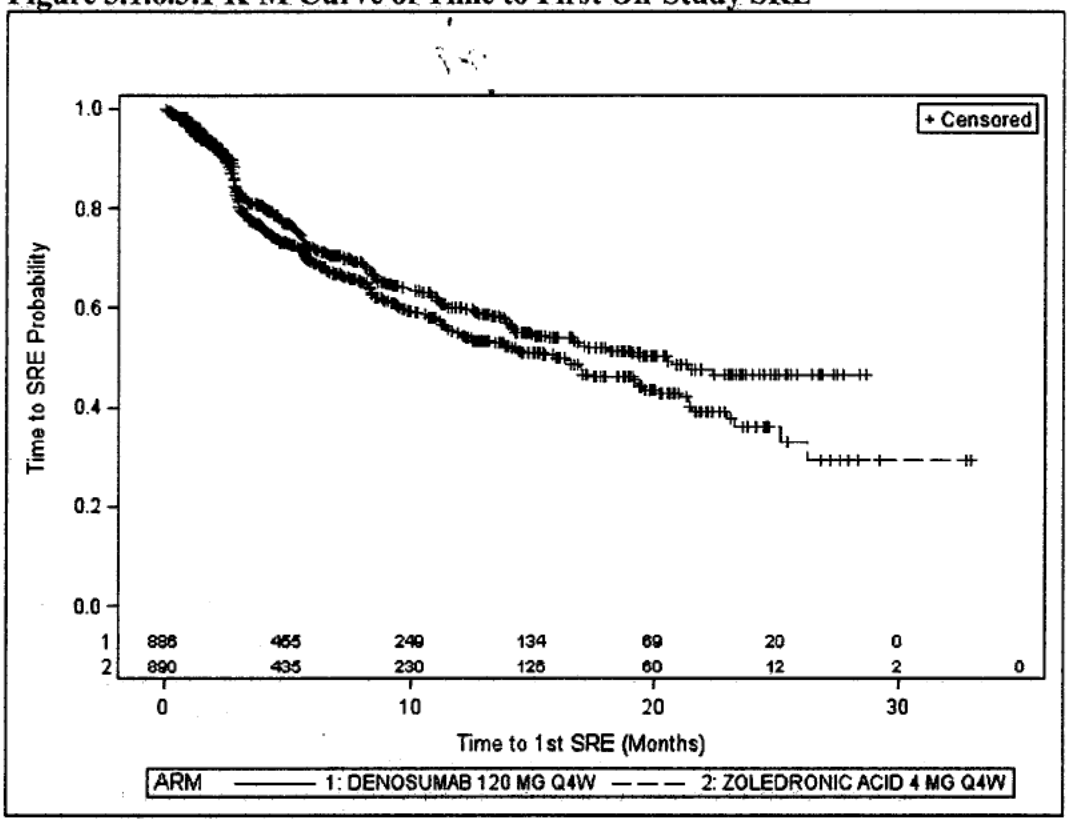


Table 3.1.6.3.2 shows the subject incidence for the components of first on-study SRE. Hierarchical ordering of on-study SRE were SCC, surgery, fracture, radiation for events occurring on same day. Fractures and radiation to bone were the most frequently reported first on-study SREs in both treatment arms. Based on the results from the WLW homogeneity test for time to first on-study SRE, there was no evidence of inconsistent effect across the four SRE components (p = 0.7908).

Table 3.1.6.3.2 Components of First On-Study SRE

	Denosumab events = 278 (31.4%)	Zoledronic Acid events = 323 (36.3%)
1st Radiation to Bone	119 (13.4%)	144 (16.2%)
1st Pathological Fracture	122 (13.8%)	139 (15.6%)
1st Surgery to Bone	13 (1.5%)	19 (2.1%)
1st SCC	24 (2.7%)	21 (2.4%)
WLW homogeneity test p-value: 0.7908		

Reviewer's comments:

There are some uncertainties about the conclusions from a non-inferiority test. The primary test of Study 244 was a non-inferiority test, and therefore involved estimation of several key parameters in the model. The precision of the estimate of the active control effect should be evaluated. Please refer to Section 3.1.4 for a detailed discussion of the estimation of HR_{PZ}.

Additional analyses to check the robustness of the test result were performed. Using the same synthesis method,

- if using 1.11, the lower bound of the 95% CI of the control effect instead of 1.40, the point estimate of HR_{PZ} in the formula, the test result was also statistically significant, with p-value = 0.0264.
- Although not statistically superior, numerically the median time to first on-study SRE and the HR favored the denosumab.

The NI testing approach also assumed that the constancy assumptions held from study to study for the estimate of the historical active-control effect. To evaluate this constancy assumption, study design features, subject population demographics and baseline characteristics, and zoledronic acid event rate from the Study 244 were compared to the historical studies used in the meta-analysis. The zoledronic acid event rates were 44% for Trials 010, 012, which were higher than 36.3% of Study 244. The median time to SRE in zoledronic acid arm was 12.2 months in Trial 010, and was not reached in Trial 011, compared with 16.3 months in Study 244. The following table summarizes the comparison of demographics and baseline characteristics, (adapted from CSR, Page 1830). These features of Study 244 and the historical studies were generally similar.

Table 3.1.6.3.3 Constancy Evaluation

	Novartis 12	Novartis 010	Novartis 011	Amgen 0244
Study Design Features	MM pamidronate disodium vs P	MM zoledronic acid vs pamidronate disodium	Other Solid Tumor zoledronic acid vs P	MM & Other Solid Tumor denosumab vs zoledronic acid
Publication reference	Theriault et al. 1999	Rosen et al. 2001	Rosen et al. 2003a	n/a
Demographic and Disease Characteristics as per inclusion criteria				
Gender	Not specified	Not specified	Not specified	Not specified
Age (yrs)	≥ 18 years	≥ 18 years	≥ 18 years	≥ 18 years
ECOG	0 – 3	0-2	0-2	0-2
Type of bone metastases	Not specified	Not specified	Not specified	Not specified
Prior type of therapy	Patient had received a regimen of chemotherapy that had not changed during at least the two months before enrollment	Antineoplastic therapy required at study entry	Cytotoxic chemotherapy at study entry	Antineoplastic therapy permitted at study entry
Corrected Serum Calcium	≤12 mg/dL	< 12 mg/dL	≤ 12 mg/dL	≥ 8.0 mg/dL and ≤ 11.5 mg/dL
Serum Creatinine	≤ 5 mg/dL	≤ 3.0 mg/dL	≤ 3.0 mg/dL	Creatinine clearance ≥ 30 mL/min*
Serum Bilirubin	≤ 2.5 mg/dL	≤ 2.5 mg/dL	≤ 2.5 mg/dL	≤ 2 x ULN
Prior bisphosphonates	Excluded if within 2 mo prior to study entry	Excluded if within 12 mo prior to study entry	Excluded if within 30 days prior to study entry	Oral bisphosphonate use for indications other than bone metastases allowed; i.v. bisphosphonates excluded

The reviewer conducted sensitivity analysis to check the robustness of the primary and secondary analysis results using the per-protocol analysis set and using the full analysis set and actual stratum (based on actual screening data versus randomization assignments from data input). These analyses were also reported by the applicant.

1. The per protocol (PP) population included patients in the ITT population who met the major inclusion criteria and who received ≥ 1 dose of active investigational product. A total of 1745 patients were included in the PP population, with 15 excluded from the denosumab arm and 16 excluded from the zoledronic acid arm from the ITT population. The results were similar to those of the ITT population. The analysis results are summarized below:

Table 3.1.6.3.4: Results of Primary Analysis in PP Population

	Denosumab N = 871	Zoledronic Acid N = 874
Number of Events (%)	268 (30.8%)	312 (35.7%)
Median Time to 1st SRE (95% CI)	19.4 (15.0, NE)	15.9 (12.0, 19.3)
p-value (Non-Inferiority)	0.001	
HR (95%CI)	0.84 (0.72, 1.00)	

2. Another sensitivity analysis was performed based on the actual strata, instead of the assigned strata. The results were consistent with the primary results.

Table 3.1.6.3.5: Results of Primary Analysis Using Verified Strata

	Denosumab N = 886	Zoledronic Acid N = 890
Number of Events (%)	278 (31.4%)	323 (36.3%)
Median Time to 1st SRE (95% CI)	20.5 (15.0, NE)	16.3 (12.2, 19.4)
p-value (Non-Inferiority)	0.001	
HR (95%CI)	0.84 (0.72, 0.99)	

Additional sensitivity analyses were also performed on certain subgroups. Please refer to Section 4.2 for results of the subgroup analyses.

Secondary Endpoints Analyses: Time to First On-Study SRE, and Time to First-and-Subsequent On-Study SRE (Superiority)

The secondary objectives of this study were to determine if denosumab was superior to zoledronic acid in time to first SRE and superior in time to first and subsequent SRE. These two tests, based on the Hochberg procedure, were to be performed only when denosumab was shown to be not inferior to zoledronic acid.

Table 3.1.6.3.6 summarizes the superiority test result for time to first on-study SRE. The adjusted p-value was 0.060, which was not statistically significant. This result was based on a stratified log-rank test.

Table 3.1.6.3.6: Results of Superiority Test for Time to First On-Study SRE

Number of Events (%)		
Median Time to 1st SRE (95% CI)		)
p-value (log-rank, adjusted)		
HR (95%CI)		

unadjusted p=0.03 (3.1.6.3.6) adjusted based on Hochberg procedure p=0.06.

Table 3.1.6.3.7 summarizes the and-subsequent on-study SRE. The not statistically significant. This resul

Table 3.1.6.3.7 Results of Time to First and Subsequent On-Study SRE

	Denosumab N = 886	Zoledronic Acid N = 890
Number of Events	392	436
Average No. of Events / Patient	0.44	0.49
p-value (AG model, adjusted)	0.145	
Rate Ratio (95%CI)	0.90 (0.77, 1.04)	

Exploratory Analyses: OS and PFS

OS and PFS were not defined as primary or secondary efficacy endpoints in this protocol, and the analysis results were considered exploratory only.

Table 3.1.6.3.8 summarizes the analysis results for OS data. The analysis showed there was no statistically significant difference in survival. The median survival was 12.0 months in the denosumab arm compared with 12.6 months in the zoledronic acid arm. The estimated HR was 0.95 with 95% CI = (0.84, 1.08).

Table 3.1.6.3.8 Results of OS Analyses

	Denosumab N = 886	Zoledronic Acid N = 890
Number of Events (%)	479 (54.1%)	474 (53.3%)
Median Survival (95% CI)	12.0 (10.7, 14.0)	12.6 (11.0, 13.9)
HR (95% CI)	0.95 (0.84, 1.08)	

Table 3.1.6.3.9 summarizes the analysis results for PFS data. The analysis showed there was no statistically significant difference in PFS. The median PFS was 5.4 months in the denosumab arm compared with 5.5 months in the zoledronic acid arm. The estimated HR was 1.01 with 95% CI = (0.91, 1.12).

Table 3.1.6.3.9 Results of PFS Analyses

	Denosumab N = 886	Zoledronic Acid N = 890
Number of Events (%)	687 (77.5%)	679 (76.3%)
Median Time to PFS (95% CI)	5.4 (4.9, 5.7)	5.5 (4.9, 5.7)
HR (95% CI)	1.01 (0.91, 1.12)	

Reviewer's comments:

Other exploratory analyses were reported in the CSR and verified by this reviewer. The following table summarizes some of the results of these analyses.

Table 3.1.6.3.10: Summary of Exploratory Analyses

Endpoints (Time to...)	Number of Events D	Z	Median (95% CI) D	Z	HR (95% CI)
1st Radiation to Bone	157	189	NE (NE, NE)	NE (26.3, NE)	0.78 (0.63, 0.97)
1st SRE or HCM	287	336	19.0 (14.2, NE)	14.4 (11.5, 17.1)	0.83 (0.71, 0.97)
Overall PD	612	600	5.7 (5.4, 6.5)	5.8 (5.5, 6.5)	1.00 (0.90, 1.12)
PD in Bone	283	292	13.9 (11.2,17.9)	13.6 (11.1,19.4)	0.98 (0.83, 1.16)
1st Symp. SRE	200	228	NE (NE, NE)	28.3 (23.2, NE)	0.84 (0.69, 1.02)
1st Radiation to Bone	157	189	NE (NE, NE)	NE (26.3, NE)	0.78 (0.63, 0.97)
1st Path Fracture	144	168	NE (27.6, NE)	NE (25.2, NE)	0.87 (0.69, 1.08)
1st SCC	27	28	NE (NE, NE)	NE (NE, NE)	1.00 (0.58, 1.70)
1st Surgery to Bone	27	31	NE (NE, NE)	NE (NE, NE)	0.86 (0.51, 1.44)

These results were consistent with the main efficacy results.

3.2 Evaluation of Safety for Study 244

Please refer to the Clinical Review of this application for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 4.1.1 presents the summary statistics of time to first on-study SRE by gender.

Table 4.1.1 Results of Time to First On-Study SRE Analysis by Gender

	Denosumab	Zoledronic Acid
Male	N = 588	N = 552
Number of Events (%)	179 (30.4%)	208 (37.7%)
Median Time to 1st SRE (95% CI)	20.7 (15.0, NE)	12.5 (9.5, 15.9)
HR (95% CI)	0.76 (0.62, 0.93)	
Female	N = 298	N = 338
Number of Events (%)	99 (33.2%)	115 (34.0%)
Median Time to 1st SRE (95% CI)	19.4 (13.9, NE)	21.0 (16.9, 23.2)
HR (95% CI)	0.99 (0.76, 1.31)	

Table 4.1.2 presents the summary statistics of time to first on-study SRE by age group (<65 vs. ≥65).

Table 4.1.2 Results of Time to First On-Study SRE Analysis by Age

	Denosumab	Zoledronic Acid
< 65	N = 587	N = 554
Number of Events (%)	185 (31.5%)	200 (36.1%)
Median Time to 1st SRE (95% CI)	21.4 (14.1 NE)	16.3 (11.7, 19.2)
HR (95% CI)	0.80 (0.65, 0.98)	
≥ 65	N = 299	N = 336
Number of Events (%)	93 (31.1%)	123 (36.4%)
Median Time to 1st SRE (95% CI)	19.4 (14.1, NE)	16.9 (11.2, NE)
HR (95% CI)	0.89 (0.68, 1.17)	

Table 4.1.3 presents the summary statistics of time to first on-study SRE by race (Caucasians vs. Non-Caucasians).

Table 4.1.3: Results of Time to First On-Study SRE Analysis by Race

	Denosumab	Zoledronic Acid
Caucasian	N = 770	N = 770
Number of Events (%)	243 (31.6%)	289 (37.5%)
Median Time to 1st SRE (95% CI)	20.5 (15.0, NE)	14.4 (11.4, 17.3)
HR (95% CI)	0.79 (0.67, 0.94)	
Non-Caucasian	N = 116	N = 120
Number of Events (%)	35 (30.2%)	34 (28.3%)
Median Time to 1st SRE (95% CI)	16.7 (12.7, NE)	NE (13.4, NE)
HR (95% CI)	1.21 (0.74, 1.98)	

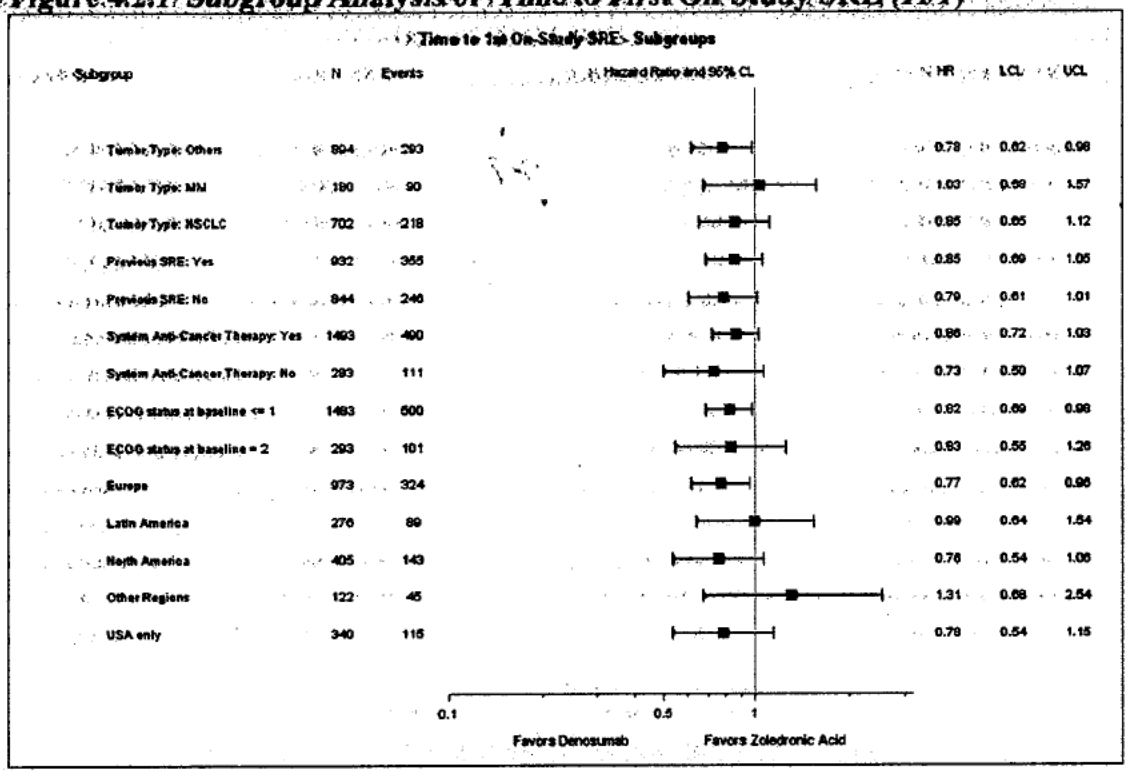
Reviewer's comments:

The analyses showed that median time to first on-study SRE was longer among male patients, younger patients (<65 years old), and Caucasians compared with the respective complementary subgroups. These observations were with the caveat that the sample sizes in the age ≥ 65 subgroup and the non-Caucasian subgroup were relatively small.

4.2 Other Special/Subgroup Populations

The applicant also reported analysis for certain subgroups. The following figure summarizes the subgroup analysis.

Figure 4.2.1 Subgroup Analysis of Time to First On-Study SRE (ITT)



Reviewer's Comments:

The subgroup analyses for time to first on-study SRE were verified by this reviewer. Most of these results were consistent with the overall result. Some of the particular subgroups are discussed in detail in the following.

A total of 180 multiple myeloma (MM) patients were enrolled in the study. Denosumab did not show benefit compared with zoledronic acid in time to first on-study SRE for this patient subgroup. The estimated median time to first on-study SRE was shorter in the denosumab arm (14.2 months) than the zoledronic acid arm (16.6 months). The estimated HR was 1.03 with 95% CI (0.68, 1.57). The following table summarizes the analysis result for this subgroup.

Table 4.2.1 Results of Time to First On-Study SRE Analysis for MM Patients

	Denosumab N = 87	Zoledronic Acid N = 93
Number of Events (%)	44 (50.6%)	46 (49.5%)
Median Time to 1st SRE (95% CI)	14.2 (8.4, NE)	16.6 (9.5, 25.2)
HR (95% CI)	1.03 (0.68, 1.57)	

In addition, the analysis result based on data from this study also showed an increased risk of death for patients in the denosumab arm compared with those in the zoledronic acid arm among the MM patients. The estimated HR was 2.26 with 95% CI (1.13, 4.50). The following table summarizes the subgroup analysis results.

Table 4.2.2 Summary of OS analysis for MM patients

	Denosumab N = 87	Zoledronic Acid N = 93
Number of Deaths (%)	23 (26.6%)	13 (14.0%)
Median Survival (95% CI)	NE	NE (28.4, NE)
HR (95% CI)	2.26 (1.13, 4.50)	

However, due to small sample size and lack of stratification at randomization, one should be cautious in interpreting this result.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary analysis showed that denosumab was non-inferior to zoledronic acid with p-value = 0.0007. The median time to first on-study SRE was 20.5 months for denosumab and 16.3 months for zoledronic acid. The hazard ratio (HR) was 0.84 with 95% confidence interval (0.71, 0.98).

Two secondary analyses, superiority in time to first on-study SRE and superiority in time to first-and-subsequent on-study SRE were tested based on the Hochberg procedure. Neither of them was statistically significant.

Subgroup analysis revealed that denosumab increased the risk of death compared with zoledronic acid among multiple myeloma patients. The estimated HR for overall survival (OS) was 2.26 with 95% CI = (1.13, 4.50).

5.2 Conclusions and Recommendations

Based on the data submitted, the study results demonstrated that denosumab was non-inferior to zoledronic acid in the primary endpoints. Whether the size of the treatment effect is adequate for approval is a clinical decision.

REFERENCES

1. Andersen PK, Gill RD. Cox's Regression Model for Counting Processes: A Large Sample Study. The Annals of Statistics 1982; 10 (4): 1100-1120.

2. Hung HM, Wang SJ, Tsong Y. Some fundamental issues with non-inferiority testing in active controlled trials. Statist. Med 2003; 22:213-225.

3. Lin DY, Wei LJ, Yang I, Ying Z. Semi-parametric regression for the mean and rate functions of recurrent events. J Royal Stat Soc, Series B; 2000;62:711-730.

4. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial - The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. J Clin Oncol. 2003a, 21(16): 3150-3157.

5. Rosen LS, Gordon D, Kaminski M, et al. Long term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, doubleblind, multicenter, comparative trial. Cancer. 2003b, 98:1735-1744.

6. Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. J Clin Oncol. 1999;17(3):846-854

7. Wei LJ, Ling DY, Weissfeld L. Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distributions. Biometrika 1989, 84, 1065 -1073.

/S/

Weishi Yuan
10/25/2010

Kun He
10/25/2010

Rajeshwari Sridhara
10/25/2010

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number: 125320 / 7

Drug Name: Denosumab

Indication(s): [redacted] (b) (4)

Applicant: Amgen

Date(s): Received Date: May 19, 2010

PDUFA Date: November 18, 2010

Review Priority: Priority

Biometrics Division: V (HFD 711)

Statistical Reviewer: Jenny (Jing) Zhang, Ph.D.

Concurring Reviewers: Kun He, Ph.D., Team Leader

Rajeshwari Sridhara, Ph.D., Director

Medical Division: Oncology Biologics Products

Clinical Team: Michael Axelson, M.D., Clinical Efficacy Reviewer

Shan Pradhan, M.D., Clinical Safety Reviewer

Steven Lemery, M.D., Team Leader

Project Manager: Melanie Pierce

Keywords: Non-inferiority, Synthesis method, Andersen and Gill method, WLW homogeneity test, Skeletal related event

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The Applicant is seeking approval for single-agent Xgeva® (denosumab) for [redacted] (b) (4)

The primary support for efficacy in this submission came from 3 randomized, double-blind, non-inferiority Phase III studies comparing denosumab with zoledronic acid (ZA) in the treatment of bone metastases in patients with hormone-refractory prostate cancer (Study 20050103), advanced breast cancer (Study 20050136), and advanced cancer (excluding breast and prostate cancer) or multiple myeloma (Study 20050244). The primary efficacy endpoint for all 3 studies was non-inferiority of time to first on-study skeletal-related event (SRE). Co-secondary efficacy endpoints were superiority of time to first on-study SRE and time to first and subsequent SRE. This review will discuss in detail studies 20050103 and 20050136. Please see Dr. Vivian Yuan's statistical review of BLA 125320 / 7 for results and discussion of Study 20050244.

A total of 1901 patients (950 on denosumab, 951 on ZA) were randomized in prostate cancer study 20050103 (study 103). The median time to first on-study SRE in the intent-to-treat (ITT) population was 20.7 months and 17.1 months in the denosumab and ZA arms, respectively. The corresponding hazard ratio (HR) was 0.82 with 95% confidence interval (CI) (0.71, 0.95). The non-inferiority test p-value using the Cox model and synthesis method (Hung et al., 2003) was 0.0002. Given the achievement of non-inferiority, the superiority stratified log-rank test p-value for time to first on-study SRE was 0.0082. Thus, study 103 demonstrated superiority of denosumab as compared with ZA with respect to time to first on-study SRE for patients with hormone-refractory prostate cancer. Additionally, denosumab did not show a detriment in overall survival as compared to ZA.

A total of 2046 patients (1026 on denosumab, 1020 on ZA) were randomized in breast cancer study 20050136 (study 136). The median time to first on-study SRE in the ITT population was 26.4 months in the ZA arm and not reached in the denosumab arm. The corresponding HR was 0.82 with 95% CI (0.71, 0.95). The non-inferiority test p-value using the Cox model and synthesis method (Hung et al., 2003) was < 0.0001. Given the achievement of non-inferiority, the superiority stratified log-rank test p-value for time to first on-study SRE was 0.0097. Thus, study 136 demonstrated superiority of denosumab as compared with ZA with respect to time to first on-study SRE for patients with advanced breast cancer. Additionally, denosumab did not show a detriment in overall survival as compared to ZA.

Both studies 103 and 136 showed that denosumab was superior to ZA in the treatment of bone metastases in patients with hormone-refractory prostate cancer and advanced breast cancer, respectively. Whether the results support the approval of denosumab for the proposed indications will depend on the clinical team's evaluation of the overall benefit-to-risk ratio.

1.2 Brief Overview of Clinical Studies

Study 20050103 (Prostate Cancer)

Study 20050103 was a randomized, double-blind, multicenter, phase III, non-inferiority trial comparing denosumab with zoledronic acid (ZA) in the treatment of bone metastases in patients with hormone-refractory prostate cancer. Patients were randomized 1:1 to receive either denosumab 120 mg subcutaneously (SC) and ZA placebo intravenously (IV) once every 4 weeks (Q4W) or ZA 4 mg IV and denosumab placebo SC Q4W in a blinded manner until completion of the primary efficacy and safety analyses. Randomization was stratified by previous SRE (yes or no), PSA level (< 10 ng/mL or ≥ 10 ng/mL), and current (i.e. within 6 weeks before randomization) chemotherapy (yes or no).

The main inclusion criteria included men ≥18 years of age with histologically-confirmed prostate cancer; current or prior radiographic evidence of at least one bone metastasis; documented failure of at least one hormonal therapy as evidenced by a rising PSA; and ECOG performance status of 0, 1, or 2. The primary efficacy endpoint was non-inferiority of time to first on-study skeletal-related event (SRE), consisting of 4 components: spinal cord compression, surgery to bone, pathologic fracture, and radiation to bone. Time to first on-study SRE for superiority and time to first and subsequent SRE were co-secondary efficacy endpoints. Exploratory endpoints included overall survival (OS) and progression-free survival (PFS).

If the true HR (of denosumab vs. ZA) is 0.90, the planned sample size of 1870 patients to observe 745 first SREs would provide 90% power to detect non-inferiority based on a synthesis approach (Hung et al., 2003) designed to demonstrate that denosumab preserves at least 50% of the effect of ZA. Assuming a true HR of 0.8 for both secondary endpoints and a correlation coefficient of 0.6 between the two endpoints, this sample size would also provide 90% power to detect superiority of denosumab to ZA for at least one of the two secondary endpoints. The data cutoff date for the primary efficacy analysis was October 30, 2009.

Study 20050136 (Breast Cancer)

Study 20050136 was a randomized, double-blind, multicenter, phase III, non-inferiority trial comparing denosumab with zoledronic acid (ZA) in the treatment of bone metastases in patients with advanced breast cancer. The treatment arms, dosage, schedules, and efficacy endpoints were the same as Study 20050103. Randomization was stratified by previous SRE (yes or no), prior oral bisphosphonate use (yes or no), current (i.e. within 6 weeks before randomization) chemotherapy (yes or no), and region (Japan or other). The main inclusion criteria included adults with histologically or cytologically confirmed breast adenocarcinoma; current or prior radiographic evidence of at least one bone metastasis; and ECOG performance status of 0, 1, or 2.

If the true HR (of denosumab vs. ZA) is 0.90, the planned sample size of 1960 patients to observe 745 first SREs would provide 97% power to detect non-inferiority based on a synthesis approach (Hung et al., 2003) designed to demonstrate that denosumab preserves at least 50% of the effect of ZA. Assuming a true HR of 0.8 for both secondary endpoints and a correlation

coefficient of 0.6 between the two endpoints) this sample size would provide 90% power to detect superiority of denosumab to ZA for at least one of the two secondary endpoints. The data cutoff date for the primary efficacy analysis was March 6, 2009.

1.3 Statistical Issues and Findings

Study 20050103 (Prostate Cancer)

Table 1 summarizes the efficacy results for study 103, including both non-inferiority (NI) and superiority (Sup) endpoints. Denosumab (D) decreased the proportion of subjects with a first on-study SRE compared with zoledronic acid (ZA); 341 (35.9%) versus 386 (40.6%) subjects, respectively. The median time to first on-study SRE in the intent-to-treat (ITT) population was 20.7 months and 17.1 months in the D and ZA arms, respectively. The corresponding hazard ratio (HR) was 0.82 with 95% confidence interval (CI) (0.71, 0.95). The non-inferiority test p-value using the Cox model and synthesis method (Hung et al., 2003) was 0.0002. Given the achievement of non-inferiority, the superiority stratified log-rank test p-value for time to first on-study SRE was 0.0082. The HR (95% CI) and p-value for time to first and subsequent SRE using the Andersen-Gill method (Andersen and Gill, 1982) adjusted for multiplicity by the Hochberg procedure was 0.82 (0.71, 0.94) and 0.0088, respectively.

Table 1: Study 103 (Prostate) - Efficacy Results

Endpoint (Time to…)	Median D	Median ZA	HR (95% CI)	p-value	Note for p-value
1st SRE (NI)	20.7	17.1	0.82 (0.71, 0.95)	0.0002	Cox model, synthesis method
1st SRE (Sup)	20.7	17.1	0.82 (0.71, 0.95)	0.0082	Log-rank, adjusted
1st and subsequent SRE (Sup)	NA	NA	0.82 (0.71, 0.94)	0.0088	Cox model, adjusted

Table 2 presents some of the key exploratory endpoints, including overall survival (OS) and progression-free survival (PFS).

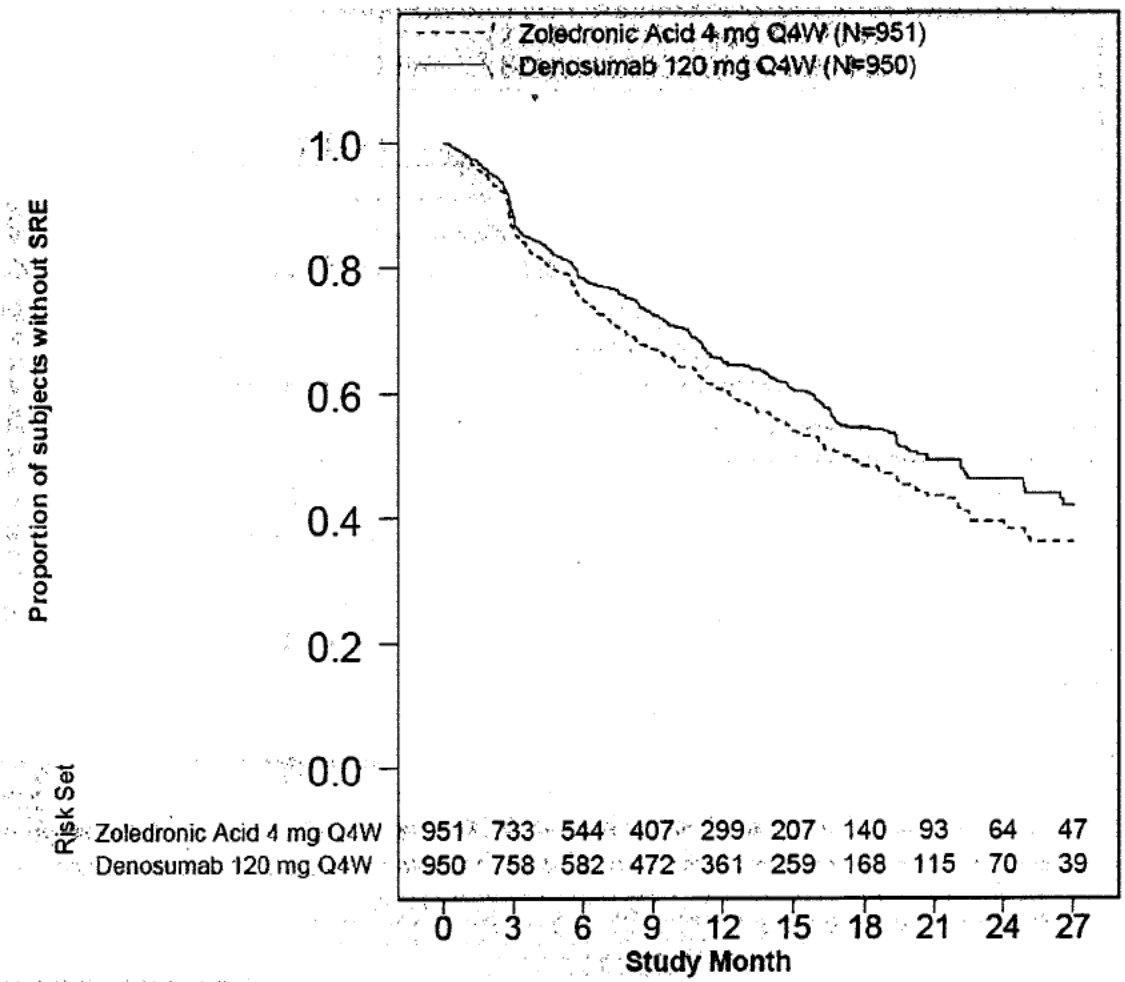
Table 2: Study 103 (Prostate) - Exploratory Endpoints

Endpoint (Time to…)	Number of events (%) D	Number of events (%) ZA	Median (in mos.) D	Median (in mos.) ZA	HR (95% CI)
1st SRE or HCM	340 (35.8)	384 (40.4)	20.7	17.1	0.83 (0.72, 0.96)
OS	474 (49.9)	461 (48.5)	19.4	19.8	1.05 (0.91, 1.20)
PD in bone	387 (40.7)	402 (42.3)	13.7	11.1	0.93 (0.80, 1.08)
Overall PD	667 (70.2)	630 (66.2)	8.4	8.4	1.03 (0.91, 1.15)
PFS	767 (80.7)	735 (77.3)	8.1	8.0	1.03 (0.92, 1.14)
1st symptomatic SRE	241 (25.4)	289 (30.4)	NR	24.2	0.78 (0.66, 0.93)

HCM = hypercalcemia of malignancy; PD = disease progression

Figure 1 presents the Kaplan-Meier curve for time to first on-study SRE by treatment for the ITT population.

Figure 1: Study 103 (Prostate) – Time to First On-Study SRE



Study 20050136 (Breast Cancer)

Table 3 summarizes the efficacy results for study 136, including both non-inferiority (NI) and superiority (Sup) endpoints. Denosumab (D) decreased the proportion of subjects with a first on-study SRE compared with zoledronic acid (ZA); 315 (30.7%) versus 372 (36.5%) subjects, respectively. The median time to first on-study SRE in the ITT population was 26.4 months in the ZA arm and not reached in the denosumab arm. The corresponding hazard ratio (HR) was 0.82 with 95% CI (0.71, 0.95). The non-inferiority test p-value using the Cox model and synthesis method (Hung et al., 2003) was < 0.0001. Given the achievement of non-inferiority, the superiority stratified log-rank test p-value for time to first on-study SRE was 0.0097. The HR (95% CI) and p-value for time to first and subsequent SRE using the Andersen-Gill method (Andersen and Gill, 1982) adjusted for multiplicity by the Hochberg procedure was 0.77 (0.68, 0.87) and 0.0012, respectively.

Table 3: Study 136 (Breast) – Efficacy Results

Endpoint (Time to...)	Median D	Median ZA	HR (95% CI)	p-value	Note for p-value
1st SRE (NI)	NR	26.4	0.82 (0.71, 0.95)	<0.0001	Cox model, synthesis method
1st SRE (Sup)	NR	26.4	0.82 (0.71, 0.95)	0.0097	Log-rank, adjusted
1st and subsequent SRE (Sup)	NA	NA	0.77 (0.66, 0.89)	0.0012	Cox model, adjusted

Figure 2 presents the Kaplan-Meier curve for time to first on-study SRE by treatment for the ITT population.

Figure 2: Study 136 (Breast) – Time to First On-Study SRE

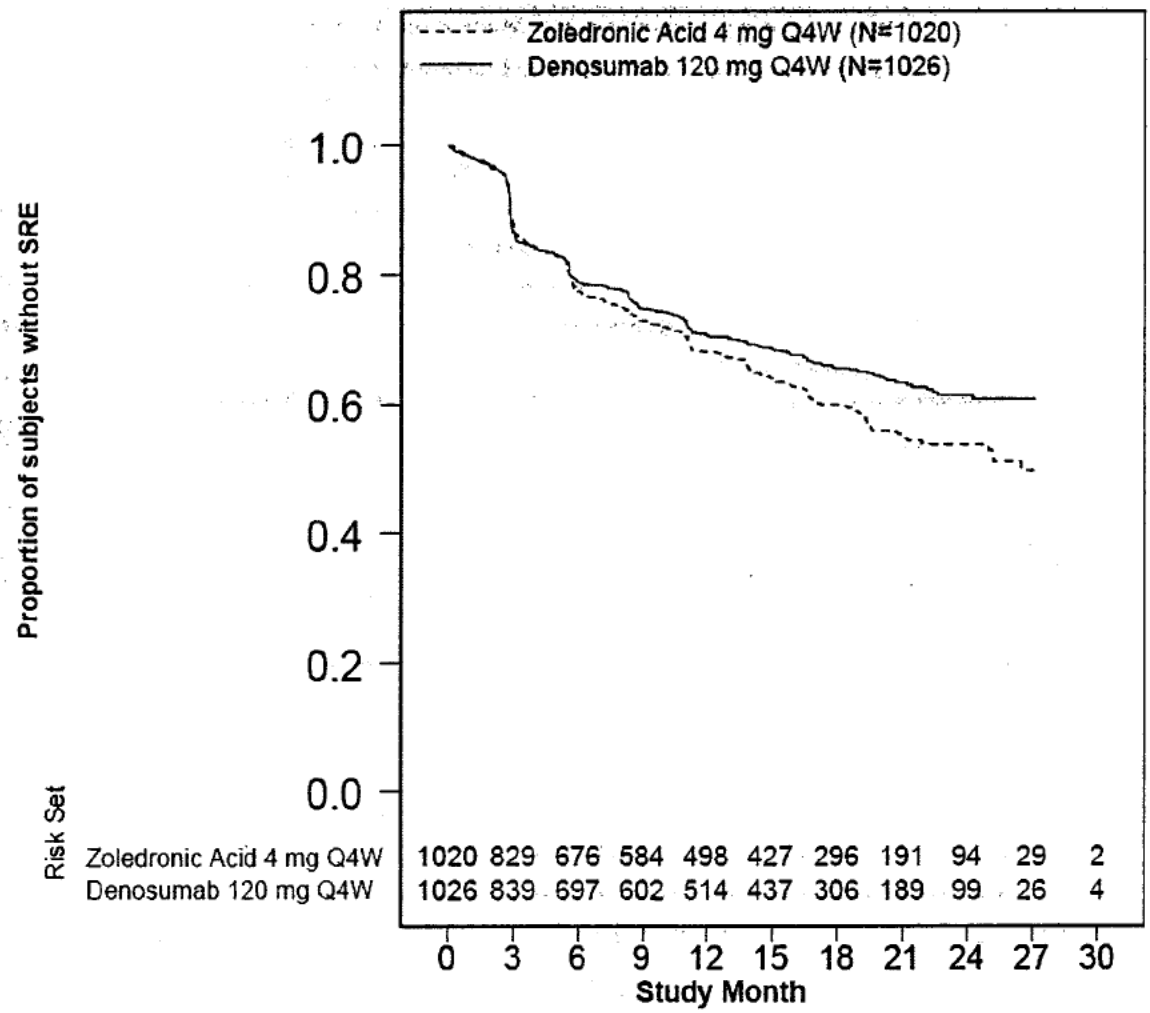


Table 4 presents some of the key exploratory endpoints, including overall survival (OS) and progression-free survival (PFS).

Table 4: Study 136 (Breast) - Exploratory Endpoints

Endpoint (Time to...)	Number of events (%) D	Number of events (%) ZA	Median (in mos.) D	Median (in mos.) ZA	HR (95% CI)
1st SRE or HCM	323 (31.5)	383 (36.5)	NR	25.2	0.82 (0.70, 0.95)
OS	301 (29.3)	305 (29.9)	29.4	NR	0.96 (0.82, 1.13)
PD in bone	446 (43.5)	449 (44.0)	16.6	16.4	0.99 (0.87, 1.13)
Overall PD	648 (63.2)	664 (65.1)	12.1	12.6	1.01 (0.90, 1.13)
PFS	683 (66.6)	698 (68.4)	11.8	11.7	1.01 (0.91, 1.13)
1st symptomatic SRE	156 (15.2)	198 (19.4)	NR	NR	0.76 (0.61, 0.93)

HCM = hypercalcemia of malignancy; PD = disease progression

2. INTRODUCTION

2.1 Overview

The Applicant is seeking approval for single-agent Xgeva® (denosumab) for the (b) (4) (b) (4)

The primary support for efficacy in this submission came from 3 randomized, double-blind, non-inferiority Phase III studies comparing denosumab with zoledronic acid (ZA) in the treatment of bone metastases in patients with hormone-refractory prostate cancer (Study 20050103), advanced breast cancer (Study 20050136), and advanced cancer (excluding breast and prostate cancer) or multiple myeloma (Study 20050244). The primary efficacy endpoint for all 3 studies was non-inferiority of time to first on-study skeletal-related event (SRE). Co-secondary efficacy endpoints were superiority of time to first on-study SRE and time to first and subsequent SRE. This review will discuss in detail studies 20050103 and 20050136. Please see Dr. Vivian Yuan's statistical review of BLA 125320 / 7 for results and discussion of Study 20050244.

2.2 Data Sources

The path to the CDER Electronic Document Room is:
\\cbsap58\m\eCTD_Submissions\STN125355.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Objective

The primary objective of studies 20050103 and 20050136 was to determine if denosumab is non-inferior to ZA with respect to time to first on-study SRE in patients with hormone-refractory prostate cancer and advanced breast cancer, respectively.

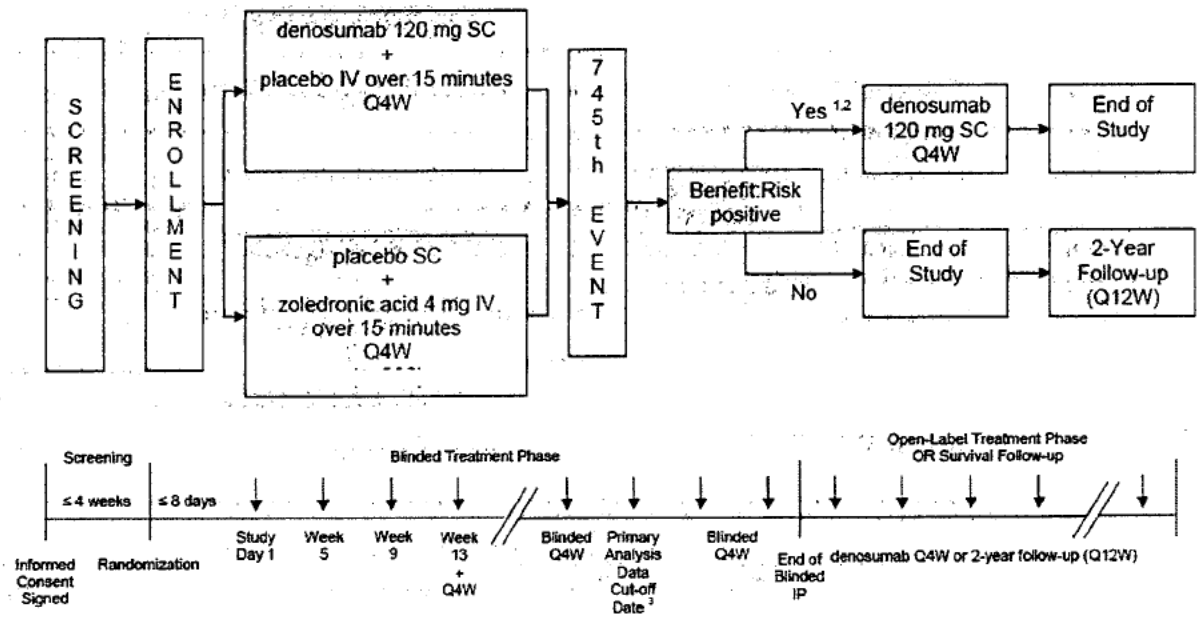
3.1.2 Study Design

Both Study 20050103 and 20050136 were randomized, double-blind, multicenter, phase III, non-inferiority trials comparing denosumab with zoledronic acid (ZA) in the treatment of bone metastases. Patients were randomized 1:1 to receive either denosumab 120 mg subcutaneously (SC) and ZA placebo intravenously (IV) once every 4 weeks (Q4W) or ZA 4 mg IV and denosumab placebo SC Q4W in a blinded manner until completion of the primary efficacy and safety analyses.

If denosumab was determined to have a positive benefit-to-risk profile compared to ZA, all patients still on-study at that time would be offered open-label denosumab at 120 mg SC for up to 2 years. However, if the benefit-to-risk ratio was not positive, then all patients would be followed for survival for 2 years after the last dose of blinded denosumab.

Figure 3 shows the study design and treatment schema for both studies.

Figure 3: Study 103 and 136 - Study Design and Treatment Schema



The primary efficacy endpoint was non-inferiority of time to first on-study skeletal-related event (SRE), consisting of 4 components: spinal cord compression, surgery to bone, pathologic fracture, and radiation to bone. Time to first on-study SRE for superiority and time to first and subsequent SRE were co-secondary efficacy endpoints. Exploratory endpoints included overall survival (OS) and progression-free survival (PFS).

Study 20050103 (Prostate Cancer)

Study 20050103 was conducted at 342 centers; 10.6% of all patients were from the United States; 3.8% of enrolled patients were African-American. Randomization was stratified by previous SRE (yes or no); PSA level (< 10 ng/mL or ≥ 10 ng/mL); and current (i.e. within 6 weeks before randomization) chemotherapy (yes or no). The main inclusion criteria included men ≥18 years of age with histologically-confirmed prostate cancer; current or prior radiographic evidence of at least one bone metastasis; documented failure of at least one hormonal therapy as evidenced by a rising PSA; and ECOG performance status of 0, 1, or 2.

If the true HR (of denosumab vs. ZA) is 0.90, the planned sample size of 1870 patients to observe 745 first SREs would provide 90% power to detect non-inferiority based on a synthesis approach (Hung et al., 2003) designed to demonstrate that denosumab preserves at least 50% of the effect of ZA. Assuming a true HR of 0.8 for both secondary endpoints and a correlation coefficient of 0.6 between the two endpoints, this sample size would also provide 90% power to detect superiority of denosumab to ZA for at least one of the two secondary endpoints.

Study 20050136 (Breast Cancer)

Study 20050136 was conducted at 322 centers with 13.9% of all patients from the United States. Randomization was stratified by previous SRE (yes or no), prior oral bisphosphonate use (yes or no), current (i.e. within 6 weeks before randomization) chemotherapy (yes or no), and region (Japan or other). The main inclusion criteria included adults with histologically or cytologically confirmed breast adenocarcinoma; current or prior radiographic evidence of at least one bone metastasis; and ECOG performance status of 0, 1, or 2.

If the true HR (of denosumab vs. ZA) is 0.90, the planned sample size of 1960 patients to observe 745 first SREs would provide 97% power to detect non-inferiority based on a synthesis approach (Hung et al., 2003) designed to demonstrate that denosumab preserves at least 50% of the effect of ZA. Assuming a true HR of 0.8 for both secondary endpoints and a correlation coefficient of 0.6 between the two endpoints, this sample size would provide 90% power to detect superiority of denosumab to ZA for at least one of the two secondary endpoints.

3.1.3 Efficacy Measures

Time to first on-study SRE

The primary efficacy endpoint of both study 103 and 136 was time to first on-study SRE, defined as the time from randomization to first occurrence of on-study SRE. If there is no known event, then the patient will be censored at his/her end of study date on the CRF or the primary analysis data cutoff date, whichever comes first. First on-study SRE was determined hierarchically (spinal cord compression, surgery, fracture, radiation) for events occurring on same day.

Time to first and subsequent on-study SRE

Time to first on-study SRE is defined above. Time to a subsequent SRE is defined, similar to time to first on-study SRE, as the time from randomization to a subsequent occurrence of on-study SRE, which has to be at least 21 days after the previous SRE.

Overall survival (OS)

OS was defined as the time from randomization to death from any cause. If the patient is still alive or lost to follow-up at the primary analysis data cutoff date, survival time will be censored at his/her last contact date or the primary analysis data cutoff date, whichever comes first.

Skeletal Morbidity Rate (SMR)

SMR was defined as the ratio of the number of occurrences of any SRE for a patient, allowing 1 event per assessment period (e.g. 3 weeks), divided by the patient's time at risk. Time at risk for each assessment period was defined as the duration from the start of the assessment period to the first SRE. If no SRE was reported for an assessment period, the entire duration of the assessment period was considered at risk. Time at risk during the study was the sum of time at risk of each assessment period of the study.

3.1.4 Sample Size Considerations

Given the non-inferiority study designs, estimates of the effect on time to first on-study SRE of placebo vs. ZA in patients with hormone-refractory prostate cancer and advanced breast cancer were needed to serve as the basis for determining the percentage of the effect of ZA that should be preserved by denosumab in order to be considered non-inferior.

Study 20050103 (Prostate Cancer)

For study 103, the estimated effect on time to first on-study SRE of placebo versus ZA was based on one historical randomized, double-blind, superiority trial of placebo versus ZA in men with hormone-refractory metastatic prostate cancer (Novartis 039; Saad et al., 2004). The estimated median time to first SRE was 16.0 months and 10.5 months in the 4 mg ZA and placebo arms, respectively. The corresponding HR of placebo over ZA was 1.48 with 95% CI (1.10, 1.98) and standard error of 0.147.

If the true HR (of denosumab vs. ZA) is 0.90, observing 745 first SREs would provide 90% power to detect non-inferiority based on a synthesis approach (Hung et al., 2003) designed to demonstrate that denosumab preserves at least 50% of the effect of ZA. Assuming a true HR of 0.8 for both secondary endpoints and a correlation coefficient of 0.6 between the two endpoints, this sample size would also provide 90% power to detect superiority of denosumab to ZA for at least one of the two secondary endpoints.

The median time to first on-study SRE for the ZA-treated patients with prostate cancer is expected to be about 16 months (Saad et al., 2004). With 1870 patients, an enrollment period of

32 months, 5% lost to follow-up rate, and 30% annual death rate, the study should reach the primary analysis cutoff date in approximately 38 months.

Study 20050136 (Breast Cancer)

For study 136, the estimated effect on time to first on-study SRE of placebo versus ZA was based on 4 historical trials in patients with advanced breast cancer (Hortobagyi et al., 1996; Theriault et al., 1999; Rosen et al., 2001, 2004; Kohno et al., 2005). Table 5 summarizes the estimated effects from each of the 4 historical trials. The pooled estimated HR of placebo over ZA for all breast cancer patients was 1.58 with 95% CI (1.23, 2.02) and standard error of 0.127.

Table 5: Study 136 (Breast) - Historical Trials

Study	Drugs	Therapy	N	HR (95% CI)	Pooled HR
Novartis 019	P vs. pamidronate	Chemotherapy	382	1.51 (1.1, 2.0)	1.36
Novartis 018	P vs. pamidronate	Hormone therapy	372	1.23 (0.9, 1.6)	(1.10, 1.67)
Novartis 010	ZA vs. pamidronate	Chemotherapy	531	0.96 (0.7, 1.32)	0.889
		Hormone therapy	599	0.83 (0.62, 1.12)	(0.71, 1.10)
		Pooled HR of P vs. ZA for non-Japanese subjects			1.53 (1.13, 2.06)
Japan 1501	P vs. Z	---	228	1.695 (1.09, 2.67)	
		Pooled HR of P vs. ZA for advanced BC patients			**1.58 (1.23, 2.02)**

P = placebo; BC = breast cancer

If the true HR (of denosumab vs. ZA) is 0.90, observing 745 first SREs would provide 97% power to detect non-inferiority based on a synthesis approach (Hung et al., 2003) designed to demonstrate that denosumab preserves at least 50% of the effect of ZA. Assuming a true HR of 0.8 for both secondary endpoints and a correlation coefficient of 0.6 between the two endpoints, this sample size would provide 90% power to detect superiority of denosumab to ZA for at least one of the two secondary endpoints.

The median time to first on-study SRE for the ZA-treated patients with breast cancer is assumed to be about 16 months (obtained from discounting the result of Rosen et al. [2004] due to differences in baseline characteristics and demographics between study 136 and Novartis 010). With 1960 patients, an enrollment period of 21 months, combined lost to follow-up and death rate of 30% per year, the study should reach the primary analysis cutoff date in approximately 33 months.

Reviewer's Comments:

1. Novartis 018, 019, and Japan 1501 were all randomized, double-blind, superiority trials. However, Novartis 010 was itself a non-inferiority trial comparing ZA with pamidronate.

2. The estimated HR from Japan 1501 was from a multiple events analysis, not directly time to first on-study SRE. The relationship between the hazard ratios from a single event analysis and a multiple events analysis is unclear.

3.1.5 Constancy Assumption

One of the key assumptions on which the non-inferiority design relies upon is that of constancy; that is, the estimate of the historical active-control effect is applicable to the current study. Evaluation of this assumption for the ZA effect on time to first on-study SRE for studies 103 and 136 was based on the historical trials (Section 3.1.4) used to derive the HR of placebo versus ZA and the observed data from each of the current trials.

Study 20050103 (Prostate Cancer)

Table 6 provides a comparison of the study design features of the historical study Novartis 039 and the current prostate cancer study 103.

Table 6: Study 103 (Prostate) – Assessment of Constancy Assumption

Study Design Features	Novartis 039	Amgen 0103	Similarity
	HRPC	HRPC	(Yes/No)
	zoledronic acid vs Placebo	denosumab vs zoledronic acid	
Publication reference	Saad et al, 2002	n/a	n/a
Demographic and Disease Characteristics as per inclusion criteria			
Gender	Male	Male	yes
Age (yrs)	Not provided	≥ 18 years	n/a
ECOG	0-2	0-2	yes
Type of bone metastases	Not specified	Not specified	yes
Baseline PSA	3 consecutive rises, last one above 4 ng/mL	3 consecutive rises, last one above 4 ng/mL	yes
Baseline testosterone	Castrate range (< 50 ng/dL)	Castrate range (< 50 ng/dL)	yes
Prior type of therapy	Antineoplastic therapy permitted at study entry; initiation of chemotherapy at study entry excluded	Antineoplastic therapy permitted at study entry	yes
Pain at baseline	Bone pain requiring strong narcotic therapy excluded*	Not specified	yes*
Corrected Serum Calcium	≥ 8.0 mg/dL and ≤ 11.6 mg/dL	≥ 8.0 mg/dL and ≤ 11.5 mg/dL	yes
Serum Creatinine	≤ 3.0 mg/dL	Creatinine clearance ≥ 30 mL/min*	yes*
Serum Bilirubin	Not reported	≤ 2 x ULN	n/a
Prior bisphosphonates	Excluded	Oral bisphosphonates for non-oncology indications allowed with 6 mo washout period	yes
Study Duration (treatment phase)	15 mo (core)	Expected ~ 15 mo (event driven)	yes
Dose and Administration of zoledronic acid	4 or 8 mg** over 5 to 15 min*** every 3 weeks	3-4 mg* over at least 15 min every 4 weeks	yes

Study Design Features	Novartis 039 HRPC zoledronic acid vs placebo	Amgen 103 HRPC denosumab vs zoledronic acid	Similarity (Yes/No)
Trigger for Withholding Study Medication In Case of On-study Deterioration in Renal Function	Increase ≥ 0.5 mg/dL if baseline creatinine < 1.4 mg/dL; increase ≥ 1.0 mg/dL if baseline creatinine ≥ 1.4 mg/dL	Increase ≥ 0.5 mg/dL if baseline creatinine < 1.4 mg/dL; increase ≥ 1.0 mg/dL if baseline creatinine ≥ 1.4 mg/dL	yes
Calcium and vit D supplementation	500 mg calcium and 400-500 IU vitD	500 mg calcium and 400-500 IU vitD	yes
Endpoint Definitions	SRE and change of antineoplastic therapy for bone pain	SRE and HCM	yes
Endpoint Analysis (primary)	Proportion of patients with at least 1 SRE*	Time to first on-study SRE or HCM	yes*
Visit Schedule	3-weekly	Monthly	yes
Bone Survey	Every 3 mo; blinded central review	Every 3 mo; blinded central review	yes
Use of Taxotere	Some patients had taxol or taxotere	More patients may get taxotere due to 2004 approval for that indication**	yes

* This restriction on pain at baseline was not made in the other SRE trials (010 and 011 and Japanese breast cancer trial 1501).
* Time to first on-study SRE (+/- HCM) was secondary endpoint in study 039. The margin is based on the results for time to first on-study SRE.
As per recent label change, zoledronic acid (3-4 mg) has to be administered with dose adjusted to baseline renal function as calculated by Cockroft-Gault formula. Baseline creatinine clearance must be ≥ 30mL/min
** 8 mg dose skipped during trial due to renal safety issues. 4 mg group was used for the margin calculation.
*** 5 min infusion time skipped due to renal safety issues.
** To our best knowledge a clearcut effect of taxanes on bone (ie, bone markers, bone histomorphometry in bone metastases, and SRE as the relevant clinical readout) has not been shown; Only (bone) pain reduction with taxanes has been reported (Tannock et al, N Engl J Med, 2004;35:1502-12)

Reviewer's Comments:

1. The baseline demographic and disease characteristics for the ZA treatment group in study 103 were generally similar to those of the relevant historical trial ZA treatment group.

2. The median time to first on-study SRE in the ZA registration trial (from ZA label) was approximately 12 months, however, the median time to first on-study SRE of ZA in study 103 was 17.1 months. Although this does not support the constancy assumption, the potential bias would be against the denosumab arm, so non-inferiority would still be acceptable.

Study 20050136 (Breast Cancer)

Table 7 provides a comparison of the study design features of the historical studies Novartis 018, 019, 010, and Japan 1501 and the current breast cancer study 136.

Table 7: Study 136 (Breast) - Assessment of Constancy Assumption

Study Design Features	Novartis 18	Novartis 19	Novartis 010	Novartis Japan 1501	Amgen 0136	Similarity
	BC Hormone pamidronate disodium vs P	BC Chemo pamidronate disodium vs P	BC Chemo/Hormone zoledronic acid vs pamidronate disodium	BC zoledronic acid vs P	BC denosumab vs zoledronic acid	(Yes/No)
Publication reference	Hirsdult et al, 1999	Hortobagyi et al, 1996	Rosen et al, 2001 Rosen et al, 2003[7]	Kohno et al, 2005	n/a	n/a
Demographic and Disease Characteristics as per inclusion criteria						
Gender	Female	Female	Not specified	Female	Not specified	yes*
Age (yrs)	≥ 18 years	≥ 18 years	≥ 18 years	≥ 20 years	≥ 18 years	yes
ECOG	0 - 3	0 - 3	0-2	0-2	0-2	yes
Type of bone metastases	Predominantly osteolytic	Predominantly osteolytic	Not specified	At least 1 osteolytic metastsasis	Not specified	yes
Prior type of therapy	Stable hormonal therapy at study entry; prior chemotherapy allowed	Cytotoxic chemotherapy at study entry	Antineoplastic therapy required at study entry	Antineoplastic therapy permitted at study entry	Antineoplastic therapy permitted at study entry	yes
Corrected Serum Calcium	Not specified	≤ 12 mg/dL	< 12 mg/dL	≥ 8.0 mg/dL and ≤ 11.5 mg/dL	≥ 8.0 mg/dL and ≤ 11.5 mg/dL	yes
Serum Creatinine	"No significant renal impairment"	≤ 2.5 mg/dL	≤ 3.0 mg/dL	≤ 2.0 mg/dL	Creatinine clearance ≥ 30 mL/min*	yes*
Serum Bilirubin	"No significant hepatic impairment"	≤ 2.5 mg/dL	≤ 2.5 mg/dL	≤ 1.5 mg/dL	≤ 2 x ULN	yes
Prior bisphosphonates	Excluded if within 2 mo prior to study entry	Excluded if: within 2 mo prior to study entry	Excluded if within 12 mo prior to study entry	Excluded if within 12 mo prior to study entry	Oral bisphosphonate use for indications other than bone metastases allowed; i.v. bisphosphonates excluded	yes

Study Design Features	Novartis 18	Novartis 19	Novartis 010	Novartis Japan 1501	Amgen 0136	Similarity
	BC Hormone pamidronate disodium vs P	BC Chemo pamidronate disodium vs P	BC Chemo/Hormone zoledronic acid vs pamidronate disod.	BC zoledronic acid vs P	BC denosumab vs zoledronic acid	(Yes/No)
Stratification	ECOG status	ECOG status	Hormonal vs chemotherapy	Age, chemotherapy, hormone therapy, non-bone metastases, performance status, center	Prior SRE, prior oral bisphosphonate use, current chemo, region (Japan vs rest of world)	No
Study Duration (core phase)	1 year	1 year	13 mo	1 year	Expected ~ 12 mo (event driven)	yes
Dose and Administration of zoledronic acid	n/a	n/a	4 or 8 mg** over 5 to 15 min*** every 3-4 weeks	4 mg over 15 min every 4 weeks	3-4 mg* over at least 15 min every 4 weeks	yes
Calcium and vit D supplementation	None	None	500 mg calcium and 400-500 IU vitD	None	500 mg calcium and 400-500 IU vitD	yes
Endpoint Definitions	SRE incl. HCM	SRE incl. HCM	SRE	SRE	SRE and HCM	yes
Endpoint Analysis (primary)	Skeletal morbidity rate	Skeletal morbidity rate	Proportion with at least one SRE	SRE rate ratio	Time to first on-study SRE and SMR	yes
Visit Schedule	Monthly	Monthly	3-4 weekly	Monthly	Monthly	
Bone survey	Baseline and mo 3, 6, 12; blinded central review	Baseline and mo 3, 6, 12; blinded central review	Every 3 mo; blinded central review	Every 3 mo	Every 3 mo; blinded central review	yes

Reviewer's Comments:

1. There were two main differences in the designs of the historical studies and study 136: (1) All the historical studies excluded patients who used oral biosphosphonates within 2 (Novartis 18, 19) or 12 (Novaritis 010, Japan 1501) months before study entry, whereas study 136 allowed entry of patients with oral biosphosphonate use for indicators other than bone metastases; (2) The stratification factors between the historical studies and study 136 were quite different.

2. The baseline demographic and disease characteristics for the ZA treatment group in study 136 were generally similar to those of the relevant historical trials ZA treatment groups.

3. The median time to first on-study SRE in the ZA registration trial (from ZA label) was approximately 12 months; however, the median time to first on-study SRE of ZA in study 136 was 26.4 months. Although this does not support the constancy assumption, the potential bias would be against the denosumab arm, so non-inferiority would still be acceptable.

3.1.6 Statistical Analysis Plan

The statistical analyses were similar for studies 103 and 136. The primary and secondary efficacy endpoints were analyzed using the intent-to-treat (ITT) population, which included all randomized subjects. Supportive analyses using the per-protocol population, which included all subjects with a protocol-defined diagnosis and no major protocol violations who received ≥ 1 dose of active treatment, were also performed.

Time to first on-study SRE was analyzed using a Cox model stratified by factors used to balance randomization. A synthesis approach (Hung et al., 2003) was used for the non-inferiority test of the primary endpoint. Let HR_{DZ} denote the estimated Cox model hazard ratio, adjusted by stratification factors, of denosumab over ZA for time to first on-study SRE. Let HR_{PZ} denote the historical estimate of the hazard ratio of placebo over ZA for time to first on-study SRE. Let σ_{DZ} and σ_{PZ} be the estimated standard error for $\ln(HR_{DZ})$ and $\ln(HR_{PZ})$, respectively. According to Hung, et al, (2003), the non-inferiority (i.e. denosumab preserves at least 50% of the effect of ZA) test statistic is given by:

$$Z_{PV} = \frac{\log(HR_{DZ}) + 0.5 \times \log(HR_{PZ})}{\sqrt{\{\sigma_{DZ}^2 + 0.25 \times \sigma_{PZ}^2\}}}.$$

Non-inferiority at a significance level of 0.05 would be claimed if $Z_{PV} < -1.96$.

Testing for superiority proceeded after demonstration of noninferiority; results of a stratified log-rank test were used to determine whether or not denosumab was superior to ZA with respect to time to first on-study SRE. For time to first-and-subsequent on-study SRE, a multiple-events analysis using the Andersen and Gill approach (Andersen and Gill, 1982) was conducted. Multiple comparison adjustment using the Hochberg procedure was implemented for the two co-secondary endpoints.

Overall survival (OS) was analyzed using a Cox model adjusted for stratification factors and other baseline covariates.

The SMR was compared between treatment groups using the Cochran-Mantel-Haenszel test stratified by the stratification factors

The data cutoff dates for the primary efficacy analysis for studies 103 and 136 were October 30, 2009 and March 6, 2009, respectively.

3.1.7 Applicant's Results and Statistical Reviewer's Findings and Comments

All summaries and results presented in this section have been verified by the reviewer based on the data submitted by the Applicant.

3.1.7.1 Study Population

The primary analysis population was the intent-to-treat (ITT), which included all patients who were randomized, with study drug assignment designated according to initial randomization. Primary analyses performed on the per-protocol (PP) population gave similar results and are not presented here.

Study 20050103 (Prostate Cancer)

The ITT population for study 103 included 1901 patients (950 on denosumab; 951 on ZA). Table 8 presents the patient disposition, and Table 9 summarizes the reasons for study discontinuation.

Table 8: Study 103 (Prostate) - Patient Disposition

	Denosumab (N=950)	ZA (N=951)
On Study through Data Cut-Off	228 (24.0%)	208 (21.9%)
Discont. before Data Cut-Off	722 (76.0%)	743 (78.1%)
Received Treatment	942 (99.2%)	946 (99.5%)
Treat through Data Cut-Off	217 (22.8%)	197 (20.7%)
Discont. before Data Cut-Off	725 (76.3.%)	749 (78.8%)
Never Received Treatment	8 (0.8%)	5 (0.5%)

Table 9: Study 103 (Prostate) - Reasons for Study Discontinuation

Reason for Discontinuation, number (%) of patients	Denosumab (N = 950)	ZA (N = 951)
Death	294 (30.9%)	269 (28.3%)
Consent withdrawn	147 (15.5%)	164 (17.2%)
Disease progression	117 (12.3%)	113 (11.9%)
Adverse event	56 (5.9%)	43 (4.5%)
Subject request	52 (5.5%)	75 (7.9%)
Other	33 (3.5%)	42 (4.4%)
Lost to follow-up	9 (0.9%)	13 (1.4%)
Noncompliance	7 (0.7%)	14 (1.5%)
Protocol deviation	3 (0.3%)	4 (0.4%)
Ineligibility determined	3 (0.3%)	2 (0.2%)
Administrative decision	1 (0.1%)	4 (0.4%)

Reviewer's Comments:

1. More patients on ZA discontinued study due to subject request, noncompliance, and administrative decision as compared with those on denosumab.

2. Thirteen (1.4%) more patients on denosumab discontinued study due to an adverse event as compared to ZA.

Study 20050136 (Breast Cancer)

The ITT population for study 136 included 2046 patients (1026 on denosumab; 1020 on ZA). Table 10 presents the patient disposition, and Table 11 summarizes the reasons for study discontinuation.

Table 10: Study 136 (Breast) - Patient Disposition

	Denosumab (N=1026)	ZA (N=1020)
On Study through Data Cut-Off	468 (45.6%)	461 (45.2%)
Discont. before Data Cut-Off	558 (54.4%)	559 (54.8%)
Received Treatment	1019 (99.3%)	1014 (99.4%)
Treat through Data Cut-Off	450 (43.9%)	443 (43.4%)
Discont. before Data Cut-Off	569 (55.5%)	571 (56.0%)
Never Received Treatment	7 (0.7%)	6 (0.6%)

Table 11: Study 136 (Breast) - Reasons for Study Discontinuation

Reason for Discontinuation, number (%) of patients	Denosumab (N = 1026)	ZA (N = 1020)
Death	174 (17.0%)	169 (16.6%)
Consent withdrawn	118 (11.5%)	117 (11.5%)
Disease progression	124 (12.1%)	124 (12.2%)
Adverse event	28 (2.7%)	43 (4.2%)
Subject request	61 (5.9%)	57 (5.6%)
Other	18 (1.8%)	21 (2.1%)
Lost to follow-up	8 (0.8%)	7 (0.7%)
Noncompliance	10 (1.0%)	4 (0.4%)
Protocol deviation	2 (0.2%)	0 (0.0%)
Ineligibility determined	1 (<0.1%)	2 (0.2%)
Administrative decision	14 (1.4%)	15 (1.5%)

Reviewer's Comment:

Fifteen (1.5%) more patients on ZA discontinued study due to an adverse event as compared to denosumab, the reverse of study 103.

3.1.7.2 Randomization Stratification

Study 20050103 (Prostate Cancer)

Study 103 was stratified by previous SRE, PSA level, and current (within 6 months of randomization) chemotherapy. Table 12 presents the number of patients randomized into each strata.

Table 12: Study 103 (Prostate) - Randomization Stratification

		D (N=950)	ZA (N=951)
Previous SRE:			
	Yes	232 (24.4%)	231 (24.3%)
	No	718 (75.6%)	720 (75.7%)
PSA level:			
	<10 ng/mL	145 (15.3%)	145 (15.2%)
	≥10 ng/mL	805 (84.7%)	806 (84.8%)
Current chemotherapy:			
	Yes	132 (13.9%)	132 (13.9%)
	No	818 (86.1%)	819 (86.1%)

Study 20050136 (Breast Cancer)

Study 136 was stratified by previous SRE, prior oral bisphosphonate use, current (within 6 months of randomization) chemotherapy, and region (Japan or other). Table 13 presents the number of patients randomized into each strata.

Table 13: Study 136 (Breast) - Randomization Stratification

		D (N=1026)	ZA (N=1020)
Previous SRE:			
	Yes	378 (36.8%)	373 (36.6%)
	No	648 (63.2%)	647 (63.4%)
Prior oral bisphosphonate use:			
	Yes	42 (4.1%)	38 (3.7%)
	No	984 (95.6%)	982 (96.3%)
Current chemotherapy:			
	Yes	410 (40.0%)	408 (40.0%)
	No	616 (60.0%)	612 (60.0%)
Region:			
	Japan	69 (6.7%)	67 (6.6%)
	Others	957 (93.3%)	953 (93.4%)

3.1.7.3 Demographics and Baseline Characteristics

Study 20050103 (Prostate Cancer)

Tables 14 and 15 provide a summary of the demographic and baseline characteristics of the ITT population for study 103. Since all patients in study 103 were male, gender is not included in Table 14.

Table 14: Study 103 (Prostate) – Demographics

	D (N=950)	ZA (N=951)
Ethnic group:		
White/Caucasian	829 (87.3%)	810 (85.2%)
African American	38 (4.0%)	35 (3.7%)
Hispanic/Latino	45 (4.7%)	57 (6.0%)
Asian/Pacific Islander	23 (2.4%)	27 (2.8%)
Other	15 (1.6%)	22 (2.3%)
Age:		
Median	71.0	71.0
Mean	70.5	71.0
< 65 years	253 (26.6%)	216 (22.7%)
≥ 65 years	697 (73.4%)	735 (77.3%)

Table 15: Study 103 (Prostate) – Baseline Characteristics

	D (N=950)	ZA (N=951)
ECOG PS:		
0	418 (44.0%)	426 (44.8%)
1	464 (48.8%)	460 (48.4%)
2	68 (7.2%)	65 (6.8%)
Gleason sum at diagnosis:		
2-6	175 (18.4%)	180 (18.9%)
7	273 (28.7%)	280 (29.4%)
8-10	394 (41.5%)	408 (42.9%)
Missing	108 (11.4%)	83 (8.7%)
Castration:		
Chemical only	619 (65.2%)	637 (67.0%)
Surgical only	55 (5.8%)	37 (3.9%)
Both	276 (29.1%)	277 (29.1%)
Primary tumor stage at diagnosis:		
T1 – T2a	116 (12.2%)	98 (10.3%)
T2 or T2b – T2c*	251 (26.4%)	260 (27.3%)
T3 or T3a	257 (27.1%)	275 (28.9%)
T3b – T4	183 (19.3%)	178 (18.7%)
Tx	143 (15.1%)	139 (14.6%)
Missing	0 (0.0%)	1 (0.1%)
Regional lymph node at diagnosis:		
N0	356 (37.5%)	349 (36.7%)
N1	123 (12.9%)	121 (12.7%)
Nx	471 (49.6%)	480 (50.5%)
Missing	0 (0.0%)	1 (0.1%)

Distant metastasis at diagnosis:		
M0	410 (43.2%)	422 (44.4%)
M1	326 (34.3%)	336 (35.3%)
Mx	214 (22.5%)	192 (20.2%)
Missing	0 (0.0%)	1 (0.1%)
# of metastatic lesions in bone at baseline – by central read:		
≤ 2	632 (66.5%)	623 (65.5%)
> 2	318 (33.5%)	328 (34.5%)
Type of bone lesion at baseline:		
Osteoblastic	601 (63.3%)	537 (56.5%)
Osteolytic	32 (3.4%)	39 (4.1%)
Mixed	128 (13.5%)	150 (15.8%)
Unable to evaluate	1 (0.1%)	2 (0.2%)
Not seen	188 (19.8%)	223 (23.4%)
Visceral metastases:		
Any	161 (16.9%)	181 (19.0%)
Liver	16 (1.7%)	20 (2.1%)
Lung	26 (2.7%)	32 (3.4%)
Other	141 (14.8%)	153 (16.1%)
Time since initiation of castration to randomization:		
≤ 3 years	508 (53.5%)	513 (53.9%)
> 3 years	442 (46.5%)	437 (46.0%)
Missing	0 (0.0%)	1 (0.1%)

*One patient with primary tumor stage at diagnosis of T3c

Study 20050136 (Breast Cancer)

Tables 16 and 17 provide a summary of the demographic and baseline characteristics of the ITT population for study 136.

Table 16: Study 136 (Breast) – Demographics

	D (N=1026)	ZA (N=1020)
Gender:		
Female	1018 (99.2%)	1011 (99.1%)
Male	8 (0.8%)	9 (0.9%)
Ethnic group:		
White/Caucasian	822 (80.1%)	813 (79.7%)
African American	26 (2.5%)	25 (2.5%)
Hispanic/Latino	59 (5.8%)	59 (5.8%)
Asian/Pacific Islander	103 (10.0%)	107 (10.5%)
Other	16 (1.6%)	16 (1.6%)
Age:		
Median	57.0	56.0
Mean	56.8	56.6
< 50 years	275 (26.8%)	287 (28.1%)
≥ 50 years	751 (73.2%)	733 (71.9%)
< 65 years	751 (73.2%)	754 (73.9%)
≥ 65 years	275 (26.8%)	266 (26.1%)

Post-menopausal:		
Yes	839 (82.4%)	831 (82.2%)
No	170 (16.7%)	170 (16.8%)
Missing/NA,	9 (0.9%)	10 (0.1%)

Table 17: Study 136 (Breast) - Baseline Characteristics

	D (N=1026)	ZA (N=1020)
ECOG PS:		
0	504 (49.1%)	488 (47.8%)
1	451 (44.0%)	444 (43.5%)
2	68 (6.6%)	82 (8.0%)
3	1 (0.1%)	2 (0.2%)
Missing	2 (0.2%)	4 (0.4%)
ER/PR status:		
Negative	163 (15.9%)	163 (16.0%)
Positive	740 (72.1%)	726 (71.2%)
Unknown	121 (11.8%)	129 (12.6%)
Missing	2 (0.2%)	2 (0.2%)
Her-2 status:		
Negative	518 (50.5%)	472 (46.3%)
Positive	183 (17.8%)	194 (19.0%)
Unknown	321 (31.3%)	350 (34.3%)
Missing	4 (0.4%)	4 (0.4%)
Primary tumor stage at diagnosis:		
I	104 (10.1%)	105 (10.3%)
II	380 (37.0%)	381 (37.4%)
III	264 (25.7%)	280 (27.5%)
IV	234 (22.8%)	203 (19.9%)
Unknown	42 (4.1%)	49 (4.8%)
Missing	2 (0.2%)	2 (0.2%)
# of metastatic lesions in bone at baseline – by central read:		
≤ 2	784 (76.4%)	780 (76.5%)
> 2	242 (23.6%)	240 (23.5%)
Type of bone lesion at baseline:		
Osteoblastic	285 (27.8%)	281 (27.5%)
Osteolytic	139 (13.5%)	152 (14.9%)
Mixed	256 (25.0%)	254 (24.9%)
Unable to evaluate	4 (0.4%)	3 (0.3%)
Not seen	336 (32.7%)	336 (32.9%)
Visceral metastases:		
Any	552 (53.8%)	525 (51.5%)
Liver	211 (20.6%)	182 (17.8%)
Lung	216 (21.1%)	210 (20.6%)
Other	369 (36.0%)	369 (36.2%)

3.1.7.4 Efficacy Results

Study 20050103 (Prostate Cancer)

Table 18 summarizes the efficacy results for study 103, including both non-inferiority (NI) and superiority (Sup) endpoints. Denosumab (D) decreased the proportion of subjects with a first on-study SRE compared with zoledronic acid (ZA); 341 (35.9%) versus 386 (40.6%) subjects, respectively. The median time to first on-study SRE in the intent-to-treat (ITT) population was 20.7 months and 17.1 months in the D and ZA arms, respectively. The corresponding hazard ratio (HR) was 0.82 with 95% confidence interval (CI) (0.71, 0.95). The non-inferiority test p-value using the Cox model and synthesis method (Hung et al., 2003) was 0.0002. Given the achievement of non-inferiority, the superiority stratified log-rank test p-value for time to first on-study SRE was 0.0082. The HR (95% CI) and p-value for time to first and subsequent SRE using the multiple-events analysis method of Andersen-Gill (Andersen and Gill, 1982) adjusted for multiplicity by the Hochberg procedure was 0.82 (0.71, 0.94) and 0.0088, respectively.

Table 18: Study 103 (Prostate) - Efficacy Results

Endpoint (Time to...)	Median D	Median ZA	HR (95% CI)	p-value	Note for p-value
1st SRE (NI)	20.7	17.1	0.82 (0.71, 0.95)	0.0002	Cox model, synthesis method
1st SRE (Sup)	20.7	17.1	0.82 (0.71, 0.95)	0.0082	Log-rank, adjusted
1st and subsequent SRE (Sup)	NA	NA	0.82 (0.71, 0.94)	0.0088	Cox model, adjusted

Figure 4 presents the Kaplan-Meier curve for time to first on-study SRE by treatment for the ITT population.

Figure 4: Study 103 (Prostate) - Time to First On-Study SRE

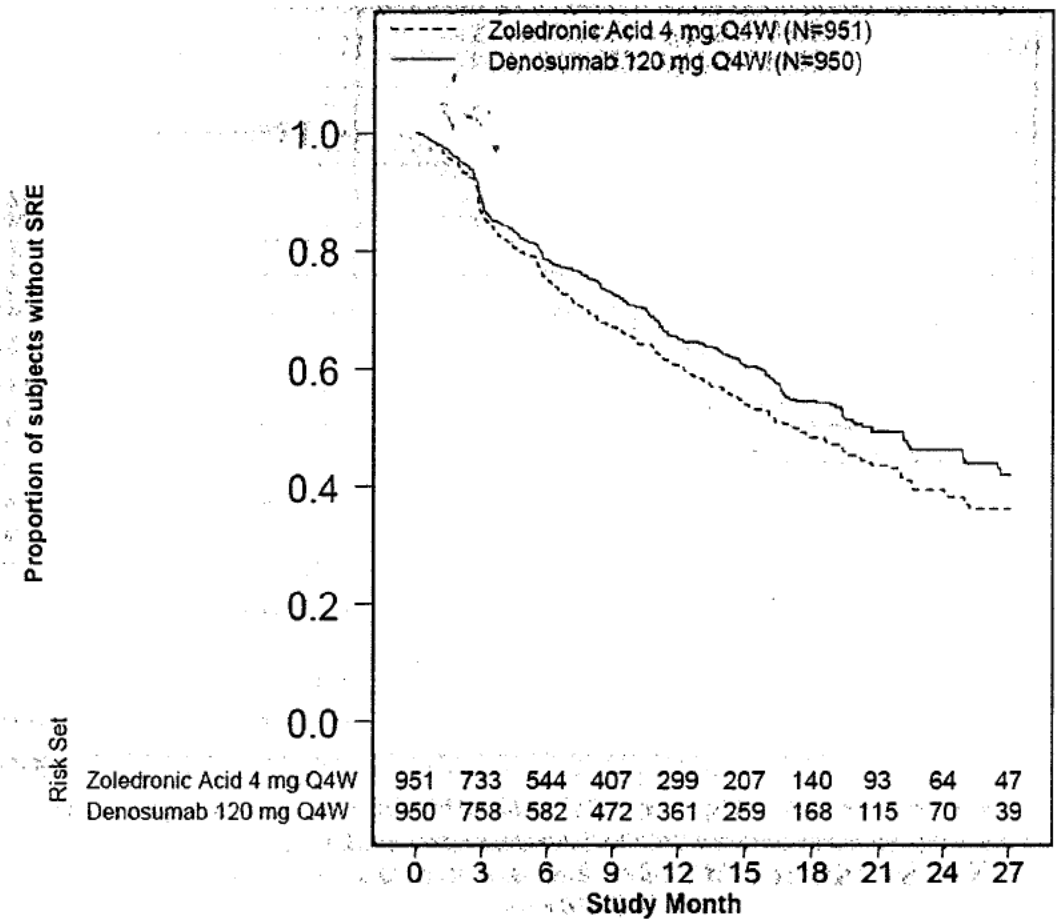


Table 19 presents the number of first on-study SREs by component. The Wei-Lin-Weissfeld (WLW) homogeneity test resulted in a p-value of 0.7059, which showed no evidence of inconsistent effects across the 4 SRE components.

Table 19: Study 103 (Prostate) - First On-Study SREs by Component

SRE	D (N=950)	ZA (N=951)
Pathologic fracture	137 (14.4%)	143 (15.0%)
Radiation to bone	177 (18.6%)	203 (21.4%)
Surgery to bone	1 (0.1%)	4 (0.4%)
Spinal cord compression	26 (2.7%)	36 (3.8%)
Total	341 (35.9%)	386 (40.6%)
WLW homogeneity test: p = 0.7059		

Table 20 presents the number of first and subsequent on-study SREs by component.

Table 20: Study 103 (Prostate) – First and Subsequent SREs by Component

SRE	D (N=494)	ZA (N=584)
Pathologic fracture	188 (38.1%)	203 (34.8%)
Radiation to bone	264 (53.4%)	330 (56.5%)
Surgery to bone	5 (1.0%)	7 (1.2%)
Spinal cord compression	37 (7.5%)	44 (7.5%)

Table 21 presents some of the key exploratory endpoints, including overall survival (OS) and progression-free survival (PFS).

Table 21: Study 103 (Prostate) – Exploratory Endpoints

Endpoint (Time to…)	Number of events (%)		Median (in mos.)		HR
	D	ZA	D	ZA	(95% CI)
1st SRE or HCM	340 (35.8)	384 (40.4)	20.7	17.1	0.83 (0.72, 0.96)
OS	474 (49.9)	461 (48.5)	19.4	19.8	1.05 (0.91, 1.20)
PD in bone	387 (40.7)	402 (42.3)	13.7	11.1	0.93 (0.80, 1.08)
Overall PD	667 (70.2)	630 (66.2)	8.4	8.4	1.03 (0.91, 1.15)
PFS	767 (80.7)	735 (77.3)	8.1	8.0	1.03 (0.92, 1.14)
1st symptomatic SRE	241 (25.4)	289 (30.4)	NR	24.2	0.78 (0.66, 0.93)

HCM = hypercalcemia of malignancy; PD = disease progression

The mean annual SMR was 0.79 (SD = 3.08) and 0.83 (SD: 1.93) for denosumab and ZA, respectively, with corresponding Cochran-Mantel-Haenzel test p-value 0.0390 The annual patient-year adjusted SRE incidence was 75.6% and 94.7% for denosumab and ZA, respectively.

Reviewer's Comments:

1. Denosumab was shown to be superior to ZA with respect to the primary endpoints in hormone-refractory prostate cancer patients.

2. There was no difference in progression endpoints and overall survival between denosumab and ZA.

Study 20050136 (Breast Cancer)

Table 22 summarizes the efficacy results for study 136, including both non-inferiority (NI) and superiority (Sup) endpoints. Denosumab (D) decreased the proportion of subjects with a first on-study SRE compared with zoledronic acid (ZA); 315 (30.7%) versus 372 (36.5%) subjects, respectively. The median time to first on-study SRE in the ITT population was 26.4 months in the ZA arm and not reached in the denosumab arm. The corresponding hazard ratio (HR) was 0.82 with 95% CI (0.71, 0.95). The non-inferiority test p-value using the Cox model and synthesis method (Hung et al., 2003) was < 0.0001. Given the achievement of non-inferiority,

the superiority stratified log-rank test p-value for time to first on-study SRB was 0.0097. The HR (95% CI) and p-value for time to first and subsequent SRB using the multiple-events analysis method of Andersen-Gill (Andersen and Gill) 1982) adjusted for multiplicity by the Hochberg procedure was 0.77 (0.68, 0.87) and 0.0012, respectively.

Table 22: Study 136 (Breast) - Efficacy Results

Endpoint (Time to...)	Median D	Median ZA	HR (95% CI)	p-value	Note for p-value
1st SRE (NI)	NR	26.4	0.82 (0.71, 0.95)	< 0.0001	Cox model, synthesis method
1st SRE (Sup)	NR	26.4	0.82 (0.71, 0.95)	0.0097	Log-rank, adjusted
1st and subsequent SRE (Sup)	NA	NA	0.77 (0.66, 0.89)	0.0012	Cox model, adjusted

Figure 5 presents the Kaplan-Meier curve for time to first on-study SRE by treatment for the ITT population.

Figure 5: Study 136 (Breast) - Time to First On-Study SRE

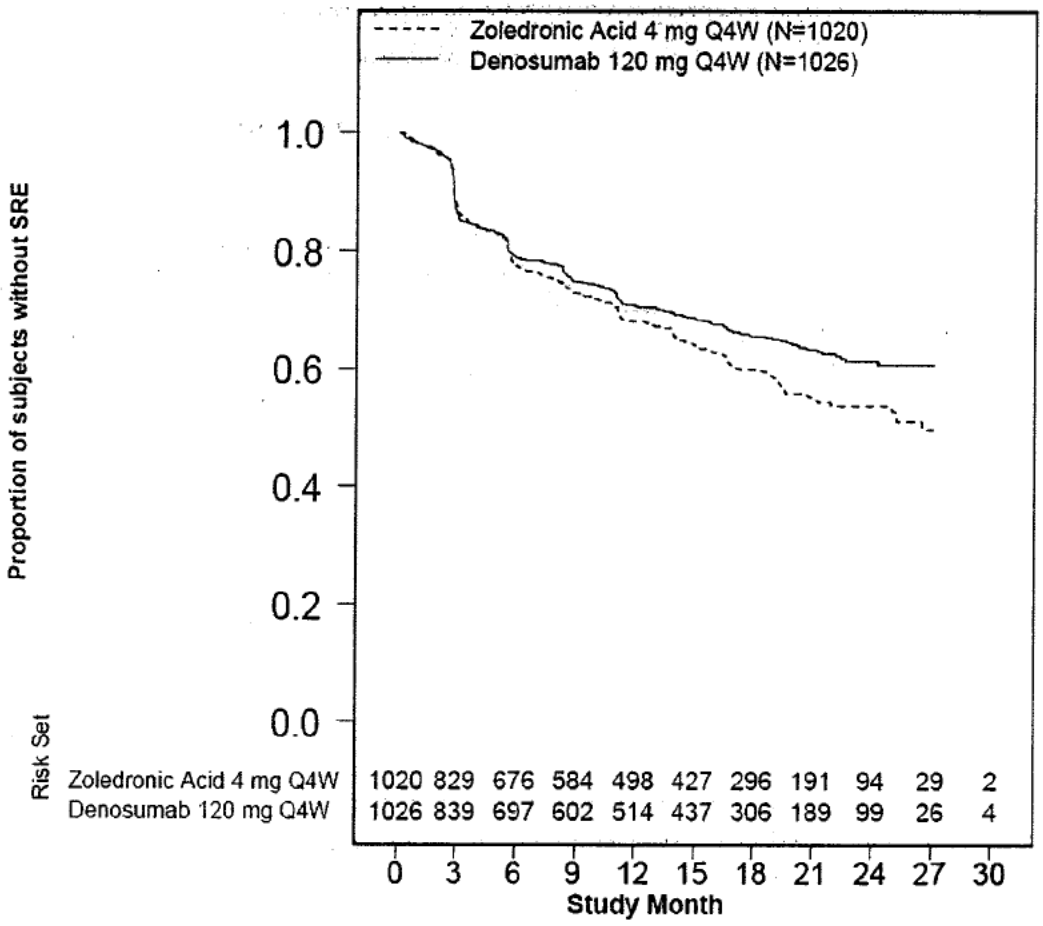


Table 23 presents the number of first on-study SREs by component. The Wei-Lin-Weissfeld (WLW) homogeneity test resulted in a p-value of 0.4775, which showed no evidence of inconsistent effects across the 4 SRE components.

Table 23: Study 136 (Breast) - First On-Study SREs by Component

SRE	D (N=1026)	ZA (N=1020)
Pathologic fracture	212 (20.7%)	238 (23.3%)
Radiation to bone	82 (8.0%)	119 (11.7%)
Surgery to bone	12 (1.2%)	8 (0.8%)
Spinal cord compression	9 (0.9%)	7 (0.7%)
Total	315 (30.7%)	372 (36.5%)
WLW homogeneity test: p = 0.4775		

Table 24 presents the number of first and subsequent on-study SREs by component.

Table 24: Study 136 (Breast) - First and Subsequent SREs by Component

SRE	D (N=474)	ZA (N=608)
Pathologic fracture	309 (65.2%)	388 (63.8%)
Radiation to bone	129 (27.2%)	189 (31.1%)
Surgery to bone	22 (4.6%)	19 (3.1%)
Spinal cord compression	14 (3.0%)	12 (2.0%)

Table 25 presents some of the key exploratory endpoints, including overall survival (OS) and progression-free survival (PFS).

Table 25: Study 136 (Breast) - Exploratory Endpoints

Endpoint (Time to…)	Number of events (%)		Median (in mos.)		HR
	D	ZA	D	ZA	(95% CI)
1st SRE or HCM	323 (31.5)	383 (36.5)	NR	25.2	0.82 (0.70, 0.95)
OS	301 (29.3)	305 (29.9)	29.4	NR	0.96 (0.82, 1.13)
PD in bone	446 (43.5)	449 (44.0)	16.6	16.4	0.99 (0.87, 1.13)
Overall PD	648 (63.2)	664 (65.1)	12.1	12.6	1.01 (0.90, 1.13)
PFS	683 (66.6)	698 (68.4)	11.8	11.7	1.01 (0.91, 1.13)
1st symptomatic SRE	156 (15.2)	198 (19.4)	NR	NR	0.76 (0.61, 0.93)

HCM = hypercalcemia of malignancy; PD = disease progression

The mean annual SMR was 0.45 (SD = 1.02) and 0.58 (SD: 1.34) for denosumab and ZA, respectively, with corresponding Cochran-Mantel-Haenzel test p-value 0.0041 The annual patient-year adjusted SRE incidence was 48.8% and 63.1% for denosumab and ZA, respectively.

Reviewer's Comments:

1. Denosumab was shown to be superior to ZA with respect to the primary endpoints in hormone-refractory prostate cancer patients.

2. Although the sample size calculation for the number of first on-study SREs was 745; only 687 events were observed in study 136. However, with 687 events, the study still had approximately 96% power for non-inferiority and 87% power for superiority.

3. There was no difference in progression endpoints and overall survival between denosumab and ZA.

3.2 Evaluation of Safety

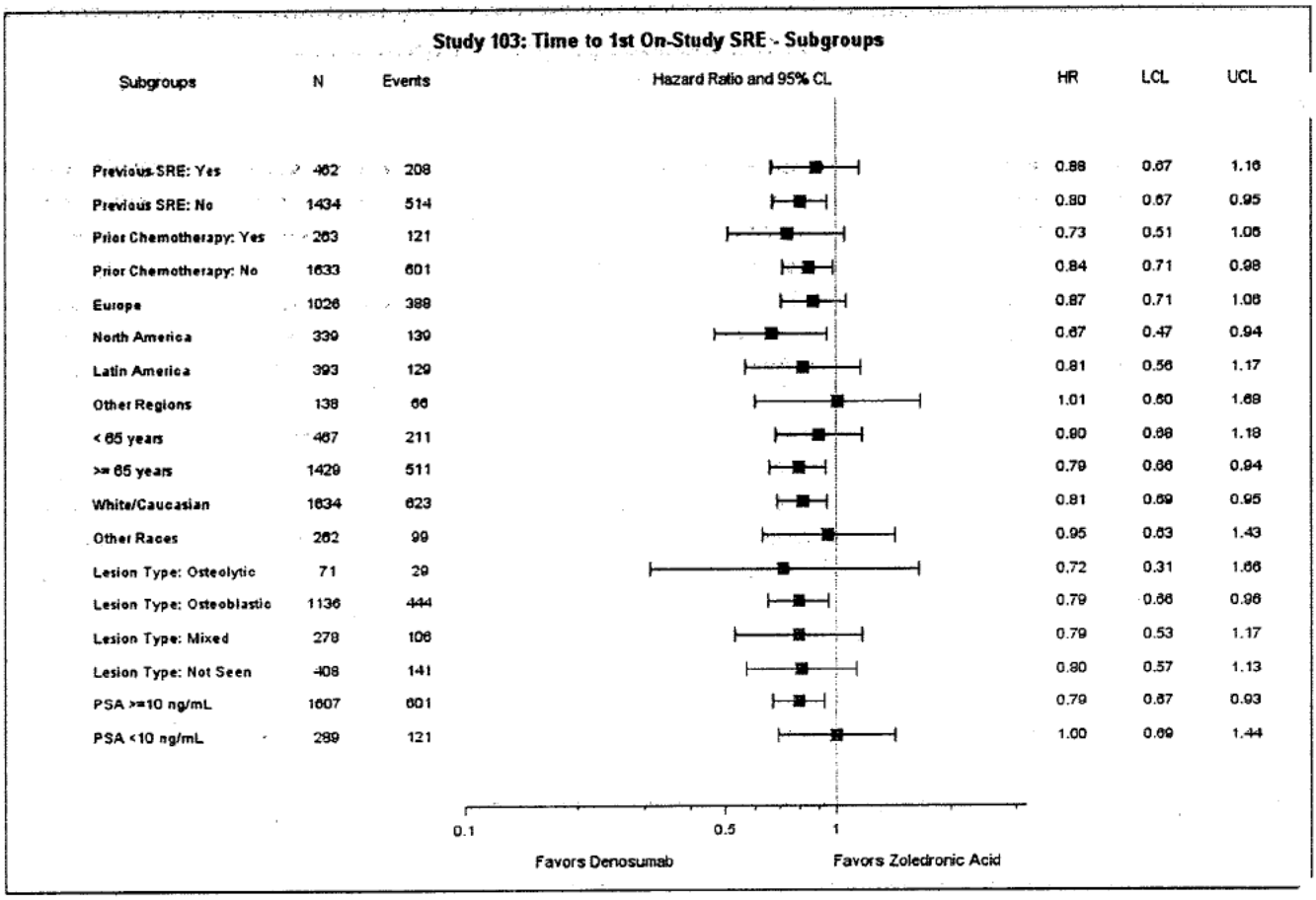
Please refer to the Clinical Review of this application for the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Study 20050103 (Prostate Cancer)

Figure 6 presents the hazard ratios (HRs) and 95% CIs (lower confidence level [LCL], upper confidence level [UCL]) of the subgroup analyses of time to first on-study SRE conducted for study 103.

Figure 6: Study 103 (Prostate) - Time to First On-Study SRE Subgroup Analyses



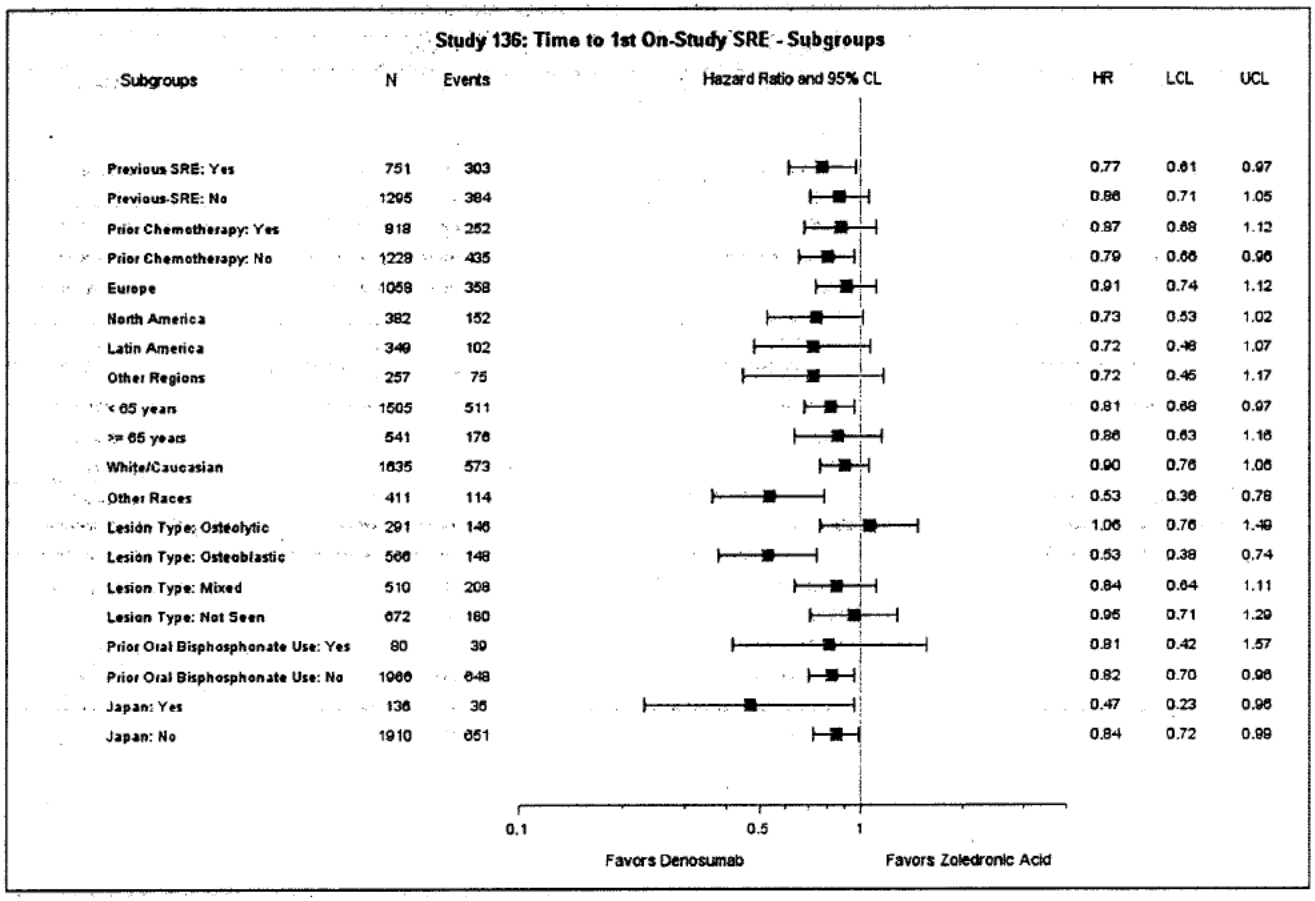
Reviewer's Comment:

These analysis results showed that the HRs favored denosumab in most subgroups in study 103, and are generally consistent with the primary analysis results.

Study 20050136 (Breast Cancer)

Figure 7 presents the hazard ratios (HRs) and 95% CIs (LCL, UCL) of the subgroup analyses of time to first on-study SRE conducted for study 136.

Figure 7: Study 136 (Breast) - Time to First On-Study SRE Subgroup Analyses



Reviewer's Comment:

These analysis results showed that the HRs favored denosumab in most subgroups in study 103, and are generally consistent with the primary analysis results.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study 20050103 (Prostate Cancer)

Table 26 summarizes the efficacy results for study 103, including both non-inferiority (NI) and superiority (Sup) endpoints. The median time to first on-study SRE in the intent-to-treat (ITT) population was 20.7 months and 17.1 months in the denosumab (D) and zoledronic acid (ZA) arms, respectively. The corresponding hazard ratio (HR) was 0.82 with 95% confidence interval (CI) (0.71, 0.95). The non-inferiority test p-value using the Cox model and synthesis method (Hung et al., 2003) was 0.0002. Given the achievement of non-inferiority, the superiority stratified log-rank test p-value for time to first on-study SRE was 0.0082. The HR (95% CI) and p-value for time to first and subsequent SRE using the multiple-events analysis method of Andersen-Gill (Andersen and Gill, 1982) adjusted for multiplicity by the Hochberg procedure was 0.82 (0.71, 0.94) and 0.0088, respectively.

Table 26: Study 103 (Prostate) - Efficacy Results

Endpoint (Time to…)	Median		HR (95% CI)	p-value	Note for p-value
	D	ZA			
1st SRE (NI)	20.7	17.1	0.82 (0.71, 0.95)	0.0002	Cox model, synthesis method
1st SRE (Sup)	20.7	17.1	0.82 (0.71, 0.95)	0.0082	Log-rank, adjusted
1st and subsequent SRE (Sup)	NA	NA	0.82 (0.71, 0.94)	0.0088	Cox model, adjusted

Table 27 presents some of the key exploratory endpoints, including overall survival (OS) and progression-free survival (PFS).

Table 27: Study 103 (Prostate) - Exploratory Endpoints

Endpoint (Time to…)	Number of events (%)		Median (in mos.)		HR (95% CI)
	D	ZA	D	ZA	
1st SRE or HCM	340 (35.8)	384 (40.4)	20.7	17.1	0.83 (0.72, 0.96)
OS	474 (49.9)	461 (48.5)	19.4	19.8	1.05 (0.91, 1.20)
PD in bone	387 (40.7)	402 (42.3)	13.7	11.1	0.93 (0.80, 1.08)
Overall PD	667 (70.2)	630 (66.2)	8.4	8.4	1.03 (0.91, 1.15)
PFS	767 (80.7)	735 (77.3)	8.1	8.0	1.03 (0.92, 1.14)
1st symptomatic SRE	241 (25.4)	289 (30.4)	NR	24.2	0.78 (0.66, 0.93)

HCM = hypercalcemia of malignancy; PD = disease progression

Study 20050136 (Breast Cancer)

Table 28 summarizes the efficacy results for study 136, including both non-inferiority (NI) and superiority (Sup) endpoints. The median time to first on-study SRE in the ITT population was 26.4 months in the ZA arm and not reached in the denosumab arm. The corresponding hazard ratio (HR) was 0.82 with 95% CI (0.71, 0.95). The non-inferiority test p-value using the Cox model and synthesis method (Hung et al., 2003) was < 0.0001. Given the achievement of non-inferiority, the superiority stratified log-rank test p-value for time to first on-study SRE was 0.0097. The HR (95% CI) and p-value for time to first and subsequent SRE using the multiple-events analysis method of Andersen-Gill (Andersen and Gill, 1982) adjusted for multiplicity by the Hochberg procedure was 0.77 (0.68, 0.87) and 0.0012, respectively.

Table 28: Study 136 (Breast) - Efficacy Results

Endpoint (Time to...)	Median D	Median ZA	HR (95% CI)	p-value	Note for p-value
1st SRE (NI)	NR	26.4	0.82 (0.71, 0.95)	< 0.0001	Cox model, synthesis method
1st SRE (Sup)	NR	26.4	0.82 (0.71, 0.95)	0.0097	Log-rank, adjusted
1st and subsequent SRE (Sup)	NA	NA	0.77 (0.66, 0.89)	0.0012	Cox model, adjusted

Table 29 presents some of the key exploratory endpoints, including overall survival (OS) and progression-free survival (PFS).

Table 29: Study 136 (Breast) - Exploratory Endpoints

Endpoint (Time to...)	Number of events (%) D	Number of events (%) Z	Median (in mos.) D	Median (in mos.) ZA	HR (95% CI)
1st SRE or HCM	323 (31.5)	383 (36.5)	NR	25.2	0.82 (0.70, 0.95)
OS	301 (29.3)	305 (29.9)	29.4	NR	0.96 (0.82, 1.13)
PD in bone	446 (43.5)	449 (44.0)	16.6	16.4	0.99 (0.87, 1.13)
Overall PD	648 (63.2)	664 (65.1)	12.1	12.6	1.01 (0.90, 1.13)
PFS	683 (66.6)	698 (68.4)	11.8	11.7	1.01 (0.91, 1.13)
1st symptomatic SRE	156 (15.2)	198 (19.4)	NR	NR	0.76 (0.61, 0.93)

HCM = hypercalcemia of malignancy; PD = disease progression

5.2 Conclusions and Recommendations

Study 20050103 (Prostate Cancer)

The median time to first on-study SRE in the ITT population was 20.7 months and 17.1 months in the denosumab and zoledronic acid (ZA) arms, respectively. The corresponding hazard ratio was 0.82 with 95% confidence interval (0.71, 0.95). The synthesis method non-inferiority test p-value was 0.0002, and the superiority log-rank test p-value was 0.0082. Thus, study 103 showed

that denosumab was statistically significantly superior to ZA with respect to time to first on-study SRB for hormone-refractory prostate cancer patients.

Study 20050136 (Breast Cancer)

The median time to first on-study SRB in the ITT population was 26.4 months in the ZA arm and not reached in the denosumab arm. The corresponding hazard ratio was 0.82 with 95% CI (0.71, 0.95). The synthesis method non-inferiority test p-value was < 0.0001, and the superiority log-rank test p-value was 0.0097. Thus, study 136 showed that denosumab was statistically significantly superior to ZA with respect to time to first on-study SRE for advanced breast cancer patients.

Both studies 103 and 136 showed that denosumab was superior to ZA in the treatment of bone metastases in patients with hormone-refractory prostate cancer and advanced breast cancer, respectively. Whether the results support the approval of denosumab for the proposed indications will depend on the clinical team's evaluation of the overall benefit-to-risk ratio.

REFERENCES

Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Statistics*. 1982;10(4):1100-1120.

Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Engl J Med*. 1996;335:1785-1791.

Hung HM, Wang S, Tsong Y, et. al. Some fundamental issues with non-inferiority testing in active controlled trials. *Statistics Med*. 2003;22:213-225.

Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese woman with bone metastases from breast cancer: a randomized placebo-controlled trial. *J Clin Oncol*. 2005;23:3314-3321.

Rosen LS, Gordon DH, Dugan W, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer*. 2004;100:36-43.

Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer*. 2001;7(5):377-387.

Saad F, Gleason D, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory cancer. *J Natl Cancer Inst*. 2004;96:879-882.

Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. *J Clin Oncol*. 1999;17(3):846-854.

/S/

Jing (Jenny) Zhang
10/25/2010

Kun He
10/25/2010

Rajeshwari Sridhara
10/25/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 125320/7 **Applicant: Amgen** **Stamp Date: 5/14/2010**

Drug Name: denosumab **NDA/BLA Type: supplement**

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

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

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	x			
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Welshi Yuan for vivian Tyan 7/7/10
Reviewing Statistician Date

Kuh He 7/7/10
Supervisor/Team Leader Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 30, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Microbiology Review: Denosumab: BL STN 125320/7

Reference the product quality and facilities reviews.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 30, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Clinical Pharmacology Team Leader Review: Denosumab: BL STN 125320/7

Team leader sign-off is located in the clinical pharmacology review.

Clinical Pharmacology Review

BLA	125320-7
Type/Category	New indication, efficacy supplement
Brand Name	XGEVA
Generic name	Denosumab
Proposed Indication	(b) (4)
Dosage Form	Injection
Route of Administration	Subcutaneous
Dosing Regimen and Strength	120 mg every 4 weeks; 70 mg/ml
Applicant	Amgen, Inc.
OCP Division	Clinical Pharmacology 5
OND Division	Biologic Oncology Products
Submission Date	19-May-2010
Primary Reviewer	Stacy S. Shord, PharmD
Secondary Reviewer	Hong Zhao, PhD
Pharmacometrics Primary Reviewer	Bahru Habtemariam, PharmD
Pharmacometrics Secondary Reviewer	Christine Garnett, PharmD

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Denosumab is a fully human IgG_2 monoclonal antibody that inhibits receptor activation of nuclear receptor factor κB (RANK) ligand. Denosumab as Prolia™ was approved on 10-Jun-2010 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. The approved dose was 60 mg administered as a subcutaneous (SC) injection every six months (Q6M) and the approved formulation was 60 mg/mL in a prefilled syringe or single use vial.

In the current submission, the applicant proposes a new indication of the [(b) (4)] [(b) (4)] at a dose of 120 mg SC every 4 weeks (Q4W) with a 70 mg/mL single use vial. In the phase 3 registration trials, denosumab 120 mg SC Q4W was statistically superior [20050136: HR 0.82 (95% CI: 0.71, 0.95) p =0.01] [20050103: HR 0.82 (95% CI 0.71, 0.94) p=0.004] or non-inferior [20050244: HR 0.84 (95% CI: 0.71, 0.98) p=0.0007] to zoledronic acid 15 mg IV Q4W in delaying skeletal related events (SRE). A SRE is a composite endpoint inclusive of radiation, surgery, pathologic fracture, and spinal cord compression.

Exposure-response (ER) analyses were performed using PK data obtained from the subset of 183 patients in the phase 3 clinical trials. Logistic regression showed the probability of SRE decreased with increasing denosumab trough concentrations. Similarly, a Kaplan-Meier plot of the proportion of patients without on-study SRE stratified by serum trough concentration quartiles showed that the time to the first SRE for patients in the higher third and forth concentration quartiles were longer than in patients in the two lower concentration quartiles. These findings suggest the selection of the clinical dose is acceptable, but not optimal.

The most common adverse events observed in clinical trials with denosumab treatment include nausea, anemia, fatigue, and back pain. Hypocalcemia occurred in about 6% of subjects administered denosumab and about 3.5% of subjects administered zoledronic acid in the phase 3 trials. No pharmacokinetic/adverse event (PK/AE) relationship was identified between denosumab serum concentrations and the probability of hypocalcaemia. The probability of hypocalcemia increases with decreasing renal function in the renal impairment trial. A PMR to examine the safety of denosumab in patients with severe renal impairment with respect to the higher incidence of hypocalcemia identified in this population and the management of this risk is being requested.

A PMR under PREA to study denosumab in pediatric patients is being requested.

1.1 RECOMMENDATIONS

The overall Clinical Pharmacology and Biopharmaceutics data submitted to support the approval of this supplemental BLA are acceptable provided that a satisfactory agreement is reached regarding the labeling.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

No PMR or PMC are requested from a clinical pharmacology perspective.

Optional OCP Inter-Divisional Briefing was held on Friday, October 15, 2010 and the following individual attended: Christine Garnett (DPM), Andrew Jackson (DCP1), Elizabeth Shang (DCP2), Arun Agrawal (DCP2), Aakansha Khandelwal (DCP5), Bijal Pandhi (DCP5), Pengfei Song (DCP5), Jun Yang (DCP5), Young-Jin Moon (DCP5), Jian Wang (DCP5), Brian Booth (DCP5), and Michael Axelson (DBOP).

Signatures:

Stacy S Shord, Pharm.D. Reviewer Division of Clinical Pharmacology 5	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology 5
Bahru Habtemariam, Pharm.D. Pharmacometrics Reviewer Division of Clinical Pharmacology 5	Christine Garnett, Pharm.D. Pharmacometrics Team Leader Division of Pharmacometrics

Cc: DBOP: RPM – **M Pierce**; MTL – **S Lemery**; MO – **M Axelson, S Pradhan**
DCP-5: DDD – **B Booth**; DD – **NA Rahman**
DPM: DD – **J Gobburu**

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Introduction: In this current submission, the applicant proposes a new indication of the [redacted] (b) (4) at a dose of 120 mg subcutaneous (SC) every 4 weeks (Q4W). This supplement includes four human pharmacokinetic (PK) trials conducted in healthy volunteers, two PK trials conducted in patients with advanced cancer, a renal impairment trial; two phase 2 clinical trials and three registration trials, as well as three comparability trials and a population PK analysis. Most of the early clinical trials were previously submitted and reviewed as part of the original BLA.

Clinical Dose Selection: The applicant justifies selection of the 120 mg SC Q4W dose over other tested dosages (30 mg to 180 mg, Q4W or Q12W) based on maximal reduction of the bone turnover biomarker urinary N-terminal telopeptide (uNTx) corrected for urinary creatineint (uCr) and sustainment of this reduction during the dosing interval.

Clinical Efficacy Trials: Denosumab 120 mg SC Q4W was administered to patients with cancer metastatic to the bone in three registrational trials. Treatment with denosumab has demonstrated at minimum non-inferior to zoledronic acid 15 mg IV Q4W for delaying skeletal related events (SRE). A SRE is a composite endpoint inclusive of radiation, surgery, pathologic fracture, and spinal cord compression. Zoledronic acid along with another intravenous bisphosphonate is the current standard of care for delaying SRE in patients with solid tumors metastatic to the bone. SRE was also used as the primary endpoint in the registrational trials supporting the approval of these active comparators.

Pharmacokinetics: The PK of denosumab was characterized in a phase 2 trial in 255 women with breast cancer metastatic to the bone. Patients were randomized to receive denosumab 30, 120, or 180 mg SC Q4W or 60 or 180 mg SC every 12 weeks (Q12W) or zoledronic acid 15mg IV Q4W. The mean ± S.D. maximal observed serum concentration C_{max} was 13.5 ± 6.1 mcg/ml following the first 120 mg dose. The accumulation ratio was 1.9 ± 1.7 following the third dose and 2.5 ± 5.3 following the fifth dose. The terminal elimination half-life was 28.8 ± 9.5 days following multi-doses at the proposed clinical dosage regimen. The three registration trials included a PK substudy in which sparse PK samples were collected. The mean serum trough concentrations demonstrated an accumulation ratio of 2.0 to 2.8 during the first six months of treatment, with no additional accumulation after 6 months.

Population Pharmacokinetic Analysis: A population PK analysis was conducted with data obtained from subjects enrolled into 20 clinical trials. Denosumab was administered as a single intravenous infusion, or single or multiple SC doses administered as weight-based or fixed doses given at dosing intervals of Q4W, Q12W or Q6M (every 6 months). First order absorption to the central compartment with linear distribution to the peripheral compartment followed by target-mediated clearance until saturation of the target was assumed. The absolute bioavailability was estimated to be 62%. The distribution half-life is 15 hours and the beta elimination half-life is 38 days at higher doses once non-linear target mediated clearance is saturated. Clearance is 3.1 mL/hr and the volume of distribution is 4 L. Subjects with multiple myeloma demonstrated 71% (95% CI: 68% to 74%) higher clearance compared to healthy volunteers and patients with osteoporosis or solid tumors. Denosumab clearance and volume of distribution values were proportional to body weight. The steady-state exposure (AUC) following repeat SC administration of 120 mg Q4W was 48% higher in a 45 kg subject and was 46% lower in a 120

kg subject than the exposure in a typical 66 kg subject.

Exposure-Response Analysis: Exposure-response (ER) analyses were performed using data obtained from the PK estimated for 183 subgroup patients in the phase 3 clinical trials. Logistic regression showed the probability of SRE decreased with increasing denosumab trough concentrations. Similarly, a Kaplan-Meier plot of the proportion of patients without an on-study SRE, stratified by serum trough concentration quartiles, showed that patients in the higher third and forth quartiles had a longer time to the first on-study SRE than that in patients in the two lower concentration quartiles. Patients treated with denosumab in the highest BSA quartile (Q4: BSA >2 m^2) and patients with multiple myeloma had increased on-study SRE compared to patients in the lower three BSA quartiles and patients with other tumor types. However, patients with BSA quartile >2 m^2 and patients with multiple myeloma administered zoledronic acid also had an increased on-study SRE. Therefore, BSA and multiple myeloma might be independent predictors of a higher incidence of on-study SRE.

Immunogenicity: Binding anti-denosumab antibodies were detected in 9 of 2,842 (<1%) subjects who participated in the five clinical trials not previously submitted (study no. 20050136, 20050244, 20050103, 20040113, 20060446). These antibodies were detected at baseline and weeks 18, 25 (n=2), weeks 35, 47, 49 (n=2), and week 57 after the first dose. Neutralizing antibodies were not detected in these subjects.

Comparability: In this current submission, the applicant proposes a 70 mg/mL single use vial instead of the approved 60 mg/mL single use vial or prefilled syringe. In a single-dose, parallel group clinical trial, 116 healthy volunteers were randomized 1:1 to receive a single 120 mg subcutaneous (SC) dose administered as either two-60 mg/mL injections or one-120 mg/1.7 mL injection. Samples were collected over 18 weeks to measure denosumab serum concentrations and serum C-terminal telopeptide (sCTX). The geometric mean ratios of the $AUC_{0\text{-}18\ wks}$ (1.07, 90% CI: 0.95, 1.20) and the C_{max} (1.01, 90% CI: 0.91, 1.11) indicate that these two formulations are pharmacokinetically comparable. The geometric mean ratio of the area under the effect curve ($AUEC_{0\text{-}18\ wks}$ 0.96, 90% CI, 0.92, 1.00) and the maximal inhibition (I_{max} 0.97, 90% CI 0.94, 1.00) of sCTx demonstrate that these two formulations are pharmacodynamically comparable. The comparable PK and PD results support the use of the safety, PK and PD data from earlier clinical trials with the 60 mg/mL formulation for the new dose strength of 70 mg/mL single use vial in this marketing application.

2 QUESTION BASED REVIEW

Refer to the original BLA 125,320 (Submission Date: 19-Dec-2008).

Four original BLAs, BLA125320, 125331, 125332 and 125333 were submitted 19 December 2008 and jointly reviewed by the Divisions of Clinical Pharmacology 3 and 5 and Pharmacometrics for the following four proposed indications: treatment (1) and prevention (2) of osteoporosis, and treatment and prevention of bone loss in patients undergoing hormone ablation therapy for breast cancer (3) and prostate cancer (4), respectively. Denosumab as Prolia™ was approved on 10-Jun-2010 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. The labeled dose is 60 mg administered as a subcutaneous (SC) injection every six months (Q6M) and the formulation is 60 mg/mL solution in a prefilled syringe or single use vial.

2.1 General Attributes of the Therapeutic Protein

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

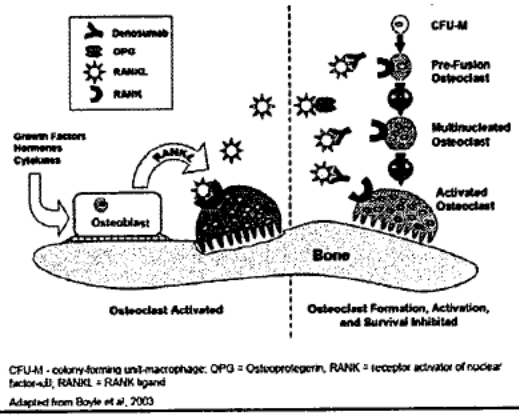
The highlights of the chemistry and physical-chemical properties of the drug substance are described in the original BLA review as follows: Denosumab (molecular weight: 147 kDa) is a human IgG_2 κ-type monoclonal antibody that binds to the receptor activator of nuclear factor-κB ligand (RANKL; a member of the tumor necrosis factor [TNF] family of proteins).

Denosumab drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by SC injection, supplied in a 70 mg/ml vial presentation with a 1.7 ml deliverable volume to support dosing of 120 mg Q4W.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The proposed mechanism of action is described in the original BLA review as follows: Denosumab binds to RANKL and prevents the activation of RANK leading to the inhibition of the formation, activation, and survival of osteoclasts (**Figure 1**). The resulting reduction in the number and function of osteoclasts decreases bone resorption and increases cortical and trabecular bone mass, volume, and strength (Kostenuik, 2005). The proposed indication is for the (b) (4)

Figure 1. Mechanism of action for denosumab



CFU-M - colony-forming unit-macrophage; OPG = Osteoprotegerin; RANK = receptor activator of nuclear factor-κB; RANKL = RANK ligand

Adapted from Boyle et al, 2003

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose is 120 mg SC Q4W. The median and maximum period for on-study assessment for the three registration trials is listed in **Table 1**.

Table 1. On study assessment

Trial Number	On-Study Period	
	Median (mo)	Maximum (mo)
20050103	12	41
20050136	17	34
20050244	7	30

2.2 GENERAL CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Summary of Clinical Pharmacology Trials: Among 10 clinical trials to support the clinical pharmacology evaluation of denosumab, 9 trials were submitted as part of the original BLA (**Table 2**). The current submission included one additional PK comparability trial (20060446).

The current submission also provides results of a population PK analysis with data collected in healthy volunteers, women diagnosed with low bone mineral density or osteoporosis and patients diagnosed with advanced cancer and bone metastases. The population PK analysis includes denosumab serum concentration-time data from 20 clinical trials, including nine PK data-rich trials (20010123, 20010124, 20030148, 20030164, 20040176, 20050241, 20050227, 20060286 and 20060446), six phase 2 trials (20010223, 20040113, 20040114, 20050134, 20050172 and 20040215) and three phase 3 trials (20040132, 20040135, and 20030216). A total of 24,603 serum concentrations from 2,315 subjects were included in this analysis.

Models were developed to characterize the effect of denosumab concentration with response to dose and regimen on the time course of urinary N-telopeptide (uNTx) levels corrected for urinary creatinine (uCr) following SC administration to patients with advanced cancer. A population pharmacokinetic/pharmacodynamic (PK/PD) analysis was conducted in patients diagnosed with advanced cancer. The dataset includes data from 331 patients enrolled into one of five clinical trials: 20010123, 20040176, 20040113, 20050136 and 20050244.

No metabolism or *in vitro* metabolic drug-drug interaction studies that used human biomaterials have been performed for denosumab, since it is a monoclonal antibody not subjecting to cytochrome P450 metabolism.

Table 2. Summary of clinical pharmacology trials

Healthy Volunteers				
Trial Number	**Primary Objective**	**Design**	**Subject Number**	**Treatment**
20010124	Evaluate the safety and tolerability when administered SC or IV to postmenopausal women	Phase 1, multicenter, randomized, placebo-controlled, double-blind, dose escalation	104	Single dose: AMG 162 SC or IV 0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg or placebo (3:1) Multiple dose: AMG 162 0.1 mg/kg SC Q3M x 2 doses
20030148	Evaluate the single-dose PK and PD profile in healthy men ≥ 50 years	Phase 1, randomized, placebo-controlled, double-blind, dose escalation	51	Single dose: AMG 162 0.1, 0.3, 1.0, or 3.0 mg/kg SC or placebo SC (4:1)

20030164	Evaluate the safety and tolerability after single SC administration in Japanese postmenopausal women	Phase 1, randomized, placebo-controlled, double-blind, dose escalation	45	Single dose: AMG 162 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg SC or placebo SC (3:1)
20030180	Evaluate single-dose PK and PD with a range of doses administered SC to healthy postmenopausal women	Phase 1, randomized, double-blinded, placebo-controlled, dose escalation	46	Single dose: AMG 162 0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg SC or placebo SC (3:1)
Patients with Cancer Metastatic to the Bone				
20010123	Evaluate the safety and tolerability of a single SC injection compared with pamidronate in subjects with cancer-related bone metastases	Phase 1, multicenter, parallel-dosing, randomized, double-blind, double-dummy, active-controlled	54	AMG 162 0.1, 0.3, 1, or 3 mg/kg SC with IV saline over 4 hours or pamidronate 90 mg IV over 4 hours with SC saline (3:1)
20040176	Characterize the safety profile of denosumab in Japanese subjects with breast cancer metastatic to bone	Open label, multi-center, ascending-dose study	19	60 mg SC x 1 dose or 180 mg SC x 1 dose or 180 mg SC Q4W x 3 doses
Intrinsic Factors – Renal Function				
20040245	Evaluate the single-dose PK in subjects with various degrees of renal function	Open-label study, renal impairment	55	60 mg SC x 1 dose
Comparability				
20050227	Provide PK, PD and safety on ACO and ATO	Open label, randomized, single dose, parallel group comparability	122	1 mg/kg SC Manufactured at ACO or ATO
20060286	Provide PK, PD and safety on BI Pharma and ATO	Open label, randomized, single dose, parallel group comparability	116	60 mg SC Manufactured at BI Pharma and ATO
20060446	Provide PK, PD, and safety on 60 and 70 mg/mL denosumab formulations	Open label, randomized, single-dose, parallel-group comparability	116	120 mg SC as two 1.0 mL injections of 60 mg/mL formulation or one 1.7 mL injection of 70 mg/mL formulation

Summary of Clinical Trials: Serum samples were obtained for assessment of denosumab concentrations, anti-denosumab antibodies, and exploratory biomarkers in a phase 2 clinical trial study 20040114 (extrinsic factor) that was submitted and reviewed as part of the original BLA.

Serum samples were obtained before, during, and after the treatment period for assessment of denosumab concentrations, anti-denosumab antibodies, and exploratory biomarkers in one additional phase 2 trial identified as study 20040113 (dense sampling) and three phase 3 clinical trials in subjects with advanced cancer: 20050103, 20050136 and 20050244 (sparse sampling).

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The applicant conducted two phase 2 and three phase 3 clinical trials in advanced cancer to support this application. **Table 3** summarizes the response endpoints and biomarkers evaluated in each of these trials.

Table 3. Summary of response endpoints or biomarkers in phase 2 and 3 clinical trials

Trial Number	Primary Objective	Primary Endpoint	Other Endpoints
20040113	Evaluate the effect of different doses and schedules of denosumab on the percentage change from baseline uNTx at week 13.	uNTx / uCr	uNTx/ uCr Bone turnover markers SRE Hypercalcemia Adverse events PK Pain
20040114	Determine the effectiveness of denosumab in reducing uNTx/Cr to below 50 nM/mM in subjects with advanced cancer and bone metastases who had uNTx/Cr levels > 50 nM/mM during prestudy IV bisphosphonate treatment	uNTx/uCr	uNTx/ uCr Bone turnover markers SRE Hypercalcemia Adverse events PK
20050136	Determine if denosumab is non-inferior to zoledronic acid with respect to the first on-study SRE, surgery to bone, or spinal cord compression) in subjects with advanced breast cancer and bone metastases.	SRE	SRE Hypercalcemia Skeletal morbidity Overall survival Disease progression Bone turnover markers PSA (20050103 only) Pain Quality of life Resource utilization Adverse events Anti-denosumab antibody PK
20050244	Determine if denosumab is non-inferior to zoledronic acid with respect to the first on-study SRE, surgery to bone, or spinal cord compression) in subjects with advanced breast cancer and bone metastases or lytic bone lesions from multiple myeloma.		
20050103	Determine if denosumab is non-inferior to zoledronic acid with respect to the first on-study occurrence of a SRE in men with hormone-refractory prostate cancer and bone metastases.		

Abbreviations:
PSA prostate specific antigen
SRE skeletal related event
uNTx urinary N-terminal telopeptide
uCr urinary creatinine

For the phase 2 trial 20040113, the primary endpoint was defined as the percentage change in uNTx/uCr from baseline to week 13 and summarized using median percentage change (with 25th and 75th percentile, minimum, and maximum) and the mean percentage change with 95% confidence intervals (CI) for each treatment group, for all denosumab groups combined, and by randomization stratification factors and treatment group.

For the phase 2 trial 20040114, the primary endpoint was defined as the proportion of subjects with uNTx/Cr < 50 nM/mM at week 13 and the proportion with associated 95% CI was calculated for each treatment group and for the denosumab Q4W and Q12W groups combined.

For the phase 3 registrational trials, the primary endpoint was defined as skeletal related events (SRE), a composite endpoint which includes a pathologic fracture, radiation to the bone, surgery to the bone or spinal cord compression. The definition and assessment of SRE in these trials is consistent with those used in the registrational trials that supported the approval of the active comparator, zoledronic acid, for a similar indication.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Denosumab is the major circulating moiety and it was measured using a validated, conventional sandwich enzyme-linked immunosorbent assay (ELISA). See the original BLA review, Section 2.6 for analytical method.

2.3 EXPOSURE-RESPONSE

2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Denosumab 120 mg SC Q4W was non-inferior to zoledronic acid 15 mg IV Q4W in one of the three registration trials and was superior to zoledronic acid in two of the three registration trials (**Table 4**).

Table 4. Summary of clinical endpoints in the three phase 3 registration trials

Endpoint	Denosumab vs Zoledronic Acid Hazard Ratio or Rate Ratio [a]							
	Study 20050136		Study 20050244		Study 20050103		Overall	
	Pt Est (95% CI)	p-value	Pt Est (95% CI)	p-value	Pt Est (95% CI)	p-value	Pt Est (95% CI)	p-value
Time to first on-study SRE (noninferiority)[b]	0.82 (0.71, 0.95)	< 0.0001	0.84 (0.71, 0.98)	0.0007	0.82 (0.71, 0.95)	0.0002	0.83 (0.76, 0.90)	< 0.0001
Time to first on-study SRE (superiority)[c]	0.82 (0.71, 0.95)	0.0101	0.84 (0.71, 0.98)	0.0309	0.82 (0.71, 0.95)	0.0085	0.83 (0.76, 0.90)	< 0.0001
Time to first-and-subsequent SRE[d]	0.77 (0.66, 0.89)	0.0006	0.90 (0.77, 1.04)	0.1447	0.82 (0.71, 0.94)	0.0044	0.82 (0.75, 0.89)	< 0.0001
Time to first on-study SRE or HCM[e]	0.82 (0.70, 0.95)	0.0074	0.83 (0.71, 0.97)	0.0215	0.83 (0.72, 0.96)	0.0134	0.83 (0.76, 0.90)	< 0.0001
Time to first on-study radiation to bone[c]	0.74 (0.59, 0.94)	0.0121	0.78 (0.63, 0.97)	0.0256	0.78 (0.66, 0.94)	0.0071	0.77 (0.69, 0.87)	< 0.0001
Time to first on-study pathological fracture[c]	0.83 (0.70, 0.99)	0.0404	0.87 (0.69, 1.08)	0.2048	0.89 (0.71, 1.10)	0.2797	0.86 (0.76, 0.96)	0.0093

Adapted from Clinical Overview, table 3, page 48

There is evidence of exposure-response (ER) for effectiveness in the phase 3 efficacy trials showing that the clinical endpoint SRE is influenced by drug exposure at the proposed dose of 120 mg SC Q4W. ER analyses were performed using a subset from whom trough PK samples were obtained (n=183).

As shown below, the probability of SRE decreased with increasing denosumab trough concentrations (**Figure 2**). Similarly, Kaplan-Meier curves show that the time to the first on-study SRE for patients in the third and forth quartiles (Q3 and Q4) of serum denosumab trough concentrations were longer than in patients within the lower two quartiles (**Figure 3**). The trough concentration ranges in each quartile were: Q1 < 12,100 ng/mL, Q2: 12,100-16,900 ng/mL, Q3: 16,900-23,100 ng/mL, and Q4: > 23,100 ng/mL.

Figure 2. Probability of on-study SRE vs. quartiles of denosumab steady-state trough concentrations

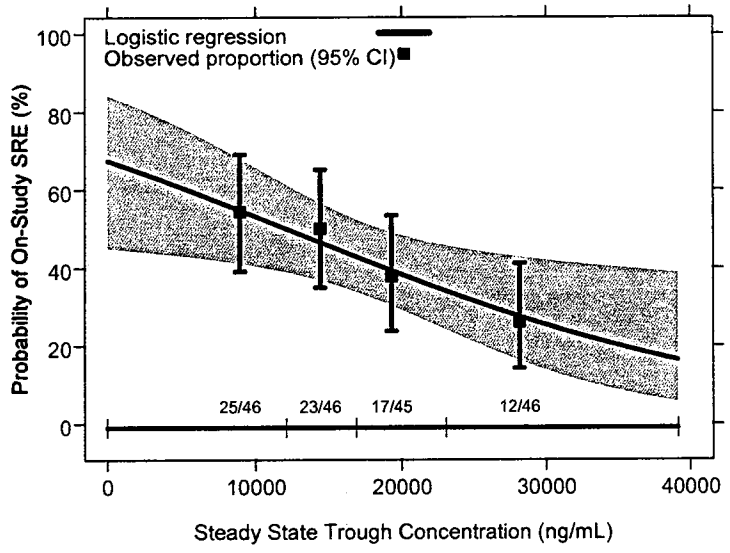
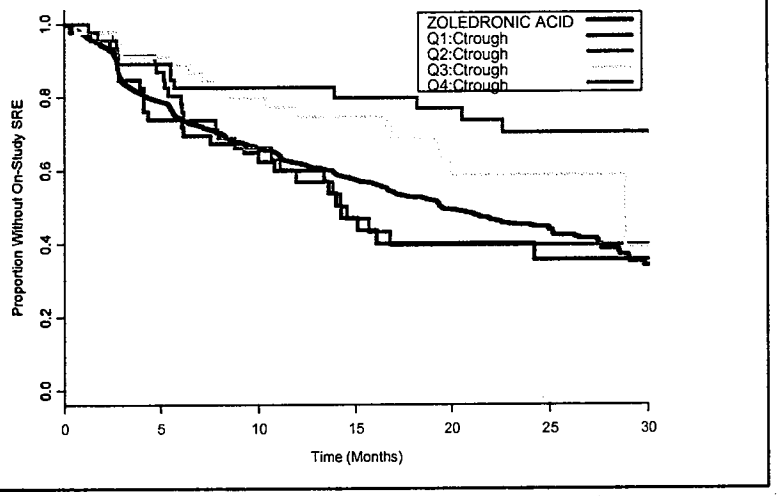


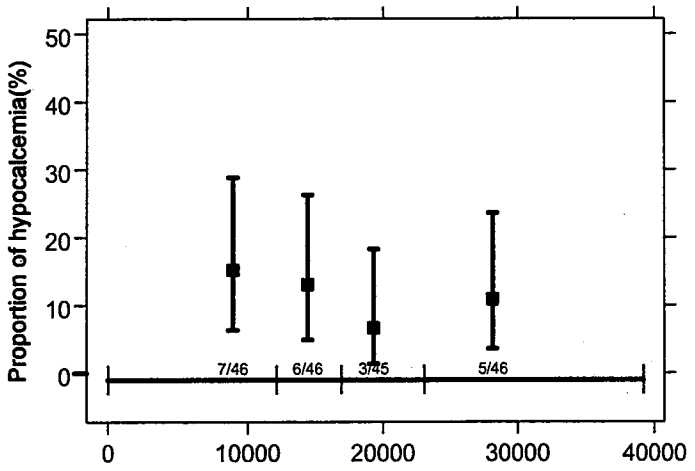
Figure 3. Probability of on-study SRE vs. quartiles of denosumab steady-state trough concentrations



2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Serum calcium levels were measured during the three registration phase 3 trials. Using serum calcium levels from these trials, logistic regression was performed to assess the relationship between probability of all-grade hypocalcaemia and denosumab steady-state trough concentrations. Analysis was performed for the subset of patients that had denosumab trough concentration data (n=183). **Figure 4** below shows that the probability of hypocalcaemia is flat across all denosumab concentrations. Therefore, the probability of hypocalcaemia does not appear to increase with increasing denosumab trough concentrations.

Figure 4. Probability of hypocalcaemia vs. quartile of denosumab steady-state trough concentrations



2.3.3 Does this drug prolong the QT or QTc interval?

See the original BLA review for a summary of the nonclinical studies and clinical trails (section 2.2.4.3). **The QT-IRT review concluded the applicant's ECG evaluations appear adequate and** there are no large effects on the QT interval due to denosumab. The evaluation included 13,500 subjects enrolled into clinical trials and who received at least one dose of denosumab. Dosages included single and repeat doses Q4W, Q12W and Q6M with a single dose up 210 mg. The maximum treatment duration appears to be about 2 years.

Electrocardiograph (ECG) assessments were not conducted in the phase 3 registration trials for patients with advanced cancer, but were included in the phase 2 dose finding trial submitted in this application. Of note, this ECG data was reviewed as part of the review conducted by QT-IRT following submission of the original BLA, although the clinical trial was not submitted to support the initial marketing application. In the trial 20040113, 255 patients with metastatic breast cancer to the bone were randomized 4:1 to receive one of five doses of SC denosumab (30, 120, or 180 mg Q4W or 60 or 180 mg Q12W) or zolendroic acid 15 mg IV Q4W. ECG assessments were completed on day 1, week 13, week 25 and at the end of the trial and serum calcium levels were measured on day 1 and weeks 2, 5, 9, 10, 11, 12, 13, 17, 18, 19, 20, 21, and 25. **Table 5** summarized the ECG assessment for this clinical trail. No effect on the QTc interval was identified.

Table 5. Summary of baseline, maximum and maximum change in QTcF interval

Parameter	Bisphosphonate IV Q4W (N = 43)	Denosumab 30 mg Q4W (N = 42)	Denosumab 120 mg Q4W (N = 41)	Denosumab 180 mg Q4W (N = 43)	Denosumab 60 mg Q12W (N = 42)	Denosumab 180 mg Q12W (N = 43)	Total (N = 211)
Baseline QTcF Interval in msec							
N	41	40	40	41	40	41	202
Mean	401.0	396.3	388.7	396.6	403.1	405.2	398.0
SD	23.1	46.9	42.7	44.0	38.9	27.1	40.5
Median	401.1	398.8	399.4	400.5	406.5	402.1	401.3
Min, Max	353, 448	286, 563	247, 459	227, 475	295, 488	302, 458	227, 563
Post-Baseline Maximum QTcF Interval in msec							
N	38	40	39	39	38	41	197
Mean	422.2	413.4	414.0	409.2	410.1	415.5	412.5
SD	25.2	31.5	32.2	28.3	29.2	33.0	30.7
Median	424.3	407.4	418.3	410.8	408.8	413.3	410.8
Min, Max	352, 471	356, 509	330, 495	324, 474	319, 481	282, 483	282, 509

Parameter	Bisphosphonate IV Q4W (N = 43)	Denosumab 30 mg Q4W (N = 42)	Denosumab 120 mg Q4W (N = 41)	Denosumab 180 mg Q4W (N = 43)	Denosumab 60 mg Q12W (N = 42)	Denosumab 180 mg Q12W (N = 43)	Total (N = 211)
Post-Baseline Maximum Change QTcF Interval in msec							
N	36	38	38	37	36	39	188
Mean	23.4	17.9	25.2	8.5	10.0	14.2	15.3
SD	25.4	41.2	41.5	39.4	32.4	21.5	36.1
Median	24.3	14.7	16.9	8.2	6.6	11.1	10.2
Min, Max	-24, 66	-132, 123	-40, 134	-85, 126	-55, 111	-36, 85	-132, 134

Adapted from denosumab ECG summary dated 26 Nov 2008, page 104, table 42

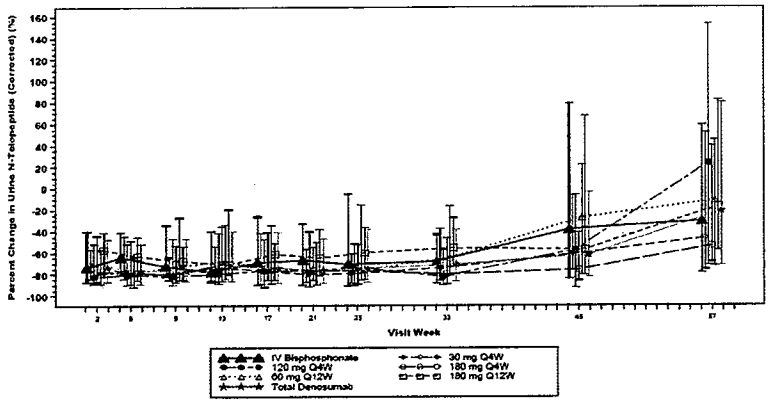
2.3.4 Is the dose and dosing regimen selected consistent with the known ER relationship?

The dose selection of 120 mg SC Q4W, which was based on safety and uNTx/Cr reduction described for the phase 2 dose-ranging trial 20040113, appears acceptable, but not optimal. The primary objective of this trial was to evaluate the effect of different doses and schedules of denosumab on the percentage change from baseline in uNTx/Cr at week 13 in subjects with breast cancer metastatic to the bone who had not previously received intravenous bisphosphonate therapy. The secondary objectives were to characterize the safety profile and long-term efficacy on bone turnover markers of denosumab administered SC at doses of 30, 60, 120, or 180 mg, by evaluating the effect of denosumab on SRE and hypocalcaemia and the PK parameters of denosumab at different doses and schedules.

The primary endpoint was the median percentage change of uNTx from baseline to week 13. The applicant reported the median reduction in uNTx/Cr was 73% in the combined denosumab groups and 78% in the bisphosphonate group and that the 120 mg Q4W dosage demonstrated the greatest median uNTx/Cr suppression (80%) (**Figure 5**). The applicant concluded that denosumab 120mg Q4W demonstrated greatest median reduction in uNTx levels and the reduction was sustained throughout the dosing interval. Furthermore, the applicant supported the selection of the proposed clinical dose by stating that denosumab 120 mg SC Q4W provides a greater proportion of subjects with normalized uNTx/Cr levels (< 50 nM/mM) relative to 30 mg Q4W dosing; a maximal proportion of subjects with uNTx/Cr suppression > 90% compared to the lowest Q4W dose and Q12W dosing, and a substantial reduction in the absolute variability in uNTx/Cr as compared with baseline. Denosumab was well tolerated across all dosing groups.

A validated analytical procedure was used to determine NTx in human urine (study no. 105414). The nominal standards were defined as 23 nM/BCE to 3000 nM/BCE [BCE = bone collagen equivalent]; the accuracy was 96% to 103% and the precision was 2% to 7% (sample analysis). The quality control levels were defined as 150, 500 and 2000 nM/BCE; the accuracy was 93% to 105% and the precision was 5% to 6% (sample analysis). The concentration values reported are acceptable.

Figure 5. Median percent change in uNTx/Cr from baseline over time by treatment group



Adapted from Summary of Clinical Pharmacology Studies, page 74, figure 20

Our analysis demonstrated a median reduction of 80% (quartiles, 40% to 89%) at week 13 after receiving multiple doses of 120 mg SC Q4W (**Table 6**). Smaller median reductions were reported for denosumab 30 mg SC Q4W (median 71%; quartiles 50% to 86%) and denosumab 180 mg SC Q4W (median 71%; quartiles 41% to 86%). The reductions were not sustained during the dosing interval for patients receiving denosumab Q12W.

Table 6. Median reduction of uNTx/Cr in study no. 20040113

Dosage / Week	2	5	9	13	17	21	25
30 mg Q4W	71%	78%	80%	71%	76%	80%	79%
120 mg Q4W	82%	81%	80%	80%	77%	76%	74%
180 mg Q4W	77%	76%	80%	71%	74%	77%	76%
60 mg Q12W	79%	78%	74%	68%	76%	77%	77%
180 mg Q12W	57%	53%	68%	71%	61%	65%	60%

The applicant selected 120 mg SC Q4W for further clinical testing in the three registration trials for patients diagnosed with cancer metastatic to the bone. Denosumab was superior (20050136 and 20050103, secondary endpoint) or noninferior (20020244, primary endpoint) to zoledronic acid in delaying SRE in these three trials.

The population PK analysis of denosumab trough concentrations shows lower exposure in patients with large body size (assessed by weight or BSA) and patients with multiple myeloma. Therefore, denosumab dosing regimen could be further optimized to obtain similar exposure across different body sizes and tumor type. There is no convincing ER relationship to recommend a specific dose modification scheme for patients with a high BSA or multiple myeloma in the present submission, because a small subset of patients in the registration trials participated in the PK substudy. The sponsor should address this issue in future submissions by obtaining adequate trough concentration samples and performing robust ER analyses. Of note,

in the clinical trial of patients with advanced malignancies involving bone (n=1776), mortality was higher in the subgroup of patients with multiple myeloma (hazard ratio 2.3 [95% CI: 1.1, 4.5]; n = 180). Randomization was stratified by tumor type (non-small cell lung cancer vs. multiple myeloma vs. other). This finding in patients with multiple myeloma is incorporated in the product labeling.

2.4 WHAT ARE THE PK CHARACTERISTICS OF THE DRUG?

See the original BLA review, section 2.2.5 for a description of the pharmacokinetics of denosumab.

Dense PK Sampling: During the phase 2 dose finding trial 20040113, PK samples were collected at the following times: pre-dose, and at weeks 2, 5, 9, 10-12, 13, 17, 18-20, 21, 25, 33, 45, and 57. Serum denosumab concentrations were measured using a validated conventional sandwich enzyme-linked immunosorbent assay (study no. 102110). The method validation was described in the review of the original BLA, section 2.6. The nominal standard curve was defined as 0.6 ng/ml to 40 ng/ml; the accuracy was 89% to 108% and the precision was 3%. The quality control levels were defined as 0.8, 3.5 and 35 ng/ml; the accuracy was 94% to 104% and the precision was 7% to 10%. The concentration values reported were acceptable. **Table 7** lists a summary of the PK parameters following single and multiple doses in this trial.

Table 7. Mean denosumab pharmacokinetic parameters after multiple-dose administration

Q4W Dosing											
Dose Group		Dose 1		Dose 3			Dose 5			Dose 6	
		C_{max} (ng/mL)	AUC_{0-tau} (ng·day/mL)	C_{max} (ng/mL)	AUC_{0-tau} (ng·day/mL)	AR_1	C_{max} (ng/mL)	AUC_{0-tau} (ng·day/mL)	AR_2	$C_{4\ week}$ (ng/mL)	$t_{1/2,\beta}$ (day)
30 mg	N	33	33	39	39	-	39	39	-	34	19
	Mean	3190	67900	7300	152000	2.24	7830	168000	2.47	6090	26.1
	SD	1390	28600	3940	81300	2.84	4320	80100	2.80	3360	10.1
	%CV*	43.4	42.1	54.0	53.4	1.27	55.2	47.8	1.14	55.1	38.8
120 mg	N	34	34	36	36	-	35	35	-	35	29
	Mean	13500	287000	22800	539000	1.88	27100	723000	2.52	20500	28.8
	SD	6130	130000	9440	215000	1.66	14800	684000	5.26	13500	9.5
	%CV*	45.5	45.3	41.4	40.0	0.883	54.7	94.5	2.09	65.8	32.9
180 mg	N	36	36	39	39	-	38	38	-	33	28
	Mean	22000	478000	46300	1030000	2.15	45300	1090000	2.27	38200	34.8
	SD	7300	154000	20300	381000	2.48	15300	356000	2.31	13000	12.4
	%CV*	33.2	32.1	43.9	37.1	1.16	33.8	32.7	1.02	34.0	35.6

Adapted from Summary of Clinical Pharmacology Studies, page 77, table 4

Sparse PK Sampling: PK samples were collected in subpopulation during the conduct of the three registration trials. Patients with cancer metastatic to the bone were randomized to receive denosumab 120 mg SC Q4W or zoledronic acid 15 mg IV Q4W. Samples for the measurement of serum denosumab concentrations were obtained from a subset of approximately 247 subjects pre-dose, then at weeks 5, 9, 13, 25, 49, 73, 97, and at the end-of-study visit. The mean C_{max} after one dose was 6.2, 7.1, and 9.7 µg/mL in trial 20050244, 20050103, and 20050130, respectively. The accumulation ratio after the third and fifth dose ranged from 2- to 2.8-fold. No additional accumulation was reported after the fifth dose.

Serum denosumab concentrations were measured using a validated conventional sandwich enzyme-linked immunosorbent assay (study no. 102110). The method validation was described in the review of the original BLA, section 2.6. The nominal standard curve was defined as 0.8 ng/ml to 35 ng/ml; the accuracy was 93% to 108% and the precision was 1% to 4%. The quality

control levels were defined as 2, 3.5 and 20 ng/ml; the accuracy was 93% to 104% and the precision was 6% to 7%. The concentration values reported were acceptable.

Population PK Analysis: The population PK analysis included serum denosumab concentrations collected in 2,315 subjects enrolled into 20 clinical trials (**Table 8**). First order absorption from the subcutaneous site into the central compartment with target mediated drug clearance until saturation of the target was assumed. Covariates analyzed were body weight, age, race, disease, and concurrent treatment.

Denosumab absolute bioavailability following SC administration is estimated to be 62%. The distribution half-life is about 15 hours once non-linear target-mediated clearance is saturated. The volume of distribution at steady-state is about 4 L and the clearance is about 3 mL/h after the target-mediated clearance pathway was saturated. The beta phase elimination half-life is about 38 days.

Table 8. Clinical trials included in population PK analysis

Phase 1 (dense)	Phase 2 (sparse)	Phase 3 (sparse)
20010123	20010223	20040132
20010124	20040113	20040135
20030148	20040114	20030216
20040164	20050134	20050136
20040176	20050172	20050244
20050241	20040215	
20050227		
20060286		
20060446		

The key findings of the population PK analysis are:

- A two-compartment target-mediated drug disposition model with linear distribution to the peripheral compartment, parallel linear and non-linear elimination, and first-order absorption following SC administration.
- Denosumab exhibited time-independent kinetics and its systemic exposure is consistent following repeat SC administration of 120 mg Q4W, with accumulation of 186%.
- Denosumab linear clearance, inter-compartmental clearance, and volumes of the central and peripheral compartments were proportional to body weight. The steady-state exposure following repeat SC administration of 120 mg Q4W to 45 kg and 120 kg subjects were, respectively, 48% higher and 46% lower than exposure of a typical 66 kg subject.
- Overall, cancer patients tend to have higher clearance, in particular, subjects with multiple myeloma had 71% (95% CI: 68% to 74%) higher clearance that resulted in lower exposure compared to healthy subjects.
- Subjects with solid tumors (breast cancer, prostate cancer, giant cell tumors, and other solid tumors without multiple myeloma) had 15% to 39% (95% CI: 11% to 46%) higher clearance compared to healthy subjects.
- PK of denosumab were similar between healthy subjects and osteopenic or osteoporotic postmenopausal women.

2.5 INTRINSIC FACTORS

2.5.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

The covariates included in the population PK analysis were body weight, age, race and disease type. No notable differences in denosumab PK were identified for age or race.

Body Weight: The sponsor's population PK analysis indicated that the clearance and volume parameters were correlated with body weight. Patients with small body weight had higher exposure, whereas those with higher body weight had lower exposure. Consistent with the sponsor's population PK analysis results, linear regression using body surface area (BSA) and steady state trough concentration showed that trough concentration decreases as BSA increases (p-value=0), as shown in **Figure 6** below.

Disease Type: The sponsor's analysis showed patients with multiple myeloma had 71% faster clearance relative to healthy volunteers. **Figure 7** shows that multiple myeloma patients had lower steady state trough concentrations than patients with other tumor types. The median steady state trough concentration of multiple myeloma and other tumor type patients were 12 mcg/mL and 17 mcg/mL, respectively, which show that denosumab concentrations were 40% lower in patients with multiple myeloma. Because there were only eight patients with multiple myeloma with trough concentrations, the 40% lower concentration estimate might not be reliable. Disease status, with the exception of patients with multiple myeloma, does not appear to affect the PK of denosumab (**Figure 8**), based on the sponsor's comparison of trough concentrations after administration of denosumab 120 mg SC Q4W in different patient populations at 1, 3 and 6 months following the first dose.

Figure 7. Denosumab steady-state trough concentrations in patients with multiple myeloma (n=8) and other tumor types (n=175).

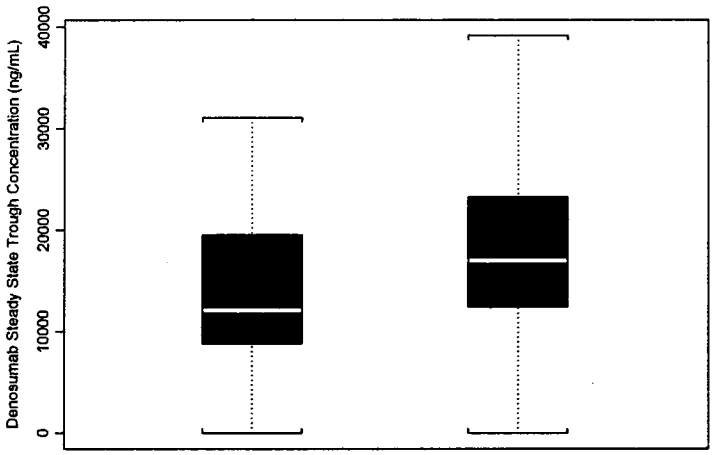
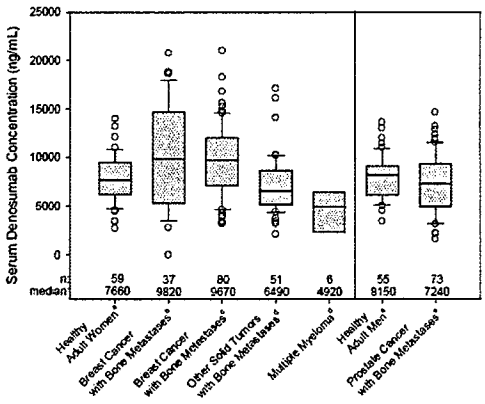
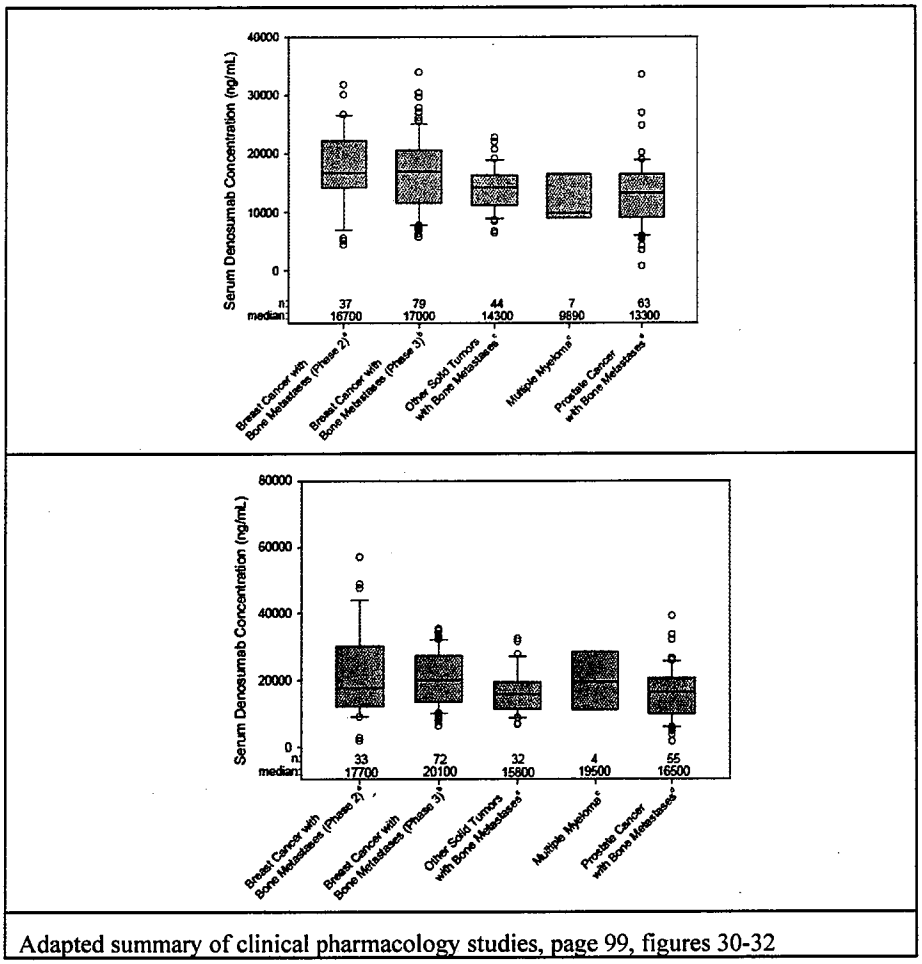


Figure 8. Trough serum denosumab concentrations at 1 (top), 3 (middle) and 6 (bottom panel) months during administration of denosumab 120 mg SC to different patient populations





Adapted summary of clinical pharmacology studies, page 99, figures 30-32

Potential of Exposure Difference on Efficacy for Denosumab Treated Patients: Patients in the highest BSA quartile (Q) (Q4: BSA >2 m^2) had increased on-study SRE compared to patients in the lower three quartiles (**Figure 9**). The analysis was conducted by computing BSA quartiles for all patients enrolled into the phase 3 trials (n=5,551). Patients with missing BSA data were excluded from the analysis (n=172). The Kaplan-Meier estimates of the median time to the first on-study SRE and the number of SRE events during the trial are shown in **Table 9**. The median time could not be computed for Q1-Q3 for subjects administered denosumab, because 50% of the subjects did not experience an event during the trial. In addition, **Figure 10** shows that patients with multiple myeloma had increased risk on-study SRE compared to patients with other tumor types.

Table 9. Kaplan-Meier estimate of median time (days) to first SRE by treatment and BSA quartiles

Group	Number of Patients	Number of SRE	Median Time to SRE (Months)	95% CI
ZA Treated Patients	2861	1081	19.4	18.6-21.4
Den Treated Patients	2862	934	27.7	24.2-NR
Q1: BSA <1.7	685	204	NR	22.6-NR
Q2: BSA 1.7–1.8	689	218	NR	22.4-NR
Q3: BSA 1.8–2.0	703	223	NR	22.4-NR
Q4: BSA >2.0	699	258	22.1	19 -27.7

ZA = Zoledronic Acid
Den = Denosumab
NR = Time to the first on-study SRE not reached because insufficient number of patients had SRE events to calculate median time to event.

Figure 9. Kaplan-Meier plot of time to first on-study SRE by BSA quartile

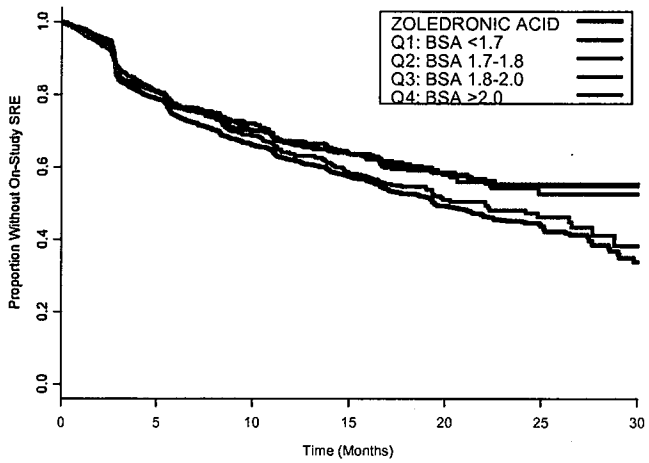
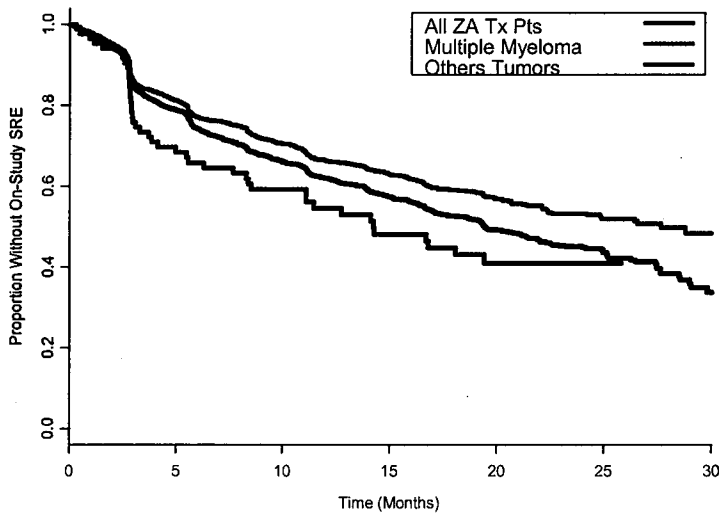
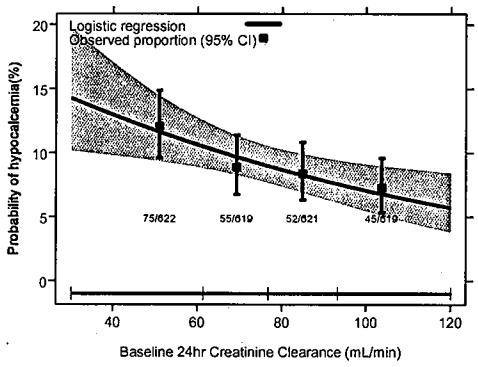


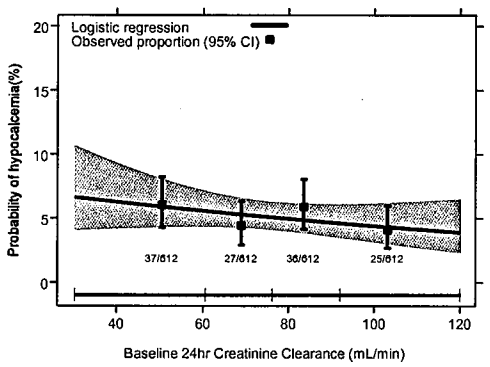
Figure 10. Kaplan-Meier Plot of time to first on-study SRE by tumor type



Potential Safety Difference for Denosumab Treated Patients: Baseline 24-hour creatinine clearance (CrCL) (n= 5679) were available from patients administered denosumab (n=2839) and zoledronic acid (n=2840) that took part in the phase 3 registrational trials. Logistic regression analysis was performed to characterize the relationship between the probability of hypocalcemia and baseline CrCL, using the subset of patients with baseline CrCL values less than 120 mL/min (n= 4935). As shown below, the probability of hypocalcemia increases with decreasing baseline creatinine clearance (**Figure 11, left panel**) in patients treated with denosumab. On the other hand, for patients in the zoledronic acid arm, the probability of hypocalcemia did not increase with decreasing CrCL (**Figure 11, right panel**).

Figure 11. Probability of hypocalcemia vs. baseline creatinine clearance for denosumab (left) and zolendronic acid (right panel)



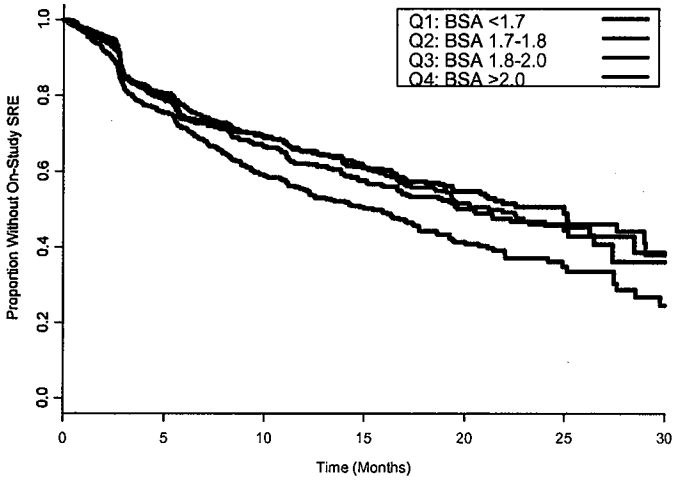


2.5.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments, if any, are recommended for each group?

2.5.2.1 *Body Weight*

Patients administered zoledronic acid that were in highest BSA quartile (Q4: BSA >2 m^2) also had an increased risk of on-study SRE compared to patients in the lower quartiles (**Figure 12**). This finding indicates that a higher BSA might be an independent predictor of an on-study SRE.

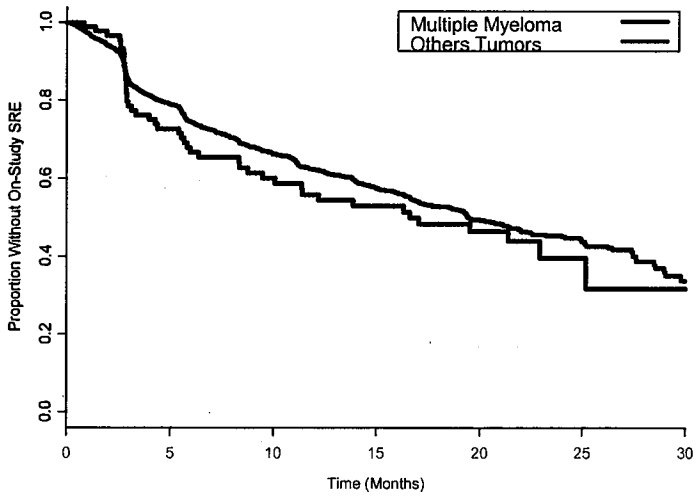
Figure 12. Kaplan-Meier plot of time to first on-study SRE by BSA quartile for zoledronic acid



2.5.2.2 *Disease Type*

Furthermore, **Figure 13** indicates that, in patients with multiple myeloma administered the active comparator zolendroic acid had shorter time to event, which suggests that multiple myeloma could be an independent predictor of on-study SRE. These findings make the denosumab exposure-response analysis results inconclusive.

Figure 13. Kaplan-Meier plot of time to first on-study SRE by tumor type in patients treated with zoledronic acid



2.5.2.3 *Elderly*

The PK of denosumab were not affected by age greater than 65 years based on the population PK analysis. See the original BLA review.

2.5.2.4 *Pediatric patients*

The safety and effectiveness of denosumab in pediatric patients have not been established. Treatment with denosumab might impair bone growth in children with open growth plates and may inhibit eruption of dentition. The results from the nonclinical study R20080340 indicated that recombinant RANKL inhibitors were associated with inhibition of bone growth, incisor growth and molar eruption in neonatal rats. Histopathology revealed altered morphology of the proximal tibial growth plate. In another nonclinical study (sponsor no. 102090), denosumab administered SC to cynomolgus monkey produced drug-related changes in the femur, left tibia and sternum consisting of an enlarged epiphyseal growth plate, decreased chondroclasis, decreased osteoclasts and decreased osteoblasts. This risk will be discussed at the upcoming Pediatric Oncology Drug Advisory Committee (ODAC) meeting in the end of November, 2010. After discussion with Pediatric Review Committee (PeRC), a Post Marketing Requirement (PMR) under PREA will be conveyed to the applicant to conduct clinical studies with denosumab in pediatric patients with relevant diseases.

2.5.2.5 *Race/Ethnicity*

The PK of denosumab were not substantially affected by race. The clearance values were higher in Black and Hispanics (21%, 95% CI: 12%, 30%; and 24%, 95% CI: 17% to 31%, respectively) compared to the clearance values for Asians and Whites. But these percent differences are within the reported variability at high concentrations estimated for patients enrolled into phase 2 and 3 trials.

2.5.2.6 *Renal Impairment*

A dedicated renal impairment trial (study no. 20040245) was conducted and reviewed as part of the original BLA submission. In brief, the PK of denosumab were not notably affected by varying degrees of renal function. The incidence of hypocalcemia appears affected by renal function. The incidence of hypocalcemia was 0%, 8%, 23%, 22%, and 25% in patients with normal renal function; mild, moderate, severe impairment; and end stage renal dysfunction requiring dialysis (ESRD). See section 2.3.2.2 of the review of the original BLA review. A PMR will be conveyed to the applicant to investigate the higher risk and management of hypocalcemia in subjects with varying degrees of renal function.

2.5.2.7 *Hepatic Impairment*

Hepatic impairment trial with denosumab has not been conducted, since denosumab is a monoclonal antibody and it is not eliminated by hepatic metabolism.

2.5.2.8 *What pregnancy and lactation use information is available?*

There are no adequate and well-controlled trials of denosumab conducted in pregnant women. In an embryofetal developmental study, cynomolgus monkeys received denosumab SC weekly during organogenesis at doses up to 6.5-fold higher than the recommended human dose of 120 mg Q4W, based on body weight (mg/kg). No evidence of maternal toxicity or fetal harm was observed during the first trimester. Potential adverse developmental effects resulting from

exposures during the second and third trimesters have not been assessed in animals.

It is not known whether denosumab is excreted into breast milk. Animal studies in pregnant mice lacking the RANK/RANKL signaling pathway indicate that maturation of the maternal mammary gland is altered and lead to impaired lactation postpartum.

2.5.3 Does genetic variation impact exposure and/or response?

The applicant did not examine genetic variation as a covariate of exposure and/or response as part of the original BLA or this supplemental submission.

2.5.4 Immunogenicity

2.5.4.1 *What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?*

The incidence of anti-denosumab antibodies was less than 1% in the four additional clinical trials submitted with this marketing application that enrolled patients with cancer (**Table 10**). In the immunogenicity summary provided by the applicant, the incidence of anti-denosumab antibodies was less than 1% in a total of 2,926 patients diagnosed with cancer. In the PK comparability trial (20060286), two of 116 subjects tested positive for anti-denosumab binding antibodies at weeks 0 and 18.

Table 10. Immunogenicity reported in clinical trials for patients with advanced cancer

Trial Number	Subject Number in Trial	Subjects with Binding Anti-Denosumab Antibodies	Subjects with Neutralizing Anti-Denosumab Antibodies
20040113	250	3 (weeks 33, 45 and 57)	0
20050103	821	2 (weeks 25,49)	0
20050136	1007	1 (week 49)	0
20050244	648	1 (week 25)	0
Total	2,726	7 (0.2%)	0

2.5.4.2 *Does the immunogenicity affect the PK and/or PD of the therapeutic protein?*

The applicant states that the serum denosumab concentrations and changes in uNTx/Cr for these seven subjects were within ranges observed for other subjects in the trials (**Table 11**).

Table 11. Effect of antidenosumab binding antibodies on denosumab serum and uNTx/Cr concentrations

Study	Subject	Time of Positive Ab Result (week)	Denosumab Serum Concentration (ng/mL)[a]	Denosumab Serum Concentration Range[b] (ng/mL)	uNTX/Cr Concentration (nmol/mmol)	uNTX/Cr Concentration Range (nmol/mmol)
20040113	113301017	57	267	BLQ - 3080	6.89	4.21 - 417
20040113	113302004	33	1480	4.12 - 26100	11.6	3.63 - 146
20040113	113403008	45	7040	1.76 - 7960	NA	NA
20040114	114650017	13	31000	12900 - 50900	47.1	4.94 - 54.4
20040114	114655037[c]	1,33	4900	1980 - 22300	177	4.13 - 177
20050134	134204001	1	7440	2870 - 25800	NA	NA
20050136	136447013[d,e]	49	NA	NA	6.46	2.20 - 289
20050244	244113008[d,e]	1	NA	NA	4.95	1.74 - 421
20050103	103321001[d,e]	49	NA	NA	5.20	2 - 365
20050103	103461001[d,e]	25	NA	NA	31.5	2 - 365

Adapted Summary of Clinical Pharmacology Studies, table 14, page 142

2.5.4.3 *Do the anti-product antibodies have neutralizing activity?*

Neutralizing antibodies have not been detected in any subject who tested positive for binding antibodies in these clinical trials.

2.5.4.4 *What is the impact of anti-product antibodies on clinical efficacy?*

The denosumab immunogenicity incidence is low and was not associated with any clinical consequences.

2.5.4.5 *What is the impact of anti-product antibodies on clinical safety?*

No evidence of altered safety profiles has been observed in the subjects who tested positive for binding antibodies.

2.6 EXTRINSIC FACTORS

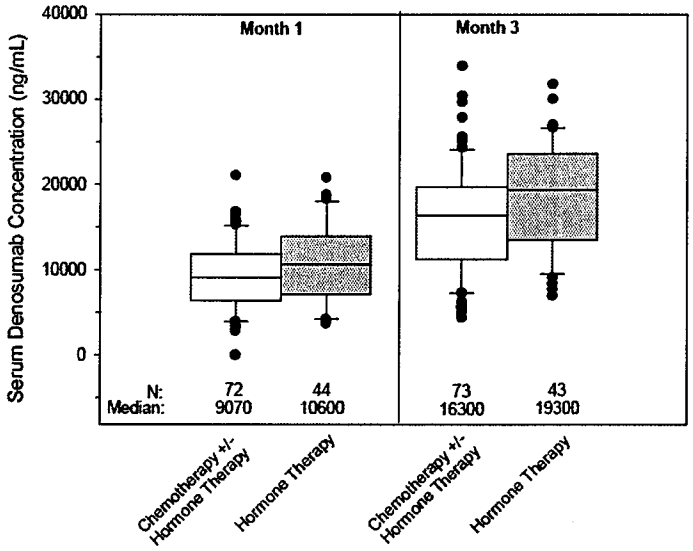
2.6.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

None of these extrinsic factors have been evaluated for their influence on denosumab ER in the original or in this current application.

2.6.2 What are the drug-drug interactions?

The applicant examined the effect of concomitant exposure to chemotherapy and or hormone therapy (20040113 and 20050136) and prior bisphosphonate therapy (20040113 and 20040114) on the denosumab PK (trough concentrations) and PD (uNTx/Cr). Women with metastatic breast cancer participating in study nos. 20040113 or 20050136 were stratified by whether they were receiving chemotherapy (with or without hormone therapy) or hormone therapy at study entry. **Figure 14** depicts the trough serum denosumab concentrations stratified based on concurrent therapy. The median reduction in the bone turnover marker, uNTx/Cr at 3 months was not affected by concurrent therapy (**Table 12**). Current anticancer therapy does not appear to clinically significantly influence the PK or PD of denosumab.

Figure 14. Trough serum denosumab concentrations of denosumab 120 mg SC Q4W to women with breast cancer receiving chemotherapy versus hormone therapy.



Adapted from Summary of Clinical Pharmacology Studies, page 107, figure 34

Table 12. Median reduction in uNTX/Cr at week 13 during administration of 120 mg denosumab Q4W to subjects with metastatic breast cancer receiving chemotherapy and/or hormone therapy

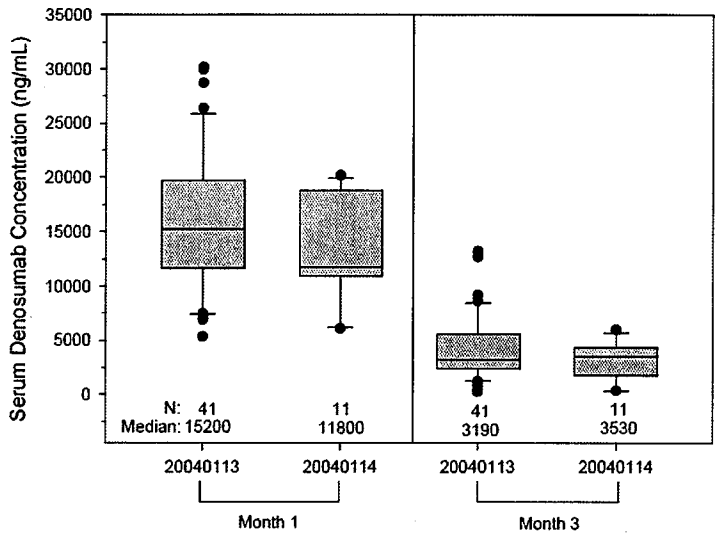
	Chemotherapy With or Without Hormone Therapy (N = 82)	Hormone Therapy (N = 50)
n	71	41
Median	-79.6	-85.3
Q1,Q3	-87, -66	-89, -55
Min, Max	-98, 134	-95, 133

N = total number of subjects
n = number of subjects at timepoint

Adapted from Summary of Clinical Pharmacology Studies, Table 9, page 108.

The denosumab PK and PD were compared between women with breast cancer metastatic to the bone in subjects who received bisphosphonate intravenous therapy (20040114) and in subjects who had not received bisphosphonate intravenous therapy (20040113). Only subjects with breast cancer in study 20040114 were included in the analysis, since only with patients with breast cancer were included in study 20040113. Only the dosing regimen of 180 mg Q12W was selected for the comparison, since the proposed clinical dose was not administered in study 20040114. Serum denosumab concentrations at 1 and 3 months post dose (**Figure 15**) and reductions in uNTx/Cr at 1 and 3 months (**Table 13**) after denosumab administration were not clinical significantly different in patients with and without previous treatment with intravenous bisphosphonate therapy.

Figure 15. Trough serum denosumab concentrations at 1 and 3 months during administration of denosumab 120 mg SC Q4W to women with (20040114) and without (20040113) previous intravenous bisphosphonate therapy



Adapted from Summary of Clinical Pharmacology Studies, Figure 33, page 105.

Table 13. Median reduction in uNTX/Cr at 1 and 3 months during administration of 180 mg denosumab Q12W to subjects with metastatic breast cancer to the bone not previously treated with bisphosphonate therapy (Study 20040113) vs. subjects who were previously treated with bisphosphonates (Study 20040114)

	Month 1		Month 3	
	20040113 (N = 43)	20040114 (N = 13)	20040113 (N = 43)	20040114 (N = 13)
n	41	12	40	12
Median	-63.2	-80.7	-70.8	-69.9
Q1,Q3	-86, -45	-89, -74	-80, -20	-79, -63
Min, Max	-94, 250	-97, -18	-96, -490	-93, -37

N = total number of subjects
n = number of subjects at timepoint

Adapted from Summary of Clinical Pharmacology Studies, Table 8, page 105.

2.7 GENERAL BIOPHARMACEUTICS

2.7.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable, because the proposed drug product is a monoclonal antibody.

2.7.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

See the original BLA review, section 2.5 for general biopharmaceutics. In summary, the drug product identified as CP1 was used in the initial human PK trials in healthy volunteers. The manufacturing process was subsequently optimized leading to drug product designated as CP2 and all subsequent clinical trials were conducted with this drug product. Comparability between CP1 and CP2 was demonstrated with nonclinical studies. CP2 was initially manufactured at Amgen Thousand Oaks (ATO) then at Amgen Colorado (ACO). A human PK and PD comparability trial submitted with the original BLA demonstrated the drug products manufactured at the two sites were comparable. Both ATO and ACO products were used in the phase 3 clinical trials supporting this marketing application.

2.7.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Not applicable for an intravenous drug product.

2.7.4 Were the PK and PD of the to-be-marketed formulation comparable to the clinical trial formulation?

The drug product Prolia™ was approved as a 60 mg/ml prefilled syringe or single use vial. With this submission, the applicant is introducing a 70 mg/ml single use vial to facilitate administration of the higher dose. The applicant conducted an open label, single dose, randomized, parallel group trial (study 20060446) to evaluate the PK and PD comparability of a single 120 mg SC dose administered as either two-60 mg/ml injections or one-120 mg/1.7 ml (70 mg/ml) injection. One hundred sixteen (116) healthy volunteers were randomized 1:1 to receive denosumab 120 mg SC as either two injections or one injection. PK samples were drawn pre-dose and then at the following times post dose: 1, 4, 8, 12, and 24 hours and 3, 4, 5, 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, 99, 113, and 127 days. The applicant stated that sampling duration would capture about 95% of the exposure. The applicant stated that assuming a true standard deviation of 0.36 (based on AUC data from healthy volunteers), a study with 90% power to detect the 90% CIs for the ratio of the geometric means to be between 0.8 and 1.25, assuming a true ratio of 1.0, required 58 subjects per group. The geometric mean ratios of the $AUC_{0\text{-}18weeks}$ and C_{max} demonstrate PK comparability (**Table 14**).

Denosumab in human serum was measured using a validated analytical procedure (Amgen method MET-001831). The method validation was described in the review of the original BLA, section 2.6 analytical methodologies. The nominal standard curve was defined as 10 ng/ml to 3000 ng/ml; the accuracy was 97% to 103% and the precision was 2% to 4% (sample analysis). The quality control levels were defined as 60, 400 and 2000 ng/ml; the accuracy was 99% to 102% and the precision is 2% (sample analysis). The concentration values reported are acceptable.

Table 14. Geometric mean ratio of the PK parameters following the administration of either 60 mg/mL or 70 mg/mL formulations

	2 x 1.0 mL x 60 mg/mL (A)		1 x 1.7 mL x 70 mg/mL (B)		Ratio of	Confidence Interval	
Parameter	N	LSM	N	LSM	A/B	Lower 90%	Upper 90%
$AUC_{0\text{-}18\ weeks}$ (day*ug/mL)	56	576.27	55	539.21	1.07	0.95	1.20
C_{max} (ug/mL)	58	11.16	56	11.09	1.01	0.91	1.11

Adapted Clinical Study Report 20060446, page 50, table 10-1.

Serum C-terminal telopeptide (sCTx) was measured pre-dose and at the following times post dose: 2, 3, 4, 5, 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, 99, 113, and 127 days. CTx is a marker of bone resorption similar to NTx. **Table 15** lists the ratio of the geometric mean area under the effective concentration curve and the maximum decrease from baseline. The data suggests that these two formulations are pharmacodynamically comparable.

A validated method was used to measure CTx in human serum (no. MET-000049, validation report 105941) and the analytical method is described in the original BLA, section 2.6. The method demonstrated dilutional linearity for 1:2 and 1:10 dilutions. The nominal standard levels ranged from 0.026 ng/mL to 2.79 ng/mL; the accuracy was 94% to 107% and the precision was 2% to 7% (sample analysis). The QC levels were 1.7 ng/mL, 0.5402 ng/mL and 0.145 mg/mL; the accuracy was 93% to 107% and the precision was 4% to 7% (sample analysis). The concentration values reported were acceptable.

Table 15. Geometric mean ratio of the PD parameters following the administration of either 60 mg/mL or 70 mg/mL formulations

	2 x 1.0 mL x 60 mg/mL (A)		1 x 1.7 mL x 70 mg/mL (B)		Ratio of	Confidence Interval	
Parameter	N	LSM	N	LSM	A/B	Lower 90%	Upper 90%
$AUEC_{0\text{-}18\ weeks}$ (day*(% Inhibition))	56	9822.55	55	10245.89	0.96	0.92	1.00
I_{max} (% Inhibition)	58	84.50	58	87.33	0.97	0.94	1.00

Adapted Clinical Study Report 20060446, page 51, table 10-2.

2.7.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product?

Not applicable for this submission.

2.8 ANALYTICAL SECTION

See original BLA review , section 2.6 analytical sections for a description of the assays used to measure denosumab serum concentrations, CTx in human serum and anti-denosumab binding and neutralizing antibodies in serum samples collected in the clinical trials.

An ELISA method was validated for quantitative measurement of uNTx corrected for urine creatinine (PK0502NTHuUrr3). This bone turnover marker was used to select the dose for the phase 3 trials after completion of the phase 2 dose finding trial (20040113). uNTx reduction was the primary endpoint in the phase 2 trial and the dose selected was based on sustained, maximal reduction of uNTx levels.

The NTx in human urine assay is a solid phase competitive inhibition ELISA in which the microtiter plate is coated with NTx. Any NTx present in a standard, quality control or unknown sample will compete with the bound NTx for binding sites of a monoclonal antibody specific for NTx and labeled with horseradish peroxidase. After washing, a substrate solution is added to the wells to react with the peroxide and create a colorimetric signal that is inversely proportional to the amount of NTx in the sample. The colorimetric reaction is stopped and the intensity of the color is measured as 450 nm with 650 nm as reference. The standard curve is used to convert the optical density to concentration units. The standards and quality controls were prepared by diluting Osteomark Calibrator with Osteomark Calibrator Diluent. The standard curve was defined as 62.5 nM/BCE to 2857 nM/BCE with the LLOQ of 62.5 nM/BCE. The following summary of the validation was recorded:

- Endogenous NTx was detected in 93% of normal human urines tested.
- Sixty percent (60%) of urines had NTx spike recovery of 80% to 120%.
- Cross reactivity with CTx was observed at 1.2 ng/mL.
- Dilutional linearity was demonstrated at 1:2 and 1:10.
- Stability up to 4 freeze-thaw cycles.
- Stable up to 1.5 years at -60°C to -80°C.
- Stable up to 1 hour at 34°C to 40°C and up to 5 hours at ambient room temperature.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. An underline indicates the content that was added to the proposed draft labeling by the agency and the ~~strikethrough~~ indicates content taken out by the agency from the proposed draft labeling.

(b) (4)

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

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	BLA125355
Submission Number (Date)	May 14, 2010
Compound	Denosumab
Clinical Division	DBOP
Primary PM Reviewer	Bahru A Habtemariam, Pharm.D.
Secondary PM Reviewer	Christine Garnett, Pharm.D.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there evidence of exposure-response for efficacy in the pivotal phase 3 trials?

Yes, there is evidence of exposure-response for effectiveness in the pivotal phase three efficacy studies showing that the clinical endpoint, skeletal related events (SREs), is influenced by drug exposure at the proposed dose 120 mg every 4 weeks.

Efficacy, safety, and trough concentration data were available from pivotal phase 3 trials as summarized in **Table 1** below. In all of the three studies, patients were randomized to receive either denosumab 120 mg every 4 weeks or zoledronic acid (ZA) 4 mg every 4 weeks. The studies were designed to show whether denosumab is noninferior to (ZA) with respect to skeletal related events (SRE) including fractures, radiation to bone, spinal cord compression and surgery to bone.
As shown below, the probability of SRE decreased with increasing denosumab trough concentrations (**Figure 1**). Similarly, Kaplan-Meier curves show time to first on-study SRE for patients in the third and forth quartile trough concentration (Q3 and A4) were longer than in patients with the bottom two concentrations quartiles (**Figure 2**). The concentration ranges in each quartiles were: Q1 < 12100 ng/mL, Q2: 12100-16900 ng/mL, Q3: 16900-23100 ng/mL, and Q4: > 23100 ng/mL

Table 1. Summary of Clinical Studies and Data Used for Exposure-Response Analyses

Study	N	Patient Population	Treatment Arm	Endpoint	PK subset
20050103	1901	Prostate Cancer	ZA vs. Denosumab	SRE	82
20050244	1776	Adv. Cancer (ex BRCA & Pros)	ZA vs. Denosumab	SRE	92
20050136	2046	Breast Cancer	ZA vs. Denosumab	SRE	73

Figure 1. Probability of SRE vs. Steady State Trough Concentrations.

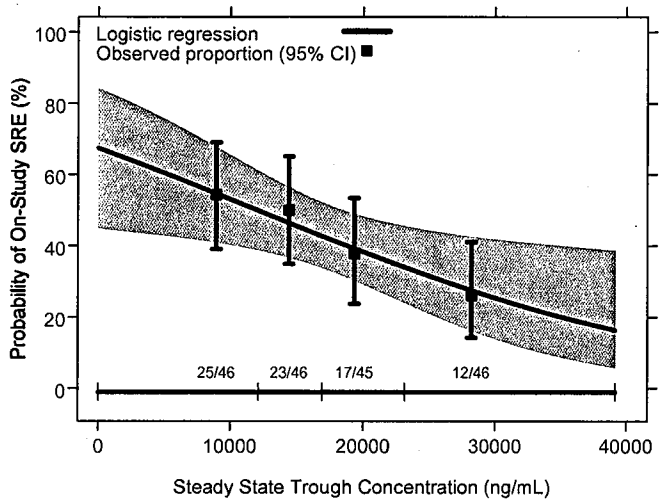
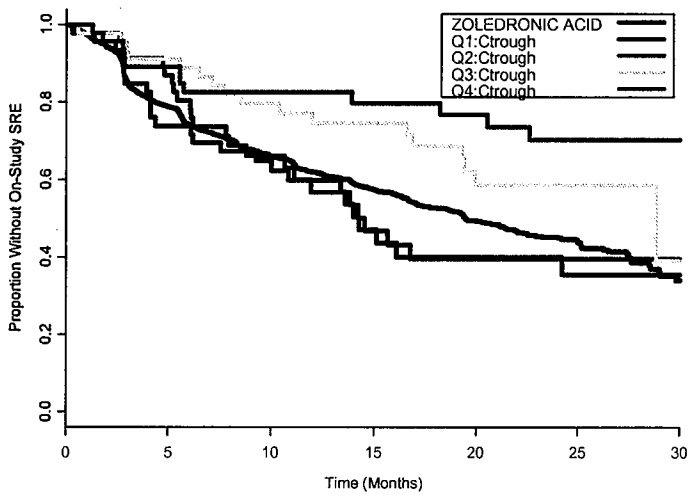


Figure 2. Proportion of Patients Without On-Study SRE Stratified by Denosumab Trough Concentration (Ctrough) Quartiles. The Dark Curve Represents All ZA Treated Patients.

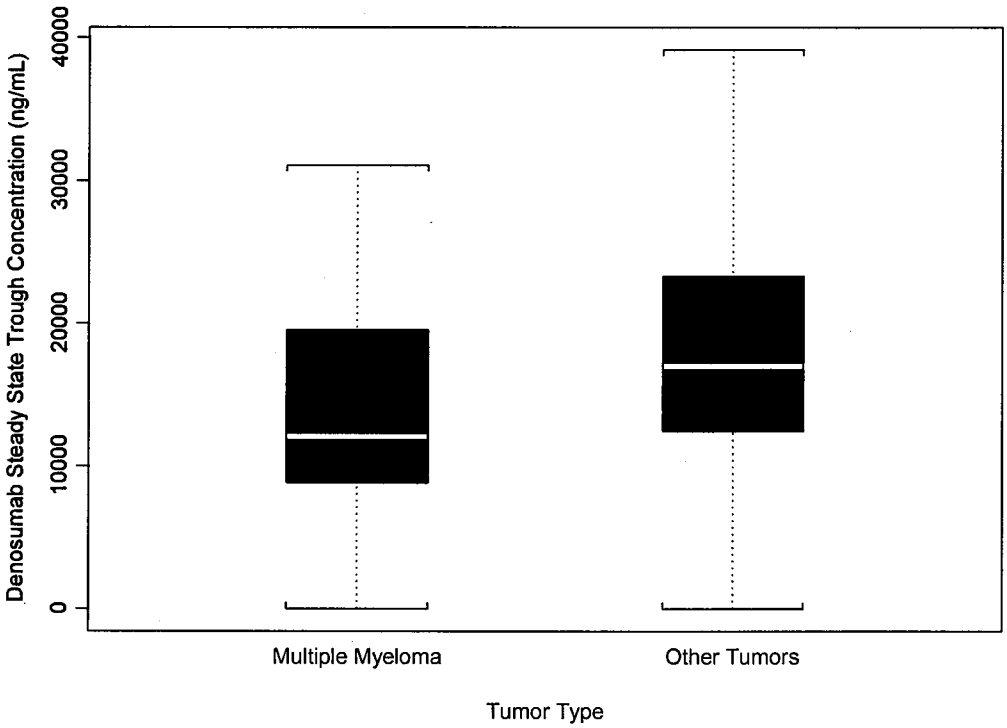


1.1.2 Are there patient covariates that account for denosumab concentration variability?

The sponsor's population pharmacokinetic analysis indicated that the clearance and volume parameters were correlated with body weight. Patients with small body weight were determined to have high exposure whereas those with high body weight were determined to have lower exposure. In addition, the sponsor's analysis showed patients with multiple myeloma had 71% faster clearance relative to healthy volunteers. Consistent with the sponsor's population PK analysis results, linear regression using body surface area (BSA) and steady state trough concentration showed that trough concentration decreases as BSA increases (p-value=0), as shown on **Figure 3** below. Similarly, **Figure 4** shows that multiple myeloma patients have lower steady state trough concentrations than patients with other tumor types. The median steady state trough concentration of multiple myeloma and other tumor type patients were 12073 and 17005 ng/mL, respectively, which shows that denosumab concentrations were lower by 40% in multiple myeloma patients. There were 8 multiple myeloma patients with trough concentrations.

Figure 3. Linear Regression Plot of Steady State Denosumab Trough Concentration Vs. Baseline BSA.

Figure 4. Denosumab Steady State Trough Concentrations by Tumor Type



1.1.3 Is there evidence of efficacy difference by body size and tumor type?

Denosumab

Patients in the highest BSA quartile (Q4: BSA >2 m^2) had increased risk on-study SRE compared to patients in the lower three BSA quartiles (**Figure 5**). The analysis was conducted by computing BSA quartile for all patients in phase 3 studies (n=5551). Patients with missing BSA data were excluded from analysis (n=172). The Kaplan-Meier estimates of median time to first SRE and number of SRE events during the study are shown in **Table 2**. Median time could not be computed for Q1-Q3 in the denosumab group because 50% of patients did not experience an event during the studies.

Table 2. Kaplan-Meier Estimate of Median Time (months) to First SRE by Treatment and BSA Quartile Groups

Group	Number of Patients	Number of SRE	Median Time to SRE (Months)	95% CI
ZA Treated Patients	2861	1081	19.4	18.6-21.4
Den Treated Patients	2862	934	27.7	24.2-NR
Q1: BSA <1.7	685	204	NR	22.6-NR
Q2: BSA 1.7–1.8	689	218	NR	22.4-NR
Q3: BSA 1.8–2.0	703	223	NR	22.4-NR
Q4: BSA >2.0	699	258	22.1	19 -27.7

Den= Denosumab, NR= Time to SRE not reached because insufficient number of patients had SRE events to calculate median time to event.

Figure 5. Kaplan-Meier Plot of Time to First On-Study SRE by BSA Quartile (Denosumab Arm)

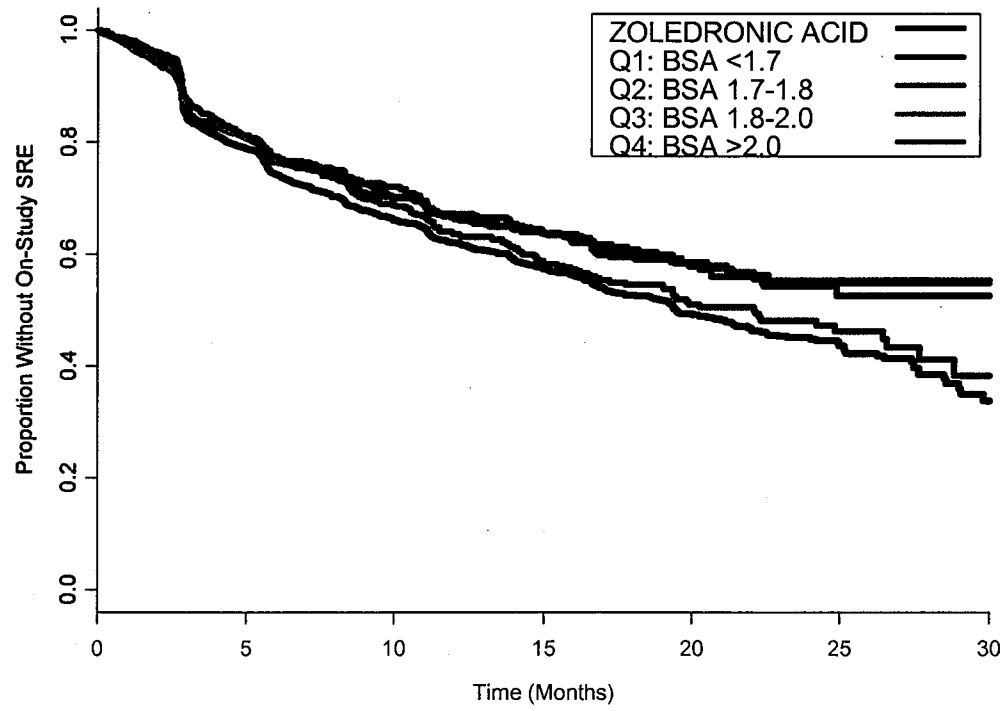
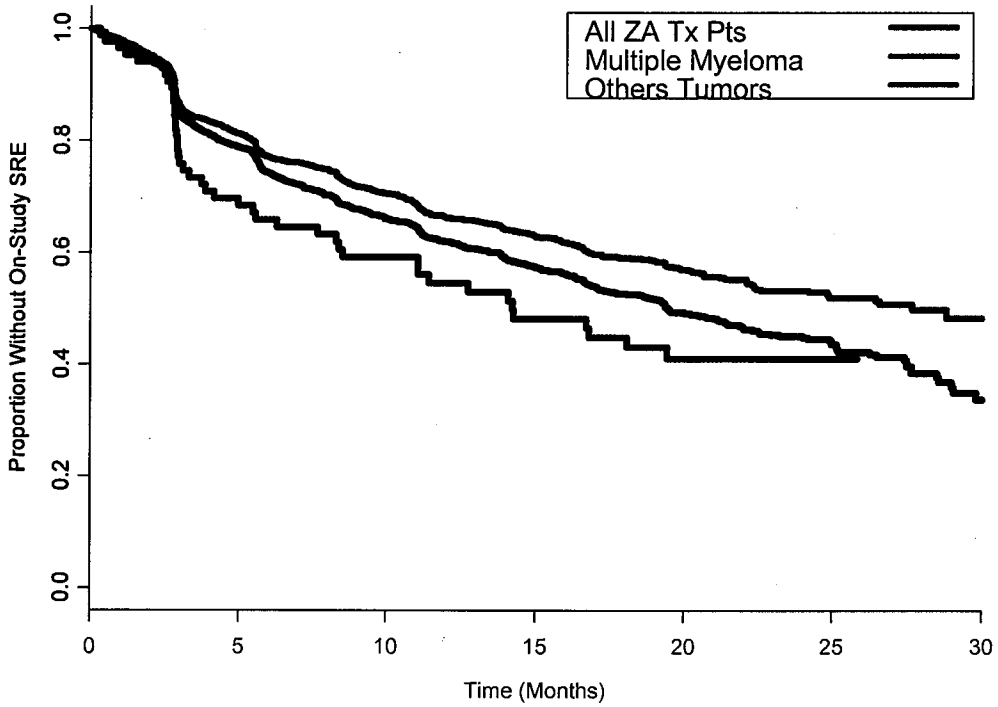


Figure 6. Kaplan-Meier Plot of Time to First On-Study SRE by Tumor Type (Denosumab Arm)



Zoledronic Acid

Patients the zoledronic acid arm that were in highest BSA quartile (Q4: BSA >2 m^2) had increased risk on-study SRE compared to patients in the lower three quartiles (**Figure 7, Table 3**). In addition, **Figure 8** the shows in both denosumab and zoledronic acid arms, patients in the top BSA quartile had 1.25-fold higher SRE events relative to patients in the lowest BSA quartiles. This finding indicates that high BSA could be an independent predictor of on-study SRE. Furthermore, **Figure 9** indicates that, in the zoledronic acid arm, multiple myeloma patients have shorter time to event, which indicates that multiple myeloma could be an independent predictor of on-study SRE.

Table 3. Kaplan-Meier Estimate of Median Time (Months) to First SRE (Zoledronic Acid Arm).

Group	Number of Patients	Number of SRE	Median Time to SRE (Months)	95% CI
ZA Treated Patients	2858	1081	19.4	18.6-21.4
Q1: BSA <1.7	699	244	25	20.8-27.4
Q2: BSA 1.7–1.8	690	255	20.4	16.8-28.5
Q3: BSA 1.8–2.0	696	245	21.2	19.1-29
Q4: BSA >2.0	690	306	15.4	12.3-17-7

Figure 7. Kaplan-Meier Plot of Time to First On-Study SRE by BSA Quartile (Zoledronic Acid Arm).

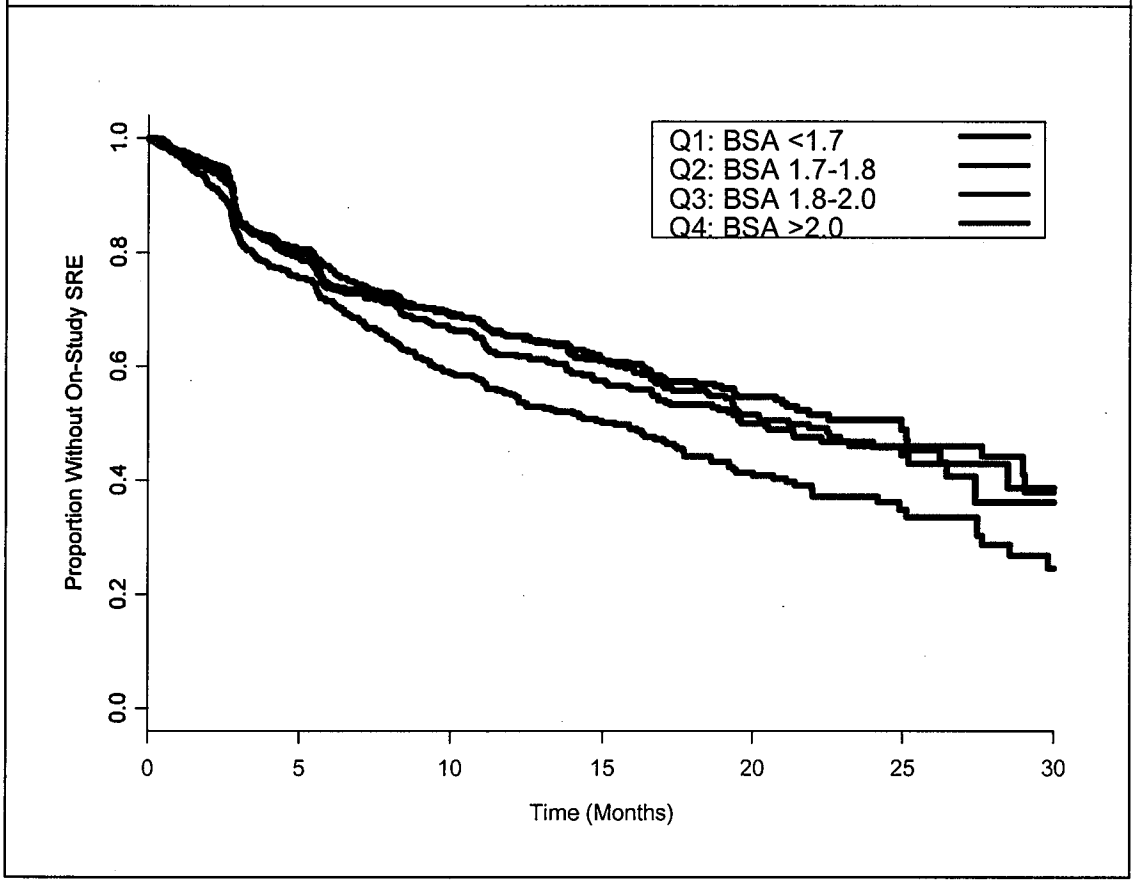


Figure 8. SRE Fold Increase by BSA Quartiles Relative to patients with BSA < 1.7 m^2 (lowest BSA quartile).

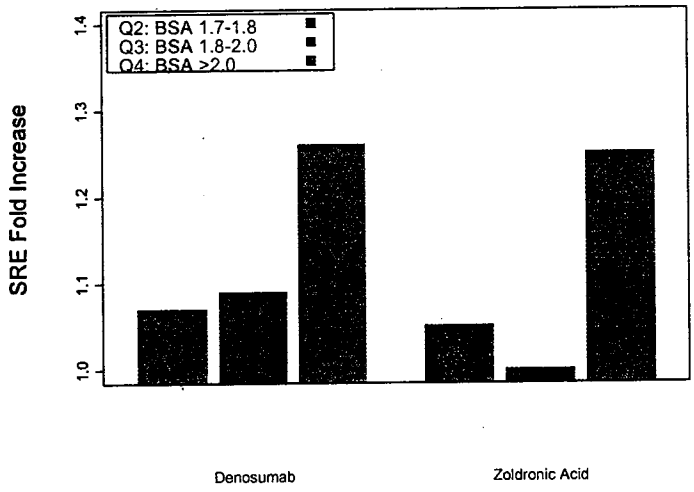
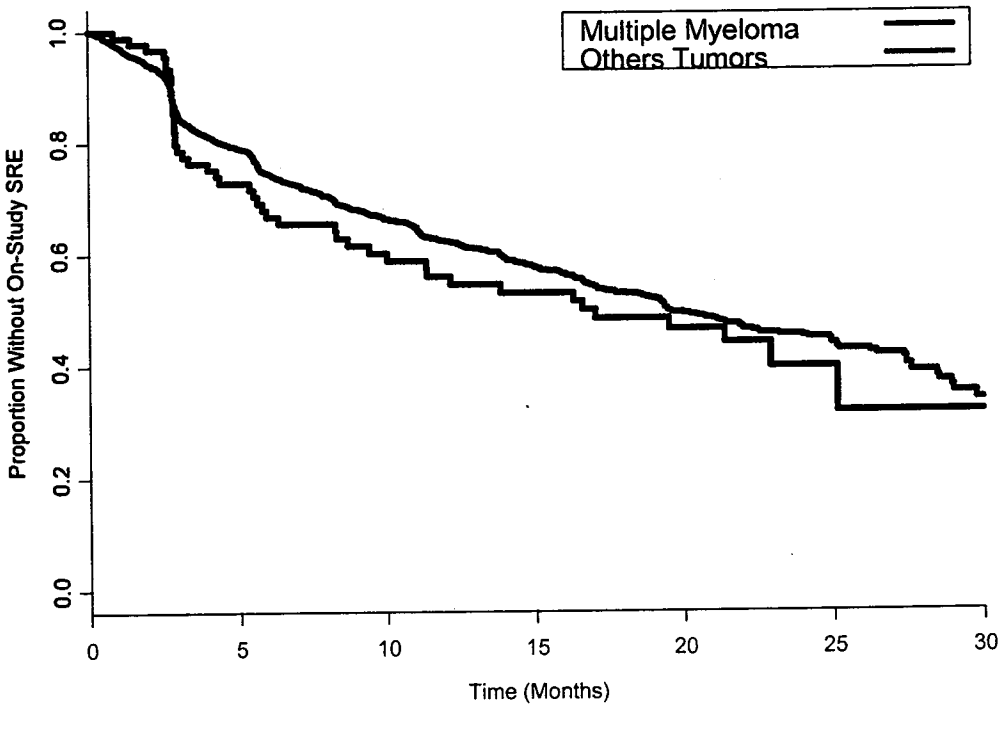


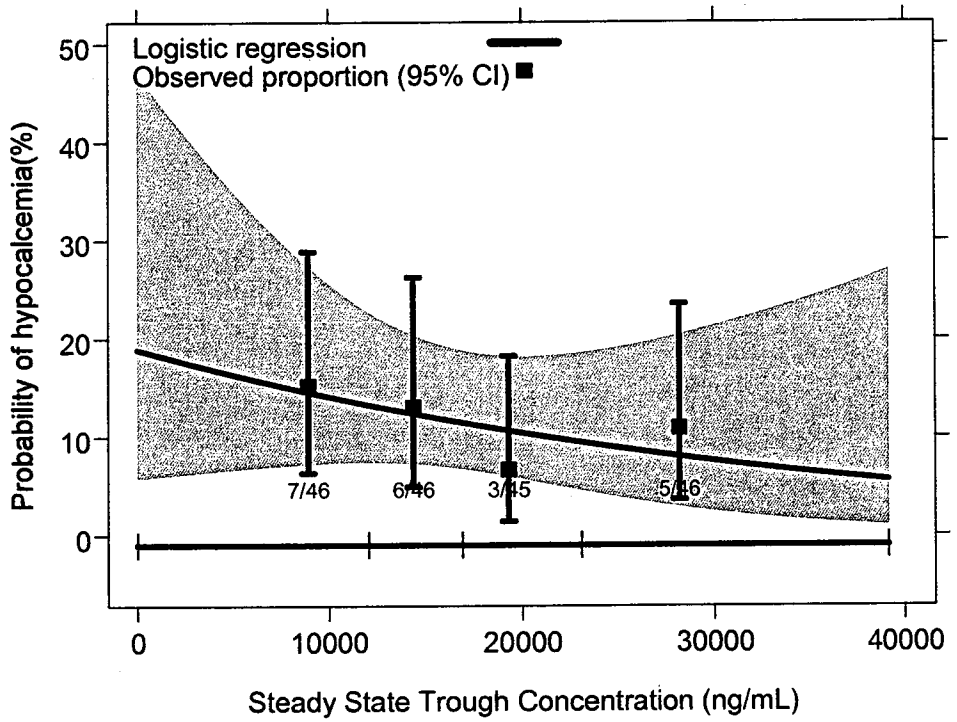
Figure 9. Kaplan-Meier Plot of Time to First On-Study SRE by Tumor Type (Zoledronic Acid Arm).



1.1.4 Is there exposure-response relationship for hypocalcemia?

No. Blood calcium levels measurements were available from the three pivotal phase 3 studies. Using blood calcium data from the pivotal studies, logistic regression was performed to assess the relationship between probability of all-grade hypocalcaemia and steady state trough denosumab concentrations. Analysis was performed for the subset of patients that had denosumab trough concentration data (n=183). **Figure 10** below shows that the probability of hypocalcemia does not appear to increase with increasing denosumab concentrations. Therefore, probability of hypocalcemia does not appear to be increasing with increasing denosumab concentrations.

Figure 10. Probability of Hypocalcemia vs. Steady State Trough Concentrations.



1.1.5 Is there relationship between creatinine clearance and hypocalcemia?

Baseline 24-hour creatinine clearance CrCL data (n= 5679) were available from denosumab and zoledronic acid treated patients that took part in pivotal phase 3 trials (**Table 4**). Logistic regression analysis was performed to characterize the relationship between the probability of hypocalcemia and baseline CrCL, using subset of patients with baseline CrCL values less than 120 mL/min (n= 4935). As shown below, the probability of hypocalcemia increases with decreasing baseline creatinine clearance (**Figure 11**) in

patients treated with denosumab. On the other hand, for patients in the zoledronic acid arm, the probability of hypocalcemia did not increase with decreasing CrCL (**Figure 12**).

Table 4. Summary of Available CrCL Data from the three Phase 3 Studies

Arm	Number of Patients with baseline CrCL data	Number of Patients with baseline CrCL < 120
Denosumab	2839	2481
Zoledronic Acid	2840	2454
Total	5679	4935

Figure 11. Probability of Hypocalcemia vs. Baseline CrCL (Denosumab Arm).

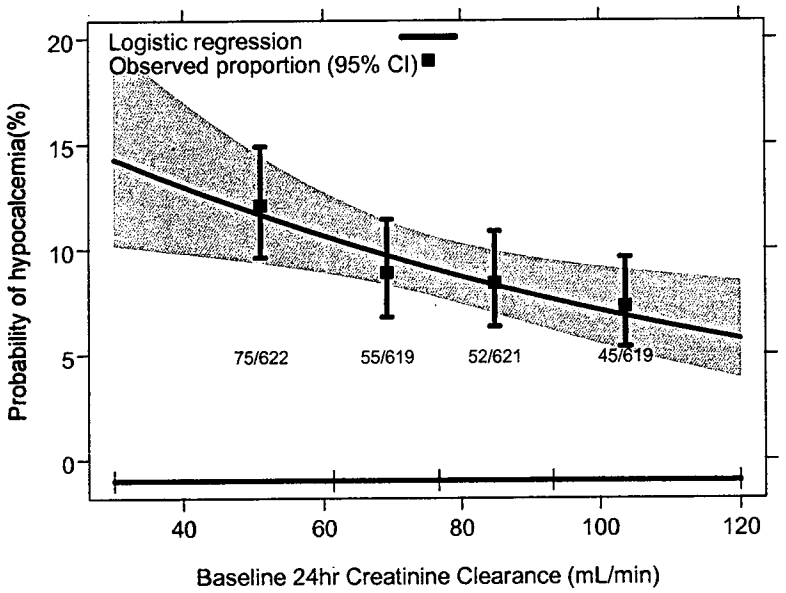
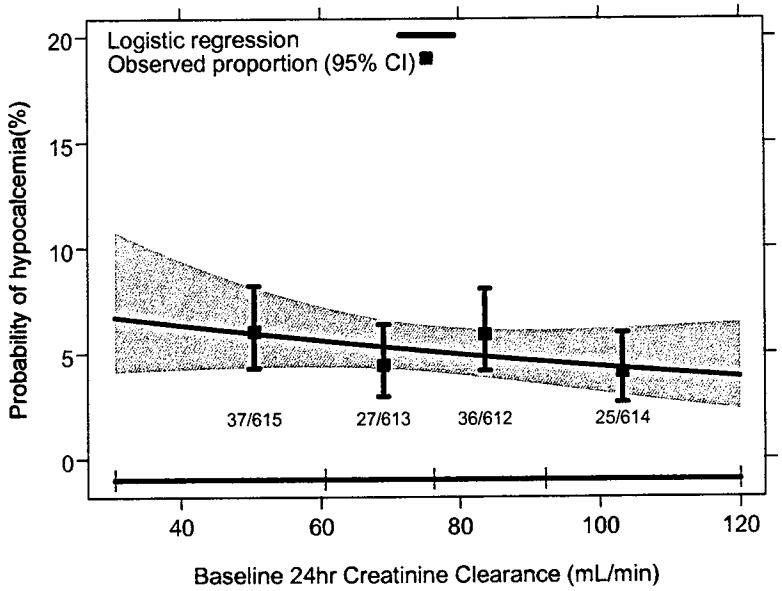


Figure 12. Probability of Hypocalcemia vs. Baseline CrCL (Zoledronic Acid Arm).



1.2 Recommendations

The exposure-response analysis indicates that patients with higher steady state denosumab concentrations have lower probability of SRE. Our analysis further indicates that patients with BSA > 2.0 and patients with multiple myeloma have lower denosumab steady state trough concentrations, which could lead to lower efficacy. However, there is no convincing exposure-response data to recommend a particular dose modification scheme for high BSA or multiple myeloma patients in the present submission. The sponsor should address this issue in future submissions by obtaining adequate trough concentration samples and performing exposure-response analyses.

1.3 Label Statements

2 RESULTS OF SPONSOR'S ANALYSIS

Population PK Analysis Findings

- A two-compartment target-mediated drug disposition model with linear distribution to the peripheral compartment, parallel linear and non-linear elimination, and first-order absorption following subcutaneous administration describes the pharmacokinetics of denosumab in healthy subjects, osteopenic and osteoporotic postmenopausal women and subjects with cancer.
- Denosumab exhibited time-independent kinetics and its systemic exposure is consistent following repeat subcutaneous administration of 120 mg every 4 weeks, with accumulation of 186%.
- Denosumab linear clearance, inter-compartmental clearance, and volumes of the central and peripheral compartments were proportional to body weight. The steady-state exposure following repeat subcutaneous administration of 120 mg every 4 weeks to 45 kg and 120 kg subjects were, respectively, 48% higher and 46% lower than exposure of the typical 66 kg subject.
- Overall, cancer patients tend to have higher clearance, in particular, subjects with multiple myeloma had 71% (95%CI: 68-74%) higher clearance that resulted in lower exposure compared to healthy subjects.
- Subjects with solid tumors (breast cancer, prostate cancer, giant cell tumors, and other solid tumors without multiple myeloma) had 15-39% (95%CI: 11-46%) higher clearance compared to healthy subjects.
- Pharmacokinetics of denosumab were similar between healthy subjects and osteopenic or osteoporotic postmenopausal women.

Population PK/PD Analysis Findings:

- An inhibitory sigmoid maximal inhibition model is suitable to characterize the relationship between the bone resorption marker, uNTx/Cr, and denosumab concentration
- The maximum uNTx/Cr suppression in subjects with advanced breast cancer or solid tumors other than prostate cancer was estimated to be 93% and the denosumab concentration providing half-maximal inhibition of the uNTx/Cr was estimated to be 41 ng/mL.
- Age, sex, weight and race had no notable impact on denosumab pharmacodynamic parameters.
- Relative to subjects with advanced breast cancer or solid tumors other than prostate cancer, multiple myeloma subjects had on average 53% lower uNTx/Cr at baseline, 24% lower IMax, 29% higher IC50 and 23 to 49% higher denosumab linear clearance.
- Simulation analyses reveal denosumab at a dose of 120 mg Q4W regimen results in: greater proportion of subjects with uNTx/Cr suppression >90% relative to Q12W dosing and the lowest Q4W dose with the maximal proportion of subjects with uNTx/Cr suppression >90%; and

Reviewer's comments:
Sponsor's population PK analysis is adequate and results are consistent with results of reviewer's analysis using trough concentration data from phase 3 studies. However, the biomarker used in the population PK/PD analysis, uNTx/Cr, does not seem useful in predicting clinical outcome, skeletal related events, in the phase 3 trials.

3 REVIEWER'S ANALYSIS

3.1 Introduction

The sponsor performed population PK analysis of denosumab to identify sources of denosumab PK variability. However, the sponsor did not perform any exposure-response analysis beyond pharmacodynamic analysis using PK and biomarker data. The reviewers performed additional analyses to further elucidate the exposure-response properties of denosumab.

3.2 Objectives

Exposure-response and dose-response analyses were performed to address the following:

1) To understand the exposure-response properties of denosumab
2) To identify patient characteristics that are source of exposure and response variabilities
3) To characterize the exposure-safety relationship in regards to hypocalcaemia

3.3 Methods

3.3.1 Data Sets

Data sets used are summarized in **Table 1** below.

Table 1: Analysis Data Sets.

Study Number	Name (desctiption)	Link to EDR
20050103	apc.xpt (PK)	\\cbsap58\M\eCTD_Submissions\STN125355\0000\m5\datasets\20050103\analysis\datasets
20050136	apc.xpt (PK)	\\cbsap58\M\eCTD_Submissions\STN125355\0000\m5\datasets\20050136\analysis\datasets
20050244	apc.xpt (PK)	\\cbsap58\M\eCTD_Submissions\STN125355\0000\m5\datasets\20050244\analysis\datasets
20050103, 20050136, and 20050244	aslbase.xpt (Demo)	\\cbsap58\M\eCTD_Submissions\STN125355\0000\m5\datasets\ise\analysis\datasets
20050103, 20050136, and 20050244	asleff.xpt (efficacy)	\\cbsap58\M\eCTD_Submissions\STN125355\0000\m5\datasets\ise\analysis\datasets
20050103, 20050136, and 20050244	aslsaf.xpt (safety)	\\cbsap58\M\eCTD_Submissions\STN125355\0000\m5\datasets\iss\analysis\datasets

3.3.2 Software

S-PLUS was used for the reviewer's analyses.

3.4 Results

See section 1.1

4 APPENDIX A: SYNOPSIS OF SPONSOR'S POPULATION PK ANALYSIS

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 PRODUCT LABELING

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

4.3 STUDY REPORTS

22 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

4.4 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125355/7	Brand Name	Under review
OCP Division (I, II, III, IV, V)	V	Generic Name	Denosumab
Medical Division	DBOP	Drug Class	Oncology
OCP Reviewer	Jun Yang, Ph.D.	Indication(s)	(b) (4) [redacted]
OCP Team Leader	Hong Zhao, Ph.D.	Dosage Form	Single-use vial 120mg (70mg/mL)
Pharmacometrics Reviewer		Dosing Regimen	120mg q4W
Date of Submission	5/19/2010	Route of Administration	Subcutaneously
Estimated Due Date of OCP Review	11/4/2010	Sponsor	Amgen
Medical Division Due Date		Priority Classification	Priority
PDUFA Due Date	11/18/2010		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		Previously reviewed
multiple dose:	x	1		Previously reviewed
Patients-				
single dose:	x	2		Previously reviewed
multiple dose:	x	6	5	One was previously reviewed
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	x	1	1	Previously reviewed
hepatic impairment:				
PD -				
Phase 2:	x	2	2	
Phase 3:	x	3	3	
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	2	2	
Phase 3 clinical trial:	x	3	3	
Population Analyses -				
Data rich:				
Data sparse:	x	2	2	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		25	18	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	x			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		x		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		x		
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___YES_____

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

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

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

24 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125355/7	Brand Name	Under review
OCP Division (I, II, III, IV, V)	V	Generic Name	Denosumab
Medical Division	DBOP	Drug Class	Oncology
OCP Reviewer	Jun Yang, Ph.D.	Indication(s)	(b) (4)
OCP Team Leader	Hong Zhao, Ph.D.	Dosage Form	Single-use vial 120mg (70mg/mL)
Pharmacometrics Reviewer		Dosing Regimen	120mg q4W
Date of Submission	5/19/2010	Route of Administration	Subcutaneously
Estimated Due Date of OCP Review	11/4/2010	Sponsor	Amgen
Medical Division Due Date		Priority Classification	Priority
PDUFA Due Date	11/18/2010		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		Previously reviewed
multiple dose:	x	1		Previously reviewed
Patients-				
single dose:	x	2		Previously reviewed
multiple dose:	x	6	5	One was previously reviewed
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	x			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		x		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		x		
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__YES_____

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

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

Reviewing Clinical Pharmacologist — Date: 7/12/2010

Team Leader/Supervisor — Date: 7/13/2010

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 18, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Labeling Memo: Denosumab: BL STN 125320/7

FDA's proposed labeling revisions sent to Amgen on November 18, 2010.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 17, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Financial disclosure Memo: Denosumab: BL STN 125320/7

Financial disclosure information can be found on page 25 of the clinical review.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

Memorandum

Label Review

Application Number:	STN 125320/7
Name of Drug:	XGEVA™ (denosumab)
Sponsor:	Amgen, Inc.
Material Reviewed:	XGEVA ™ (denosumab) Labeling
Submission Dates:	August 23, 2010, November 11, 2010

EXECUTIVE SUMMARY

The carton and container labels for XGEVA™ (denosumab) were reviewed and found to comply with the following regulations : 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100, USPC Official 10/1/10-2/1/11, USP 33/NF 28. Labeling deficiencies were identified, addressed and mitigated. Please see comments in the conclusions section.

Background:

STN 125320/7 is a supplement to the Biologic License Application (BLA) for denosumab for the [redacted] (b) (4) The product is a monoclonal antibody supplied as a sterile, preservative-free, clear, and colorless to slightly yellow solution in 120 mg/1.7 mL glass vials.

Labels Reviewed:

XGEVA™ (denosumab) Carton label
XGEVA™ (denosumab) Container label
XGEVA™ (denosumab) Prescribing Information

Review

Proposed Vial label submitted August 23, 2010

I. Container

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
   a. The proper name of the product – denosumab – is displayed along with the proprietary name (XGEVA). This conforms to the regulation.

   b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. The manufacturer is listed as Amgen LTD, License no 1080. This conforms to the regulation.

   c. The lot number or other lot identification – The lot number is located on the container label. This conforms to the regulation.

   d. The expiration date – The expiration date is displayed on the container label. This conforms to the regulation.

   e. The recommended individual dose, for multiple dose containers – This product is supplied in a single use vial and prefilled syringe. A statement appears on the label to this effect. This conforms to the regulation.

f. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is located on the label. This conforms to the regulation.

g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – The container label is too small to display the Medication guide statement. The label is too small to add the statement; therefore the statement is located on the carton. This conforms to the regulation.

2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This section does not apply.

3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – This conforms to the regulation.

4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a label.

5. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. This conforms to the regulation.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

C. 21 CFR 201.5 Drugs; adequate directions for use – This is not needed for the vial label as the minimum requirements are listed in 21 CFR 610.60.

D. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proprietary and proper name. This conforms to the regulation.

E. 21 CFR 201.10 Drugs; statement of ingredients – Per 601.2(c)(1), this product is exempt from 610.62 and is regulated by 201.10. The established name, denosumab, is in parenthesis and has the prominence commensurate of the proprietary name, XGEVA. This conforms to the regulation.

F. 21 CFR 201.15 Drugs; prominence of required label statements – All required statements ("Rx Only" and storage conditions) are prominent and do not overlap. This conforms to the regulation.

G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is listed on the label. This conforms to 21 CFR 610.60.

H. 21 CFR 201.25 Bar code label requirements – Bar code appears on the label. This conforms to the regulation.

I. 21 CFR 201.50 Statement of identity – The established name (denosumab) is stated on the label. The established name and proprietary name (XGEVA) conform to 21 CFR 201.10. This conforms to the regulation.

J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents is declared on the label. The containers are marked "Single-Use". This conforms to the regulation.

K. 21 CFR 201.55 Statement of dosage – The statement "120 mg/1.7 mL" followed by "(70 mg/ mL)/mL" and "Single Use Vial" are displayed on the label. This conforms to the regulation.

L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only" and other pertinent information. This conforms to the regulation.

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

A. 21 CFR 610.61 Carton/Package Label –

a. The proper name of the product – The proper name (denosumab) and the proprietary name (XGEVA) are displayed on the front and back panels of the carton. This conforms to the regulation.

b. The name, addresses, and license number of the manufacturer. The manufacturer is listed as "Amgen LTD, Thousand Oaks, CA 91320-1799" on the primary panel and "US License no 1080" is listed on the side panel. This conforms to the regulation.

c. The lot number or other lot identification – The lot number is on the top panel of the carton. This conforms to the regulation.

d. The expiration date – The expiration date is listed below the lot number on the top panel of the carton. This conforms to the regulation.

e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative" –The statement "No Preservative" is displayed on the carton. This conforms to the regulation.

f. The number of containers, if more than one – There is only one package container per drug. Each package contains one vial of drug and is marked "Single-use Vial". This conforms to the regulation.

g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as a concentration of 120 mg/ 1.7 mL followed by (70 mg/mL) per container.

h. The recommended storage temperature – The statement "Store at 2°-8°C (36° to 46°F) is displayed on the front panel of the carton. This conforms to the regulation.

i. The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product – The statements "Protect from direct sunlight", "Do not freeze", and "Avoid excessive shaking." This conforms to the regulation.

j. The recommended individual dose if the enclosed container(s) is a multiple-dose container – Only one single-use vial per package, therefore, this does not apply.

k. The route of administration recommended, or reference to such directions in an enclosed circular – The statement "For Subcutaneous Use Only" is located on the front panel of the carton.

l. Known sensitizing substances, or reference to enclosed circular containing appropriate information –none listed.

m. The type and calculated amount of antibiotics added during manufacture – none listed. This conforms to the regulation.

n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information. USPC Official 10/1/10-2/1/11, USP 33/NF 28, <1091> Labeling of Inactive Ingredients, the list of all inactive ingredients must be in alphabetical order. - Inactive ingredients are listed on the carton in alphabetical order. This conforms to the regulation.

o. The adjuvant, if present –None present. This conforms to the regulation.

p. The source of the product when a factor in safe administration. None listed. This conforms to the regulation.

q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – None used. This conforms to the regulation.

r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No

U.S. standard of potency" – "No U.S. Standard of Potency" is displayed on the carton. This conforms to the regulation.

s. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is located on the carton. This conforms to the regulation.

B. 21 CFR 610.62 Proper name; package label; legible type *[Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]* – This is an exempted product (monoclonal antibody products for in vivo use). Therefore the label does not need to conform to this regulation.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown – Amgen Manufacturing Ltd. is the only manufacturer listed on the label. This regulation does not apply.

D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. – No distributor is listed. This regulation does not apply.

E. 21 CFR 610.65 Products for export – [redacted] (b) (4) . This conforms to the regulation.

F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – Bar code appears on the carton label. This conforms to the regulation.

G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the front panel of the carton. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

H. 21 CFR 201.5 Drugs; adequate directions for use – The label states "See Package Insert for Full Prescribing Information." This conforms to the regulation.

I. 21 CFR 201.6 Drugs; misleading statements – The names shown on the carton label are (XGEVA) and (denosumab). Therefore, this cannot be confused with any other drug, device, food, or cosmetic. This conforms to the regulation.

J. 21 CFR 201.10 Drugs; statement of ingredients – Per 601.2(c)(1), this product is exempt from 610.62 and is regulated by 201.10. The established name, denosumab, is in parenthesis and has the prominence commensurate of the proprietary name, XGEVA. This conforms to the regulation.

K. 21 CFR 201.15 Drugs; prominence of required label statements – All required statement ("Rx Only", "Do not freeze", "Avoid excessive shaking") are prominent and do not overlap. This conforms to the regulation.

L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot identification number on the carton label. This conforms to 21 CFR 610.60 and 21 CFR 201.17.

M. 21 CFR 201.25 Bar code label requirements – Bar code appears on the carton label. This conforms to the regulation.

N. 21 CFR 201.50 Statement of identity – The established name (denosumab) is stated on the label. The established name (denosumab) and proprietary name (trade name) conform to 21 CFR 201.10. This conforms to the regulation.

O. 21 CFR 201.51 Declaration of net quantity of contents – Net quantity of contents is declared on the carton label. This conforms to the regulation.

P. 21 CFR 201.55 Statement of dosage – The statement "120 mg/mL" followed by "(70 mg/ mL)" and "Single Use Vial" are displayed on the label. This conforms to the regulation.

Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only" and other pertinent information. This conforms to the regulation.

III. Conclusions and Recommendation

The following deficiencies were noted in the initial review of the denosumab container and carton labels:

A. Carton

1. Per 21 CFR 201.51(g), the declaration of net quantity of contents shall express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by NF or the USP for filing ampules. (b) (4) Change made and acceptable.

Kimberly Rains, Pharm.D.
Regulatory Project Manager
CDER/OPS/OBP

Concurrence:

Sarah Kennett, Ph.D.
Product Reviewer
CDER/OPS/OBP/DMA

Patrick Swann, Ph.D.
Deputy Director
CDER/OPS/OBP/DMA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 10, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Labeling Memo: Denosumab: BL STN 125320/7

General Comments:

1. Present the numerical strength as 120 mg/1.7 mL within the orange circle.

2. Add the statement "Discard Unused Portion" following the statement "Single Use Vial".

Carton Labeling:

3. Per 21 CFR 201.51(g), the declaration of net quantity of contents shall express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by NF or the USP for filing ampules. Please remove the statement, '[redacted]' (b) (4) from all labeling.

4. Currently, most of the information on the principal display panel is bolded. Only use bolding to highlight the most important information (e.g. strength and route of administration).

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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 8, 2010

TO: Melanie Pierce, Regulatory Project Manager
Shan Pradhan, Medical Officer
Division of Biologic Oncology Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

BLA: 125320/7

APPLICANT: Amgen Inc.

DRUG: Denosumab (XGEVA)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: (b) (4)

CONSULTATION REQUEST DATE: 7/8/2010

DIVISION ACTION GOAL DATE: 11/18/2010

PDUFA DATE: 11/18/2010

I. BACKGROUND:

Amgen seeks licensure to market denosumab, a fully human IgG2 monoclonal antibody that binds to and inhibits the action of receptor activator of nuclear factor kappa B (RANK) ligand,

for the [redacted] (b) (4) The RANK ligand is essential for the formation, activation and survival of osteoclasts, the sole cell type responsible for bone resorption. Therefore, denosumab binding to RANK ligand prevents RANK activation and inhibits the formation, activation, and survival of osteoclasts. As a consequence, bone resorption and cancer-induced bone destruction is reduced, according to the applicant. As a result of its unique and specific mechanism of action, denosumab is being investigated for use in patients with advanced malignancies involving bone to delay or prevent the occurrence of skeletal related events (SREs; for example, pathological fracture, spinal cord compression, radiation to bone, or surgery to bone). Denosumab is currently licensed under the trade name Prolia™ for the treatment of postmenopausal women with osteoporosis at high risk for fracture.

The application is supported primarily by data from 3 pivotal studies sponsored by Amgen and designed to demonstrate non-inferiority versus zoledronic acid for the composite primary efficacy endpoint of a skeletal related event (SRE), defined as one of the following; pathologic fracture (vertebral or nonvertebral), radiation therapy to bone (including use of radioisotopes), surgery to bone, or spinal cord compression. The following pivotal studies were targeted for inspection.

- Study 20050103 entitled, "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer", planned for 1870 subjects enrolled and actually enrolled 1904 subjects. The study was conducted in 342 centers in 39 countries. This study was conducted under IND 9838.

- Study 20050136 entitled, "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects with Advanced Breast Cancer", planned for 1960 subjects enrolled and the study actually enrolled 2049. The study was conducted in 322 centers in 35 countries. This study was conducted under IND 9838.

- Study 20050244 entitled, "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma", planned for 1690 subjects enrolled and the study actually enrolled 1779. The study was conducted in 321 centers in 33 countries. This study was conducted under IND 9838.

Six clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811); that of Dr. Ronaldo Damiao (site number 686 of Study 20050103), Dr. Karim Fizazi (site number 503 of Study 20050103), Dr. Alexey Manikhas (site number 346 of Study 20050136), Dr. Jose R. Pereira (site number 672 of Study 20050244), Dr. Maciej Krzakowski (site number 386 of Study 20050244), and Dr. Veena Charu (site number 115 of Study 20050103; site number 107 of Study 20050244). Sites above were chosen based upon analysis of site-specific efficacy data, number and types of protocol deviations, patient enrollment per site, and investigator financial conflict of interest disclosures. Specifically, the foreign CI sites were

selected because they represent high enrollment across the 3 pivotal studies. In addition, Site #686 (Dr. Damiao) and Site #503 (Dr. Fizazi) each had a high number of on-study protocol deviations for Study 103, and Site #503 (Dr. Fizazi) reported site-specific efficacy results that were significantly different than the efficacy results reported by other sites. Site #672 (Dr. Pereira) and Site #386 (Dr. Krzakowski) each had a high number of on-study protocol deviations for Study 244. Site #346 (Dr. Manikhas) reported site-specific efficacy results that were significantly different than the efficacy results reported by other sites for Study 136. (b) (6) (b) (6) (b) (6)

One CRO, (b) (4) was inspected in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810). This CRO was responsible for central review of primary efficacy endpoint components for all three pivotal trials (studies 20050103, 20050136, and 20050244 share a common composite primary efficacy endpoint of 'time to first on-study skeletal-related event'). This high priority CDER Sponsor/Monitor/CRO Domestic Inspection was also linked to and conducted in conjunction with a FY 2010 – High Priority CDER For-Cause CRO Inspection. The for-cause assignment was issued in follow-up to information received from the FDA Office of Criminal Investigations concerning allegations of noncompliance related to validation and auditing practices, potentially impacting data integrity. In addition to the 3 protocols above, the for-cause inspection audited a forth protocol, 20050181, entitled, "A Randomized, Multicenter Phase 3 Study to Compare the Efficacy of Panitumumab in Combination with Chemotherapy to the Efficacy of Chemotherapy Alone in Patients with Previously Treated Metastatic Colorectal Cancer," which was conducted under IND 8382.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor & Location	Protocol # and # of Subjects	Inspection Date	Final Classification
CI 1: Site #686 (Brazil) Dr. Ronaldo Damiao Hospital Universitario Pedro Ernesto Avenida 28 de Septembro 77 50 andar-Urologia Rio de Janeiro, 20551-030 Brazil	Protocol: 20050103 Site Number: 686 Number of Subjects: 42	9/27/2010 - 9/30/2010	Pending Interim classification: NAI
CI 2: Site #503 (France) Dr. Karim Fizazi Institut Gustave Roussy 39 Rue Camille Desmoulins Villejuif, 94805 France	Protocol: 20050103 Site Number: 503 Number of Subjects: 42	10/11/2010 10/15/2010	Pending Interim classification: VAI
CI 3: Site #346 (Russia) Dr. Alexey Manikhas City Oncology Dispensary 2-ya Berezovaya alleya 3/5, Saint Petersburg 197022 Russia	Protocol: 20050136 Site Number: 346 Number of Subjects: 25	9/27/2010 - 10/1/2010	Pending Interim classification: NAI

Name of CI, IRB, or Sponsor & Location	Protocol # and # of Subjects	Inspection Date	Final Classification
CI 4: Site #672 (Brazil) Dr. Jose R. Pereira Instituto do Cancer Arnaldo Vieira de Carvalho Rua Martinico Prado 2610 Andar conjuntos 101, 102, 103, & 122, Sao Paulo Sao Paulo 01224 Brazil	Protocol: 20050244 Site Number: 672 Number of Subjects: 40	9/20/2010 - 9/24/2010	Pending Interim Classification: NAI
CI 5: Site #386 (Poland) Dr. Maciej Krzakowski Instytut im. M. Sklodowskiej-Cuire-Centurm Onkologii Ulica Roentgena 5 Warszawa 02-781 Poland	Protocol: 20050244 Site Number: 386 Number of Subjects: 27	10/4/2010 – 10/8/2010	Pending Interim classification: VAI
CI 6: Site #115 (Study 20050103) **Site #107 (Study 20050244)** Dr. Veena Charu Pacific Cancer Center 1801 West Romneya Drive Suite 203 Anaheim, CA 92801	Protocol: 20050103 Site Number: 115 Number of Subjects: 6 Protocol: 20050244 Site Number: 107 Number of Subjects: 15	8/19/2010 – 8/26/2010	Pending Interim Classification: NAI
			(b) (4)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 and/or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **CI#1: Dr. Ronaldo Damiao**
   (Site Number 686)
   Hospital Universitario Pedro Ernesto
   Avenida 28 de Septembro 77
   50 andar-Urologia
   Rio de Janeiro, 20551-030
   Brazil

a. **What was inspected:** The site screened 51 subjects, 42 of those were randomized and treated and 14 subjects completed the study. The study records of 24 subjects, including all those with reported SRE's and important protocol deviations, were audited in accordance with the clinical investigator compliance program, CP 7348.811. All subjects reviewed had reported adverse events (AEs) and 17 of 24 subjects also reported serious adverse events (SAEs). The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting AEs. The study was found to be well controlled and well documented.

This study was monitored by (b) (4) and was conducted in accordance with the study protocol. Drug accountability appeared adequate. Protocol deviations were reported to the sponsor and the IRB. Source documents were available to compare with the CRF's for the subjects audited including: laboratory results from the local lab and the central lab, x-rays and reports, CT reports, radiation to bone reports, progress notes in the source documents when the subject was seen for the study visit that included the investigational product infusion information, and SAE reports. Monitor follow-up reports were available for review (reports were in English) that noted protocol deviations and action taken concerning the deviations.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125320/7. No Form FDA 483 was issued.

c. **Assessment of data integrity:** The data for Dr. Damiao's site, associated with Study 20050103 submitted to the Agency in support of BLA 125320/7, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

2. **CI#2: Dr. Karim Fizazi**
(Site Number 503)
Institut Gustave Roussy
39 Rue Camille Desmoulins
Villejuif, 94805
France

a. **What was inspected**: The site screened 48 subjects, 42 of those were randomized and treated and 5 subjects completed the study. The study records were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed 100% of informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. There was no evidence of under-reporting AEs. The study was found to be well controlled and well documented. However, the site failed to consistently re-consent subjects with updated ICDs, there were a number of subjects with missed protocol-specified periodic assessments, 5 of which included x-rays of subjects who subsequently achieved an SRE endpoint, and intravenous infusion start and stop times were not always documented.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125320/7. A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

a. Fourteen of the 48 subjects (006, 011, 012, 014, 015, 016, 020, 027, 028, 032, 035, 044, 045, and 047) did not sign all relevant informed consent forms that were approved by the ethics committee.
b. Five of the 18 subjects, with reported on study skeletal-related events, radiologic assessments (x-rays) were not always performed.

Subject	X-Rays not Performed	Date of Visit	SRE's as Endpoint
008	Week 13	9 May 07	18 September 07 (Pathologic Fracture)
011	Week 13	30 May 07	12 April 2007 12 October 2007 (Radiation to Bone)
038	Week 13	19 June 2008	11 September 2008 4 December 2008 26 March 2009 (Pathologic Fractures)
040	Week 25	25 September 2008	22 Jan 2009 (Radiation to Bone)
047	Week 13 Week 25 (X-Rays not sent to Rad-Pharm)	15 January 2009 9 April 2009	30 March 2009 Not confirmed by Central Vendor

c. A review of the source documents for subject 006 revealed the prostate specific antigen assessment for Week 73 was not taken according to study procedures.
d. The urine samples for urinary N-telopeptide assay and urine creatinine were not collected before 12 PM for the following subjects: 001, 002, 004, 006, and 022.
e. The intravenous infusion start and stop times were not always documented as per the study procedures for the following subjects: 001, 006, 014, 022, and 023.

DSI Review's Note: *Regarding inspectional observation 1.b, there was concern that these subjects (with the exception of Subject 047) may have had an SRE that went undetected when their protocol-specified x-ray assessments were missed. These subjects may have already had an SRE prior to the confirmation of SRE endpoint indicated in the table above, as reported to the agency in BLA 125320/7. The DSI reviewer discussed this observation and concern with the review division medical officer. It was suggested that if the subject had an SRE of pathologic fracture, detectable by x-ray, that there would have been significant clinical symptoms, including pain. Therefore, it is reasonable to assume that these subjects did not have a pathologic fracture at the study visit where a protocol-specified x-ray was not done. While this inspectional observation remains a regulatory violation, the finding does not appear to the significantly impact the reliability of data generated by this site.*

c. **Assessment of data integrity:** Not withstanding the regulatory violations noted above, the data for Dr. Fizazi's site, associated with Study 20050103 submitted to the Agency in support of BLA 125320/7, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

3. **CI #3: Dr. Alexey Manikhas**
(Site #346)
City Oncology Dispensary
2-ya Berezovaya alleya
3/5, Saint Petersburg 197022
Russia

a. **What was inspected**: The site screened 25 subjects, 25 of those were randomized and treated and 9 subjects completed the study. The study records were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed 100% informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. There was no evidence of under-reporting AEs. The study was found to be well controlled and well documented.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125320/7. No Form FDA 483 was issued.

c. **Assessment of data integrity:** The data for Dr. Manikhas' site, associated with Study 20050136 submitted to the Agency in support of BLA 125320/7, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

4. **CI#4: Dr. Jose R. Pereira**
(Site Number 672)
Instituto do Cancer Arnaldo
Vieira de Carvalho
Rua Martinico Prado 2610
Andar conjuntos 101, 102, 103, & 122, Sao Paulo
Sao Paulo 01224
Brazil

a. **What was inspected**: The site screened 53 subjects, 40 of those were randomized and treated and none completed the study . The study records of 25 subjects, including all those with reported SRE's and important protocol deviations, were audited in accordance with the clinical investigator compliance program, CP 7348.811. All subjects reviewed had reported AEs and 18 of 25 subjects also reported SAEs. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting AEs. The study was found to be well controlled and well documented.

This study was monitored by (b) (4), and was conducted in accordance with the study protocol. Drug accountability appeared adequate. Protocol deviations were reported to the sponsor and the IRB. Source documents were available to compare with the CRF's for the subjects audited including: laboratory results from the local lab and the central lab, x-rays and reports, CT reports, radiation to bone reports, progress notes in the source documents when the subject was seen for the study visit that included the investigational product infusion information, and SAE reports. Monitor follow-up reports were available for review (reports were in English) that noted protocol deviations and action taken concerning the deviations.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125320/7. No Form FDA 483 was issued.

c. **Assessment of data integrity:** The data for Dr. Pereira's site, associated with Study 20050244 submitted to the Agency in support of BLA 125320/7, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

5. **CI #5: Dr. Maciej Krzakowski**
(Site #386)
Instytut im. M.
Sklodowskiej-Cuire-Centurm Onkologii
Ulica Roentgena 5
Warszawa 02-781
Poland

a. **What was inspected:** The site screened 31 subjects, 27 of those were randomized and treated and no subjects completed the study. The study records were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed 100% informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR

b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. There was no evidence of under-reporting AEs. The study was found to be well controlled and well documented. However, the site failed to consistently re-consent subjects with updated ICDs, there were several instances where protocol-specified periodic assessments were done out-of-window, and concomitant medications were not always documented.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125320/7. A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

a. Subject 005 signed version 1 (June 12, 2006) of the ICD on February 27, 2007. The subject's end of treatment date was April 11, 2007. On February 14, 2007 version 2 of the ICD was approved by the ethics committee but was not signed by the subject.
b. A review of the source documents for subject 027 revealed the skeletal surveys (x-ray) for Week 25 and Week 61 were not taken according to the study procedures stated in the protocol. Section 7.6, entitled, Skeletal Surveys (x-rays), states: Skeletal survey must be conducted every 12 weeks and no more than 7 days before administration of the next dose of investigational products. Yet, the Week 25 visit was on August 4, 2008 and the x-rays were taken July 24, 2008, 11 days before the study visit and treatment. The Week 61 visit was on April 8, 2009, and the x-rays were taken May 7, 2009, 29 days after the study visit and treatment.
c. A review of medical records for Subjects 005 and 012 revealed all concomitant medications were not reported on the case report forms. Subject 005 was prescribed Tramal (Tramadol) for pain on April 2, 2007 but it was not listed on the subject's CRF. Subject 012 was prescribed Furagin for urinary tract infection on January 26, 2008 but it was not listed on the subject's CRF.

DSI Reviewer's Note: *The FDA field investigator provided additional inspectional observations, not listed on the Form FDA 483, that are worth noting here. A review of the source documents relating to the protocol deviation reported for subject 023 regarding clarification of the IP box number administered on Day 1 revealed subject 023 received both denosumab and zoledronic acid on the first day of dosing. Subject 023 was randomized to receive denosumab. On January 3, 2008 (Day 1), subject 023 was administered Box 057756 instead of Box 057765. Box 057756 was to be given to subject 013 who was randomized to receive zoledronic acid.*

c. **Assessment of data integrity:** The Review Division should determine the impact that dosing errors for Subject #023 may have on analyses; however, given that this is an isolated occurrence it seems unlikely that results would be significantly impacted. Not withstanding the other inspectional observations noted above, the data for Dr. Krzakowski's site, associated with Study 20050244 submitted to the Agency in support of BLA 125320/7, appear generally reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

6. **CI #6: Dr. Veena Charu**
(Site #115, Study 20050103)
(Site #107, Study 20050244)
Pacific Cancer Center
1801 West Romneya Drive, Suite 203
Anaheim, CA 92801

a. **What was inspected**: For Study 20050103 the site screened 17 subjects, 15 of those were randomized and treated, 2 subjects completed the study. The study records of 15 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. For Study 20050244 the site screened 6 subjects, 6 of those were randomized and treated; all 6 subjects completed the study. The study records of all 6 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811.

The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: Generally, the investigator's execution of the protocols was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting AEs. The study was found to be well controlled and well documented.

Consistent with the routine clinical investigator compliance program assessments, for each study, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125320s7. No Form FDA 483 was issued.

c. **Assessment of data integrity:** The data for Dr. Charu's site, associated with Study 20050103 and Study 2005244 submitted to the Agency in support of BLA 125320/7, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Damiao, Dr. Fizazi, Dr. Manikhas, Dr. Pereira, Dr. Krzakowski, and Dr. Charu, and study (b) (4) currently known as (b) (4) the study data collected appear reliable and may be used in support of BLA 125320/7.

The FDA field investigators did not note any deficiencies for Dr. Damiao, Dr. Manikhas, Dr. Pereira, and Dr. Charu, and none were issued a Form FDA 483.

A Form FDA 483 was issued to Dr. Fizazi because the site failed to consistently re-consent subjects with updated ICDs, there were a number of subjects with missed protocol-specified periodic assessments, 5 of which included x-rays of subjects who subsequently achieved an SRE endpoint, and intravenous infusion start and stop times were not always documented. There was initial concern that subjects that had an SRE, but that had missed a previous, protocol-specified x-ray assessment may have already had an SRE that went undetected until the next x-ray assessment was conducted. The DSI reviewer discussed this observation and concern with the review division medical officer. It was suggested that if the subject had an SRE of pathologic fracture, detectable by x-ray, that there would have been significant clinical symptoms. Therefore, it is reasonable to assume that these subjects did not have a pathologic fracture at the study visit where a protocol-specified x-ray was not done. Therefore, while this inspectional observation remains a regulatory violation, the finding does not appear to the significantly impact the reliability of data generated by this site.

A Form FDA 483 was issued to Dr. Krzakowski because the site failed to consistently re-consent subjects with updated ICDs, there were several instances where protocol-specified periodic assessments were done out-of-window, and concomitant medications were not always documented. These inspectional observations were limited to a few subjects, do not appear to be systemic in nature, and should not affect the overall reliability of the data generated by this site.

The FDA field investigators reported that the services provided by the CRO, as described in the Master Service Agreement, include the Communication Plan, receipt of media and

digitization of hard copy images, Image Quality Assessment, central reading of images, Adjudication of Radiology Results, and data transmission to sponsor. The CRO was not responsible for quality control of the instruments (radiographic or scanners) maintained and operated by the clinical investigator sites. The inspection of the CRO found that records and procedures were clear, and generally well organized. The primary efficacy endpoint data were verifiable at the CRO site for the 6 FDA audited clinical sites. The FDA field investigators were able to confirm that all SREs found in data listings submitted to BLA 125320/7 pertaining to the 6 FDA audited clinical sites, a total of 64 "vender confirmed SREs," were accurate against source documents found at the site. The inspection revealed deficiencies in the firm's approval and execution of the independent review charter(s) for each audited study. In addition, the inspection revealed that the firm failed to ensure that a radiologist was board-certified, failed to maintain copies of all original source documents utilized in the adjudication of radiology results, and failed to obtain financial disclosure information in a timely manner. A Form FDA 483 was issued, citing 5 inspection observations. However, preliminary review of the EIR and exhibits found no evidence that these 5 inspectional observations, which while consistent with regulatory violations and/or violations of the independent review charters, actually did not appear to significantly impact the quality or integrity of data promulgated by RadPharm, Inc. Therefore, the data generated by (b) (4). for Protocols 20050103, 20050136, and 20050244 appear acceptable in support of the respective indication.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the outstanding EIRs and supporting inspection evidence and exhibits.

/Lauren Iacono-Connors/
Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

/Jean Mulinde for Tejashri Purohit-Sheth/
Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 30, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Advisory Committee Memo: Denosumab: BL STN 125320/7

There was no Advisory Committee meeting for efficacy supplement 125320/7.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 28, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/7; Proposed PMC/PMR language

The following Post Marketing Commitment and Post Marketing Requirement proposals were sent to Amgen via electronic mail On October 28, 2010:

POST-MARKETING COMMITMENT:

Overall Survival:

1. To submit a final report that includes updated results for overall survival for trials 20050103 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer;" 200050136 entitled "A Randomized, Double-blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects With Advanced Breast Cancer;" and 20050244 entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma." The final report should also include the primary and derived datasets and analysis programs used to generate the overall survival results reported.

   The original protocol for clinical trial 20050103 was submitted to FDA on XX,XX, XXXX, and began patient accrual on May 12, 2006. The original protocol for clinical trial 20050136 was submitted to FDA on XX, XX, XXXX, and began patient accrual on April 27, 2007. The original protocol for clinical trial 20050244 was submitted to FDA on XX, XX, XXXX, and began patient accrual on June 21, 2006.

   The timetable you submitted on October 07, 2010 states that you will conduct the trials according to the following milestone:

   Final Report Submission: October 1, 2012.

POST-MARKETING REQUIREMENTS:

Hypocalcemia:

1. To conduct a clinical trial to determine the safety of denosumab 120 mg administered every four weeks by subcutaneous injection in patients with severe renal insufficiency

(creatinine clearance less than 30 mL/min) and in patients receiving dialysis. The number of patients enrolled in the trial and the frequency and duration of plasma sampling will be sufficient to estimate the incidence and severity of hypocalcemia, hypomagnesemia, and hypophoshatemia in this patient population. The final report should include the primary and derived datasets and analysis programs used to generate the safety and laboratory analyses.

The timetable you submitted on XX/XX/XXXX states that you will conduct this study according to the following schedule:

Final Protocol Submission:	XX/XX/XXXX
Trial Completion Date:	XX/XX/XXXX
Final Report Submission:	XX/XX/XXXX

Required Pediatric Assessments:

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

We are deferring submission of your pediatric studies until INSERT DATE because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

2. A phase 1, open-label, dose-finding pharmacokinetic, pharmacodynamic, and safety study in pediatric patients ages 0 to 18 years who are diagnosed with solid tumors metastatic to bone. The study will determine whether a safe dose can be administered to patients in subsequent phase 2 and phase 3 studies.

The timetable you submitted on **XX/XX/XXXX** states that you will submit this study report according to the following timetable.

Final Protocol Submission: **December 30, 2011**
Study Completion Date: XX/XX/XXXX
Final Report Completion: **September 30, 2014**

3. A phase 2, open-label, single-arm study in pediatric patients ages 0 to 18 with solid tumors with bone metastases to determine the safety, including effects on growing bones, and activity of denosumab in the prevention of skeletal related events.

The timetable you submitted on **XX/XX/XXXX** states that you will submit this study report according to the following timetable.

This study must not be initiated until at least one month after you have submitted the complete study report for post marketing requirement 2.

Final Protocol Submission: **XX/XX/XXXX**
Study Completion Date: **XX/XX/XXXX**
Final Report Submission: **XX/XX/XXXX**

4. A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of denosumab for the prevention of skeletal related events in pediatric patients ages 0 to 18 with solid tumors and bone metastases.

This study must not be initiated until at least one month after you have submitted the complete study report for post marketing requirements 2 and 3.

The timetable you submitted on **XX/XX/XXXX** states that you will submit this study report according to the following timetable

Final Protocol Submission: **XX/XX/XXXX**
Study Completion Date: **XX/XX/XXXX**
Final Report Submission: **XX/XX/XXXX**

Submit final study reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment(s)**".

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

FINAL REVIEW

Date: October 27, 2010

To: Patricia Keegan, M.D., Director
Division of Biologic Oncology Products (DBOP)

Through: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK)
10/27/10

From: **Scientific Lead,** Elizabeth A. Donohoe, M.D.,
Risk Management Analyst, DRISK

Suzanne Robottom, Pharm.D, Team Leader, DRISK

Subject: Final review of the proposed risk management approach for Xgeva (denosumab)

Drug Name (Established Name): Xgeva (denosumab)

Therapeutic Class: RANK ligand inhibitor

Dosage and Route: 120 mg every 4 weeks subcutaneous injection

Application Type/Number: BLA 125320/7

Applicant: Amgen

OSE RCM #: 2010-1313

1 Introduction

This review addresses the risk management approach for denosumab as it pertains to the efficacy supplement currently under review in Division of Biologic Oncology Products (DBOP) for the treatment of patients with bone metastases from solid tumors to prevent skeletal-related adverse events. DBOP requested the Office of Surveillance and Epidemiology's (OSE) Division of Risk Management (DRISK) review of the proposed Medication Guide (MG) submitted by Amgen.

2 Background

In December 2008, the denosumab BLA was submitted for approval for the following four indications involving two different review divisions (DRUP and DBOP):

- Treatment of post-menopausal osteoporosis (PMO)
- Prevention of PMO
- Treatment of bone loss associated hormone ablation therapy in patients with prostate or breast cancer
- Prevention of bone loss associated with hormone ablation therapy in patients with prostate or breast cancer

During this initial review cycle, only one indication (for the treatment of PMO), after Amgen responded to the Complete Response action, received approval on June 1, 2010. Denosumab was approved under the trade name "Prolia" and the remaining applications were converted to efficacy supplements under the Prolia BLA.

Prolia is administered subcutaneously by a healthcare professional. The dose for treatment of PMO is 60 mg administered every six months. It is available in two formulations: single-dose 60 mg prefilled syringe and single-use 60 mg vial. It was approved with a REMS consisting of a Medication Guide (MG) and communication plan (CP) to ensure that the benefits of the drug outweigh the following risks: serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover (including osteonecrosis of the jaw (ONJ)).

With this efficacy supplement, Amgen proposes to market denosumab under a different trade name (Xgeva). For this indication, denosumab is given as a 120 mg subcutaneous injection to be administered by a healthcare professional. It is only available in a single-use 120 mg vial. Initially, (b) (4)

(b) (4)

(b) (4)

2 Materials Reviewed

- DBOP mid-cycle meeting for denosumab, August 26, 2010
- Sponsor's response to the 74-day letter, dated August 23, 2010
- (b) (4)
- Proposed label, submitted August 16, 2010
- 74-day letter, dated July 30, 2010
- CR letter for denosumab, dated October 19, 2009
- Donohoe E. 2010-05-19 denosumab 125320 DRISK REMS final. Signed May 19, 2010.

3 Safety Concerns

DBOP outlined the following safety concerns for Xgeva at the August 26, 2010 mid-cycle meeting:[1]

- Hypocalcemia: Hypocalcemia is not directly addressed through the Prolia REMS but it is a safety concern highlighted by both Amgen and DBOP. The 10.22.10 draft labeling states an incidence of 18% in denosumab-treated patients compared to 9% of patients treated with zoledronic acid (3.1% severe vs 1.3%, respectively). Of patients who experienced severe hypocalcemia, 33% experienced 2 or more episodes of severe hypocalcemia and 16% experienced 3 or more episodes. The clinical significance of hypocalcemia can vary from an asymptomatic condition to life-threatening tetany depending on the duration, severity, and rapidity of development. Typically, clinical signs and symptoms are observed only with decreases in ionized calcium concentration (normally 4.5-5.5 mg/dL). It is not clear if any of cases associated with denosumab were life-threatening.
- Hypocalcemia in patients with severe chronic kidney disease (CKD)/end-stage renal disease (ESRD): The draft labeling states that the risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance of less than 30 mL/min or receiving dialysis. In one study, 8 of 17 patients with a creatinine clearance less than 30 mL/min or receiving dialysis experienced corrected serum calcium levels less than 8.0 mg/dL as compared to 0 of 12 patients with normal renal function.
- ONJ: ONJ was confirmed in 1.8% of denosumab-treated patients compared to 1.3% of patients in the zoledronic acid group. In patients with ONJ, the median

[1] Data reflects draft labeling submitted by Amgen on 10.22.10. Clinical Review not yet available to DRISK.

time to ONJ was 14 months (range 4 – 25) in the denosumab group versus 14 months (range 5 – 30) for zoledronic acid. When events occurring during an extended treatment phase of approximately 4 months in each trial are included, the incidence of confirmed ONJ was 2.2% in patients who received denosumab and 1.6% in patients who received zoledronic acid.

- Decreased survival in patients diagnosed with multiple myeloma: The current raft labeling states a hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n = 180.

At this time, DRISK has not been provided a draft of the medical officer's review. A full understanding of the risks and anticipated actions by DBOP from their perspective is not known.

4 Discussion

When considering the appropriate risk management approach for Xgeva, a number of factors must be considered. These considerations are discussed below and organized by the safety concern highlighted at the mid-cycle meeting for the bone metastases efficacy supplement and the risks addressed through the approved Prolia REMS.

- Dermatologic adverse events: Dermatologic adverse reaction is a risk addressed through the Prolia REMS.

  Based on the Prolia labeling, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a higher rate in the Prolia group (10.8%) compared to the placebo group (8.2%). Most of these events were not specific to the injection site.

  It is unclear if this risk is serious.

  DBOP has not highlighted this risk as concerning.

- Serious infections: Serious infection is addressed in the Prolia REMS.

  By nature, cancer treatments are immunosuppressive and increase the risk of infection to patients. As a common consequence of cancer treatment, oncologists and possibly oncology patients are aware of and used to monitoring for infection.

  In addition, due to the advanced nature of the disease in patients with bone metastases, this population is monitored closely by specialists. However, women with PMO can be otherwise healthy with no other medical conditions thus seeking only routine/annual medical care. Therefore, the need to communicate this type of risk information about denosumab to oncologists and oncology patients is less crucial because there is more regular patient/physician interaction for monitoring.

- Hypocalcemia: As stated above, due to the advanced nature of the disease, patients with bone metastases are generally more closely monitored relative to women treated with denosumab for PMO. However, we do note that this risk did occur more frequently with denosumab compared to zoledronic acid. If the presentation of severe hypocalcemia is more aggressive, this risk would be more concerning.

- Use of denosumab in patients with severe CKD/ESRD: The concern for use in this population relates mainly to an increased risk of hypocalcemia. It is currently included in the Prolia PI and not addressed in the REMS. Use in "specific

populations" can be addressed through labeling or through REMS. However, it is not clear if serious sequalae resulted from any of the hypocalcemia cases.

As part of good medical practice, any drug initiated in a CKD/ESRD patient should be carefully evaluated. Further, dialysis patients receive frequent mineral/electrolyte monitoring in conjunction with dialysis and hypocalcemia would be detected.

- Oversuppression of bone turnover (including risk of ONJ): This is a risk addressed in the Prolia REMS and highlighted by DBOP.

  It is practical to take into account other anti-resorptive agents that are also associated with ONJ and have similar (one or both) indications to denosumab. There are two bisphosphonates currently approved (zoledronic acid, pamidronate) for hypercalcemia of malignancy and for treatment in patients with bone metastases.[2] In addition, there are four bisphosphonates approved for prevention and/or treatment of PMO.[3] For the drugs approved for treatment/prevention of PMO, a REMS consisting of a MG was required (as of 10.13.10) to address the risk of atypical factures and diasphyseal femoral fracture with increased duration of bisphosphonate exposure. A REMS was not required for those bisphosphonates approved only hypercalcemia of malignancy/bone metastases to address the risk of atypical fracture.

  To date, REMS (MG or otherwise) have not been required to communicate the risk of ONJ, to patients treated with anti-resorptive agents. Any possible future requirement for a REMS for Xgeva would require consideration for similar strategies for the bisphosphonates used in the treatment of hypercalcemia of malignancy/bone metastases.

- Decreased survival in multiple myeloma treated with denosumab: DBOP also raised a concern with decreased survival for multiple myeloma patients treated with denosumab.

  "Increased mortality in patients with multiple myeloma" is a Warning and addressed under "Important Limitations to Use" in the Indication section.

  It is worth noting that REMS with elements to assure safe use to restrict distribution have been required to minimize use in certain patient populations where decreased survival is a concern (e.g., erythropoietin stimulating agents (ESAs), romiplostim, eltrombopag). The Agency has approached this type of risk through labeling as a first step (ESAs) and through proactive restricted distribution at the time of initial approval (romiplostim and eltrombopag).

  In absence of a better understanding of the decreased survival data associated with denosumab use in multiple myeloma patients, it is difficult to determine whether this risk should trigger any additional risk mitigation measures. The strategy to address this risk would be more appropriately directed at healthcare professionals than

---

[2] Zoledronic acid is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Pamidronate is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma.

[3] Ibandronate (Boniva), Alendronate (Fosamax), zoledronic acid (Reclast), Risedronate (Actonel, Atelvia).

patients because this information should be considered at the time the decision to treat with denosumab.

In addition, the impact and possible consequences of taking a different risk management approach for a drug moiety must be explored. If a MG is not required for Xgeva, the main concern would be the possibility of a PMO patient receiving Xgeva instead of Prolia and not receiving a MG. This would compromise the communication of risk information to the PMO patient. Because Xgeva is only available as a single-use 120 mg vial which is a higher dose than recommended for PMO treatment (120 mg for solid tumor with bone metastases vs 60 mg for PMO), it more likely that a solid tumor patient would receive Prolia (2 vials of Prolia = 1 Xgeva dose). Therefore, while possible, it seems unlikely that a PMO patient would receive Xgeva and not receive a MG.

While it is difficult to argue against, at minimum, providing patients information about a drug they are prescribed[4], it may be reasonable at this time not to require a MG or other additional risk management strategies under a REMS for Xgeva for the following reasons:

- Similar agents indicated for the treatment of sequalae from bone metastases are available with certain risks (hypocalcemia, ONJ) that are associated with denosumab. Oncologists are familiar with adverse effects of anti-resorptive agents. These risks have not triggered a REMS for the bisphosphonates.
- Risk of infection is a well-known risk to oncologists and possibly cancer patients who have undergone cancer treatment.
- Patients with advanced disease (such a solid tumor with bone metastases) are in regular contact with their oncologists.
- The standard practice in CDER is to provide the most important risk information in MGs. Feedback from some oncology professional societies suggest that, as currently written, Medication Guides over-warn patients and do not provide enough information on the potential benefit to the patient.
- The need to communicate risks may be different across patient populations particularly if the monitoring practices and life expectancy are different.
- The likelihood a PMO patient receives Xgeva is low.
- As a general therapeutic area, oncology drug products have substantial toxicities. Requiring patient-directed material may be best reserved to communicate the most serious risks which may affect a patient's decision to be treated or to be aware of certain signs and symptoms. Denosumab does not appear to have toxicities comparable to anti-neoplastic agents.

While the points above are reasons not to require a MG or additional risk management strategies, just as many valid reasons in support of MG could be made. For example:

---

[4] There are 3 broad regulatory criteria for requiring a MG includes (in brief): (1) patient labeling could prevent serious adverse effects; (2) product has serious risks (relative to benefits) of which patient should be made aware…; (3) patient adherence is crucial to the drug's effectiveness.

- The risk benefit profile of denosumab should be considered in the context of a supportive care agent which is different than an agent that may be curative.
- Certain adverse events associated with denosumab may be worse than standard of care and there are alternative treatment options available. Hypocalcemia and ONJ associated with denosumab were more frequent in the denosumab group compared to zoledronic acid. Decreased survival in multiple myeloma patients appears to be unique to denosumab.

5 Conclusion and Recommendation

After review of the comparison of the risk management approaches for drugs with similar risks and/or similar indications, it is reasonable not to require additioanl risk mitigation measures to address the risks of dermatologic adverse events, infection, hypocalcemia, use in severe CKD/ESRD, and ONJ.

We are unable to assess adequately the risk of decreased survival in multiple myeloma patients treated with denosumab in the context of the appropriate risk management approach without further information from DBOP.

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	October 26, 2010
Application Type/Number:	BLA 125320/7
To:	Pat Keegan, MD, Director Division of Biologic Oncology Products
Through:	Carlos Mena-Grillasca, RPh, Team Leader CMena 10/26/10 Carol Holquist, RPh, Director CHolquist 10/26/10 Division of Medication Error Prevention and Analysis (DMEPA)
From:	Judy Park, PharmD, Safety Evaluator CMena for Judy Park 10/26/10 Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Xgeva (Denosumab) Injection 120 mg/1.7 mL (70 mg/mL)
Applicant:	Amgen, Inc.
OSE RCM #:	2010-1310

1 INTRODUCTION

This review responds to a request from the Division of Biologic Oncology Products for DMEPA review of the container label, carton and insert labeling for Xgeva (Denosumab) Injection to identify areas that could lead to medication errors. In addition, DMEPA reviewed the Pharmacovigilance Plan for Xgeva (Denosumab) to evaluate the proposed post-marketing activities aimed to minimize potential medication errors.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis,[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container label and carton labeling submitted on August 23, 2010 and working draft insert labeling dated September 24, 2010 to identify vulnerabilities that could lead to medication errors (see Appendices A and B).

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed container label, carton and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations and comments for the insert labeling and Pharmacovigilance Plan in Section 3.1 for discussion during the review team's labeling meetings. We request the recommendations for the container label and carton labeling in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Sue Kang at 301-796-4216.

3.1 COMMENTS TO THE DIVISION

A. Pharmacovigilance Plan

1. To address the risk of medication errors with concomitant therapy of Prolia and Xgeva the Applicant is proposing to:
   a. Include a warning statement in the Prescribing Information of both products to alert prescribers that the same active ingredient is present in Prolia and Xgeva and that patients should not be receiving both products. DMEPA finds this acceptable.
   b. (b) (4) DMEPA recommends that this statement be included in Section 17 – Patient Counseling Information as described below (comment B. 2.).
   c. Communication activities to healthcare practitioners regarding the existence of the two drug products, their dual proprietary name status, different product presentation and dosing regimens, and associated indications. DMEPA finds this acceptable.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Insert Labeling

1. Under *Dosage Form and Strengths* sections in Highlights and Full Prescribing Information, present the strength as total drug content (i.e. 120 mg/1.7 mL).
2. Section 17- Patient Counseling Information section. Add the warning information included under section 5.1 "Drugs with same Active Ingredient".

3.2 COMMENTS TO THE APPLICANT

A. General Comments

1. Present the numerical strength as 120 mg/1.7 mL within the orange circle.
2. Add the statement "Discard Unused Portion" following the statement "Single Use Vial".

B. Carton Labeling

1. Delete the statement [redacted] (b) (4)
2. Currently, most of the information on the principal display panel is bolded. Only use bolding to highlight the most important information (e.g. strength and route of administration).

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 26, 2010

From: Melanie Pierce MDP, DBOP/OODP/CDER

Subject: BLA 125320/7; Information request denosumab

John,

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for denosumab.

We have the following requests for additional information:

FDA's results for the breakdown of the components of first on-study SREs was slightly different from the results in CSR for Studies 103, 136 and 244. In addition, the reviewer's results of OS analysis for the multiple myeloma patients in Study 244 were slightly different from the CSR.

Attached please find the SAS code the reviewer used to generate the results and please inform FDA where the analysis procedures were different from Amgen's.

CODES FOR COMPONENTS OF SRES:

```
/*verify Time to 1st SRE*/
title 't2sre dataset';
data t2sre1;
set mine244.at2sre;
where fullset='Y';
patno=1*subjid;
trt=1; if armcd='ZA4Q4W' then trt=0; *1=Denosumab, 0=Zometa;
keep patno usubjid trt randdt rfendt TUMORAS SREAS CATXAS srcat srstdt srehcm sre21dw;
run;
data baseline;
set mine244.aslbase;
if fullset = 'Y';
if ecogb=. then ecogb=99;
if sex = 'F' and menost=' ' then menost='missing';
if tstage = '' then tstage = 'missing';
run;
* merge with baseline data;
proc sort data = t2sre1; by usubjid; run;
proc sort data = baseline; by usubjid; run;
data t2sre;
merge t2sre1 baseline;
by usubjid;
data firstsre;
set t2sre;
by patno;
retain fsre censre sredt ;
if first.patno then do; fsre='CEN'; censre=0; sredt=rfendt; end;
```

```
if srcat ne 'CENSOR' and srcat ne 'HYPERCALCEMIA OF MALIGNANCY' and censre=0 then
do; fsre=srcat; censre=1; sredt=srstdt; end;

if last.patno then output;

drop rfendt srcat srstdt srehcm;

run;

data firstsre;

set firstsre;

t2sre=(sredt-randdt+1)/30.4375;

run;

proc freq data=firstsre;

tables trt*fsre/ nocol nopercent;

run;

data test;

set firstsre;

keep usubjid fsre censre sredt patno;

format sredt date9.;

run;

proc freq data = firstsre;

tables fsre*trt;

run;
```

OS for MM patients:

```
data asleff;

set mine244.asleff;

proc contents data = asleff; run;

data eff244;

set mine244.asleff;

if fullset = 'Y';

if sre = 'Y' then sren = 1;
```

```
else if sre ='N' then sren =0; * censor = 1 event = 0;
if armcd = 'A120Q4W' then trt = 1; * denosumab(treatment)=1;
else if armcd = 'ZA4Q4W' then trt =0; * zometa(control)=0;
tfsrem = tfsred/30.4375; *tranfer days into months;
label tfsrem = 'Time to 1st SRE (Months)';
run;
data eff244;
set eff244;
allPD=0; if alldp='Y' then allPD=1; *1=event, 0=censored;
PFS=0; if adpdth='Y' then PFS=1;
bonePD=0; if bonedp='Y' then bonePD=1;
death=0; if survivl='N' then death=1;
symsre=0; if ASYMPSRE ='Y' then symsre = 1;
t2allPD=talldpd/30.4375;
t2PFS=tadpdthd/30.4375;
t2bonePD=tbonedpd/30.4375;
t2death=tdeathd/30.4375;
t2symsre=TFSSRED/30.4375;
run;

proc sort data =baseline;
by usubjid;
proc sort data = eff244;
by usubjid;
data mm;
set all244;
if tumoras ='MULTIPLE MYELOMA';*
proc freq data = mm;
tables (sren death)*trt/norow nopercent;
```

```
run;
** Main Kaplan-Meier/Log-rank Test Analysis Macro with strata **;
%macro logrk(dataset, tmtodt, censor, cen01, strata, trt, title);
** Statified log-rank test: to obtain p-value **;
proc lifetest data = &dataset;
time &tmtodt*&censor(&cen01);
strata &strata / group = &trt;
* test &trt;
title &title;
run;
** Kaplan-Meier curve: to obtain the quantiles including the median **;
proc lifetest data =&dataset plot = (s);
time &tmtodt*&censor(&cen01);
strata &trt;
run;
** stratified Cox proportional hazards regression: to obtain hazard ratio **;
proc phreg data = &dataset;
model &tmtodt*&censor(&cen01) = &trt/ ties= efron rl;*ties=discrete;
strata &strata;
run;
%mend;
%LET strat244 = %str(TUMORAS SREAS CATXAS);
%logrk(mm, t2death, death, 0, TUMORAS SREAS CATXAS, trt, "OS MM");
```

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 26, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Labeling Memo: Denosumab: BL STN 125320/7

FDA's proposed labeling revisions sent to Amgen on October 26, 2010.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 26, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Wrap-up memo: Denosumab: BL STN 125320/7

A Wrap-up meeting was held on October 26, 2010 to discuss all outstanding issues with the denosumab application. Representatives from all review disciplines were present.

The review team reported that most reviews were complete. All review disciplines recommended approval of the application with the exception of DSI, which tentatively recommended approval pending the outcome of the final inspections which were still on-going.

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	October 21, 2010
Application Type/Number:	BLA 125320/7
Through:	Carlos Mena-Grillasca, RPh, Team Leader CMena 10/21/2010 Carol Holquist, RPh, Director C Holquist 10/21/2010 Division of Medication Error Prevention and Analysis (DMEPA)
From:	Judy Park, PharmD, Safety Evaluator CMena for Judy Park 10/21/2010 Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name(s):	Xgeva (Denosumab) Injection 120 mg/1.7 mL (70 mg/mL)
Applicant:	Amgen, Inc.
OSE RCM #:	2010-1500

This document contains proprietary and confidential information that should not be released to the public.

CONTENTS

EXECUTIVE SUMMARY

This review summarizes DMEPA's evaluation of the proposed proprietary name, Xgeva, for denosumab injection. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Xgeva, acceptable for this product.

If the approval of this BLA is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from Amgen on July 23, 2010 for an assessment of the proposed proprietary name, Xgeva, regarding potential name confusion with other proprietary or established drug names in the usual practice settings. DMEPA reviewed the previous proposed name, (b) (4) under IND phase (IND 9838) in OSE RCM #2008-1363 dated June 15, 2009, and found the name unacceptable. The Applicant also submitted an independent proprietary name safety assessment by Drug Safety Institute in support of the dual proprietary name, Xgeva.

1.2 PRODUCT INFORMATION

Xgeva (denosumab) injection represents a product line extension for the approved denosumab product, Prolia. Prolia was approved on June 1, 2010. Denosumab is a receptor activator of nuclear factor kappa B (RANK) ligand inhibitor. Table 1 on page 4 summarizes the different product characteristics between the two products.

Table 1: Summary of Product Characteristics of Xgeva vs. Prolia

	Xgeva	Prolia
Indication	(b) (4) (b) (4)	Treatment of postmenopausal women with osteoporosis at high risk for fracture
Strength	70 mg/mL	60 mg/mL
Dose	120 mg (1.7 mL) subcutaneous	60 mg (1 mL) subcutaneous
Frequency of Administration	Every 4 weeks	Once every 6 months
How Supplied	Single use vial	Single use vial; Prefilled syringe

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2, 2.3, and 2.4 identify specific information associated with the methodology for the proposed proprietary name, Xgeva.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'X' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

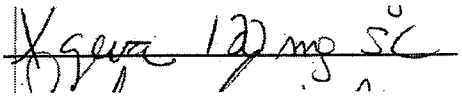
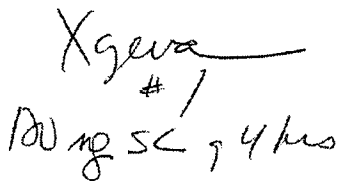
To identify drug names that may look similar to Xgeva, the DMEPA safety evaluators also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (5 letters), upstrokes (one, capital letter 'X'), down strokes (one, lower case letter 'g'), cross strokes (one, upper case letter, 'X'), and dotted letters (none). Additionally, several letters in Xgeva may be vulnerable to ambiguity when scripted (See Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look or sound similar to Xgeva.

When searching to identify potential names that may sound similar to Xgeva, the DMEPA safety evaluators search for names with similar number of syllables (3), stresses (X-ge-va, x-GE-va, x-ge-VA), and placement of vowel and consonant sounds. Additionally, the DMEPA safety evaluators consider that pronunciation of parts of the name can be misinterpreted (See Appendix B). The Applicant's intended pronunciation is *X-gee-va with emphasis on 'X'* was also taken into consideration. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient and outpatient medication orders and verbal prescription was communicated during the FDA prescription studies.

Figure 1. Xgeva Prescription Study (conducted on August 10, 2010 and August 13, 2010)

HANDWRITTEN MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: 	Xgeva 120 mg subcutaneously
Outpatient Medication Order: 	

[1] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[2] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

2.3 FDA ADVERSE EVENT REPORTING SYSTEM

Since denosumab is currently marketed under Prolia, the Division of Medication Error Prevention searched the FDA Adverse Event Reporting System (AERS) on September 21, 2010 to identify post-marketing reports of medication errors associated with Prolia. AERS was searched using the active ingredient "denosumab" and trade name "Prolia" as well as the MedDRA Higher Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues."

2.4 EXTERNAL STUDIES

2.4.1 Proprietary Name Risk Assessment of Xgeva

For this product the Applicant submitted an external evaluation of the proposed proprietary name. The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in the usual practice settings.

After the Safety Evaluator has determined the overall risk associated with the proposed name, the Safety Evaluator compares the findings to their overall assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

2.4.2 Failure Mode and Effects Analysis of Naming Convention

The Applicant submitted two studies, Failure Mode and Effects Analysis (FMEA) for denosumab (dated April 17, 2009) and Public Health Study (dated January 30, 2009), both conducted by Drug Safety Institute. The FMEA study was designed to evaluate the risk associated marketing denosumab under a single proprietary name versus dual proprietary names and the Public Health Study was to evaluate the appropriateness and preference of marketing denosumab as a single proprietary name versus dual proprietary names.

2.4.2.1 DSI FMEA

The DSI FMEA evaluated two scenarios (described below) in which participants brainstormed for possible medication errors that could lead to the creation of situations called failure modes. Failure modes are customized to each scenario because they reflect a unique process such as ordering, storing, prescribing, dispensing and/or administration of denosumab under a single proprietary name or dual proprietary names. The two scenarios evaluated using these methodologies were:

1. The existence of 'Brand X' with multiple indications and strengths
2. The co-existence of [redacted] (b) (4) (former proposed name before Xgeva) and Prolia

The failure modes for each scenario were rated by six members of the DSI staff using a pre-determined scale of 1 to 10 based on the following criteria: likelihood, severity, and detectability of each failure mode. Each criterion was given a score by each team member using the operational definitions provided in the table on page 6:

Table 2: The 10 point scale used in the FMEA study

Value	Likelihood of Occurrence	Severity of Effect	Detectability
1	Remote	None	Immediately detectable
2	Very low	Very minor effect	Found early
3	Low	Minor	Usually found
4	Low to moderate	Low to moderate	Probably found
5	Moderate	Moderate	May be found
6	Moderate to high	Moderate to high	Less than 50% chance of detection
7	High	High	Unlikely to be detected
8	Very High	Very High	Very unlikely to be detected
9	Extremely High	Hazardous	Extremely unlikely to be detected
10	Almost Certain	Disastrous	Almost impossible to detect

The resultant scores from each of the six team members were averaged for each of the three criteria. The averaged scores for likelihood, severity, and detectability were then multiplied to determine the Risk Priority Number (RPN) which takes into account how risky a failure mode is and also the ability to detect the associated risk. The higher the RPN, the greater the risk is for failure.

2.4.2.2 DSI Public Health Study

The study participants included 200 physicians, 200 retail and hospital pharmacists and 200 patients (oncology and post-menopausal patients). The participants were presented with the following information and then asked to choose their preference of either a single proprietary name or dual proprietary name: indications of use of denosumab, usual dose for the different indications of use, and strength and packaging (prefilled syringe and vial for 60 mg dose vs. vial for 120 mg dose).

Then the participants were presented with the full product profile for denosumab (therapeutic classification, indication, dosage strength, frequency of administration, dosage form, route of administration, usual dosage, how supplied, storage requirements, and prescribing population) and asked questions about likelihood of medication error occurring if the product was marketed under a single brand name 'Brand X' with choices of "very unlikely," "somewhat unlikely," "somewhat likely," and "very likely."

The participants were also presented with the product profile of dual proprietary names, Reclast and Zometa, for zoledronic acid comparing the pair to 'Brand X' and asked naming strategy questions.

3 RESULTS

The following sections discuss the findings from DMEPA database searches, Expert Panel Discussion (EPD), Adverse Events Reporting System (AERS), and Independent Studies submitted by the Applicant.

3.1 DATABASE AND INFORMATION SOURCES

The DMEPA Safety Evaluators' database searches yielded a total of nine names as having some similarity to the name, Xgeva.

Seven names were thought to look like Xgeva by the DMEPA Safety Evaluators. These include: Frova, Revia, Xiaflex, Xigris, Xpect, Xyrem, and Xyzal. The remaining two names, Abreva and Lexiva, were thought to sound like Xgeva.

Additionally, DMEPA Safety Evaluators did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of September 17, 2010.

3.2 CDER EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA Safety Evaluators (see Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Xgeva.

DDMAC had no concerns regarding the proposed proprietary name from a promotional perspective, and did not offer any additional comments relating to the proposed proprietary name.

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 36 practitioners responded. Twenty one practitioners interpreted the name correctly as 'Xgeva', with correct interpretations all occurring in the written studies. The two misinterpretations in the written studies occurred with the letter 'g' where one practitioner misinterpreted as 'q' and another as 'y.' All the practitioners in the verbal study misinterpreted the letter 'X' as 'Ex.' Additionally, practitioners in the verbal study misinterpreted the letter 'gi' as 'ge,' 'che,' 'ti,' 'ji,' or 'tee,' None of the responses in any of the studies identified a currently marketed drug name.

3.4 FDA ADVERSE EVENT REPORTING SYSTEM

The AERS search did not retrieve any cases of medication errors with denosumab injection.

3.5 EXTERNAL STUDIES

3.5.1 External Proprietary Name Sound/Look-Alike Assessment

In the proposed name risk assessment submitted by the Applicant, Drug Safety Institute (DSI) found the name acceptable. They identified and evaluated a total of 21 drug names thought to have some potential for confusion with the name Xgeva. Five of the 21 names (Abreva, Lexiva, Xigris, Xyrem and Xyzal) were previously identified in the DMEPA Safety Evaluators' searches or the Expert Panel Discussion.

The remaining 16 names were not identified by DMEPA Safety Evaluators and will be evaluated in the Safety Evaluator Risk Assessment.

3.5.2 External Failure Mode and Effects Analysis of Naming Convention

To determine whether or not there would be problems marketing this product under two different names and strengths, DSI conducted an FMEA and a Public Health Survey.

3.5.2.1 DSI FMEA

DSI's FMEA evaluated two scenarios: a (1) single proprietary name and (2) dual proprietary names. The FMEA on the single proprietary name for multiple indications and strengths, uncovered 15 failure modes. The Risk Priority Number (RPN) for these failures ranged from 9 to 65, with an average value of 34. The top three failure mode error types for this naming convention were wrong dose and frequency, omission of dose, and omission of therapy. The RPN value for the top three failure modes was 65, 56 and 56 with an average score of 59.

The dual proprietary name strategy scenario uncovered five failure modes. The RPN for these failures ranged from 8 to 31 with an average value of 16. The top three failure modes for the dual proprietary name strategy were wrong dose (two failure modes with the same medication error outcome) and dual therapy. The RPN value for the top three failure modes was 31, 15 and 14 with an average score of 20.

The DSI concluded that the FMEA demonstrated that the safest strategy to consider is where denosumab is available and marketed under two separate proprietary names. They also stated the data supports that marketing denosumab under a single proprietary name or two separate proprietary names are "viable strategies from a safety perspective."

3.5.2.2 DSI Public Health Study

When the full product profile of denosumab (using both indications of use) was shown to the healthcare professional participants, they felt a medication error is "very/somewhat unlikely" to occur when a single proprietary name strategy is used. However, when product profiles of denosumab were presented separately for Xgeva and Prolia, the results were more favorable in support of a dual proprietary name strategy. When the healthcare professional participants were shown the product profile of denosumab (both indications) and the existing products, Reclast and Zometa, only 59% found that a dual proprietary name strategy was preferred over a single proprietary name strategy.

When the full product profile of denosumab was shown to patient participants, 69% of the participants felt that unique proprietary name for each use would be better than one proprietary name for both uses. When the product profiles for denosumab were shown separately, 80% of participants agreed that the names should be different from one another.

3.6 COMMENTS FROM THE DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS (DBOP)

3.6.1 Initial Phase of Review

In a response to the OSE August 10, 2010 e-mail, DBOP had no issues regarding the proposed name, Xgeva, at the initial phase of the name review.

3.6.2 Midpoint of Review

On October 20, 2010 DMEPA notified DBOP via e-mail that we had no objections to the proposed proprietary name, Xgeva. Per e-mail correspondence from DBOP on October 20, 2010 they indicated that the review team does not have any issues with the proposed proprietary name, Xgeva.

3.7 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator identified five additional names, Extina, Extavia, Tyvaso, Tyzeka and Tyzine, thought to look similar to Xgeva and represent a potential source of drug name confusion.

Thus, a total of 30 names were identified for their similarity to Xgeva from the combined searches: nine names identified in section 3.1, 16 names identified in an external name study, and five names identified by the primary safety evaluator.

4 DISCUSSION

Xgeva is the proposed proprietary name for denosumab. This proposed name, Xgeva, was evaluated from a promotional and safety perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name. DMEPA and DBOP concurred with this assessment.

4.2 SAFETY RISK ASSESSMENT

Two broad categories of failures were evaluated by DMEPA. Risk of confusion within the Denosumab product line and risk of confusion outside the product line.

4.2.1 Denosumab Product Line Extension

The proposed Xgeva (denosumab) injection will be an extension of the denosumab product line manufactured by the Applicant and marketed under the proprietary name, Prolia. Although both products contain the same active ingredients, they have a different indication of use, dose, strength, and frequency of administration. See Table 1 on page 3 for a comparison of Xgeva and Prolia characteristics. The Applicant proposes a new and different proprietary name for this product. The Applicant submitted an independent study, which used two different methods of evaluation (FMEA and Public Healthy Survey) assessing the risks associated with the various nomenclature approaches. However, these methods have several limitations and as such were not useful for our analysis nor they fully support the strategy to use two different proprietary names.

One of the limitations of the DSI FMEA study is the make-up of the FMEA team, who are all staff members of DSI and none of which appear to be practicing professionals. In addition, all but one of the members comprising the FMEA team are pharmacists, and do not represent a multi-disciplinary team of healthcare professionals (i.e. practitioners, pharmacists, nurses, etc.). Another limitation is the non-validated prioritization of risk that DSI employs. The 10 point scale used to calculate the Risk Priority Number (RPN) (see Table 2 on page 6) is an arbitrary and subjective rating scale. Since name confusion is a preventable error, any identified failure as a result of a potential confusion should be considered carefully and not evaluated based on a subjective and unreliable PNR. Additionally, the FMEA for use of a single proprietary names provided failures that would also be seen with two proprietary names but these were not captured in the dual proprietary name FMEA.

The limitation of DSI's Public Health Study is the rating scale used in the study for participants to assess the risk of errors. The participants were allowed to choose from "very likely," "somewhat likely," "very unlikely," and "somewhat unlikely." There were no objective criteria set for the rating scale for participants to assess the difference of choosing one option from another. Additionally, the study results demonstrated conflicting findings. The healthcare professionals initially felt medication errors are unlikely to occur when a single proprietary name strategy is used given the full product profile of denosumab; however, the results favored dual proprietary name strategy when the product profiles were shown separately for each indication. The percentage of "very or somewhat unlikely" risk of error with dual proprietary name was not significantly different (48.8% to 56.6% vs. 61.8% to 71.3%). The study or survey did not provide conclusive data that favored one approach over the other. It just confirmed that either strategy has some risk.

We remain concerned for the potential for concomitant therapy since postmarketing experience with other drug products has shown concomitant therapy to be a common type of error when an active ingredient is marketed under two or more names. [3] Also, errors still may occur when prescribers order either product using the established name. This is a failure not considered in DSI's FMEA.

DBOP initially objected to the use of a dual proprietary name for this product (see OSE Review #2008-1363 dated June 15, 2010). However, upon further discussions between DBOP, DRUP and DMEPA, it was agreed that the data currently available did not indicate a significant safety risk associated with concomitant therapy of denosumab. Given that the product will have different doses, strengths, and

[3] The Institute for Safe Medication Practices. "Revatio=Sildenafil=Viagra". January 2009

frequency of administration it may be better managed under a separate name. Thus decreasing the likelihood of dosing confusion.

4.2.2 Xgeva Assessment of Risk Outside of the Denosumab Product Line

In total, 30 names were identified and evaluated by DMEPA for their similar sound or appearance to Xgeva. We determined no other aspects of the name are a source of potential confusion. Ten of the 30 names were eliminated for the following reasons (see Appendices D and E): nine names lacked convincing orthographic and/or phonetic similarity to the proposed proprietary name, Xgeva, and one name was a discontinued product with no generics available.

Failure mode and effect analysis (FMEA) was applied to determine if the proposed proprietary name could potentially be confused with the remaining 20 names and lead to medication errors. This analysis determined that the name similarity to Xgeva was unlikely to result in medication errors with any of the 20 products for the reasons presented in Appendix F. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Xgeva, is not promotional nor is it vulnerable to name confusion that could lead to medication errors. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Xgeva, for this product at this time. Our conclusion is consistent with the external risk assessment conducted by Drug Safety Institute that was provided by the Applicant. The Applicant will be notified via letter.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this BLA is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation. If you have further questions or need clarifications, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Xgeva, and have concluded that it is acceptable.

The proposed proprietary name, Xgeva, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

6 REFERENCES

1. Micromedex Integrated Index (http://csi.micromedex.com)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

5. Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. U.S. Patent and Trademark Office (http://www.uspto.gov)

USPTO provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. ***Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at*** *(www.thomson-thomson.com)*

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. ***Natural Medicines Comprehensive Databases*** *(www.naturaldatabase.com)*

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. ***Stat!Ref*** *(www.statref.com)*

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. ***USAN Stems*** *(http://www.ama-assn.org/ama/pub/category/4782.html)*

USAN Stems List contains all the recognized USAN stems.

14. ***Red Book Pharmacy's Fundamental Reference***

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. ***Lexi-Comp*** *(www.lexi.com)*

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. ***Medical Abbreviations Book***

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [4]

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [5] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[6] DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products

---

[4] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[5] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[6] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

because similarly in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	**Considerations when searching the databases**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a

variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND review Division or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their comments or concerns with the proposed proprietary name and any

clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[7] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that

[7] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's

credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. (See Section 4 for limitations of the process).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in name, Xgeva	Scripted may appear as	Spoken may be interpreted as
Capital 'X'	'F,' 'T,' 'R'	Ex, Ax
Lower case 'g'	's,' 'p,' 'q,' 'y,' 'z'	jee, ji, ch, t
Lower case 'e' or 'a'	any vowel	any vowel
Lower case 'v'	'n,' 'r,' 's,' 'u,' 'z'	b

Appendix C: FDA Prescription Study Responses for Xgeva

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Xgeva	Xgeva	Exgiva
Xgeva	Xgeva	Exgeva
Xgeva	Xgeva	Excheba
Xgeva	Xgeva	Excheiva
Xgeva	Xgeva	Exgiva
Xgeva	Xyeva	Exgeva
Xgeva	Xgeva	Exgiva
Xqueva	Xgeva	Extiva
Xgeva	Xgeva	Exjiva
Xgeva	Xgeva	Exteeva
Xgeva	Xgeva	Excheva
	Xgeva	Exjiva
		Exgiva

Appendix D: Proprietary names that lack convincing orthographic and/or phonetic similarities

Proprietary Name	Similarity to Xgeva or Source
Boniva	DSI
Cimzia	DSI
Invega	DSI
Ixiaro	DSI
Je-Vax	DSI
Xenical	DSI
Xiaflex	Look
Xopenex	DSI
Zebeta	DSI

Appendix E: Proprietary name of a discontinued product with no generics available

Proprietary Name	Similarity to Xgeva	Status	Source
Tequin (Gatifloxacin)	DSI	Discontinued	Clinical Pharmacology Online

Appendix F: Products with multiple differentiating product and/or orthographic/phonetic characteristics that minimize the risk for medication errors

Product name with potential for confusion	Similarity to Xgeva	Dosage Form/ Strength	Usual Dose	Differentiating product or orthographic/phonetic characteristics (Product vs. Xgeva)
Xgeva (Denosumab)	**NA**	**Injectable: 120 mg/1.7 mL (70 mg/mL)**	**120 mg subcutaneously every 4 weeks**	**NA**
Abreva (Docosanol) *Over-the-counter*	Sound	Topical cream: 10%	Apply 5 times/day	**Dosage form:** cream vs. injectable **Route:** topical vs. subcutaneous **Frequency:** 5 times daily vs. every 4 weeks **Availability:** over-the-counter vs. prescription

Arzerra (Ofatumumab)	DSI	Injectable: 100 mg/5 mL	300 mg initial dose (dose 1), followed 1 week later by 2,000 mg weekly for 7 doses (doses 2 to 8), followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses (doses 9 to 12).	**Route:** intravenous vs. subcutaneous **Dose:** 300 mg or 2000 mg vs. 120 mg **Orthographic differences:** Beginning letters (Ar vs. X), length (7 vs. 5 letters)
Extavia (Interferon Beta-1B)	Look and Sound	Injectable: 0.3 mg/vial	Initial dose: 0.0625 mg (0.25 mL) subcutaneously every other day; increase to 0.25 mg (1 mL) subcutaneously every other day	**Frequency:** every other day vs. every 4 weeks **Dose:** 0.0625 mg to 0.25 mg vs. 120 mg **Orthographic differences:** Upstroke vs. downstroke in similar position ('t' vs. 'g') **Phonetic difference:** 'ta' vs. 'ge'
Extina (Ketoconazole)	Look and Sound	Topical foam: 2%	Apply to affected area twice daily	**Dosage form:** foam vs. injectable **Route:** topical vs. subcutaneous **Frequency:** twice daily vs. every 4 weeks
Frova (Frovatriptan Succinate)	Look	Tablet: 2.5 mg	1 tablet (2.5 mg) orally once. Max dose: 3 tablets/day	**Dosage form:** tablet vs. injectable **Route:** oral vs. subcutaneous **Dose:** 2.5 mg (1 tablet) vs. 120 mg
Kariva (Ethinyl Estradiol/ Desogestrel)	DSI	Tablet: 0.02 mg/0.15 mg (21 tablets) and 0.01 mg (5 tablets)	1 tablet orally once daily	**Dosage form:** tablet vs. injectable **Route:** oral vs. subcutaneous **Dose:** 1 tablet vs. 120 mg **Frequency:** once daily vs. every 4 weeks
Lexiva (Fosamprenavir Calcium)	Sound	Tablet: 700 mg Oral solution: 50 mg/mL	1400 mg once or twice daily or 700 mg twice daily (depending on if administered with ritonavir and ritonavir's dose)	**Dosage form:** tablet or oral solution vs. injectable **Route:** oral vs. subcutaneous **Dose:** 700 mg or 1400 mg vs. 120 mg **Frequency:** once or twice daily vs. every 4 weeks
Ostiva (Multivitamin) **Discontinued (according to Clinical Pharmacology online)*	DSI	Tablet	1 tablet orally once daily	**Dosage form:** tablet vs. injectable **Route:** oral vs. subcutaneous **Frequency:** once daily vs. every 4 weeks
Pexeva (Parooxetine Mesylate)	DSI	Tablet: 10 mg, 20 mg, 30 mg, 40 mg	10 mg to 60 mg orally once daily	**Dosage form:** tablet vs. injectable **Route:** oral vs. subcutaneous **Dose:** 2.5 mg or 50 mg vs. 120 mg **Frequency:** once daily vs. every 4 weeks

Revia (Naltrexone Hydrochloride)	Look	Tablet: 50 mg	Depends on indication of use: 25 mg or 50 mg orally once daily	**Dosage form:** tablet vs. injectable **Route:** oral vs. subcutaneous **Dose:** 2.5 mg or 50 mg vs. 120 mg **Frequency:** once daily vs. every 4 weeks
Sustiva (Efavirenz)	DSI	Tablet: 600 mg Capsules: 50 mg, 200 mg	Adult: 600 mg once orally daily or 300 mg orally once daily co-administered with voriconazole Children: 200 mg to 600 mg	**Dosage form:** tablet or capsules vs. injectable **Route:** oral vs. subcutaneous **Dose:** 200 mg to 600 mg vs. 120 mg **Strength:** 50 mg, 200 mg, 600 mg vs. 120 mg/1.7 mL (70 mg/mL) **Frequency:** once daily vs. every 4 weeks
Tyvaso (Treprostinil Sodium)	Look	Inhalation solution: 0.6 mg/mL	3 to 9 breaths per treatment session; 4 treatment sessions per day	**Dosage form:** inhalation solution vs. injectable **Route:** inhalation vs. subcutaneous **Dose:** 3 to 9 breaths vs. 120 mg **Frequency:** 4 times daily vs. every 4 weeks
Tyzeka (Telbivudiune)	Look	Tablet: 600 mg Oral solution: 100 mg/5 mL	600 mg once daily Renal adjustment: 10 mL to 30 mL once daily or 1 tablet every 24 h, 48h, 72 h or 96 h.	**Dosage form:** tablet and oral solution vs. injectable **Route:** oral vs. subcutaneous **Dose:** 600 mg or 10 to 30 mL vs. 120 mg **Frequency:** once daily to every 96 hours vs. every 4 weeks
Tyzine (Tetrahydrozoline Hydrochloride)	Look	Nasal solution: 0.05%, 0.1% Nasal spray: 0.1%	2 to 4 drops or 3 to 4 sprays in each nostril as needed	**Dosage form:** solution or spray vs. injectable **Route:** intranasal vs. subcutaneous **Dose:** 2 to 4 drops or 3 to 4 sprays vs. 120 mg **Frequency:** as needed vs. every 4 weeks
Viagra (Sildenafil Citrate)	DSI	Tablet: 25 mg, 50 mg, 100 mg	25 mg to 100 mg 30 to 60 minutes prior to intercourse	**Dosage form:** tablet vs. injectable **Route:** oral vs. subcutaneous **Dose:** 25 mg to 100 mg vs. 120 mg **Strength:** 25 mg, 50 mg, 100 mg vs. 120 mg/1.7 mL (70 mg/mL)
Xigris (Drotrecogin Alfa)	Look	Injectable: 5 mg/vial, 20 mg/vial	24 mcg/kg/hr infused over 96 hours	**Route:** intravenous infusion vs. subcutaneous **Dose:** 24 mcg/kg/hr vs. 120 mg **Strength:** 5 mg/vial and 20 mg/vial vs. 120 mg/1.7 mL (70 mg/mL)

Xpect (Guaifenesin) *Over-the-counter*	Look	Tablet: 400 mg	200 mg to 400 mg orally every 4 hours	**Dosage form:** tablet vs. injectable **Route:** oral vs. subcutaneous **Dose:** 200 mg to 400 mg vs. 120 mg **Frequency:** every 4 hours vs. every 4 weeks **Availability:** over-the-counter vs. prescription
Xyrem (Sodium Oxybate)	Look	Oral solution: 500 mg/mL	6 g to 9 g per night in two divided doses (4 hours apart)	**Dosage form:** oral solution vs. injectable **Route:** oral vs. subcutaneous **Dose:** 6 g to 9 g vs. 120 mg **Frequency:** two divided doses vs. every 4 weeks
Xyzal (Levocetrizine Hydrochloride)	Look	Tablet: 5 mg Oral solution: 2.5 mg/ 5 mL	Adult: 5 mg orally once daily in the evening 6 to 11 yo: 2.5 mg orally once daily in the evening 6 month to 5 yo: 1.25 mg once daily in the evening	**Dosage form:** tablet or oral solution vs. injectable **Route:** oral vs. subcutaneous **Dose:** 1.25 mg, 2.5 mg or 5 mg vs. 120 mg **Frequency:** once daily vs. every 4 weeks
Zenieva (Hydrogel wound dressing)	DSI	Topical emulsion	Apply topically three times daily	**Dosage form:** emulsion vs. injectable **Route:** topical vs. subcutaneous **Frequency:** three times daily vs. every 4 weeks

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: October 19, 2010
To: Administrative File, STN 125320/7
From: Donald C. Obenhuber, Ph.D., CDER/OC/DMPQ/MAPCB/BMT DO 11/9/10
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PH 11/9/10
Subject: PAS: resubmission of all of the data found in 125355/0
Applicant: Amgen, Inc.
US License: 1080
Facility: Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos
Puerto Rico 00777 USA
FEI No. 1000110364
Product: Prolia (Denosumab)
Dosage: 120 mg (70 mg/mL), subcutaneous injection, single use vial
Indication: (b) (4)
PDUFA date: 18 November 2010

Recommendation: The drug product part of this application is recommended for approval from sterility assurance and product quality microbiology perspective.

Review Summary

Denosumab, is a fully human IgG2 monoclonal antibody that inhibits receptor activator of nuclear factor kappa B ligand, (b) (4) tosumab drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in a 70 mg/mL to support the 120 mg every 4 weeks dosing schedule proposed for the (b) (4)
Since the 60 mg/mL vial previously submitted under BLA 125320 and the proposed 70 mg/mL vial for (b) (4) contain the same drug substance and were developed in parallel based on the same formulation, the majority of the CMC information has remained unchanged between the applications.

Assessment

Description of the Composition of the Drug Product (3.2.P.1):

Denosumab is supplied as a sterile, single use, preservative free solution for subcutaneous injection in a vial containing 70 mg/mL denosumab. This vial presentation is intended to be used in the treatment of patients with (b) (4) (b) (4) (b) (4). The drug product has the same composition as the drug substance (70 mg/mL denosumab, 18 mM acetate, and 4.6% (w/v) sorbitol at a pH of 5.2), so no dilution is required for drug product manufacture. The acetate-sorbitol formulation for drug product has been used throughout clinical development. The vial presentation consists of a 3 cc (b) (4) glass vial, (b) (4) stopper (b) (4) and aluminum seal with flip-off cap.

Table 1. Drug Product (Formulated Bulk) 70 mg/mL Vial Batch Formula

Formula Ingredients	Target Concentration in Formulated Bulk	Amount per 1 kg	Amount per 64 kg Batch	Amount per 80 kg Batch
Denosumab drug substance[a]	70 mg/mL	1.0 kg	64 kg	80 kg

[a] This batch formula example is for drug substance at 70 mg/mL. Denosumab drug substance is supplied at a concentration of 70 ± 7 mg/mL. The drug substance and formulated bulk density are both 1.034 g/mL.

Manufacture (3.2.P.3):

Manufacturers (3.2.P.3.1):

The finished drug product is manufactured at the following facility:

Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos
Puerto Rico 00777 USA
FEI No. 1000110364

The site was inspected May 19-27, 2010 by SJN-DO and classified NAI. The BTP and TRP profiles were updated and are acceptable.
A PAI for Denosumab and surveillance inspection of Amgen, Juncos was conducted July 27 to September 11, 2009. The initial classification was Official Action Indicated (OAI) related to broken syringes complaints. A final evaluation of the compliance status of the drug product manufacturing site was VAI.

This site was also inspected by SJN-DO September 21 - October 1, 2010 to cover reported Epogen drug product vial delamination events. The inspection was initially classified VAI. DMPQ believes that these observations have no direct impact on the denosumab (Prolia) manufacturing responsibilities at this site. Therefore, we find this site to be acceptable for the purposes of this supplement.

Description of the Manufacturing Process and Process Controls (3.2.P.3.3)

(b) (4)

[redacted]

25 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Stability (3.2.P.8)

The 70 mg/mL vial presentation consists of a 3 cc (b) (4) glass vial with a 13 mm (b) (4) stopper and an aluminum seal with a plastic flip-off dust cover. The container closure system used for the stability program is identical to those used in clinical trials and for commercial distribution.

Currently, up to 36 months of data from the primary stability lots, and 18 months of data from the commercial lots manufactured at AML have been obtained, along with 18 months of supporting stability data as outlined in Table 1. Additional stability timepoints will continually be evaluated based on the testing program presented in Table 3.

Table 1. Summary of Denosumab 70 mg/mL Vial Lots in the Stability Program

Lot Number	Strength (mg/mL)	Drug Substance Parent Lot Number	Drug Substance Site	Drug Substance Date of Manufacture	Drug Product Fill Site	Drug Product Date of Manufacture	Stability Program	Latest Stability Time Point Tested (Months)
049A063049	70	049A050663	ATO	Oct 2005	ATO	Jan 2006	Primary	36
049A063045	70	049A052429	ATO	Nov 2005	ATO	Mar 2006	Primary	36
049A074424	70	049C053511	ACO	Nov 2005	ATO	Apr 2006	Primary	36
049A066143	70	049C048022	ACO	Jul 2006	ATO	Nov 2006	Primary	36
00100078218 (00100061908)	70	049D108163	BIP	Jul 2007	AML	May 2008	Commercial	18
00100078228 (00100061918)	70	049D108926	BIP	Aug 2007	AML	May 2008	Commercial	18
00100078238 (00100061928)	70	049D108163 049D108926 049D108927	BIP	Jul 2007	AML	May 2008	Commercial	18
049A119057	70	049D108163	BIP	Jul 2007	ATO	Jan 2008	Supporting	18
049A119058	70	049D108926	BIP	Jul 2007	ATO	Jan 2008	Supporting	18
049A119059	70	049D108163	BIP	Jul 2007	ATO	Jan 2008	Supporting	18
A0309160900	60	049C053511	ACO	Nov 2005	ATO	Jan 2006	Reference Standard	36

ACO = Amgen Colorado
ATO = Amgen Thousand Oaks, California
BIP = Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
AML = Amgen Manufacturing Limited
a Amgen inspection lot number
b Amgen fill lot number

Table 2. Stability 70 mg/mL Vial Storage Conditions

Condition Name	Condition Abbreviation	Temperature Range
Recommended	5°C	2°C to 8°C
Accelerated	20°C	27°C to 30°C
Stress	37°C	35°C to 39°C

Table 3. Stability Test Schedule During Development

	Time Point (Months)												
Temperature	0	0.5	1	2	3	6	9	12	18	24	30	36	48
5°C	X		X		X	X	X	X	X	X	X	X	X
20°C			X		X	X	X	X					
37°C		X	X	X	X	X							

Drug product lots are stored at the recommended storage condition of 5°C with testing scheduled for the 0, 3, 6, 9, 12, 18, 24, 30, 36, and 48 month time points. In addition, for experimental purposes, other storage conditions were evaluated during development as outlined in Table 2. These experimental temperature conditions are performed to compare relative rates of degradation, to assess the effect of temperature stress on the product and to support potential temperature deviations. The test schedule employed to date for the primary, commercial and supporting programs are shown in Table 3. Testing regimens for storage conditions may vary according to individual study protocols.

Container Closure Integrity Container closure integrity is assessed via the vacuum decay leak detection technique as part of the commercial program. All time points tested to date have met acceptance criteria.

Sterility Sterility is maintained in 70 mg/mL vial stored at 5°C for up to 36 months.

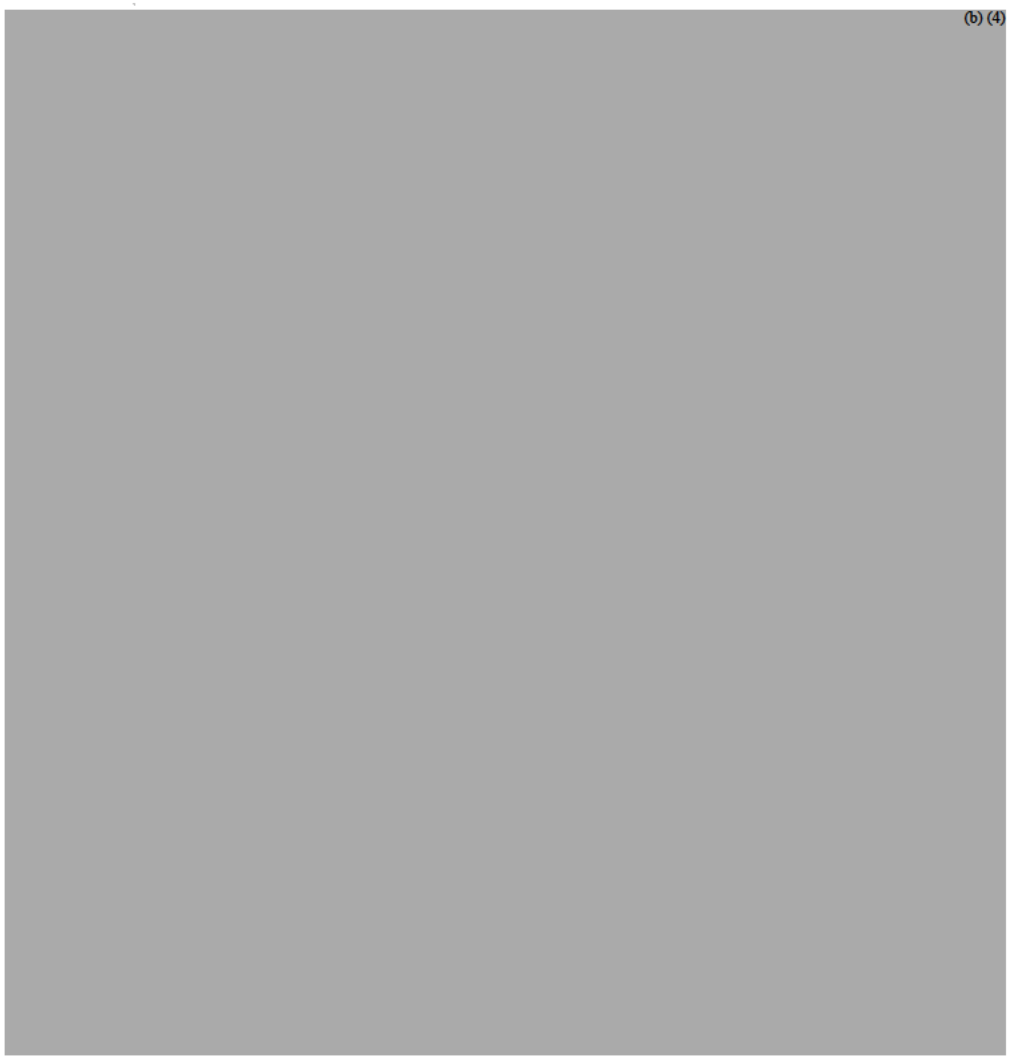
Data at the recommended storage condition were used to estimate a shelf-life which confirms that the upper and lower 95% confidence intervals on the mean are within specification limits through 36 months of storage at 5°C. Therefore, a 36 month shelf life for 70 mg/mL vial stored at 5°C was recommended.

Post Approval Stability Testing

(b) (4)

[redacted]

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



Environmental Assessment:

Denosumab is subject to a categorical exclusion under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31(c), based on consideration of its effects when exposed to the environment.

Denosumab is considered to be a nonhazardous, biodegradable product. Patients injected with Denosumab are expected to fully metabolize it with negligible excretion of intact, biologically-active protein from the body. Any breakdown products are not expected to remain in the environment for any significant period as a biologically-active protein because of their susceptibility to biodegradation by a wide range of environmental microflora. The environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment.

cGMP Status:

This site was also inspected by SJN-DO September 21 - October 1, 2010 to cover reported Epogen drug product vial delamination events. The inspection was initially classified VAI DMPQ believes that these observations have no direct impact on the denosumab (Prolia) manufacturing responsibilities at this site. The manufacturing processes covered are considered acceptable from a GMP perspective.

Conclusion

I. The BLA is recommended for approval from a sterility assurance and product quality microbiology perspective.

II. Information and data in this submission not related to drug product sterility assurance was not evaluated and should be reviewed by an OBP reviewer.

III. No additional inspectional follow-up items were identified.

Cc: WO51: Obenhuber
WO51: Hughes
WO22: Melanie Pierce
HFD-328, eCTD Blue Files (STN 125320/7)

Archived File: S:\archive\BLA\125320.7.rev.mem.PAS.10-19-2010.doc

To: Pohlhaus, Timothy
Subject: FW: TB-EER for 125320/7

Tim,
Could you please let me know the current status for Amgen Juncos considering the issue with the recent BPDR for EPOGEN and [redacted] (b) (4) I'm supposed to complete the review by next week.
Thanks,
Don

From: Pohlhaus, Timothy
Sent: Monday, August 16, 2010 3:30 PM
To: Obenhuber, Donald
Cc: CDER-TB-EER; Pohlhaus, Timothy
Subject: RE: TB-EER for 125320/7

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for Amgen's STN 125320/7. Please see the attached form for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this supplement.

Timothy J. Pohlhaus, Ph.D.
Staff Fellow
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 1333
Silver Spring, MD 20993
Phone - (301) 796-5224

From: Obenhuber, Donald
Sent: Friday, August 13, 2010 4:01 PM
To: CDER-TB-EER
Cc: Suvarna, Kalavati
Subject: TB-EER for 125320/7

Please complete a review and evaluation of the attached TB-EER for 125320/7. Please let me know if there are any questions.

Thanks, Don

Donald C. Obenhuber, PhD
Microbiologist
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave
W051, RM 4245, HFD-320
Silver Spring, Maryland 20903

(301) 796-3214
donald.obenhuber@fda.hhs.gov

From: Dillon, Laura
Sent: Wednesday, February 03, 2010 12:43 PM
To: CDER-TB-EER
Cc: Obenhuber, Donald; Suvarna, Kalavati; Hughes, Patricia; Rothman, Barry; Dillon, Laura
Subject: TB-EER for 125320/0/48

Please complete a review and evaluation for 125320/0/48. This is a response to the Denosumab BLA complete response. I've attached a scanned version of the TB-EER from when the sites were last evaluated in August 2009.

Regards,
Laura

Laura A. L. Dillon, M.S.
Program Analyst
Food and Drug Administration
Center for Drug Evaluation and Research
OC/DMPQ/BMT
10903 New Hampshire Avenue
Bldg. 51, Rm. 4359
Silver Spring, MD 20993
301-796-3204 (office)
301-847-8743 (fax)
Laura.Dillon@fda.hhs.gov

**Division of Drug Marketing,
Advertising, and Communications**

Internal Consult

****Pre-decisional Agency Information****

To: Melanie Pierce, Regulatory Project Manager
Division of Biologic Oncology Products (DBOP)
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications (DDMAC)

Carole C Broadnax 10/21/10

Date: October 21, 2010

Re: **Prolia (denosumab) Injection**
BLA 125320-7 (formerly 125355-0)
Comments on draft product labeling

In response to DBOP's Request for Consultation dated June 10, 2010, DDMAC has reviewed the proposed physician labeling (PI) for Prolia. The version of the PI used in this review was sent via email to DDMAC from DBOP on October 19, 2010.

Supplement 7 provides for a new indication – (b) (4) (b) (4)

DDMAC offers the following comments:

Section	Statement from Draft	Comment
HIGHLIGHTS **INDICATIONS AND USAGE**		Major limitations of use must be briefly noted in the Highlights – Indications and Usage section. DDMAC recommends that the Important Limitation of Use that Prolia is not indicated for the prevention of skeletal related events in patients with multiple myeloma be briefly noted in this section.

		DDMAC notes that the Zometa (zoledronic acid) label approved November 2009 contains an important limitation of use in this section.
HIGHLIGHTS - INDICATIONS AND USAGE **FULL PRESCRIBING INFORMATION - 1 INDICATIONS AND USAGE** **FULL PRESCRIBING INFORMATION - CLINICAL TRIALS**	**HIGHLIGHTS - INDICATIONS AND USAGE** • (b) (4) **FULL PRESCRIBING INFORMATION - 1 INDICATIONS AND USAGE** **1.1 Bone Metastasis from Solid Tumors** [TRADENAME2] is indicated for the prevention of skeletal related events in patients with bone metastases from solid tumors. **FULL PRESCRIBING INFORMATION - CLINICAL TRIALS** • (b) (4) And • (b) (4)	The indication should generally match the population that was studied in the clinical trial. The Clinical Trials section uses the language (b) (4) however, the Indication statement does not use this language. (b) (4) If not, DDMAC recommends revising the indication statement to be consistent with the population studied in the clinical trial and to prevent broadening of the indication.
HIGHLIGHTS - DOSAGE AND ADMINISTRATION **And**	**HIGHLIGHTS - DOSAGE AND ADMINISTRATION** • Instruct patients to take (b) (4) (b) (4) calcium daily	Should patients and healthcare professionals also be instructed to take/administer magnesium as indicated in section 5.1 (Hypocalcemia) of the Full

HIGHLIGHTS - WARNINGS AND PRECAUTIONS **And** **FULL PRESCRIBING INFORMATION - DOSAGE AND ADMINISTRATION Recommended Dosage (2.1)** **And** **FULL PRESCRIBING INFORMATION - PATIENT COUNSELING INFORMATION Hypocalcemia (17.1)**	and (b) (4) IU vitamin D daily (2.1) **HIGHLIGHTS - WARNINGS AND PRECAUTIONS** • (b) (4) **FULL PRESCRIBING INFORMATION - DOSAGE AND ADMINISTRATION Recommended Dosage (2.1)** • Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia *[see Warnings and Precautions (5.1)]*. **PATIENT COUNSELING INFORMATION Hypocalcemia (17.1)** • (b) (4)	Prescribing Information (FPI)?
HIGHLIGHTS **ADVERSE REACTIONS**	• (b) (4)	The presentation of the Highlights most common adverse reactions is inconsistent with the FPI - Section 6 most common adverse reactions. Section 6 of the FPI states, "The most common adverse reactions in patients receiving [TRADENAME2] (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (see Table 1)." DDMAC recommends revising

		the most common Adverse Reactions in the Highlights and the FPI - section 6 to ensure they are consistent with each other. DDMAC recommends using the term "adverse **reactions**" throughout the label instead of the term "adverse events." [emphasis added]
HIGHLIGHTS **USE IN SPECIFIC POPULATIONS**	• (b) (4)	(b) (4) DDMAC recommends that this information be deleted from the Highlights – Use in Specific Populations section.
FULL PRESCRIBING INFORMATION **DOSAGE FORMS AND STRENGTHS**	• 120 mg denosumab (**70 mg/mL**) in 1.7 mL solution, single-use vial.. [emphasis added]	DDMAC recommends not using a "slash mark" (/) to separate doses since it is commonly mistaken for the number 1. Instead use "per." For example do not use 70 mg/mL. Use 70 mg per mL.
FULL PRESCRIBING INFORMATION **WARNINGS AND PRECAUTIONS** (b) (4)	(b) (4)	
FULL PRESCRIBING INFORMATION - ADVERSE REACTIONS	**FULL PRESCRIBING INFORMATION - ADVERSE REACTIONS**	DDMAC recommends avoiding using "IV" as it is commonly mistaken for

Clinical Trials Experience (6.1) And **FULL PRESCRIBING INFORMATION - CLINICAL TRIALS Treatment of Patients with Advanced Malignancies Involving Bone (14.1)**	**Clinical Trials Experience (6.1)** • Patients who received **IV** bisphosphonates were excluded, as were patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure. And **FULL PRESCRIBING INFORMATION - CLINICAL TRIALS Treatment of Patients with Advanced Malignancies Involving Bone (14.1)** • In all three trials, patients were randomized to receive 120 mg [TRADENAME2] subcutaneous every 4 weeks or 4 mg zoledronic acid **IV** every 4 weeks. [emphasis added]	Roman number IV. Instead use "intravenous."
FULL PRESCRIBING INFORMATION **USE IN SPECIFIC POPULATIONS** **Pregnancy Category C (8.1)** **And** **FULL PRESCRIBING INFORMATION** **USE IN SPECIFIC POPULATIONS** **Pediatric Use (8.4)**	**FULL PRESCRIBING INFORMATION - USE IN SPECIFIC POPULATIONS Pregnancy Category C (8.1)** • In genetically engineered mice in which the gene for RANK ligand (RANKL; (b) (4) has been deleted (a "knockout mouse"), the absence of RANKL caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. **FULL PRESCRIBING INFORMATION - USE IN SPECIFIC POPULATIONS Pediatric Use (8.4)** • In neonatal rats, inhibition of RANKL (**target of [TRADENAME2]**) with a	The mechanism of action language (b) (4) will be used promotionally. DDMAC recommends that this language be deleted.

	construct of osteoprotegerin bound to Fc (OPG-Fc) at doses less than or equal to 10 mg/kg was associated with inhibition of bone growth and tooth eruption. [emphasis added]	
FULL PRESCRIBING INFORMATION - USE IN SPECIFIC POPULATIONS Renal Impairment (8.6) **And** **FULL PRESCRIBING INFORMATION - CLINICAL PHARMACOLOGY Pharmacokinetics (12.3)**	**FULL PRESCRIBING INFORMATION - USE IN SPECIFIC POPULATIONS Renal Impairment (8.6)** • (b) (4) **And** **FULL PRESCRIBING INFORMATION - CLINICAL PHARMACOLOGY Pharmacokinetics (12.3)** • (b) (4)	(b) (4) Is this information clinically relevant? If not, DDMAC recommends that this language be deleted.
FULL PRESCRIBING INFORMATION - CLINICAL PHARMACOLOGY Pharmacodynamics (12.2)	• (b) (4)	(b) (4)
FULL PRESCRIBING INFORMATION - CLINICAL TRIALS (b) (4) **and** **Table 2:** (b) (4) (b) (4)	(b) (4) And **Table 2:** (b) (4) (b) (4)	In general, (b) (4) (b) (4) (b) (4) ims (b) (4) If not, DDMAC recommends deleting these claims. (b) (4)

	Malignancies Involving Bone • (b) (4)	(b) (4) (b) (4) g (b) (4) (b) (4) If not, DDMAC recommends deleting these claims.
FULL PRESCRIBING INFORMATION - CLINICAL TRIALS (b) (4)	(b) (4) (b) (4)	

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 19, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Team Meeting Memo: Denosumab: BL STN 125320/7

A team meeting was held on October 19, 2010 to discuss the progress of the denosumab application review. Representatives from all review disciplines were in attendance.

All review disciplines provided updates regarding the status of their reviews and reported that most reviews are either complete or close to complete. Post-marketing commitments and requirements were also discussed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 19, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Labeling Memo: Denosumab: BL STN 125320/7

FDA's proposed labeling revisions sent to Amgen on October 19, 2010.

DEPARTMENT OF HEALTH AND HUMAN SERVICES | Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: October 18, 2010
To: Administrative File, STN 125320/7
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT 10/18/2010
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PFH 10/20/2010
Subject: Supplemental BLA
US License: #1080
Applicant: Amgen, Inc.
Mfg Facility: **For drug substance:** Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard, Boulder, CO 80301. USA.
FEI No. 3003072024

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany
FEI No. 3002806518

For drug product: Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA
FEI No. 1000110364.

Product: Trade name to be determined (Denosumab, AMG 162)
Dosage: Single-use, sterile, preservative-free solution for subcutaneous injection supplied in a vial; strength:120 mg (70 mg/mL).
Indication: (b) (4)
Due Date: October 25, 2010 (GRMP); November 18, 2010 (PDUFA)

Recommendation for Approvability: The drug substance section of the supplement is recommended for approval from a CMC microbiology product quality perspective.

SUMMARY:

Denosumab is a fully human IgG2 monoclonal antibody that inhibits the RANK ligand. It is derived from the Xeno-mouse™ technology and produced in CHO cells. The application contains information to support commercial production of denosumab drug substance at Amgen Colorado (ACO) located in Boulder, Colorado, and Boehringer Ingelheim Pharma (BIP), located in Biberach an der Riss, Germany, as well as drug product manufacture at Amgen Manufacturing Limited (AML), Puerto Rico.

The original BLA (STN 125320) for the 60 mg/mL strength denosumab was approved on June 1, 2010 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. The sBLA STN 125320/7 for the 70 mg/mL strength for the (b) (4) was submitted in eCTD format. This review covers the evaluation of the drug substance aspects of the sBLA STN 125320/7 from a microbiology product quality perspective.

ASSESSMENT:

This is a supplemental BLA requesting approval of denosumab (AMG 162), a fully human IgG2 monoclonal antibody that inhibits the receptor activator of the nuclear factor kappa B (RANK) ligand, for the (b) (4). Denosumab is produced in the Chinese hamster ovary (CHO) cells. The application contains information to support commercial production of denosumab drug substance at Amgen Colorado (ACO) located in Boulder, Colorado, and Boehringer Ingelheim Pharma (BIP), located in Biberach an der Riss, Germany, as well as drug product manufacture at Amgen Manufacturing Limited (AML), Puerto Rico.

Denosumab drug product is supplied as a sterile, preservative-free solution for administration by subcutaneous injection. The drug product contains 70 mg/mL denosumab, 18 mM acetate (1 mg/mL) and 4.6% (w/v) sorbitol (46 mg/mL) at pH 5.2.

This assessment only covers the drug substance aspects of the application. For drug product aspects of the application, please see the review by Dr. Donald Obenhuber.

3.2.S. DRUG SUBSTANCE

3.2.S.1. GENERAL INFORMATION

Denosumab is a fully human IgG2 monoclonal antibody that inhibits the RANK ligand. It is derived from the Xeno-mouse™ technology and produced in CHO cells.

This section should be reviewed by OBP/DMA reviewer.

3.2.S.2. MANUFACTURE

3.2.S.2.1. MANUFACTURE(S)

(b) (4)

Manufacture, release and stability testing, and storage of drug substance and raw materials. Also, storage of working cell bank:
Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard Boulder, CO 80301 USA
FEI No. 3003072024

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 65 88397 Biberach an der Riss, Germany
FEI No. 3002806518

Storage of master cell bank, raw material testing and release, drug substance release and stability testing, and storage:
Amgen Inc. (ACO) Longmont Facility
4000 Nelson Road Longmont, CO 80503 USA
FEI No. 3002892484

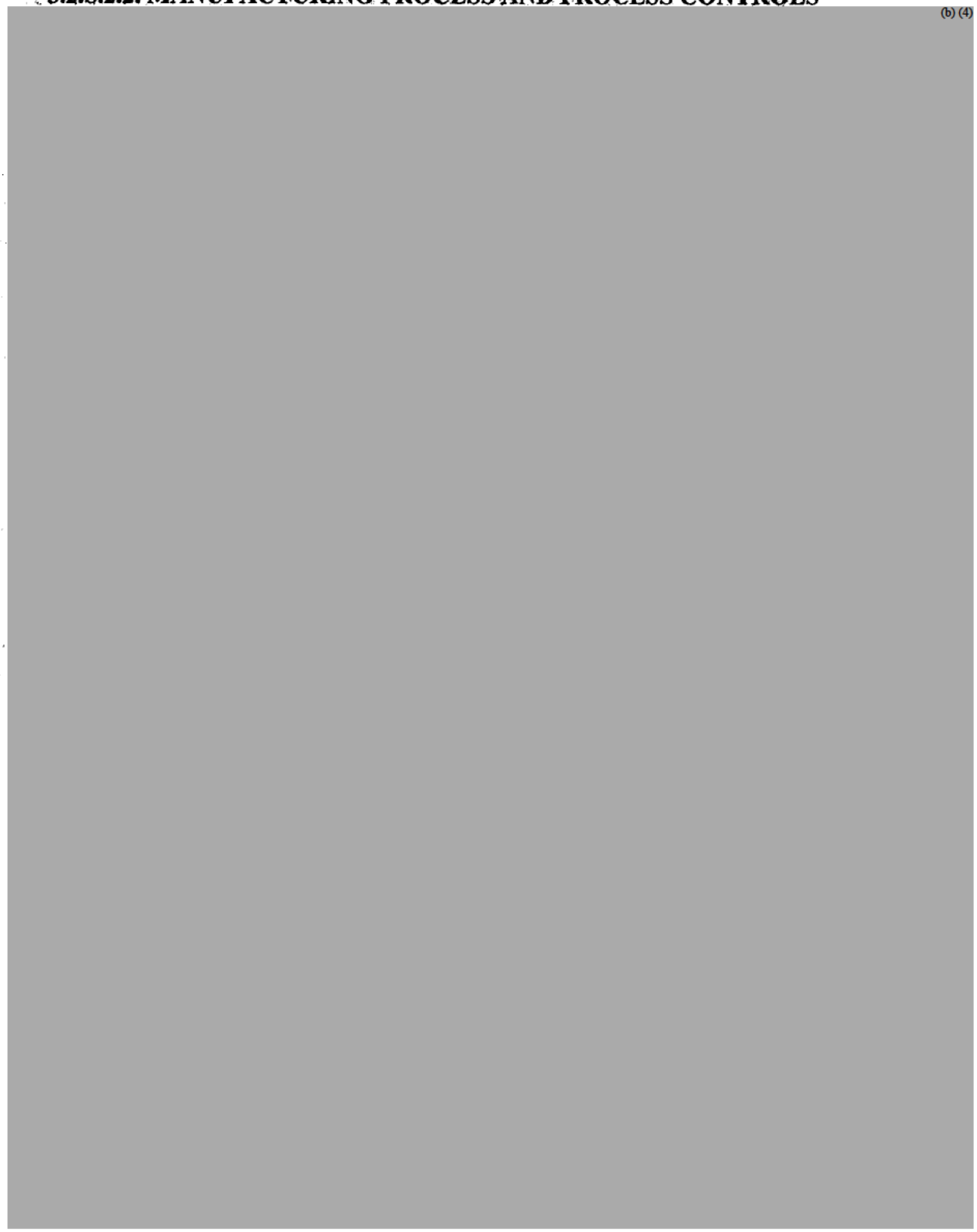
Raw material testing and release, and drug substance storage, release and stability testing:
Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA
FEI No. 1000110364

(b) (4)

Review comments: The manufacturing sites are same as the original BLA 125320 except for testing laboratories. The CGMP status of the manufacturing sites is acceptable.

3.2.S.2.2: MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)



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

(b) (4)

[redacted]

2.3.S.7. STABILITY:

Based on the stability data collected to date, a shelf life of 36 month was proposed for the drug substance. The stability data update should be reviewed by the OBP/DMA reviewer.

SATISFACTORY

3.2.A. APPENDICES:

3.2.A.1. FACILITIES AND EQUIPMENT:

(b) (4)

[redacted]

ENVIRONMENTAL ASSESSMENT:

Denosumab is subject to a categorical exclusion under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31(c). Denosumab is considered to be a nonhazardous, biodegradable product. The environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment.

cGMP STATUS:

There are no pending or ongoing compliance actions to prevent approval of STN 125320/7 at this time. The status of the drug substance manufacturing and release and stability testing sites as of 10/18/2010 is shown below:

Establishment	FEI	Inspection date	Classification	Profile
Amgen Inc. (ACO) LakeCentre Facility 5550 Airport Boulevard Boulder, CO 80301 USA	3003072024	August 23 - September 3, 2010	VAI	BTP and TRP
Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma) Birkendorfer Strasse 6588397 Biberach an der Riss Germany	3002806518	May 15-26, 2010	VAI	TRP and SVS
Amgen Inc. (ACO) Longmont Facility, 4000 Nelson Road Longmont, CO 80503 USA	3002892484	August 23 - September 3, 2010	VAI	BTP
Amgen Manufacturing, Limited (AML) State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777	1000110364	May 19-27, 2010	NAI	BTP and TRP

(b) (4)

[redacted]

CONCLUSION:

I. Sections 3.2.S of the sBLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The sBLA is recommended for approval from a CMC microbiology product quality perspective.

II. CMC product specific information and data should be reviewed by the OBP/DMA reviewer.

III. There are no follow-up inspection items associated with this supplement.

CC: DMPQ/BMT/Building 51, Suvarna
DMPQ/BMT/Building 51, Hughes, Patricia
HFD-107, Pierce, Melanie
DMPQ/BMT/Building 51, eCTD Files (STN:125320)

Archived File: S:\archive\BLA\125320\STN125320\7.rev.mem.BLA.10-18-2010.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 15, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/7; Teleconference (denosumab)

FDA Attendees:
Patricia Keegan, Division Director
Steve Lemery, Clinical Team Leader
Shan Pradhan, Clinical Reviewer
Michael Axelson, Clinical Reviewer
Hong Zhao, Clinical Pharmacology Team Leader
Grace Carmouze, Safety Project Manager
Melanie Pierce, Project Manager

Amgen Attendees:
Paul Eisenberg, SVP Regulatory Affairs (Telecon in MD)
Roger Dansey, Executive Director, Clinical Development (Thousand Oaks)
Steven Galson, VP Regulatory Affairs (Telecon in MD)
Brad Glasscock, Director Regulatory Affairs (Telecon)
Roy Baynes, VP, Global Development (Telecon in MD)
Sean Harper, SVP Global Development (Telecon in MD)
Sandra Milligan, Executive Director Regulatory Affairs (Thousand Oaks)
Laura Bloss, Executive Director, Clinical Development (Telecon)
Desmond Padhi, Executive Director, Clinical Development (Telecon in Canada for meeting)
John Bergan, Sr. Manager Regulatory Affairs (Thousand Oaks)
Jose Vega, VP Regulatory Affairs (Safety)
Andre Daniels, Executive Director Regulatory Affairs (Safety) (Telecon in Canada for meeting)
Bill Haddock, Director Regulatory Affairs (Safety) (Thousand Oaks)

This was an FDA-initiated teleconference that began at 2:30pm:

FDA proposed the following PMRs/PMCs for denosumab application 125320/7:

1. FDA proposed a small study to determine the risk of hypocalcemia in patients with severe compromised renal function to determine if this patient population can use denosumab safely. Amgen agreed.

2. FDA Proposed a PMR to discuss the safety and efficacy of denosumab in the pediatric population. Amgen agreed and will follow-up with more detailed plans and timelines after the pediatric ODAC scheduled for November 28, 2010.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 5, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/7; Information request denosumab

John,

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for denosumab.

We have the following requests for additional information:

Clinical Pharmacology:

1. Provide the bioanalytical report (including analytical procedure, method summary, assay performance, sample re-analysis) for the measurement of serum denosumab concentrations for the following clinical trials: 20050136, 20050244, 20050103, 20040113, and 20060446. Provide the method validation report (including assay range, inter-assay and intra-assay accuracy and precision, selectivity, specificity, stability, and dilutional linearity) if the ELISA was modified since provision of method validation report107381.

2. Provide the method validation report (including assay range, inter-assay and intra-assay accuracy and precision, selectivity, specificity, stability, and dilutional linearity) for the bioanalytical assay developed and validated to measure N-terminal telopeptide (NTX) in human urine and the bioanalytical report (including analytical procedure, method summary, assay performance, sample re-analysis) for dose-finding clinical trial 20040113.

Provide the indicated reports no later than Friday, October 15, 2010.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 5, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/7; Information request denosumab

John,

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for denosumab.

We have the following requests for additional information:

Clinical Pharmacology:

1. Provide the bioanalytical report (including analytical procedure, method summary, assay performance, sample re-analysis) for the measurement of serum denosumab concentrations for the following clinical trials: 20050136, 20050244, 20050103, 20040113, and 20060446. Provide the method validation report (including assay range, inter-assay and intra-assay accuracy and precision, selectivity, specificity, stability, and dilutional linearity) if the ELISA was modified since provision of method validation report107381.

2. Provide the method validation report (including assay range, inter-assay and intra-assay accuracy and precision, selectivity, specificity, stability, and dilutional linearity) for the bioanalytical assay developed and validated to measure N-terminal telopeptide (NTX) in human urine and the bioanalytical report (including analytical procedure, method summary, assay performance, sample re-analysis) for dose-finding clinical trial 20040113.

Provide the indicated reports no later than Friday, October 15, 2010.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Maternal Health Team Review

Date: September 29, 2010 **Date Consulted:** June 9, 2010

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D. 9/29/2010
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Biological Oncology Products (DBOP)

Drug: denosumab injection for subcutaneous use

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of denosumab injection for subcutaneous use labeling, BLA 125320/7

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of denosumab labeling.

INTRODUCTION

AMGEN submitted a BLA (125355) on May 19, 2010, for denosumab injection for subcutaneous use, for the [redacted] (b) (4) The application was resubmitted as Prior Approval Efficacy Supplement, BLA 125320/7 on July 23, 2010, for administrative purposes. A priority review was requested and granted for this application.

Prolia (denosumab injection for subcutaneous use) was approved June 1, 2010, for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Amgen is proposing a separate tradename and separate labeling for this oncology-use denosumab product and several tradenames are currently under review.

The Division of Drug Biologic Products (DBOP) consulted MHT to review the Pregnancy and Nursing Mothers labeling subsections of denosumab injection for subcutaneous use, for the [redacted] (b) (4)

BACKGROUND

Denosumab

Denosumab is a human monoclonal antibody (IgG2) that inhibits receptor activator of nuclear factor kappa B (RANK) ligand (a TNF-family molecule). RANK ligand (RANKL), also known as osteoprotegerin ligand, is a key regulator (with its receptor RANK) of bone remodeling and essential for the development and activation of osteoclasts. RANKL also regulates T cell/dendritic cell survival and lymph node organogenesis and is involved with the formation of lactating mammary glands in pregnancy.[1] Published reports[2,3] of reproductive and developmental toxicity studies in pregnant and neonatal mice lacking the RANKL signaling pathway resulted in fetal lymph node agenesis (prenatal exposure), and impaired dentition and bone growth (neonatal exposure). Pregnant mice showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum. Reproductive and developmental toxicity studies were performed in cynomolgus monkeys; however, maternal dosing was only done during the period of organogenesis, so the effects of denosumab on later fetal development were not assessed. In addition, lymph nodes were not examined in the fetal monkeys, even though previous mouse studies demonstrated that signaling via RANKL was necessary for lymph node development. Neither perinatal nor postnatal studies were performed in cynomolgus monkeys.

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team has developed a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate

---

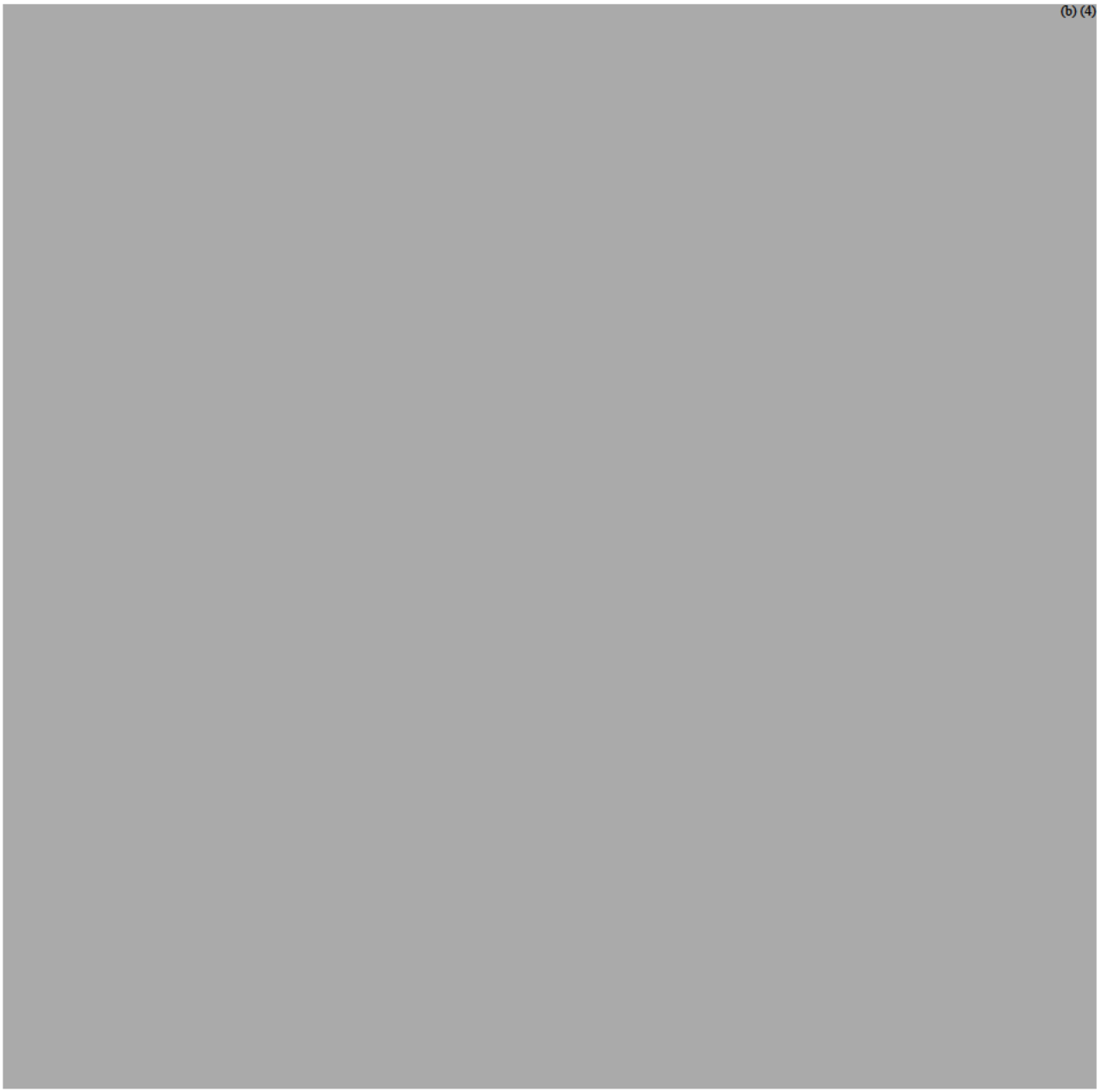
[1] Nakashima T, Wada T, Penninger J. RANKL and RANM as novel therapeutic targets for arthritis. Curr Opin in Rheumat, 2003, 15:280-7

[2] Fata j, Kong, y, Li, j, Sasaki, t, Irie-Sasaki J, Moorehead R, Elliott R, Scully s, Voura E, Lacey D, Boyle, W, Khokha R, Penninger J. The osteoclast differentiation factor osteoprotegerin-ligand is essential for mammary gland development. Cell, Sept 2000; 103:41-50

[3] Hororweg K, Cupedo T. Development of human lymph nodes and peyer's patches. Sem in Immune, 2008, 20:166-70

regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides MHT's suggested revisions to the Sponsor's proposed Pregnancy and Nursing Mothers subsections of denosumab injection, for sucuntaeous unjection for the treatment of patients with bone metastases from solid tumors.



(b) (4)

Sponsors Proposed Pregnancy and Nursing Mothers Labeling (July 23, 2010 version)

(b) (4)

DISCUSSION AND CONCLUSIONS

Denosumab injection for subcutaneous use was approved on June 1, 2010, for the treatment of postmenopausal women with osteoporosis at high risk for fracture. This review presents labeling recommendations for the pregnancy and nursing mothers subsections of denosumab labeling for an efficacy supplement currently under review for the (b) (4) (b) (4)

The sponsor did not submit any additional nonclinical developmental and reprotoxicty data with this denosumab application; however, (b) (4) . The Sponsor failed to include a required Pregnancy Category classification for the pregnancy subsection of labeling. Prolia (denosumab injection for subcutaneous use) was approved with a pregnancy category C classification. Pregnancy Categories will disappear with implementation of the Final Rule for Pregnancy and Lactation Labeling publishes. Until that time, a pregnancy category is required by regulation [21 CFR 201.57(c)(9)(i)(A)] for all systemically available prescription drug products. The Sponsor appropriately included information about their Pregnancy Surveillance Program in the labeling for this denosumab product. This continues to be the appropriate method for monitoring pregnancy outcomes with denosumab use.

MATERNAL HEALTH TEAM LABELING RECOMMENDATIONS

Provided below are the MHT labeling recommendations that were agreed upon with DBOP at a labeling meeting held on September 28, 2010.

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 14, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Team Meeting Memo: Denosumab: BL STN 125320/7

A team meeting was held on September 14, 2010 to discuss the progress of the denosumab application review. Representatives from all review disciplines were in attendance.

The review team provided updates regarding the status of their reviews and discussed initial labeling issues.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 2, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/7; Information request denosumab

Information request sent to Amgen via electronic mail on September 2, 2010.

Please address the following request from our statistical reviewer:

Please submit the SAS program file "t_sre_morbidity.sas" referenced in Table 14-4.4.1 of studies 103 and 136.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 2, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/7; Information request denosumab

Information request sent to Amgen via electronic mail on September 2, 2010.

Please address the following request from our statistical reviewer:

Please submit the SAS program file "t_sre_morbidity.sas" referenced in Table 14-4.4.1 of studies 103 and 136.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 1, 2010
To:	Patricia Keegan, M.D., Division Director **Division of Biologic Oncology Products (DBOP)**
Through:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	TRADENAME (denosumab) Injection
Application Type/Number:	BLA 125320/7 (formerly BLA 125355/0)
Applicant/sponsor:	Amgen Inc.
OSE RCM #:	2010-1313

The Division of Biologic Oncology Products (DBOP) requested that the Division of Risk Management (DRISK) review proposed patient labeling for Biologic Labeling Application (BLA) 125320/7 submitted by Amgen, Incorporated on May 14, 2010 for TRADENAME (denosumab)Injection.

DBOP issued a 74-Day Deficiency letter on July 30, 2010, informing the Applicant of potential review issues. DBOP requested that the Applicant [redacted] On August 23, 2010, Amgen Inc. submitted an Information Amendment: Response to Day 74 Questions. [redacted] This memo serves to close-out the consult request for RCM 2010-1313 for Denosumab Injection.

CC List

DBOP:

Patricia Keegan

Melaine Pierce

Shan Pradhan

Michael Orr

OSE/DRISK:

Sharon Mills

LaShawn Griffiths

Barbara Fuller

Mary Dempsey

Mary Willy

Claudia Karwoski

Elizabeth Donohoe

OSE/Management Staff:

Sue Kang

Robert Pratt

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 26, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Mid-Cycle Meeting Memo: Denosumab: BL STN 125320/7

A Mid-cycle meeting was held on August 26, 2010 to discuss the progress of supplement 125320/7. The clinical, statistical, nonclinical, and clinical pharmacology review disciplines presented for pre-specified time periods at the meeting.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 25, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/7; Information request denosumab

The following information request was sent to Amgen via electronic mail on 8.25.10:

Please provide details and direct references of how the hazard ratios and related 95% CIs were obtained from Novartis Studies 012, 018, and 019. This is related to the derivation of the NI margin used for Study 136 and Study 244.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 24, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Team Meeting Memo: Denosumab: BL STN 125320/7

A team meeting was held on August 24, 2010 to discuss the progress of the denosumab application review. Representatives from all review disciplines were in attendance.

The team provided updates regarding the status of their reviews.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 20, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/7; Information request denosumab

The following information request was sent to Amgen via electronic mail on 8.20.10:

Please submit your SAS code for the WLW method. The file name you reference in the clinical study report is "t_sre_time_wlw.sas." Please submit the file for all three studies (103, 136 and 244).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 5, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Team Meeting Memo: Denosumab: BL STN 125320/7

A team meeting was held on August 5, 2010 to discuss the progress of the denosumab application review. Representatives from all review disciplines were in attendance.

The review team provided updates regarding the status of their reviews and discussed the mid-cycle review presentation.

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Biologic Oncology Products

Application Number: 125320/7

Name of Drug: Denosumab

Applicant: Amgen, Incorporated

Material Reviewed:

Submission Date: May 14, 2010

Receipt Date: May 19, 2010

Submission Date of Structure Product Labeling (SPL): May 14, 2010

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

1. Highlights:

   a. The highlights limitation statement must appear in bold type.

   b. CONTRAINDICATIONS is a required heading – if no contraindications are known it must state "None."

   c. To report SUSPECTED ADVERSE REACTIONS, please insert a valid toll-free number and web address.

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by September 1, 2010
This updated version of labeling will be used for further labeling discussions.

Instructions to PM:

- Convey comments to applicant in 74-day letter or separate communication.
- Request applicant to re-submit labeling addressing the identified deficiencies. Ideally, resubmitted labeling should be submitted by mid-cycle. If not, specify a date before labeling discussions begin.
- Before labeling review and revision begins, ensure that updated (revised) labeling has been submitted and use this labeling for further labeling discussions.

_____
Melanie Pierce
Senior Regulatory Health Project Manager

Supervisory Comment/Concurrence:

_____
Karen D. Jones
Chief, Project Management Staff

Drafted: M. Pierce 7.28.10
Revised/Initialed:7.30.10
Finalized: 7.30.10
Filename: N:\\DBOP\current reviewers\Pierce\BLAs\denosumab\125320-7\communications\letters\74-day Letter 125320/7.doc
CSO LABELING REVIEW OF PLR FORMAT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 15, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/7; formerly 125355/0Information request denosumab

---

John,

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Vectibix™ (panitumumab).

We have the following requests for additional information:

1. Please identify where the transfer of obligation document, legally transferring the sponsor responsibilities to the CRO, is located in the BLA
2. Please identify where there a referenced contract agreement between you and (b) (4) and if so, where is it located in the BLA.

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # BLA# 125320/0	NDA Supplement #:S- BLA STN # 125320/7	Efficacy Supplement Type SE-
Proprietary Name: denosumab Established/Proper Name: XGEVA Dosage Form: Single-use vial Strengths: 120 mg in a 1.7 mL solutions		
Applicant: Amgen, Incorporated Agent for Applicant (if applicable): NA		
Date of Application: May 14, 2010 Date of Receipt: May 19, 2010 Date clock started after UN: NA		
PDUFA Goal Date: November 18, 2010	Action Goal Date (if different):	
Filing Date: July 18, 2010	Date of Filing Meeting: July 13, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NA		
Proposed indication(s)/Proposed change(s): (b) (4)		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** *http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html* ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 9838	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** *http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm* ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** *http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm*		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**NA**	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?				
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:** Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***				

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			Pediatric ODAC set for November 30, 2010
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Deferral included

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***		X		Requested Amgen submit certification on June 29, 2010
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		(b) (4) [redacted]
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	(b) (4) [redacted]			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** September 20, 2005 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** January 30, 2010; April 13, 2010	X			

If yes, distribute minutes before filing meeting				
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 13, 2010

BLA/NDA/Supp #: 125320/7

PROPRIETARY NAME: NA

ESTABLISHED/PROPER NAME: denosumab

DOSAGE FORM/STRENGTH: Single-use vial/120mg in a 1.7mL solution

APPLICANT: Amgen, Incorporated

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): (b) (4) (b) (4)

BACKGROUND: See attached document

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Melanie Pierce	Y
	CPMS/TL:	Karen Jones	N
Cross-Discipline Team Leader (CDTL)	Steven Lemery		Y
Clinical	Reviewer:	Shan Pradhan/Michael Axelson	Y
	TL:	Steven Lemery	Y
Social Scientist Review (*for OTC products*)	Reviewer:	NA	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	NA	
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	NA	
	TL:		

Clinical Pharmacology	Reviewer:	Jun Yang	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Vivian Yuan	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Michael Orr	Y
	TL:	Anne Pilaro	N
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	NA	
	TL:		
Product Quality (CMC)	Reviewer:	Sarah Kennett	Y
	TL:	Chana Fuchs	Y
Quality Microbiology *(for sterile products)*	Reviewer:	NA	
	TL:		
CMC Labeling Review	Reviewer:	Kimberly Rains	N
	TL:	Marilyn Welschenbach	N
Facility Review/Inspection	Reviewer:	Kalavati Suvarna	Y
	TL:	Patricia Hughes	N
OSE/DMEPA (proprietary name)	Reviewer:	Judy Park	Y
	TL:	Carlos Mena-Grillasca	Y
OSE/DRISK (REMS)	Reviewer:	Elizabeth Donohoe	Y
	TL:	Suzanne Robottom	N
OC/DCRMS (REMS)	Reviewer:	NA	
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Lauren Iacono-Connor	
	TL:	Leslie Ball	
Controlled Substance Staff (CSS)	Reviewer:	NA	
	TL:		
Other reviewers-DDMAC MHT	Nisha Patel Jeanine Best		N
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments:**	☒ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**: Immunogenicity reviewed by Product Quality reviewer.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: No consult necessary CMC reviewer determines the adequacy of the assessment request.	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments:**	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable ☐ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments:**	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Patricia Keegan

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

☒	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct labeling review and include labeling issues in the 74-day letter
☒	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 13, 2010

From: Melanie Pierce MMP, DBOP/OODP/CDER

Subject: Filing Meeting Minutes: Denosumab: BL STN 125332/7

This filing meeting for STN BL 125320/7 was a face-to-face, internal, FDA meeting. Attendees included Patricia Keegan, Steve Lemery, Shan Pradhan, Michael Axelson, Anne Pilaro, Michael Orr, Hong Zhao, Jun Yang, Chana Fuchs, Sarah Kennett, Vivian Yuan, Kun He, Latonia Ford, Elizabeth Donohoe, Judy Park, Carlos Mena-Grillasca, Sue Kang, Kalavati Suvarna, and Melanie Pierce.

DISCUSSION TOPICS:

- **Filing:** The team determined that the application will be filed.
- **Review Status:** The team concluded that this application is a priority review.
- **Advisory Committee:** The team determined that an advisory committee meeting is not necessary.
- **Meetings:** The team determined that standing meetings with Amgen are not necessary. Labeling and team meetings will be scheduled.
- **Consults**: DSI, DDMAC, OSE and MHT will require independent consults.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 11, 2010

From: Melanie Pierce, DBOP/OODP/CDER

Subject: First Committee Meeting Memo: Denosumab: BL STN 125355/0

Original Application: BL STN 125355/0:

Product: Denosumab

Submission Date: May 14, 2010

Received Date: May 19, 2010

Sponsor: Amgen, Incorporated

Indication: (b) (4)

This filing meeting for STN BL 125320/7 was a face-to-face, internal, FDA meeting. Attendees included Patricia Keegan, Steve Lemery, Suzanne Demko, Jeff Summers, Grace Carmouze, Shan Pradhan, Stacey Ricci, Michael Orr, Hong Zhao, Jun Yang, Chana Fuchs, Sarah Kennett, Vivian Yuan, Kun He, Mike Jones, Karen Jones, and Melanie Pierce.

The team discussed the following:

- The possibility of unbundling the application based on indication.
- Informing Amgen that the application will be converted to an efficacy supplement.
- Additional consults needed.
- Justification for the need of a Medication Guide.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 18, 2005 SKS

From: Sharon Sickafuse, CDER/OODP/DBOP

To: IND 9838

Subject: September 20, 2005, pre-Phase 3 meeting with Amgen regarding the proposed Phase 3 protocols

Meeting Date: September 20, 2005

Meeting Requestor: Amgen, Incorporated

Product: Denosumab [Human Monoclonal Antibody (AMG 162) to the Osteoprotegerin Ligand (RANKL)] and Chemotherapy

Proposed Use: [redacted] (b) (4)

Meeting Purpose: Discuss proposed Phase 3 protocols for treatment of [redacted] (b) (4) bone metastases to prevent skeletal related events or [redacted] (b) (4)

Background: The meeting package is amendment 65 submitted on August 19, 2005. FDA responses to Amgen's questions were faxed to them on September 19, 2005. The three protocols under discussion are:

20050103 "A Randomized, Double Blind, Double Dummy, Multicenter Study of Denosumab Compared with Zoledronic Acid in the Treatment of Bone Metastases in Men with Hormone Refractory Prostate Cancer"

20050136 "A Randomized, Double Blind, Double Dummy, Multicenter Study of Denosumab Compared with Zoledronic Acid in the Treatment of Bone Metastases in Advanced Breast Cancer"

20050147 "A Randomized, Double Blind, Placebo Controlled, Multicenter Phase 3 Study of Denosumab on Prolonging Bone Metastases-Free Survival in Men with Hormone Refractory Prostate Cancer"

Below are Amgen's questions, FDA's responses, and the discussion that occurred during the meeting.

Sponsor Questions and FDA Response:

1. *Does the Agency agree that the proposed 2 studies are sufficient to obtain the target indication of* [redacted] (b) (4);

FDA Response:

- The demonstration of clinical benefit in the Protocols 20050103 and 20050136, if modified to address the comments below, is adequate to support licensure.
- Please modify the primary endpoint to include only skeletal related events (SRE). [redacted] (b) (4)
- FDA cannot comment on the indication statement prior to review of the data.

Discussion: Amgen inquired if studies in other patient populations were required to support a [redacted] (b) (4) DBOP stated that they would discuss this issue with the Division of Oncology Drug Products to ensure consistency of approach with regard to labeling claims.

2. *Does the Agency agree with:*

   a. *Amgen's proposal for the primary endpoint as time to the first on study SRE* [redacted] (b) (4)

FDA Response:

- No, however, time to first on study SRE is an acceptable primary endpoint.
- The proportion of patients with a SRE, the time to symptomatic SRE, and overall survival will be important review issues in the analysis of this trial.
- The results of the non-inferiority analysis should be similar in the full analysis set and the per protocol population. Any differences in these results will need to be explained.

Discussion: Amgen expressed agreement on these points.

b. *Amgen's proposal for the overall multiplicity adjustment using the Hochberg procedure, the overall approach for the secondary endpoints (e.g., claiming superiority of Denosumab over zoledronic acid), and the approach of interim monitoring?*

FDA Response:

- The use of the Hochberg procedure to control for multiplicity is acceptable.
- If testing for non-inferiority is statistically significant, it is acceptable to then test for superiority.
- In the preamble to this question, there is a statement that the study may be stopped for evidence of superiority. Stopping rules are not included in your protocol. Please modify the protocols to provide detailed information on the study stopping rules for efficacy

Discussion: Amgen stated that they plan to revise the protocol to allow the Data Monitoring Committee to recommend early stopping if p=0.005. There is no plan to stop the study early due to early evidence of inferiority. FDA had no objections to this proposal, but will reserve finial comment pending review of the protocol and statistical analysis plan (SAP).

3. *Does the Agency agree with Amgen's proposal to use a synthesis approach and change the current protocols from the fixed margin approach?*

FDA Response: Yes, this is acceptable.

4. *Does the Agency concur with Amgen's proposed non-inferiority margin?*

FDA Response:

- This is acceptable for study 20050103.
- This is also acceptable for study 20050136. However, FDA's calculations led to a slightly greater non-inferiority cutoff. Regardless of which cutoff is chosen, the sample/event size calculation is incorrect for the assumptions provided. Based on FDA's calculations, approximately 715 events, not 1300 events, are needed to have 80% power at a Denosumab vs. zoledronic acid hazard ratio of 0.9 to rule out with at least 97.5% confidence that the Denosumab vs. zoledronic acid hazard ratio is 1.11 or greater.

Discussion: Amgen expressed agreement.

5. *Does the Agency agree with the proposed use of multiple-event analysis as a secondary analysis, thereby allowing patients with an SRE* (b) (4) *to remain in the study?*

FDA Response:

- Please provide the reference for Wei *et al* (1989). Amgen mentioned that they are now considering using the Prentice-Williams-Peterson modification of the Anderson-Gill approach. Amgen agreed to provide the reference for the Prentice *et. al.* paper.

Discussion: Amgen agreed to do this.

- Continuation of study drug following a SRE may be acceptable, if there are adequate data to justify the potential benefit to patients. Please provide evidence for the activity of Denosumab in studies 20040113 and 20040114.

Discussion: Amgen agreed to provide this information. Amgen noted that the primary endpoint for studies 20040113 and 20040114 was the bone absorption marker uNTx and determination of activity was based on this biomarker. They also agreed to provide information on any SREs in these studies. Study 20040114 is accruing slowly and Amgen could not state when this information will be available. Amgen plans to have a Data Monitoring Committee (DMC) monitor SREs and effect of continuation of Denosumab on SREs. Amgen will submit the DMC charter.

- FDA is concerned that patient continuation/discontinuation may be non-random and that conclusions concerning the continued efficacy of either study drug will be only exploratory in nature.

Discussion: Amgen acknowledged this concern.

- The acceptability of a 21-day interval in the definition of a second event cannot be determined based on the information provided. Consideration of the appropriateness of this choice will be undertaken in the review of the final study results.

Discussion: FDA said that the basis for selection of the 21 day interval is unclear. Amgen clarified that the goal is to not count the same event multiple times. The interval was based on use in previous regulatory submissions in this indication and appears to be empirically derived.

6. *Does the Agency agree:*

   a. *That providing the trials reveal a statistically significant result, BPI-SF score changes and/or changes in analgesic use for Denosumab and zoledronic acid can be included in the Prescribing Information?*

FDA Response: Results of validated, well-conducted assessments of patient reported outcomes may be included in product labeling. Statistically significant difference in the change in BFI-SF score over time will not be sufficient to support claims (see the following comments)

b. *That the between group difference in mean BPI-SF score change from baseline to end of study is a suitable score for the basis of statistical comparison?*

FDA Response:

- The difference between two groups with a similar time on study should be clinically meaningful in addition to statistically significant.

- A detailed plan for analysis of this endpoint, including the magnitude of effect to be shown, and validation of the instrument, should be provided prior to initiation of Protocols 20050103 and 20050136.

c. *With the use of superiority testing as the primary analysis of the primary pain assessment from the BPI-SF scale?*

FDA Response: The SAP provided in the pre-meeting package is insufficiently detailed to allow comment on testing procedures.

Discussion: Amgen stated that they plan to use the Brief Pain Inventory (BPI) as the primary assessment in the pain endpoint analysis plan. FDA confirmed that the BPI is accepted by the Agency for use in analgesic claims and has been adequately validated in that setting. Amgen stated that they will provide references from a comparable population that for baseline pain scores of 2-3, a 15-20% change from baseline is meaningful. FDA expressed concern that the analgesic score did not adequately capture differences in the use of pain medications which may lead to differences in the BPI. Amgen will provide additional information concerning the use of the analgesic score and its role in the analysis of the BPI. Amgen clarified that the pain secondary endpoint is tested at the same time as the SRE primary endpoint. They will provide a detailed analysis plan of the pain secondary endpoint.

7. *Does the Agency agree that the proposed study and statistical approach is sufficient to obtain an indication for the prolongation on bone metastasis free survival in patients with hormone refractory prostate cancer at high risk for developing bone metastases?*

FDA Response:

- The study design is acceptable. Overall survival, patterns of metastases, and the development of symptomatic metastases will be important review issues.

- Results from 20040138 and 20050103 should be consistent with findings in the proposed trial.

- FDA suggests that the clinical protocols provide a detailed description of the approach assessment of new lesions on bone scan; the protocols should specify the hierarchy of studies (X-ray then CT/MRI if non-diagnostic) that will be used to "confirm" the presence of metastatic disease seen on bone scan.

Discussion: Amgen stated that they agreed in principle, however the timely availability of a CT/MRI may be difficult at some non-U.S. sites and proposed a repeat x-ray instead. Amgen speculated that 20% or less of the events would be confirmed by repeat x-ray rather than CT or MRI. FDA stated that if the percentage of patients with confirmation in this manner is low (20% or less), this would be acceptable, but urged Amgen to select sites with CT and MRI capability. FDA also asked Amgen to perform an exploratory analysis to assess how the type of confirmatory method impacts the study results.

- Given the complex eligibility and stratification factors, FDA requests a description of the proposed plans to monitor study sites for adherence to entry criteria and accuracy of stratification criteria in randomization of eligible patients.

Discussion: Amgen agreed to provide this.

8. *Provided the unblinded data from the ongoing Phase 2 study (20040113) confirm a) the simulated multiple dose PK behavior and b) the safety profile observed in the aggregate blinded data, does the Agency agree that the Phase 3 program can proceed with the proposed dose regimen in Q4 2005 and Q1 2006?*

FDA Response:

- FDA cannot comment on the acceptability of dosing prior to review of the data.

- The proposed dose will, due to drug accumulation, lead to higher serum concentrations than those previously studied. Please provide a plan to monitor drug safety at this dose through use of the DMC.

Discussion: Amgen presented two overheads on this issue (see attachments). Amgen stated that based on the data provided in the two overheads, the proposed regiment for the Phase 3 study does not exceed the concentrations previously studied. Amgen does plan to use a DMC to monitor drug safety.

FDA Requests for Protocol Revisions:

9. Obtain vital signs and observe patients for an appropriate interval following the administration of Denosumab.

Discussion: Rather than modify the study, Amgen stated that they would provide data demonstrating that patients have not experienced infusion reactions when receiving Denosumab to justify not obtaining vital signs or requiring an observation period.

10. Assess for anti-Denosumab antibody levels at least three half-lives after the last dose of Denosumab.

Discussion: Amgen proposed a final evaluation of 6 months instead of three half-lives. FDA agreed to this proposal. Amgen also agreed to provide information on anti-Denoxumab antibodies in patients undergoing treatment for osteoporosis.

11. Increase the number of documented examinations of the oral cavity and provide follow-up information on all patients undergoing dental procedures.

Discussion: Amgen agreed to revise the protocol to include an examination of the oral cavity every 6 months and to provide follow-up information on all patients undergoing invasive dental procedures (i.e., not routine teeth cleaning).

12. Modify Protocol 20050147 to clarify the criteria concerning rising PSA in Section 4.1.7.

Discussion: Amgen agreed to do this.

13. Protocols 20050103 and 20050136 state that patients may be withdrawn for disease progression. If the intent is not to withdraw patients for any evidence of disease progression, but only for evidence of progression of bone metastases, please revise for clarity.

Discussion: Amgen clarified that their intent is to withdraw patients only for evidence of progression of bone metastases. They will clarify this in the protocols.

14. Include pharmacokinetic assessments of Denosumab in patients with breast and prostate cancer in at least two of the three protocols.

Discussion: Amgen agreed to do this in a subset of patients of each cancer type.

15. Provide a detailed description of the rules for censoring patients who have not experienced an event/are lost to follow up in the SAPs for Protocols 20050103 and 20050136.

Discussion: Amgen agreed to do this.

16. Protocol 20050147 includes the following stratification factor: PSA $\geq$ 8 ng/mL AND a doubling time $\leq$ 10 months (Y/N). From the paper by Smith *et. al.* it appears that such

patients have a similar prognosis. Please provide evidence that these two factors are additive in the determination of time to first bone metastasis.

Amgen will ask Dr. Smith for further information concerning the added value of each factor and submit this data to the IND.

17. Revise Protocol 20050103 for clarity with regard to:

    a. Whether patients who are given intravenous bisphosphonate will discontinue active therapy.

    b. The timing of the skeletal survey. The study calendar states that this will be performed every 4 and every 12 weeks.

18. Revise Protocol 20050136 to address the following discrepancies:

    a. Section 10.1 states that 100 mg of Denosumab will be administered while Section 6.1.1 states that this is 120 mg.

    b. Page 274 does not appear to belong to this protocol.

19. Revise Protocol 20050147 to correct the amount of Denosumab given (Section 10.1 states 100 mg, while Section 6.1 states 120 mg).

20. Protocol 20050147 should include criteria concerning the maximum time that Denosumab may be held prior to discontinuation.

Discussion: Amgen agreed to revise the protocol as requested in items 17-20 above.

FDA Requests for Informed Consent Document Revisions:

21. For Protocols 20050103 and 20050136, include information on the risk of continuation of blinded study drug following a SRE.

22. Clarify the specific conditions of when a patient may be withdrawn from the study.

23. Inform patients that a biomarker to predict SRE will be monitored.

Discussion: Amgen agreed to revise the informed consent document as requested in items 21-23 above.

FDA Requests for Additional Information:

24. Provide the charter for the independent radiology facility that will be used in the three studies.

25. All three protocols state that Denosumab is stable for four hours. If additional stability data are available, please modify all three protocols to reflect the extended stability period.

26. Provide information from the drug development program (planned and completed) concerning the timing of EKG monitoring relative to administration of Denosumab and to observed changes in calcium levels. Please also provide an overview of the results of EKG monitoring to date

Discussion: Amgen agreed to supply the information requested in items 24-26 above.

Additional Comments by Amgen:
Data from study 20040113 will be submitted in November.

Amgen stated their intent to submit a protocol for Denosumab in patients with multiple myeloma.

FDA Attendees:
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Biologic Oncology Products
Patricia Keegan, M.D.
Ellen Maher, M.D.
Kaushik Shastri, M.D.
Sharon Sickafuse, M.S.

Office of Biostatistics
Biologic Therapeutics Statistical Staff
Kyung Y. Lee, Ph.D.
Mark Rothmann, Ph.D.

Office of New Drugs
Study Endpoints and Labeling Team
Jane Scott

Musa Mayer, patient representative

Sponsor Attendees:
Amgen, Inc.
Mathew Arnold
Roy Baynes, V.P., Global Clinical Development Oncology
Robert Charnas, Ph.D., Associate Director, Regulatory Affairs
Crystina Cupp, Senior Manager, Regulatory Affairs
Roger Dansey, Director, Clinical Development Leader
Michael Elia, Senior Director, Regulatory Affairs
Carsten Goessl, M.D., Director, Clinical Scientist
Qi Jiang, Ph.D., Associate Director, Biostatistics
Susie Jun, M.S. Associate Director, Clinical Scientist
David Parkinson, V.P., Global Clinical Development Oncology
Steve Snapinn, Ph.D., Senior Director, Biostatistics
Martin Zagari, Senior Director, Outcomes Research

Attachments: Amgen's presentation on dosing
Attendee List

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 125320/S-007

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

BLA # 125320/0	BLA STN # 125320/7	If NDA, Efficacy Supplement Type:
Proprietary Name: XGEVA Established/Proper Name: denosumab Dosage Form: Single-use vial		Applicant: Amgen, Incorporated Agent for Applicant (if applicable): NA
RPM: Melanie Pierce		Division: Biologic Oncology Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is November 18, 2010	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain NA	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ Yes, dates 10.28.10
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Burst

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Version: 8/25/10

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 8/25/10

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date AP; November 18, 2010
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	11.18.10
• Original applicant-proposed labeling	5.19.10
• Example of class labeling, if applicable	NA

[3] Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	11.12.10
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 Acceptable 10.22.10
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 7.30.10 ☒ DMEPA 10.26.10 ☒ DRISK 9.01.10 ☒ DDMAC 10.21.10 ☐ CSS ☒ Other reviews MHT 9.29.10; OBP 11.17.10

Administrative / Regulatory Documents

❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	7.18.10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 9.22.10-PeRC recommendations in memo If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	 ☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	11.18.10; 11.15.10; 11.10.10; 10.28.10; 10.26.10(2); 10.19.10;

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

	10.05.10; 9.02.10; 8.25.10; 8.20.10; 7.30.10; 7.16.10 (2); 7.15.10; 6.29.10; 6.23.10
❖ Internal memoranda, telecons, etc.	10.26.10; 10.19.10; 9.14.10; 8.26.10; 8.24.10; 8.05.10; 7.13.10; 6.11.10
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 4.13.10;
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 6.09.10; 09.20.05
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	1.30.09-Structure and format
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11.18.10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11.17.10
PMR/PMC Development Templates *(indicate total number)*	☐ None 10.27.10
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL review
• Clinical review(s) *(indicate date for each review)*	11.17.10; 11.17.10; 9.23.10
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 25 of the clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 10.27.10
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 11.08.10

[5] Filing reviews should be filed with the discipline reviews.
Version: 8/25/10

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 10.25.10-concurrence is with the statistical review
Statistical Review(s) *(indicate date for each review)*	☐ None 10.25.10
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None concurrence is with the Clinical Pharmacology review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10.28.10
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 11.15.10
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11.15.10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None concurrence is with the Product Quality review 9.29.10
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 9.29.10
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☒ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed See facilities review
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Page 32 of Product Quality review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	11.10.10; 10.20.10
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: 6.23.10; 10.20.10 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.
Version: 8/25/10

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

1. Debarment Certification

Amgen hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Sandra A. Milligan, MD, JD
Executive Director, Global Regulatory Affairs and Safety

4/26/10
Date

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125320/0 | Supplement Number: 7 | NDA Supplement Type (e.g. SE5): _____

Division Name: DBOP | PDUFA Goal Date: November 18, 2010 | Stamp Date: 5/19/2010

Proprietary Name: Proposed-XGEVA

Established/Generic Name: Denosumab

Dosage Form: Sub Q Injection

Applicant/Sponsor: Amgen, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Treatment of postmenopausal women with osteoporosis at high risk for fracture
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: [redacted] (b) (4)

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☒ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☒ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit*	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☒	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☒	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

8/4/10

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

November 8, 2010

Veena Charu, M.D.
Pacific Cancer Medical Center Inc.
1801 West Romneya Drive, Ste 203
Anaheim, CA 92801

Dear Dr. Charu:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected. Between August 19 and August 26, 2010, Mr. Gene Arcy, representing the FDA, met with you and your staff to review your conduct of the following clinical investigations of the investigational drug Denosumab Injection (AMG 162), performed for Amgen Inc:

> Protocol #20050103, entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer", and
>
> Protocol #20050244, entitled "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma".

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Arcy, during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Jean M. Mulinde, M.D.

/Jean M. Mulinde, M.D./
Jean M. Mulinde, M.D.
Acting Team Leader
Good Clinical Practice Branch II
Division of Scientific Investigations
Bldg. 51, Rm. 5318
Office of Compliance
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125320/7

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

OCT 22 2010

ATTENTION: John Bergan
Senior Manager, Regulatory Affairs

Dear Mr. Bergan:

Please refer to your Biologics License Application (BLA) dated May 14, 2010, received May 19, 2010, submitted under section 351 of the Public Health Service Act, for Denosumab Injection, 70 mg/mL.

We also refer to your July 23, 2010, correspondence, received July 26, 2010, requesting review of your proposed proprietary name, Xgeva. We have completed our review of the proposed proprietary name, Xgeva and have concluded that it is acceptable.

The proposed proprietary name, Xgeva, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 23, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Melanie Pierce at (301) 796-1273.

Sincerely,

Carol Holquist 10/22/10

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Pierce, Melanie

From: Suvarna, Kalavati
Sent: Wednesday, October 20, 2010 8:29 AM
To: Pierce, Melanie
Subject: FW: Final TB-EER response for STN 125320/7 drug substance sites

From: Pohlhaus, Timothy
Sent: Friday, October 15, 2010 2:13 PM
To: Suvarna, Kalavati
Cc: Hughes, Patricia; Pohlhaus, Timothy; CDER-TB-EER
Subject: Final TB-EER response for STN 125320/7 drug substance sites

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for Amgen's STN 125320/7. Please see below for individual site compliance statuses. There are no pending or ongoing compliance actions for the drug substance sites below that would warrant withholding approval of this efficacy supplement.

Manufacture, release and stability testing, and storage of drug substance. Also, storage of working cell bank:

Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard Boulder, CO 80301 USA
FEI No. 3003072024

Inspected by DEN-DO August 23 - September 3, 2010 and classified VAI. This was a biennial GMP surveillance inspection. Although the site's profiles, BTP and TRP, have not yet been updated in FACTS, DEN-DO indicated that the site's profiles are acceptable and that they will be updated accordingly.

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 6588397 Biberach an der Riss Germany
FEI No. 3002806518

Inspected May 15-26, 2010 by IOG and initially classified VAI. The SVS and TRP profiles are currently listed in FACTS as acceptable, pending compliance officer review. Although FACTS has not yet been updated, ICB has indicated that no regulatory action will been pursued, the final classification of the inspection is VAI, and the profiles are acceptable.

Drug substance release and stability testing:
Amgen Inc. (ACO) Longmont Facility
4000 Nelson Road Longmont, CO 80503 USA
FEI No. 3002892484

Inspected by DEN-DO August 23 - September 3, 2010 and classified VAI. This was a biennial GMP surveillance inspection. Although the site's BTP profile has not yet been updated in FACTS, the DEN-DO indicated that the profile is acceptable and that it will be updated accordingly.

Drug substance storage, release and stability testing:

III. There are no follow-up inspection items associated with this supplement.

CC: DMPQ/BMT/Building 51, Suvarna
DMPQ/BMT/Building 51, Hughes, Patricia
HFD-107, Pierce, Melanie
DMPQ/BMT/Building 51, eCTD Files (STN:125320)

Archived File: S:\archive\BLA\125320\STN125320\7.rev.mem.BLA.10-18-2010.doc

cGMP STATUS:

There are no pending or ongoing compliance actions to prevent approval of STN 125320/7 at this time. The status of the drug substance manufacturing and release and stability testing sites as of 10/18/2010 is shown below:

Establishment	FEI	Inspection date	Classification	Profile
Amgen Inc. (ACO) LakeCentre Facility 5550 Airport Boulevard Boulder, CO 80301 USA	3003072024	August 23 - September 3, 2010	VAI	BTP and TRP
Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma) Birkendörfer Strasse 6588397 Biberach an der Riss Germany	3002806518	May 15-26, 2010	VAI	TRP and SVS
Amgen Inc. (ACO) Longmont Facility, 4000 Nelson Road Longmont, CO 80503 USA	3002892484	August 23 - September 3, 2010	VAI	BTP
Amgen Manufacturing, Limited (AML) State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777	1000110364	May 19-27, 2010	NAI	BTP and TRP

(b) (4)

[redacted]

CONCLUSION:

I. Sections 3.2.S of the sBLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The sBLA is recommended for approval from a CMC microbiology product quality perspective.

II. CMC product specific information and data should be reviewed by the OBP/DMA reviewer.

Review comment: The usefulness of the aerosol challenge to demonstrate container closure integrity of frozen drug substance is not known.

2.3.S.7 STABILITY:
Based on the stability data collected to date, a shelf life of 36 month was proposed for the drug substance. The stability data update should be reviewed by the OBP/DMA reviewer.

SATISFACTORY

3.2.A. APPENDICES:
3.2.A.1. FACILITIES AND EQUIPMENT:
Details of the manufacturing flow for the denosumab drug substance process and site maps of the Amgen Colorado-Lake Centre (ACO) and Boehringer Ingelheim Pharma GmbH and Co. Kg (BI Pharma) manufacturing facilities and diagrams depicting the air pressure plan, room air classification, and the flow of personnel, product, equipment, and raw materials were provided in Module 3.2.A.1, Facilities and Equipment.

The drug substance manufacture occurs in Building AC-7 at Amgen's Lake Centre multi-product facility in Boulder, Colorado. The cell culture area is dedicated for the production of mammalian products, including denosumab. The recovery area is used to manufacture both mammalian and microbial products. Other products manufactured in shared rooms at the ACO site are anakinra, palifermin, and romiplostim.

The drug substance is manufactured in G104 and F113 facilities of Boehringer Ingelheim Pharma GmBH&Co. KG, in Biberach, Germany. This is a contract manufacturing facility. Other products manufactured in the building are from the same cell type (CHO cell lines) and belong to the monoclonal antibodies, recombinant enzymes, and receptors class.

Review comment: The CGMP status of the manufacturing sites is acceptable.

ENVIRONMENTAL ASSESSMENT:
Denosumab is subject to a categorical exclusion under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31(c). Denosumab is considered to be a nonhazardous, biodegradable product. The environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment.

Batch analysis:
No new information was included in this section. The bioburden and endotoxin batch analysis data for the 70 mg/mL drug substance manufactured at ACO and BI Pharma were reviewed in the original BLA submission (see review by Dr. Kalavati Suvarna for BLA 125320/0 dated August 17, 2009).

2.3.S.5: REFERENCE STANDARD OR MATERIALS:
This section is reviewed by OBP/DMA.

2.3.S.6. CONTAINER CLOSURE SYSTEM:
The container closure system used for storage and shipping of denosumab bulk drug substance is a polycarbonate (PC) bottle with a polypropylene (PP) screw closure and (b) (4)

Upon receipt, the containers and closures are visually inspected to check for conformance to the Certificate of Analysis (COA) and for physical attributes. The containers and closures are autoclaved prior to use. Information on chemical resistance and extractables should be reviewed by OBP/DMA.

(b) (4)

Review comments: The manufacturing sites are same as the original BLA 125320 except for testing laboratories. The CGMP status of the manufacturing sites is acceptable.

3.2.S.2.2. MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)

Review comment: The changes to the manufacturing process are adequately described.

SATISFACTORY

3.2.S.2.3. CONTROL OF MATERIALS:
The section should be reviewed by OBP/DMA.

3.2.S.2.4. CONTROLS OF CRITICAL STEPS AND INTERMEDIATES:

(b) (4)

SATISFACTORY

3.2.S.2.5. PROCESS VALIDATION AND/OR EVALUATION:

(b) (4)

SATISFACTORY

2.3.S.4. CONTROL OF DRUG SUBSTANCE:

(b) (4)

Manufacture, release and stability testing, and storage of drug substance and raw materials. Also, storage of working cell bank:
Amgen Inc. (ACO) Lake Centre Facility
5550 Airport Boulevard Boulder, CO 80301 USA
FEI No: 3003072024

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 65 88397 Biberach an der Riss, Germany
FEI No: 3002806518

Storage of master cell bank, raw material testing and release, drug substance release and stability testing, and storage:
Amgen Inc. (ACO) Longmont Facility
4000 Nelson Road Longmont, CO 80503 USA
FEI No: 3002892484

Raw material testing and release, and drug substance storage, release and stability testing:
Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA
FEI No: 1000110364

(b) (4)

The original BLA (STN 125320) for the 60 mg/mL strength denosumab was approved on June 1, 2010 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. The sBLA STN 125320/7 for the 70 mg/mL strength for the treatment of patients with bone metastases from solid tumors was submitted in eCTD format. This review covers the evaluation of the drug substance aspects of the sBLA STN 125320/7 from a microbiology product quality perspective.

ASSESSMENT:

This is a supplemental BLA requesting approval of denosumab (AMG 162), a fully human IgG2 monoclonal antibody that inhibits the receptor activator of the nuclear factor kappa B (RANK) ligand, for the treatment of patients with bone metastases from solid tumors. Denosumab is produced in the Chinese hamster ovary (CHO) cells. The application contains information to support commercial production of denosumab drug substance at Amgen Colorado (ACO) located in Boulder, Colorado, and Boehringer Ingelheim Pharma (BIP), located in Biberach an det Riss, Germany, as well as drug product manufacture at Amgen Manufacturing Limited (AML), Puerto Rico.

Denosumab drug product is supplied as a sterile, preservative-free solution for administration by subcutaneous injection. The drug product contains 70 mg/mL denosumab, 18 mM acetate (1 mg/mL) and 4.6% (w/v) sorbitol (46 mg/mL) at pH 5.2.

This assessment only covers the drug substance aspects of the application. For drug product aspects of the application, please see the review by Dr. Donald Obenhuber.

3.2.S. DRUG SUBSTANCE

3.2.S.1. GENERAL INFORMATION

Denosumab is a fully human IgG2 monoclonal antibody that inhibits the RANK ligand. It is derived from the Xeno-mouse™ technology and produced in CHO cells.

This section should be reviewed by OBP/DMA reviewer.

3.2.S.2. MANUFACTURE

3.2.S.2.1. MANUFACTURE(S)

The denosumab drug substance manufacturing process consists of [redacted] (b) (4) [redacted] The denosumab drug substance manufacturing sites are (1) Amgen Inc. (ACO) located in Boulder, Colorado, and (2) Boehringer Ingelheim Pharma GmbH & Co. Kg (BIP) located in Biberach an der Riss, Germany.

The address and FEI numbers of the sites used for the manufacture of drug substance, raw material testing, storage of cell banks, contract testing laboratories, release and stability testing are listed below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: October 18, 2010
To: Administrative File, STN 125320/7
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT 10/18/2010
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PFH 10/20/2010
Subject: Supplemental BLA
US License: #1080
Applicant: Amgen, Inc.
Mfg Facility: **For drug substance:** Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard, Boulder, CO 80301. USA.
FEI No. 3003072024

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany
FEI No. 3002806518

For drug product: Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA
FEI No. 1000110364.

Product: Trade name to be determined (Denosumab, AMG 162)
Dosage: Single-use, sterile, preservative-free solution for subcutaneous injection supplied in a vial; strength 120 mg (70 mg/mL).
Indication: (b) (4)
Due Date: October 25, 2010 (GRMP); November 18, 2010 (PDUFA)

Recommendation for Approvability: The drug substance section of the supplement is recommended for approval from a CMC microbiology product quality perspective.

SUMMARY:

Denosumab is a fully human IgG2 monoclonal antibody that inhibits the RANK ligand. It is derived from the Xeno-mouse™ technology and produced in CHO cells. The application contains information to support commercial production of denosumab drug substance at Amgen Colorado (ACO) located in Boulder, Colorado, and Boehringer Ingelheim Pharma (BIP), located in Biberach an der Riss, Germany, as well as drug product manufacture at Amgen Manufacturing Limited (AML), Puerto Rico.

Pierce, Melanie

From: Ramanadham, Mahesh
Sent: Wednesday, June 23, 2010 12:05 PM
To: Pierce, Melanie
Cc: CDER-TB-EER
Subject: RE: EER Request for denosumab application 125355

Attachments: Initial TB-EER response STN125355-0.doc

Dear Melanie,

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for STN 125335/0. There are no pending or ongoing compliance actions to prevent approval of STN 125335/0. Please resubmit this TB-EER prior to the action date for an updated and final evaluation.

Initial TB-EER response STN125...

Sincerely,

Mahesh Ramanadham, PharmD/M.B.A.
LT., USPHS
Regulatory Compliance Officer
CDER, Office of Compliance
Division of Manufacturing and Product Quality,
Manufacturing Assessment and Pre-Approval Compliance Branch
(301)796-3272

From: Pierce, Melanie
Sent: Wednesday, June 09, 2010 1:54 PM
To: CDER-TB-EER
Subject: EER Request for denosumab application 125355

Hello all,
Please see the attached EER request for BLA application 125355 for denosumab. Please let me know if you need anything else or if I have omitted something.
Thank you,
Melanie

<< File: TB- EER form denosumab.doc >>

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: November 18, 2010

Applicant Name: Amgen, Incorporated
U.S. License #: 1080
STN(s):125355/0
Product(s): denosumab
Short summary of application: Original application soon to be converted to a supplemental application

---

FACILITY INFORMATION

Manufacturing Location:
Firm Name: Amgen Inc. (ACO)
Address: 5550 Airport Boulevard
Boulder, CO 80301
(LakeCentre facility)

FEI: **3003072024**

Short summary of manufacturing activities performed:
Working cell bank storage
Raw material storage, testing and release
Drug substance manufacture

---

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Drug substance in-process and release testing
Drug substance stability testing
Drug substance storage

Inspected by CDER-DMPQ June 8-12, 2009. Denosumab drug substance manufacturing processes were covered and found acceptable.

Manufacturing Location:
Firm Name: Amgen Inc. (ACO)
Address:4000 Nelson Road
Longmont, CO 80503
(Longmont facility)

FEI: 3002892484

Short summary of manufacturing activities performed:
Drug Substance Manufacturing:
Master cell bank and working cell bank storage
Raw material storage, testing and release
Drug substance in-process and release testing
Drug substance stability testing
Drug substance storage
Drug Product Manufacturing:
Drug product lot release
Drug product stability testing

Inspected January 31, 2008 by CDER-DMPQ. The BTP profile was covered, specifically including coverage of biological product raw material, drug substance, and drug product release testing, and is acceptable. The last comprehensive GMP inspection for the site was conducted by ORAHQ April 24- May 3, 2007 and was classified VAI. This site is a Tier I inspectional priority for FY '10. We find this site to be acceptable for the purposes of this BLA.

Manufacturing Location:
Firm Name: Amgen Inc. (ATO)
Address: One Amgen Center Drive
Thousand Oaks, CA 91320

FEI: 2026154

Short summary of manufacturing activities performed:
Drug Substance Manufacturing:
Master cell bank and working cell bank storage
Working cell bank production
Raw material testing, storage, and release
Drug substance storage
Drug Product Manufacturing:

Drug product storage

Inspected by LOS-DO April 7-11, 2008 and classified NAI. This inspection covered the Quality and Laboratory Systems, including the CBI, CTB, and CTL profiles.

Manufacturing Location:
Firm Name: Amgen Manufacturing Limited (AML)
Address:State Road 31
Kilometer 24.6
Juncos, Puerto Rico 00777

FEI: 1000110364
DMF 21000

Short summary of manufacturing activities performed:
Drug Substance Manufacturing:
Drug substance storage
Raw material testing, storage, and release
Drug substance lot release and stability testing
Drug Product Manufacturing:
Formulation
Fill and finish
Drug product in-process and release testing
Drug product stability testing
Packaging/Labeling
Drug product storage

Inspected July 27 – September 11, 2009 and classified VAI. The BTP and TRP profiles were covered and are considered acceptable.

Manufacturing Location:
Firm Name: Boehringer Ingelheim Pharma
GmbH & Co. Kg
Address: Birkendorfer Strasse 65
88397 Biberach an der Riss
Germany

FEI: 3002806518

Short summary of manufacturing activities performed:
Working cell bank storage
Raw material storage, testing and release
Drug substance manufacture
Drug substance in-process and release testing
Drug substance storage

Inspected by CDER-DMPQ May 11-19, 2009 and classified VAI. This was a Pre-Approval inspection for Denosumab drug substance manufacturing processes. The TRP profile was covered and is acceptable.

Pierce, Melanie

From: Suvarna, Kalavati
Sent: Wednesday, October 20, 2010 8:29 AM
To: Pierce, Melanie
Subject: FW: Final TB-EER response for STN 125320/7 drug substance sites

Melanie,

FYI, The TB-EER for denosumab application.

Thanks
Kala

From: Pohlhaus, Timothy
Sent: Friday, October 15, 2010 2:13 PM
To: Suvarna, Kalavati
Cc: Hughes, Patricia; Pohlhaus, Timothy; CDER-TB-EER
Subject: Final TB-EER response for STN 125320/7 drug substance sites

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for Amgen's STN 125320/7. Please see below for individual site compliance statuses. There are no pending or ongoing compliance actions for the drug substance sites below that would warrant withholding approval of this efficacy supplement.

Manufacture, release and stability testing, and storage of drug substance. Also, storage of working cell bank:

Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard Boulder, CO 80301 USA
FEI No. 3003072024

Inspected by DEN-DO August 23 - September 3, 2010 and classified VAI. This was a biennial GMP surveillance inspection. Although the site's profiles, BTP and TRP, have not yet been updated in FACTS, DEN-DO indicated that the site's profiles are acceptable and that they will be updated accordingly.

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 6588397 Biberach an der Riss Germany
FEI No. 3002806518

Inspected May 15-26, 2010 by IOG and initially classified VAI. The SVS and TRP profiles are currently listed in FACTS as acceptable, pending compliance officer review. Although FACTS has not yet been updated, ICB has indicated that no regulatory action will been pursued, the final classification of the inspection is VAI, and the profiles are acceptable.

Drug substance release and stability testing:
Amgen Inc. (ACO) Longmont Facility
4000 Nelson Road Longmont, CO 80503 USA
FEI No. 3002892484

Pierce, Melanie

From: Greeley, George
Sent: Friday, October 15, 2010 1:27 PM
To: Pierce, Melanie
Cc: Salis, Olga
Subject: BLA 125320 XGEVA

Importance: High

Hi Melanie,

The XGEVA (denosumab) deferral and plan was reviewed by the PeRC PREA Subcommittee on September 22, 2010.

The Division presented a deferral for patients birth to sixteen years of age.

- The PeRC recommends that the Division consider making the preclinical data a PREA PMR for this application.

The PeRC agreed with the Division to grant a deferral for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

PeRC PREA Subcommittee Meeting Minutes
September 22, 2010

PeRC Members Attending:
Lisa Mathis
Rosemary Addy
Kim Dettelbach (Cutivate and Plavix review only)
Robert "Skip" Nelson (Cutivate and Plavix review only)
Donna Katz (Did not review Natroba)
Patricia Dinndorf
Hari Sachs
Susan McCune
Tom Smith
Solomon Sobel
William Rodriguez
Wiley Chambers
David Maybee
Dianne Murphy
Alan Ou
Rachel Witten
Diane Murphy
Daiva Shetty
George Greeley
Coleen LoCicero
Peter Starke
Phillip Krause
Lily Mulugeta
Julia Pinto

Guests Attending:
Jeanine Best (PMHS)
Debbie Avant (OPT)
Allen Rudman (OCP)
Carin Kim (OB)
Catherine Lee (OPT)
Ruby Leong (OCP)
Patricia Brown (DDDP)
Amy Woitad (DDDDP)
Melissa Tassinari (PMHS)
Walt Ellenberg (OPT)
Dionna Green (OCP)
Barbara Hill (DDDP)
Dennis Bashear (OCP)
Dawn Williams (DDDP)
Yaning Wang (OCP)
Dave Kettl (DDDP)

Agenda

NDA 22-408 – Natroba (spinosad) (b) (4)
BLA 125320 – XGEVA (denosumab) Deferral/Plan
NDA 21-152 – Cutivate (fluticasone propionate) (b) (4)
NDA 20-839 – Plavix (clopidogrel) (b) (4)

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

(b) (4)

XGEVA Deferral/Plan

- BLA 125320/007, XGEVA (denosumab) Sub Q injections were studied for the (b) (4).
- This application was submitted on May 19, 2010 and has a PDUFA Goal Date of November 18, 2010.
- The sponsor plans to conduct phase I and phase II studies in patients ages birth to 18 years. A few nonclinical studies will be conducted first as this drug could possibly stunt bone growth. This product will be taken to ODAC to determine if this drug should be studied in pediatrics due to the risk of bone growth impairment and fracture.
- The ODAC will occur after the PDUFA date for this product. If the safety profile or risk/benefit profile changes then the trial can be modified. The Division could issue a PMR including all indications for this drug and then modify the PMR at a later date.
- With the concern for growing bones it might be best to look at a waiver for the youngest patient population.
- The primary studies for this indication included both a higher dose and a more frequent dosing schedule in adults that included roughly 6000 patients.
- The Division will defer studies because additional safety information is needed prior to approval.
- The PeRC recommends that the Division consider making the wanted preclinical data PREA PMRs.
- The PeRC agreed with the Division to grant a deferral because the product is ready for approval in adults.

(b) (4)

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125320/7

INFORMATION REQUEST
October 6, 2010

Amgen, Incorporated
Attention: John Bergan
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320-1799

Dear Mr. Bergan:

Please refer to your biologics license application (BLA) dated May 14, 2010 received May 19, 2010 submitted under section 351 of the Public Health Service Act for Denosumab.

Please also refer to your August 16, 2010 submission containing a proposed osteonecrosis of the jaw (ONJ) case registry.

We have reviewed the proposed ONJ case registry and have the following comments and requests for additional information:

(b) (4), (b) (5)

(b) (4), (b) (5)

If you have any questions, please contact the Regulatory Project Manager, Melanie Pierce at (301) 796-1273

Sincerely,

/ Patricia Keegan, M.D./
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

74-Day Deficiency Letter

STN: BL 125320/7

July 30, 2010

Amgen, Incorporated
Attention: John Bergan
Senior Manager, Regulatory Affairs and Safety
One Amgen Center Drive
Mail Stop 38-4C
Thousand Oaks, CA 91320-9978

Dear Mr. Bergan:

Please refer to your biologics license application (BLA), submitted May 14, 2010, received May 19, 2010, submitted under section 351 of the Public Health Service Act, for denosumab. Please also refer to our July 16, 2010 filing letter. While conducting our filing review we identified the following potential review issues:

CLINICAL:

1. Please withdraw the proposed [redacted] (b) (4)
(b) (4)

2. Submit the minutes from the closed session of the DSMB for study 20050103 or indicate where in the application that these minutes can be located.

3. Submit conflict of interest information for the adverse event adjudicators/committee members (osteonecrosis of the jaw and cardiac) or indicate where in the application that this information can be located.

4. Provide a summary analysis of the safety findings for denosumab obtained in all studies enrolling patients with multiple myeloma. Identify each study that has been conducted in patients with multiple myeloma outside of the U.S. IND. For each such study, provide a protocol synopsis to permit us to put the results in context.

LABELING:

5. With regard to the "Highlights" section of the package insert:

a. The highlights limitation statement must appear in bold type.

b. CONTRAINDICATIONS is a required heading – if no contraindications are known it must state "None."

c. To report SUSPECTED ADVERSE REACTIONS, please insert a valid toll-free number and web address.

Please address the identified deficiencies/issues and re-submit labeling by September 1, 2010. This updated version of labeling will be used for future labeling discussions.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission. We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 28, 2010.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Melanie Pierce, Regulatory Project Manager, at (301) 796-1273.

Sincerely,

/ Patricia Keegan, M.D./
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125320/0
(b) (4)
BLA 125320/5
BLA 125320/6
BLA 125320/7

INFORMATION REQUEST
July 16, 2010

Amgen, Incorporated
Attention: John Bergan
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320-1799

Dear Mr. Bergan:

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for denosumab for the treatment of patients with bone metastases from solid tumors.

On June 1, 2010, FDA approved Prolia™ (denosumab) STN 125320/0 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Therefore, BLA applications STN BL 125331/0, 125332/0, 125333/0 and 125355/0 were converted to supplements under STN BL 125320/0. The supplements are designated as follows:

1. STN BL 125320/0 Preserved: "Original application" as described under section 351 of the Public Health Service Act: Treatment of osteoporosis in postmenopausal women.

2. STN BL 125331/0-Changed to 125320/4: "Prior Approval Supplement-Efficacy" as described under 21 CFR 601.12(b) for the Prevention of osteoporosis in postmenopausal women.

3. STN BL 125332/0-Changed to 125320/5: "Prior Approval Supplement-Efficacy" as described under 21 CFR 601.12(b) for the treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer.

4. STN BL 125333/0-Changed to 125320/6: "Prior Approval Supplement-Efficacy" as described under 21 CFR 601.12(b) for the treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer.

5. STN BL 125355/0-Changed to 125320/7: "Prior Approval Supplement-Efficacy" as described under 21 CFR 601.12(b) for the [redacted]

[redacted] STN BL 125320/5, 125320/6 and 125320/7 will be managed and reviewed by the Division of Biologic Oncology Products. For additional information regarding the eCTD requirements for this STN administrative action please contact the Office of Business Process Support, Electronic Submissions esub@fda.hhs.gov.

When you submit application amendments containing information that is applicable to each supplement, please submit that information to the appropriate STN as identified above.

If you have any questions, please contact the Regulatory Project Manager, Melanie Pierce, at (301) 796-1273.

Sincerely,

/ Patricia Keegan, M.D./
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING ISSUES
July 16, 2010

Our STN: BL 125320/7

Amgen, Incorporated
Attention: John Bergan
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320-1799

Dear Mr. Bergan:

This letter is in regard to the supplement to your biologics license application (BLA), dated May 14, 2010, received May 19, 2010, submitted under section 351 of the Public Health Service Act for denosumab for the treatment of patients with bone metastases from solid tumors.

We have completed an initial review of your supplement for denosumab for the (b) (4) (b) (4) (BL STN 125320/7) to determine its acceptability for filing. Under 21 CFR 601.2(a), we filed your supplement today. The review classification for this supplement is Priority; therefore, the user fee goal date is November 18, 2010. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

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

REGULATORY:

1. Please add line numbers to the red-lined copy, FULL PRESCRIBING INFORMATION section of the package insert.

CHEMISTRY, MANUFACTURING AND CONTROLS:

2. (b) (4)

3. The proposed package insert (PI) for the 70 mg/ml presentation includes a 25°C/77°F storage period of up to (b) (4) Discussions regarding data necessary to support storage of drug product under these conditions occurred during the labeling meetings for the 60 mg/ml denosumab presentations under BLA STN 125320/0. Our concern was that in most cases the end users do not have controlled temperature conditions to assure product storage is maintained at or below 25°C when out of refrigeration. Temperatures may reach above 40°C in some areas of the United States, and drug product may be exposed to such extreme temperatures either at the physician's office or when transported by the patient after product is picked up from the pharmacy. Supporting stability data should be provided to the BLA for the 70 mg/ml presentation to allow for the inclusion of an extended storage period outside of refrigeration.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we will advise you in writing of any action we have taken and request additional information if needed.

Submit proposed content of labeling in SPL format.

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

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients (neonates: 0 – 30 days; infants: 1 – 24 months; children: 25 months – 12 years; adolescents: 13 -16 years). Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Melanie Pierce, Regulatory Project Manager, at (301) 796-1273.

Sincerely,

/ Patricia Keegan, M.D./
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125355/0

BLA ACKNOWLEDGEMENT
June 29, 2010

Amgen, Incorporated
Attention: John Bergan
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320-1799

Dear Mr. Bergan:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Denosumab

Date of Application: May 14, 2010

Date of Receipt: May 19, 2010

Our Submission Tracking Number (STN): BL 125355/0

Proposed Use: [redacted] (b) (4)

We are currently reviewing your application and have the following request for additional information:

Please provide the following regarding your request for pediatric deferral:

1. A certification for grounds for deferring the pediatric studies.

2. A summary of safety considerations based on non-clinical or clinical findings regarding the potential for adverse effects on skeletally immature patients.

3. Your rationale for requiring completion of additional non-clinical studies prior to commencing the proposed pediatric studies.

4. Timelines for protocol submission and study completion for the proposed phase 1b and phase 2 pediatric studies (if these studies are determined to be reasonably safe for the intended populations).

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

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call me Melanie Pierce at (301) 796-1273.

Sincerely,

/Karen D. Jones/
Karen D. Jones
Chief, Project Management Staff
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Pierce, Melanie

From: Pierce, Melanie
Sent: Wednesday, June 23, 2010 2:42 PM
To: 'Bergan, John'
Subject: CRO and Clinical inspection site information

John,
I know that all of the documentation for the CROs are located at Amgen, but did you provide current phone numbers for the study sites as well as the point of contact for the CRO with a phone number also?
Thanks,
Melanie

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

DRAFT RESPONSES

SPONSOR	Amgen, Incorporated
MEETING DATE:	June 9, 2009
TIME:	2:00pm-3:00pm
LOCATION:	White Oak Bldg 22, conference room 2327
APPLICATION:	IND 9838
DRUG NAME:	Denosumab {Human Monoclonal Antibody (AMG 162) to the Osteoprotegerin Ligand (RANKL)] and Chemotherapy
TYPE OF MEETING:	Type B
MEETING FORMAT	Teleconference
MEETING CHAIR:	Jeff Summers
MEETING RECORDER:	Melanie Pierce

TENTATIVE LIST OF FDA ATTENDEES:

Office of Oncology Drug Products
Division of Biologic Oncology Products

Patricia Keegan	Division Director
Joseph Gootenberg	Deputy Division Director
Jeff Summers	Clinical Team Leader
Suzanne Demko	Clinical Reviewer
Anne M. Pilaro	Pharmacology/Toxicology Supervisor
Melanie Pierce	Regulatory Project Manager

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

Chana Fuchs	Quality Team Leader
Sarah Kennett	Quality Reviewer

Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Hong Zhao,	Clinical Pharmacology Team Leader
Sarah Schrieber	Clinical Pharmacology Reviewer

Office of Biostatistics
Division of Biometrics 5

Mark Rothmann,	Biostatistics Team Leader
Kyung Yul Lee,	Biostatistics Reviewer

TENTATIVE LIST OF SPONSOR ATTENDEES:

Roy Baynes,	Vice President, Global Development
Ada Braun,	Medical Director, Clinical Development
Andre Daniels	Executive Director, Global Safety
Roger Dansey,	Executive Director, Clinical Development
Bradley Glasscock	Director, Regulatory Affairs
Graham Jang	Director, Pharmacokinetics and Drug Metabolism
Qi Jiang	Executive Director, Biostatistics
Janet Nokleby	Senior Manager, Regulatory Affairs
Makan Sarkeshik	Director, Global Safety
Steve Snapinn	Vice President, Global Biostatistics and Epidemiology
Winnie Sohn	Senior Scientist, Pharmacokinetics and Drug Metabolism
Rachelle Springer	Manager, Regulatory Affairs Operations
Jianming Wang	Senior Manager, Biostatistics

BACKGROUND

On March 6, 2009, Amgen requested a meeting to obtain guidance on the proposed Phase 3 design and statistical approaches to support the clinical development program of denosumab in early stage breast cancer.

Clinical studies are ongoing to evaluate denosumab for the (b) (4)

(b) (4)

On December 19, 2008, a BLA was submitted to the FDA for the following denosumab indications:

- BLA STN 125320/0/0 - Treatment and prevention of osteoporosis in postmenopausal women
- BLA STN 125331/0/0 Prevention of osteoporosis in postmenopausal women
- BLA STN 125332/0/0 – Treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer
- BLA STN 125333/0/0 – Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer

(b) (4)

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Linked Applications	Sponsor Name	Drug Name / Subject
IND 9838	AMGEN INC	Denosumab {Human Monoclonal Antibody (AMG 162) to the Osteoprotegerin Ligand (RANKL)] and Chemotherapy

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

/s/

MELANIE B PIERCE
06/05/2009

Pierce, Melanie

From: Nokleby, Janet [jnokleby@amgen.com]
Sent: Monday, June 08, 2009 2:44 PM
To: Pierce, Melanie
Subject: IND 9838 pre-phase 3 meeting

Hi Melanie,
As we discussed earlier, Amgen would like to cancel the pre-phase 3 meeting scheduled for tomorrow. There are some items that we would like to provide additional supportive information and we are working on some written responses to the FDA comments.

We are targeting submitting these responses to you tomorrow. I will notify you if that plan changes.

Thank you so much for your assistance in coordinating this effort.
Regards,
janet

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

SPONSOR	Amgen, Incorporated
MEETING DATE:	April 13, 2010
TIME:	1:00pm-2:30pm
LOCATION:	White Oak Bldg 22, conference room 1313
APPLICATION:	IND 9838
DRUG NAME:	Denosumab
TYPE OF MEETING:	Type B
MEETING FORMAT	Face-to-Face
MEETING CHAIR:	TBD
MEETING RECORDER:	Melanie Pierce

FDA ATTENDEES

Office of Oncology Drug Products
Division of Biologic Oncology Products

Patricia Keegan	Division Director
Suzanne Demko	Clinical Team Leader/Clinical Reviewer
Steven Lemery	Clinical Team Leader
Shan Pradhan	Clinical Reviewer
Anne M. Pilaro	Pharmacology / Toxicology Supervisor
Michael Orr	Pharmacology / Toxicology Reviewer
Melanie Pierce	Regulatory Project Manager

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

Chana Fuchs	Product Quality Team Leader
Sarah Kennett	Product Quality Reviewer

Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Hong Zhao,	Clinical Pharmacology Team Leader
Sarah Schrieber	Clinical Pharmacology Reviewer

Office of Biostatistics
Division of Biometrics 5

Kun He	Biostatistics Team Leader
Weishi Yuan	Biostatistics Reviewer

BACKGROUND

Amgen, Incorporated submitted a Type B, Pre-BLA meeting request on May 29, 2009 for "Denosumab (AMG 162; Human Monoclonal Antibody to RANK Ligand)." The meeting was scheduled for October 29, 2009, but was cancelled by Amgen on September 17, 2009 and rescheduled for April 13, 2010.

Denosumab is a fully human monoclonal IgG_2 antibody that inhibits RANK ligand (RANKL) by binding with high affinity (dissociation equilibrium constant [Kα] 3 x 10^{-12}M) and specificity to the soluble and cell membrane-bound forms of human RANKL. RANKL is an essential mediator of osteoclast formation, activation, and survival. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. Denosumab at 70 mg/mL (1.7 mL deliverable volume) is supplied in vials as a sterile, preservative-free solution intended for subcutaneous injection.

On September 20, 2005, a Type C end-of-phase 2 meeting was held to discuss the designs of the phase 3 studies intended to support an application for registration. During this meeting, agreements were reached regarding the primary endpoints, including use of the method to test for noninferiority; and the secondary endpoints, including acceptability to test for superiority if testing for noninferiority is statistically significant. In addition, the Hochberg procedure was accepted for use in overall multiplicity adjustment. Amgen also met with FDA on July 8, 2008 (with a follow-up teleconference on July 29, 2008) to discuss Chemistry, Manufacturing, and Controls (CMC) related aspects of the overall denosumab program. On January 30, 2009, a Type B meeting was held to discuss the structure and format of the proposed denosumab (b) (4) BLA. Agreements were reached regarding the content, format, and structure of the BLA, the efficacy and safety data to be included, the content of the 120-day safety update, as well as the contents of the nonclinical and CMC modules of the planned BLA. As a result of this meeting, studies 20050136 and 20050244 were identified as the key studies intended to support the proposed BLA. Subsequently, a third phase 3 study, 20050103, was also identified as supportive of the proposed (b) (4) BLA.

Amgen's meeting package contains a summary of the quality, nonclinical, and clinical content of the BLA, including key data from 3 phase 3 studies (20050136, 20050244, and 20050103) (b) (4) (b) (4) conducted under BB-IND 9838. As discussed and agreed during the January 30, 2009 meeting with FDA, Amgen still intends to submit a stand-alone biologics license application for denosumab (separate from the Bone Loss BLA) under the proprietary name (b) (4) for the treatment of (b) (4) (b) (4) FDA notes that prior advice regarding submission of a stand-alone BLA was made in the context that the BLA could be submitted to the FDA prior to approval of denosumab for any indication.

The meeting package was received March 10, 2010. The draft comments were sent to Amgen, Inc. on April 12, 2010.

---

synopsis CSRs; the results from the extension phase for study 20050103 will be provided at a later time. Amgen confirmed that all efficacy data for the primary analyses for studies 20050136, 20050244, and 20050103 and all safety data for these studies will be complete upon submission. FDA found Amgen's proposal acceptable.

3. **As further support for the primary safety analyses described in Question 2, does the FDA agree with the proposal described in Section 7.6.2 to include the integrated data from the primary blinded treatment phase form study 20050103 and the double-blind treatment phases of Studies 20050136 and 20050244 (which include the primary blinded treatment phase and the double-blind treatment phase extension) in the Integrated Analysis of Safety (IAS)?**

FDA Response: Yes. See FDA's response to question 2.

Discussion during meeting: Amgen acknowledged FDA's feedback and had no additional comments.

4. **Does the Agency require any clarifications regarding Amgen's approach for overall safety evaluation, as described in Section 7.6?**

FDA Response: No clarifications of the approach to the overall safety evaluation are required. However, include in the BLA submission the charters, procedures and meeting minutes for any adjudication committees used in evaluation of the denosumab safety data. At a minimum, include: the date the committees were appointed, a roster of committee members, what criteria were used for query of the safety databases and selection of events forwarded for committee review, criteria used for adjudication for each condition, procedures used to resolve differences of opinion among committee members. Please include minutes from all DMC meetings and minutes of classification meetings with detailed descriptions of analysis populations. Similarly, describe the data safety monitoring procedures in detail.

Discussion during meeting: Amgen acknowledged FDA's feedback and had no additional comments.

5. **Does the agency agree with the proposed updated content of the 120-day Safety update, as summarized in Section 7.8, including Amgen's proposal to provide integrated data from the double-blind treatment phases (which includes the primary blinded treatment phase and the double-blind treatment phase extension) of Studies 20050136, 20050244, and 20050103 and the synopsis clinical study report (CSR) summarizing the efficacy and safety data for the double-blind treatment phase for Study 20050103?**

FDA Response: No. The proposed update is more extensive that necessary and may be limited to case narratives for serious adverse events and case report forms for toxicity

FDA Response: No. The review status of the application will be determined after the BLA is submitted.

Discussion during meeting: Amgen acknowledged FDA's feedback and had no additional comments.

9. **Does the Agency have a status update regarding the review of Amgen's proposed proprietary name request for** [redacted] (b) (4)

FDA Response: No. The proprietary name request continues under review at this time.

Discussion during meeting: Amgen acknowledged FDA's feedback and had no additional comments.

Additional Clinical Comment:

10. Refer to addendum 1 for the Office of Oncology Drug Products general advice on planned submissions of marketing applications.

Discussion during meeting: Amgen acknowledged FDA's feedback and had no additional comments.

Statistical Comment:

11. FDA recommends that you use a stratified log-rank test for the superiority test.

Discussion during meeting: Reference slide 15: Amgen agreed that the use of a stratified log-rank test for superiority is a practical approach; however, Amgen used the stratified Cox Model to test for superiority. Amgen stated that the Cox model is equivalent to the log-rank test if there are no covariates in the Cox model and the score test is used. For the primary analysis, Amgen used a stratified Cox model which does not include covariates and the Wald test in the stratified Cox model which is almost identical to the score test. FDA stated that the log-rank test is not equivalent to the Cox model. The log-rank test is a non-parametric test while the Cox model is a semi-parametric model. It is difficult to verify the assumptions used in the Cox model. In addition, the log-rank test is preferred with new applications as it is easier to compare to historical data. Amgen proposed that because the CSR was already completed, they will provide the results for both the Cox and log-rank test in the summary of efficacy and integrated datasets. FDA agreed and stated that if the product were approved, the results of the log-rank test will be used in the label.

Clinical Pharmacology Comments:

proposed to revise this original agreement as they do not have the ability to comply with the new SDTM c3.1.2 and ADaM v2.1. FDA stated Amgen can use SDTM v 3.1.1 and ADaM v1.0 for this submission but will have to use SDTM v3.1.2 and ADaM v2.1for future submissions.

- **PHARMACOVIGILANCE PROPOSAL:**

  Discussion during meeting: Reference slide 21: Amgen proposed to implement a single global ONJ registry and asked if they could facilitate interactions between FDA and EMA. FDA will determine if interactions are needed with EMA and had no additional comments.

- **MEDICATION GUIDE AND COMMUNICATION PLAN:**

  Discussion during meeting: Reference slide 22: Amgen asked if FDA will require a medication guide. FDA determined that the need for a medication guide will be a review issue

ISSUES REQUIRING FURTHER DISCUSSION:

See action items below

ACTION ITEMS:

- Amgen will provide the CSRs for the extension phase data for study 20050103 once it is complete.
- Amgen will ensure that all efficacy and safety data will be complete upon submission.
- Amgen will provide the results from both the Cox and log-rank tests in the summary of efficacy as well as integrated datasets.

ATTACHMENTS AND HANDOUTS:

- Addendum 1-OODPs General Advice for Planned Marketing Applications
- Amgen slide deck

b) description of selected analysis datasets
c) key variables of interest, including efficacy and safety variables
d) SAS codes for sub-setting and combining datasets
e) coding dictionary used
f) methods of handling missing data
g) list of variable contained in every dataset
h) listing of raw data definitions
i) analysis data definitions
j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item)
k) documentation of programs

7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).

8) Pediatric Studies. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

9) A Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:

a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
b) Safety endpoints for Adverse Events of Special Interest (AERI)
c) Definition of Treatment Emergent Adverse Event (TEAE)
d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))
e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50

follow up, physician decision, or subject decision.

Narrative summaries should contain the following components:

a) subject age and gender
b) signs and symptoms related to the adverse event being discussed
c) an assessment of the relationship of exposure duration to the development of the adverse event
d) pertinent medical history
e) concomitant medications with start dates relative to the adverse event
f) pertinent physical exam findings
g) pertinent test results (for example: lab data, ECG data, biopsy data)
h) discussion of the diagnosis as supported by available clinical data
i) a list of the differential diagnoses, for events without a definitive diagnosis
j) treatment provided
k) re-challenge results (if performed)
l) outcomes and follow-up information
m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs upon request.

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

21) Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

22) The NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
b) Exposure-Response Relationships – important exposure-response assessments.
c) Less common adverse events (between 0.1% and 1%).
d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.

(www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

DATA STANDARDS
General Considerations

1) Follow SDTM Implementations Guide (SDTM v. 3.1.2, www.cdisc.org):

CDER has received numerous "CDISC-like" applications over the past several years in which sponsors have not followed the CDISC implementation guides.
The SDTM Implementation Guide (SDTMIG) should be followed carefully (CDISC.org). Section 3.2.2 of the SDTMIG provides general criteria conformance with the SDTM data model. These criteria should not be interpreted as the sole indication of the adequacy of submitted CDISC data, however, they should be followed unless otherwise indicated. If there is uncertainty with regards to implementation, the sponsor should discuss with the division.
2) Follow ADaM Implementation Guide (ADaM v. 2.1, www.cdisc.org):

For analysis datasets, sponsors should refer to the recently published ADaM Implementation Guide as well as the CDER Study Data Specifications Document and the CDER Analysis Data Request Document. It is expected that significant discussion between the sponsor and CDER clinical and statistical reviewers will be necessary to appropriately determine which analysis datasets as well as dataset content are needed to support application review.
3) Sponsor to discuss with review division and submit supporting documentation for non-Implementation Guide Decisions/Issues:

It is understood that CDISC data standards are evolving and that there may be instances in which the current implementation guides do not provide specific instruction as to how certain clinical trial data should be represented. In this instance, sponsors should discuss their proposed solution with the review division and submit supporting documentation at the time of submission that describes these decisions/solutions.
4) Define file: CDER would prefer that sponsors submit the define file in both .pdf and .xml formats.

5) SEND Data (pre-clinical data):

CDER is currently involved in pilot testing of the SEND standard for the submission of pre-clinical data. Sponsors who are interested in submitting SEND-compliant data should discuss with the toxicology reviewers from the appropriate review division.
6) CDISC legacy conversion and analysis data:

CDISC Conversion: It is strongly preferred that sponsors design their phase 3 trials using CDISC-defined data elements which allow for much easier SDTM domain creation (such as is possible with use of CDASH-specified CRFs). Conversion of non-CDISC data to CDISC format at the end of the drug development process is more challenging and if pursued, sponsors must ensure that converted SDTM datasets support key analyses contained in the sponsor's study/integrated reports. In addition, the accompanying analyses datasets should be derived from the SDTM data sets and also must support the analyses contained in the sponsors' reports.
7) Datasets: The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included. If the SAS programs use any macro programs, please provide all necessary macro programs.

15) **SUPPQUAL** is a dataset domain in SDTM. It is intended to include data variables that are not specified in SDTM. SUPPQUAL datasets are often used as a "waste-basket" for data elements that the sponsor is not sure what to do with. Discussion needs to occur if the sponsor intends to include important variables (that support key analyses) in the SUPPQUAL domains. One way to deal with this issue for important data elements that are likely to be needed to support review work, is to ensure that analysis datasets are prepared in a way that includes these and other relevant data elements.
16) In the **DM** domain, if ARMCD ('Planned Arm Code') equals "SCRNFAIL' then ARM ('Description of Planned Arm') must equal "Screen Failure'. Uncertainty occurs in the situation that a subject was not a screen failure, however, did not receive treatment for other reasons. The recommended solution for this situation is to use the terminology of 'NOTTXD' for the ARMCD variable and 'Not Treated' for the ARM variable, and make a comment in the define.xml that this is what was done. In addition, there is no current variable included in the **DM** domain that denotes actual therapy received which can be used to determine the safety population. For example, if a subject is randomized to one arm, but then actually receives therapy in accordance with a different arm, there is no variable in the DM dataset that captures this. The recommended solution for this is to include in the DM dataset a variable called "ACTARM" with a label of "Actual Arm". Terminology for this variable should include the name of the arm that the patient was treated under (consistent with the terminology used for the ARM variable) or "Not Treated" if the patient did not receive any therapy.
The DM variable "RFENDTC" should correspond to the date/time of last exposure to study treatment.
17) The DM domain lacks population flag variables to support analysis. The following population variables should be included in the DM domain:

EX domain **Exposure:** Provide the exposure data in a consistent format across all the studies ("one record" per dose per day).

DS domain: **Deaths:** The current SDTM version 3.1.2 does not address the need for a unique place for recording deaths. SDTM CDISC still contains several different places to record deaths. To simplify our safety analysis, for each patient who died there should be one record in the Disposition domain where DSCAT='DISPOSITION EVENT' and DSDECOD='DEATH'. When there is more than one disposition event the EPOCH variable should be used to distinguish between them so that if the death occurred during the treatment period EPOCH='TREATMENT' and if the death occurred during the follow-up period EPOCH='FOLLOW-UP'. Other values may be used for epoch depending upon the terminology used in the trial design model datasets.

AE domain (additional variable for MedDRA version harmonized): There is currently no variable in the AE domain that indicates if a variable was "treatment emergent." CDER would like the AE domain to include all adverse events recorded in any way in the patients' case report forms. An additional variable should be added to the AE domain that indicates if the event was or was not treatment emergent. This variable should be a simple yes or no (Y/N) response. In addition, the AE domain does not include variables for levels of the MedDRA hierarchy other than the preferred term or system organ class levels. To address this issue, sponsors should include the following variables: LLT (Lower Level Term), HLT (High Level

Variables

24) Required vs. Expected vs. Permissible:

CDISC data standards categorize variables as being Required, Expected, and Permissible. According to the standard, Permissible variables are optional. However, for the purposes of submission of CDISC data to CDER, all permissible variables for which data were collected or for which derivations are possible should be submitted. Examples of some of the permissible variables that CDER expects to see include:

- Baseline flags for Laboratory results, Vital Signs, ECG, Pharmacokinetic, Microbiology results
- EPOCH designators
- STDY variables in SE or other findings domains
- Exposure – total dose

25) Naming conventions (variable name and label) and variable formats should be followed as specified in the implementation guides.

26) Dates: Dates in SDTM domains should conform to the ISO8601 format. Examples of how to implement this are included in the SDTMIG. Because of the usefulness of numeric date formats in common software/systems used in CDER, it is expected that for the ADaM datasets, dates be also provided using numeric formats such as SAS and/or Oracle dates. Follow the same CDISC format for dates across all the trials and datasets.

27) USUBJID (unique subject identifier variable): Each individual patient must be assigned a single unique identifier (USUBJID) across the entire submission. An individual subject should have the same unique identifier across all datasets including SDTM and ADaM. Do not add leading or trailing spaces in any dataset.

28) Derived variables: The sponsor should be encouraged to include in the SDTM domains derived variables which essentially represent derived extensions of existing variables. An example would be the following: a creatinine clearance is derived from a patient's measured serum creatinine. This could be represented in the LB data set with LABTEST equal to calculated creatinine clearance. Of course, supporting documentation must be provided to describe the methods of calculation. Another example would be a baseline APACHE score. This score is a derivation of multiple elements of patient data, and often times, all such elements are not even completely captured in the CRF. This score could be represented in the Subject Characteristics (SC) domain. The SCTEST variable would be used with the field entry of "baseline APACHE score".

29) Imputed data variables: SDTM should not include any imputed data. If there is a need for data imputation, this should occur in an analysis dataset.

Common errors

30) Define.xml does not validate:

Please refer to www.cdisc.org/define-xml for instructions. Here sponsors can find the white paper for XML Schema Validation for Define.xml which provides guidance on validating define.xml version 1.0 documents against the define.xml XML schemas. Prior to submission, a sponsor may submit their define.xml for testing to determine whether it validates.

31) Invalid ISO8601 date format for SDTM datasets:

41) Narrative template format:

USUBJID	Narrative
01019929944	Patient made full recovery, and has no residual pain
01888777666	Patient is still hospitalized in ICU
Etc.	

Physician's Labeling Rule

Highlights
1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a)(4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

8.5 Geriatric Use *(not 8.4)*
20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."
Full Prescribing Information (FPI)
22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23) Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
24) Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]
26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection,

AMGEN

Denosumab Type B Pre-BLA Meeting

13 April 2010
White Oak Building 22, Conference Room 1313
10903 New Hampshire Avenue
Silver Spring, MD 20903

Meeting Objectives

1. Reach agreement with the Agency that the proposed clinical and nonclinical data package provide an adequate basis for BLA submission planned for May 2010
2. Reach agreement with the Agency regarding the proposed content of the 120 day Safety Update
3. Address items that require further clarification or confirmation. For all other items, please refer to Amgen's written responses

Pivotal Phase 3 Studies to be Provided in the BLA

Clinical Studies Supporting the Efficacy and Safety of Denosumab in the (b) (4)

- **20050136** – Denosumab vs. Zoledronic Acid in Subjects with Advanced Breast Cancer and Bone Metastases (N = 2046), event-driven, active-controlled
- **20050244** – Denosumab vs. Zoledronic Acid in Subjects with Other Solid Tumors and Bone Metastases or Multiple Myeloma (N = 1776), event-driven, active-controlled
- **20050103** – Denosumab vs. Zoledronic Acid in Subjects with Advanced Prostate Cancer and Bone Metastases (N = 1901), event-driven, active-controlled

AMGEN

Overall Safety Database

- **6883 subjects from 18 clinical trials included in the BLA for the Advanced Cancer Program**
- **5677 subjects in the 3 Advanced Cancer pivotal Phase 3 studies**
  - 2841 subjects treated with denosumab (120 mg Q4W) representing 3096 subject-years of therapy
  - 2836 subjects treated with zoledronic acid (4mg Q4W adjusted for renal function) representing 3046 subject-years of therapy

AMGEN

Question 2 FDA Response

- The proposed clinical data from the three phase 3 studies as well as the data summarized from the overall development program are adequate to support a BLA submission for the proposed (b) (4)
  All available safety and efficacy data should be submitted for the relevant studies. Trial synopses or abbreviated reports will not be sufficient.
- The extended blinded treatment phase for Study 20050103 will be ongoing at the time the BLA is submitted. FDA expects complete, cleaned and verified data up to the date of the data cut-off for this study to be submitted as part of the BLA, and a final study report to be submitted upon completion of the trial.

Question 2 Amgen Response

- The basis of this BLA submission is the primary analysis of phase 3 studies 20050136, 20050244, and 20050103 comprising 5732 patients (randomized). All 3 studies consist of a primary analysis phase, a short double blind extension phase, and an open label or survival follow-up phase.
- Amgen will provide the full CSRs from the completed primary analysis phases of studies 20050136, 20050244, and 20050103, which form the basis of the safety and efficacy analyses for this indication.
- Supportive information including incremental data from the double-blind (short) extension phase of studies 20050136 and 20050244 will be provided in synopsis CSRs. All analyses that were performed in the primary analysis phase were repeated and are included in the synopsis CSRs (i.e., all tables, listings, and graphs). Amgen confirms a study report including incremental data from the short double-blind extension phase will also be provided for Study 20050103 when available.
- Amgen confirms that all available safety and efficacy data will be submitted for the relevant studies.

Question 5 Amgen Response

- Amgen acknowledges the Agency's feedback and proposes a revised approach for the 120 Day safety update.
- Amgen confirms that the SAE narratives and hyperlinked CRFs for subjects who died or discontinued due to an adverse event will be provided for studies 20050136, 20050244, and 20050103.
- In addition, updated individual and integrated analyses from section 7.6.4 from the FDA briefing document will be provided.

Revised Proposal for 120 Day Safety Update Content

Study	Study Status at the 120-day Safety Update Data Cutoff	Information to be Provided in the 120-day Safety Update
Phase 3 Advanced Cancer Studies		
20050136 (OLE)	Ongoing, open-label extension phase	Case narratives for all SAEs and hyperlinked CRFs for subjects who died or withdrew due to an adverse event from the date of the DBE cutoff up to the data cutoff for the 120 Day safety update will be provided
20050244 (survival FU)	Ongoing survival follow-up	No adverse event information is being collected, as subjects are in survival follow-up. If any SAEs are reported, case narratives will provided
20050103 (DBE + OLE)	Ongoing, open-label extension phase	A safety analysis up to the end of the extended blinded treatment phase, including a synopsis CSR will be provided. Case narratives for all SAEs and hyperlinked CRFs for subjects who died or withdrew due to an adverse event from the date of the primary analysis cutoff up to the data cutoff for the 120 day safety update will be provided
Other Studies		
20080540 (OLE)	Ongoing, open-label extension phase (N= 34)	No information provided
20040114	Complete (N = 19)	
20050134	Ongoing treatment phase (N = 26)	
20040215	Ongoing follow-up phase (N = 20)	
20050147	Ongoing treatment phase	

Addendum 1: Clinical Comment 18

- **FDA Comment: Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision.**

Addendum 1: Clinical Comment 18

- **Amgen Response**
  - As previously agreed between Amgen and the FDA during the Type B meeting of January 30, 2009 and subsequent correspondence between Amgen and the Agency
    - Amgen will provide the case narratives for all patients who withdrew from investigational product or the trials due to an AE, all patients who experienced SAEs, and all patients who died during the trials.
    - Based on this previous agreement, Amgen proposes to not provide case narratives for subjects who terminated study drug or participation in the study prematurely for other reasons (ie, other, lost to follow up, physician decision, or subject decision).

Single Global ONJ Registry Questions for the Agency

(b) (4), (b) (5)

Medication Guide and Communication Plan

- **Based on FDA's current knowledge around the safety profile of the anti-resorptives, what does FDA anticipate will be required in the way of patient and physician communication for denosumab in the oncology (SRE) setting?**
  - Specifically, is it likely FDA will require a Medication Guide and/or Communication Plan?
  - If yes:
    - How would FDA like these to be submitted?
    - When would FDA like these to be submitted?
    - How can Amgen engage OSE in a timely fashion to ensure review and negotiation with a view to a PDUFA date approval?

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 9838

Amgen, Inc.
Attention: Bradley Glasscock, Pharm.D.
Director, Regulatory Affairs
One Amgen Center Dr.
Thousand Oaks, CA 91320

Dear Dr. Glasscock:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Denosumab {Human Monoclonal Antibody (AMG 162) to the Osteoprotegerin Ligand (RANKL)] and Chemotherapy."

We also refer to the meeting between representatives of your firm and the FDA on January 30, 2009. The purpose of the meeting was to discuss the proposed structure and format of the denosumab marketing application for (b) (4) (b) (4).

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

If you have any questions, call me at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

SPONSOR:	Amgen, Incorporated
MEETING DATE:	January 30, 2009
TIME:	10:00 a.m. to 11:00 a.m. (EST)
LOCATION:	White Oak Bldg. 22; Conference Room 1309
APPLICATION:	IND 009838
DRUG NAME:	Denosumab {Human Monoclonal Antibody (AMG 162) to the Osteoprotegerin Ligand (RANKL)] and Chemotherapy
TYPE OF MEETING:	Face-to-Face
MEETING CHAIR:	Patricia Keegan
MEETING RECORDER:	Melanie Pierce

LIST OF FDA ATTENDEES:

Office of Oncology Drug Products
Division of Biologic Oncology Products

Patricia Keegan	Division Director
Jeff Summers	Medical Team Leader
Suzanne Demko	Medical Officer
Anne Pilaro	Pharmacology / Toxicology Supervisor
Michael Orr	Pharmacology / Toxicology Reviewer
Melanie Pierce	Regulatory Project Manager
Norma Griffin	Regulatory Project Manager

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

Chana Fuchs	Quality Reviewer Team Leader
Sarah Kennett	Quality Reviewer

Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Sarah Schreiber	Clinical Pharmacology Reviewer

Office of Business Process Support
Division of Regulatory Review Support

Zei-Pan Huang	Supervisory Program Analyst
Constance Robinson-Kuiper	Regulatory Information Specialist

Office of Translational Sciences
Office of Biostatistics
Division of Biostatistics V
Kyung Yul Lee — Biostatistics Reviewer

Office of Translational Sciences
Office of Biostatistics
Division of Biostatistics VI
Charles Cooper — Medical Officer

Office of Drug Evaluation III
Division of Reproductive and Urologic Products
Vaishali Popat — Medical Officer / Staff Fellow

LIST OF SPONSOR ATTENDEES:

Amgen, Inc.

Steven Snapinn	Vice President, Global Biostatistics & Epidemiology
Laura Bloss	Executive Director, Clinical Development
Roger Dansey	Executive Director, Clinical Development
Bradley Glasscock	Director, Regulatory Affairs
Randy Steiner	Executive Director, Regulatory Affairs
David Feigal	Vice President Global Regulatory Affairs
Makan Sarkeshik	Director, Global Safety
Bill Dougall	Scientific Director, Preclinical Research
Susie Jun	Clinical Research Medical Director
Mike Abernathy	Senior Manager, Regulatory Affairs CMC
Qi Jiang	Executive Director, Biostatistics
André Daniels	Executive Director, Global Safety
Roy Baynes	Vice President, Clinical Development
Javier San Martin	Executive Director, Clinical Development
Barrie Nelson	Senior Manager, Biostatistical Programming
Michelle Fan	Senior Manager, Biostatistics

BACKGROUND:

Amgen, Inc. submitted a pre-BLA meeting briefing document on December 23, 2008 for Denosumab, Human Monoclonal Antibody (AMG 162) to the Osteoprotegerin Ligand (RANKL)} and Chemotherapy. Amgen is conducting a clinical program under BB-IND 9838 for the use of denosumab (proposed trade name (b) (4) in (b) (4) (b) (4) The submission of this Biologics License Application (BLA) is planned as early as December 2009. (b) (4)

The December 23, 2008 briefing document describes denosumab as a human IgG_2 monoclonal antibody to receptor activator of nuclear factor-κB ligand (RANKL), a full length immunoglobulin. Denosumab binds to RANKL with high affinity and specificity. This binding prevents RANKL from binding to RANK and inhibits the function, formation, and survival of osteoclasts, the cells that resorb bone. Inhibition of the RANKL pathway by administration of denosumab is expected to reduce the bone destruction and subsequent skeletal complications associated with bone metastases.

Denosumab will be supplied as a sterile, clear, colorless, preservative free liquid at a concentration of 70 mg/mL in vials with a deliverable volume of 1.7mL. For this indication, denosumab will be administered as a 120 mg subcutaneous (SC) injection once every 4 weeks.

Amgen's clinical development program for IND BB-IND 9838 includes three studies intended to support registration:

- Study 2005136 – A Phase 3, randomized, double blind, active control trial of 2049 patients to determine if denosumab is non-inferior to zoledronic acid in reducing the incidence of the first occurrence of skeletal-related events for patients with advanced breast cancer involving bone.
- Study 20050244 – A Phase 3, randomized, double blind, active control trial of 1799 patients to determine if denosumab is non-inferior to zoledronic acid in reducing the incidence of the first occurrence of skeletal-related events for patients with advanced solid tumors involving bone, including multiple myeloma.
- Study 20050103 – A Phase 3, randomized, double blind, active control trial of 1900 patients to determine if denosumab is non-inferior to zoledronic acid in reducing the incidence of the first occurrence of skeletal-related events for patients with advanced prostate cancer involving bone.

Amgen expects the results from Studies 20050136 and 20050244 to demonstrate a consistent treatment effect for denosumab across tumor and bone lesion types (osteolytic or osteoblastic) for the reduction in the occurrence of skeletal related events (SREs). Results from the primary analysis of these studies are expected to be available in Q2 and Q3 of 2009. Results from the primary analysis of Study 20050103 may be available in 2010, significantly after the scheduled

submission of the [redacted] (b) (4) BLA. Amgen intends to provide blinded SAE data as well as limited demographic data from this study in the BLA. If unblinded data becomes available at the time of the 120-day safety update, Amgen will provide unblinded, cleaned, and source-verified safety results from Study 20050103 in the 120-day safety update.

On December 19, 2008, a BLA was submitted to the FDA for the following denosumab indications:

- BB-IND 9837 – BLA STN 125320/0/0 - Treatment and prevention of osteoporosis in postmenopausal women
- BB-IND 11709 – BLA STN 125320/0/0 – Treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast and prostate cancer

Further, the denosumab clinical development program is evaluating treatment effects of denosumab in other settings that are not subject of the planned [redacted] (b) (4) BLA. These include:

- BB-IND 9838 – Prevention of bone metastases in men with prostate cancer at high risk of bone metastases
- BB-IND 9838 – Treatment of relapsed or plateau-phase multiple myeloma
- BB-IND 9838 – Treatment of giant cell tumor
- BB-IND 11707 – Inhibition of structural damage in subjects with rheumatoid arthritis (RA)

The meeting briefing packages were received on December 24, 2008.

Meeting Purpose: The purpose of this meeting is to discuss the proposed structure and format of the denosumab marketing application. The clinical indication is for [redacted] (b) (4)

Preliminary comments were sent to Amgen on January 28, 2009.

DISCUSSION:

Sponsor Submitted Questions and FDA Response:

Clinical/Statistical:

1. As defined in the protocols for the pivotal Phase 3 studies (20050136 and 20050244), the primary analysis is to occur on the anticipated date when approximately 745 subjects have experienced an initial on-study skeletal related event. As detailed in Appendix 1, full clinical study reports (CSRs) for these primary analyses will be prepared and included in the BLA. In addition, full CSRs will be provided for non-pivotal, Phase 2 advanced cancer clinical studies 20040113 and 20040114.

   Within Module 2 sections 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety, analyses will be presented for each individual study together with an integrated analysis of efficacy and safety for pivotal Phase 3 studies 20050136 and 20050244 to provide insight beyond the individual clinical studies. Section 6.3 describes the general plan for preparation of these clinical summaries, including the integrated analyses.

   To provide transparency on the safety profile of denosumab in placebo-controlled clinical studies in approximately 10,000 subjects in the PMO and HLT populations, Amgen Proposes to include the Summary of Clinical Safety (Module 2, Section 2.7.4) from the Bone Loss BLA (submitted to FDA on 19 December 2008 under STN 12532/0/0) in Module 5 of the Advanced Cancer BLA. Therefore, Amgen proposes to not include PMO/HALT CSRs from the Bone Loss BLA in the Advanced Cancer BLA.

   1a. Does the Agency agree with Amgen's proposal for provision of CSRs for advanced cancer pivotal studies 20050136 and 20050244 and non-pivotal studies 20040113 and 20040114 as the clinical basis of the Advanced Cancer BLA?

   FDA Response: Yes, Amgen's proposal to submit CSRs for the pivotal and non-pivotal studies is acceptable.

   Discussion during meeting: *Amgen acknowledged FDA's feedback and had no additional comments.*

   1b. Does the Agency agree with Amgen's proposal for integration and analysis of efficacy and safety data from the pivotal Phase 3 studies as described in Sections 6.3.1 and 6.3.2, in particular, does the FDA have comments on the SAPs for the Clinical Summaries of Efficacy and Safety provided in Appendix 3 and Appendix 4, and the SAPs for Studies 20050136 and 20050244 included in Appendix 6 and Appendix 7?

FDA Response: The SAP pertaining to the Clinical Summary of Safety appears acceptable. However, in addition to pooled safety data, safety data from each individual study should be submitted. Defer to Statistics Reviewer for efficacy summary.

The proposed primary analysis is not acceptable to support a broad labeling claim for the use of denosumab in the patients with (b) (4) (b) (4) For each study, substantial evidence should be provided on the efficacy of denosumab. Each comparison may be supportive of each other. Integrated analyses may be supportive.

Discussion during meeting: *Reference Amgen's responses to FDA's comments; not discussed during the meeting. Amgen agreed to provide the safety analysis and evidence of efficacy for studies 20050136 and 20050244.*

1c. **Amgen is exploring the inclusion of a "pilot" quantitative statistical analysis plan (QSAP) as part of the Advanced Cancer BLA. Is the FDA receptive to discussion on a potential "pilot" QSAP as part of the Advanced Cancer BLA during subsequent pre-submission meetings?**

FDA Response: The Division of Biologic Oncology Products (DBOP) in conjunction with the Division of Biometrics VI is agreeable to discussions regarding the optimal presentation of safety data as a Quantitative Safety Analysis Plan at the pre-BLA meeting and additional meetings as necessary.

Discussion during meeting: *Reference slide 6: Amgen agreed to provide a centralized index of all components of the safety analysis and hyperlinks to documents that comprise the safety analysis, e.g., SAPs, charters, adjudication procedures and the risk management plan. Amgen also intends to submit a draft table of contents for the pilot QSAP and a roadmap with hyperlinks to the IND for FDA review. FDA reminded Amgen that the pilot QSAP is on-going and that the guidance is still in draft format; however, FDA suggested Amgen focus on efficacy regarding the study design, data analysis and integration. FDA agreed to work with Amgen regarding the QSAP prior to the submission of the sBLA.*

1d. **Does the Agency agree with Amgen's proposal for inclusion of the Summary of Clinical Safety from the Bone Loss BLA in Module 5 of the Advanced Cancer BLA?**

FDA Response: No, Amgen's proposal to include the Summary of Clinical Safety from the bone loss BLA in Module 5 of the advanced cancer BLA is not acceptable. In general, summaries should be included in Module 2. However, if feasible, Amgen should cross reference BLA STN 125320 in the advanced cancer BLA and provide hyperlinks to the relevant data.

Discussion during meeting: *Reference slide 8. Amgen agreed to include the Summary of Clinical Safety in module 2; supporting documents and appendices will be included in module 5. Hyperlinks to BLA 1253210 will be provided as needed. FDA agreed with Amgen's proposals for module 2 and 5 but stated that the advanced cancer indication should be a stand-alone application. Any information contained in related sBLAs should not be cross-referenced, especially if the application is not approved. Amgen expressed understanding and had no additional comments.*

2. Amgen plans to submit safety data from the ongoing advanced cancer Phase 2 and 3 studies in the 120-day safety update. Section 6.4 describes Amgen's proposal for the 120-day safety update.

Does the Agency agree with the proposed content, structure, analysis, and estimated data cut off date for the 120-day safety update?

FDA Response: Yes, Amgen's overall approach for the 120-day safety update is acceptable.

Discussion during meeting: *Amgen acknowledged FDA's feedback and had no additional comments.*

3. Amgen plans to provide case report forms (CRFs) from Phase 2 and Phase 3 advanced cancer studies (Phase 2 studies 20040113, Phase 3 studies 20050136 and 20050244) for all subjects who died on study, for all subjects who withdrew from the investigational product or the study due to an adverse event and for all subjects who experienced a serious adverse event. In accordance with the approach agreed to by the FDA for the bone loss BLA, the CRFs will be hyperlinked within the common technical document (CTD) at the page level with any changes in the CRF documentation hyperlinked to the query or documentation from which the change resulted.

Does the Agency agree with Amgen's proposal for inclusion of CRFs?

FDA Response: Yes, Amgen's proposal for inclusion of CRFs is acceptable.

Discussion during meeting: *Amgen acknowledged FDA's feedback and had no additional comments.*

4. Amgen used [redacted] (b) (4) as the independent imaging vendor for the pivotal Phase 3 studies. Data from these images were used in the analysis of key components of the efficacy endpoints (i.e., identification of confirmation of fracture or spinal cord compression as skeletal related events). The imaging charters will be submitted in the BLA. In addition, the datasets included in the BLA for each study will contain the event results from each independent reader and the final decision, thereby providing each

radiologists review of each assessment. Amgen does not plan to include individual radiographic images for each patient in the BLA unless otherwise requested by the FDA.

Does the Agency agree with this proposal?

FDA Response: Yes, Amgen's proposal with regard to imaging data is acceptable.

Discussion during meeting: *Amgen acknowledged FDA's feedback and had no additional comments.*

5. Consistent with Amgen's structure of the Bone Loss BLA, the Advanced Cancer BLA will be compliant with the CDISC SDTM Implementation Guide 3.1.1 for tabulation data and observe the CDISC ADaM 1.0 for analysis data. Therefore, Amgen proposes to follow the proposals and FDA feedback on the CDISC SDTM implementation as agreed during the Bone Loss meetings in February and October 2008 (FDA minutes provided in Appendix 5 and Appendix 6).

5a. **Does the Agency agree with Amgen's proposal for inclusion of datasets in the (b) (4) BLA?**

FDA Response: Yes, Amgen's dataset plan appears adequate.

5b. **Does the Agency agree with the proposed dataset structure for the (b) (4) (b) (4) BLA which will be provided in accordance with the agreements reached for the Bone Loss BLA?**

FDA Response: Yes.

5c. **Can the agency provide a point of contact within the Office of Business Process Support that Amgen can liaise with to follow-up on questions prior to submission of the BLA?**

FDA Response : Amgen may contact Connie Robinson-Kuiperi in OBPS with any general eCTD questions via email at constance.robinson-kuiperi@fda.hhs.gov. Questions regarding datasets should be directed to Zei-Pao Huang, email: zeipao.huang@fda.hhs.gov.

5d. **Amgen expects most submission data files to be less than 400 Mb in size. In line with previous guidance, no large SDTM (tabulation) datasets will be split. At least 6 ADaM (analysis) submission datasets are expected to be 1 to 3 Gb. Amgen proposes not to split these datasets into multiple smaller component datasets in the BLA. Does the Agency agree with this proposal? If splitting is desired, please provide specific guidance to Amgen on the desired method of splitting such large ADaM datasets.**

FDA Response: This is correct, if less than 400 MB, no splitting is required. Specific guidance on splitting analysis datasets that are 1-3 GB can be obtained in consultation with Zei-Pao Huang from OBP and the review team who will be examining the data.

5e. **Amgen proposes to supply numeric preferred term codes in addition to the decodes in the ACM ADaM datasets for the pivotal Phase 3 studies (20050136 and 20050244). In addition, Amgen proposes to supply Chemical Therapeutic Subgroup (Code and Decode) variables for each concomitant medication in the ACM datasets for these two studies. This presents the most granular level within the ATC hierarchy (level 4), and allows for the Therapeutic Subgroup (ATC level 3), Therapeutic Main Group (ATC level 2), and Anatomical Main Group (ATC level 1) to be derived. In accordance with FDA feedback from the Bone Loss pre-BLA meeting in October 2008 (Appendix 6), Amgen will supply all possible level 4 ATC codes/decodes associated with each medication record, however, these will not be used for analyses conducted by Amgen.**

Does the Agency agree with this proposal?

FDA Response emailed 1.28.09: Yes.

5f. **Aside from AB, PC, and PP, Amgen plans to include 7 custom SDTM domains in one or more studies in the BLA:**

- **CE (Clinical Events; this domain is intended to contain additional information about deaths.)**
- **DF (Disorder Findings; this domain is intended to contain additional information about bone metastases, malignancies, lesions along with details of specific treatments.)**
- **HE (Healthcare Event; this domain is intended to contain additional information about hospitalizations, out-patient visits or other healthcare utilization.)**
- **LS (Lesion Findings; this domain is intended to contain additional information about specifics of lesions.)**
- **NF (Non-vertebral Fracture Assessment; this domain is intended to contain non-vertebral fracture confirmation data from facture confirmation performed by a third-party vendor. This data is qualitative in nature.)**
- **SX (Surgery Events; this domain is intended to contain additional information about surgical events, basic information such as the type of surgery and date performed)**
- **VF (Vertebral Fracture Assessment; this domain is intended to contain vertebral fracture assessment data that produced a semi-quantitative score as a result. The assessments were provided by a third-party vendor.)**

All custom domains are designed in strict adherence to the guidance for creating new domains found in the SDTM-IF 3.1.1 (Section 2.6) and as such are considered SDTM compliant. Custom domains will follow the same validation procedures as used for published domains, based on the rules for the SDTM General Observation Class on which the custom domain was based.

Does the Agency agree with this proposal?

FDA Response: Yes.

5g. **Amgen intends to remap MedDRA terms from studies that were coded in different versions to a single, consistent version in the CSS datasets and analysis. Amgen proposes to retain both the original and remapped MedDRA hierarchy in the CSS adverse events ADaM datasets, to provide transparency to the Agency on which events changed preferred term or hierarchy mapping when the data was converted from one MedDRA version to another.**

Does the Agency agree with this proposal?

FDA Response: Yes. Amgen should also note that the MedDRA version utilized for the final remapping should be indicated in your submission.

Discussion during meeting: *Regarding responses 5a-5g: Amgen acknowledged FDA's feedback and will provide the requested information in the advanced cancer BLA.*

Chemistry, Manufacturing and Controls:

6. A freestanding BLA is proposed for the (b) (4) indication and may be submitted to the FDA prior to approval of the Bone Loss BLA. Therefore, Amgen intends to provide complete Modules 2.3, and 3 in the Advanced Cancer BLA. As the majority of the Chemistry, Manufacturing, and Controls (CMC) information will be identical to that submitted in the Bone Loss BLA, Section 6.1 details Amgen's proposal for identification of information that is new in the (b) (4) and information that is updated compared to that included in the Bone Loss BLA.

Does the Agency agree with Amgen's proposal for management of the CMC Module 2.3 and Module 3 information contained in the Advanced Cancer BLA?

FDA Response: Yes. Please include only the drug substance and drug product information that would be required for registration of the 70 mg/ml vial presentation. Please clearly delineate in the BLA the information that is unique to the advanced cancer BLA, as well as identifying sections that are unchanged from what was submitted under STN 125320 as such.

Discussion during meeting: *Reference slide 10: Amgen asked if the Bone Loss BLA was granted approval prior to the submission of the* [redacted] (b) (4), *would cross-referencing the entire drug substance section be appropriate. FDA stated that it would not be possible to cross-reference or create hyperlinks for BLAs in the CBER EDR. FDA expressed concern regarding Amgen's proposal due to formulation differences in the drug product BLAs. Amgen clarified that the formulation for the drug substance are identical not the drug product. FDA stated that there will be follow-up discussions regarding cross-referenced information common to different applications.*

Nonclinical:

7. Amgen intends to provide complete Modules 2.4, 2.6, and 4 in the [redacted] (b) (4) BLA. As for the CMC information, the majority of the nonclinical information will be identical to that submitted in the Bone Loss BLSA. Section 6.2 details Amgen's proposal for identification of information that is new in the [redacted] (b) (4) BLA, and information that is updated compared to that included in the Bone Loss BLA.

Does the Agency agree with Amgen's proposal for management of the nonclinical information in Modules 2.4, 2.6, and 4 contained in the [redacted] (b) (4) **BLA?**

FDA Response: FDA disagrees with the proposal to omit the following studies from Module 4.2.1.1 of the [redacted] (b) (4) BLA:

- R2004321 Effects of denosumab (AMG 162) on bone mass and bone resorption in aged human rank ligand knock-in mice
- R2004430 Effect of denosumab (AMG 162) on bone mass and resorption in human rank ligand knock-in mice
- 103981 AMG 162: A monthly subcutaneous injection osteoporosis prevention study for 16 months in the cynomolgus monkey
- 106564 A 12-month osteoporosis "switch" study in cynomolgus monkey
- R2006458 Comparison of two anti-resorptive therapies (alendronate vs AMG 162 monoclonal anti-RANKL antibody) on murine fracture healing

For the [redacted] (b) (4) BLA, FDA requires a complete dossier of the available nonclinical data; therefore, Amgen will need to include all final study reports in Module 4.2.1.1 including the studies listed above, as this information is essential for reviewing the nonclinical pharmacologic activity of denosumab. Furthermore, while updates to the nonclinical sections of the [redacted] (b) (4) indication BLA are reasonable, module 2.6.2.2 will need to include all the information relevant for any of the proposed indications. FDA requests that all changes relative to the previously submitted PMO and HALT bone loss BLA applications are clearly indicated in the dossier.

Discussion during meeting: *Regarding responses 5a-5g: Amgen acknowledged FDA's feedback and will provide the requested information in the* (b) (4) *BLA.*

Regulatory:

8. Amgen intends to market denosumab with proprietary names for different indications. On 30 July 2008, Amgen submitted to BB-IND 9837, Serial 0507 (cross referenced to BB-IND 9838, Serial 0431) a request for FDA review of the following proposed proprietary names.

   - PROLIA™ for the indications related to PMO and HALT (being studied under BB INDs 9837 and 11709, respectively, and subject to the Bone Loss BLSA submitted on 19 December 2008)
   - (b) (4) for the indications related to (b) (4) (being studied under BB IND 9838 and subject to the (b) (4) BLA that is anticipated to be submitted in December 2009)

   Does the Agency have a status update regarding the review of Amgen's proposed proprietary name request?

   FDA Response: No. Amgen's proposed request for two proprietary names remains under FDA review.

   Discussion during meeting: *Amgen acknowledged FDA's feedback and will provide the requested information in the* (b) (4) *BLA.*

Additional Clinical Comments:

9. The BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: http://www.fda.gov/cder/mapp/6010.3.pdf.

   a. To facilitate the review, FDA requests Amgen provide analyses, where applicable, that will address the items in the template, including:
      - Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
      - Exposure-Response Relationships - important exposure-response assessments.
      - Less common adverse events (between 0.1% and 1%).
      - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
      - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
      - Marked outliers and dropouts for laboratory abnormalities.

- Analysis of vital signs focused on measures of central tendencies.
- Analysis of vital signs focused on outliers or shifts from normal to abnormal.
- Marked outliers for vital signs and dropouts for vital sign abnormalities.
- Overview of ECG testing in the development program, including a brief review of the nonclinical results.
- Overdose experience.
- Explorations for dose dependency for adverse findings.
- Explorations for time dependency for adverse findings.
- Explorations for drug-demographic interactions.
- Explorations for drug-disease interactions.
- Explorations for drug-drug interactions.
- Dosing considerations for important drug-drug interactions.
- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Discussion during meeting: *Amgen confirms that the requested information will be provided in the* (b) (4) *BLA.*

10. FDA requests that all submitted datasets include the following information. Please note that some of the information may have been discussed above in FDA's responses to Amgen's questions.

a. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration. The integrated safety dataset should include the following fields/variables:

- A unique patient identifier
- Study/protocol number
- Patient's treatment assignment
- Demographic characteristics, including gender, chronological age (not date of birth), and race
- Dosing at time of adverse event
- Dosing prior to event (if different)
- Duration of event (or start and stop dates)
- Days on study drug at time of event
- Outcome of event (e.g. ongoing, resolved, led to discontinuation)
- Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
- Marker for serious adverse events
- Verbatim term

Discussion during meeting: *Reference slide 11: Amgen agreed to provide the requested information. FDA agreed with Amgen's proposals and had no additional comments.*

b. The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the verbatim term taken from the case report form.

c. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.

d. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

e. The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.

f. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.

g. In every dataset, all dates should be formatted as ISO date format.

Discussion during meeting: *Regarding responses 10b-10h: Amgen acknowledged FDA's feedback and will provide the requested information in the* (b) (4) *BLA.*

h. Provide a comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities. Also, provide a list of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The BLA analyses of the frequency of abnormalities across treatment groups are not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

Discussion during meeting: *Reference Amgen's responses to FDA's comments; not discussed during the meeting. Amgen will provide data from patients with potentially clinically significant laboratory or vital sign abnormalities in the Summary of Clinical Safety ADaM datasets. All other requested information will be provided in the advanced cancer BLA.*

i. For patients listed as discontinued due to "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

Discussion during meeting: *Reference Amgen's responses to FDA's comments; not discussed during the meeting: Amgen reviews reasons for discontinuation and tabulates the study disposition table according to the reason for discontinuation.*

j. If Amgen and/or FDA believes that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

Discussion during meeting: *Amgen acknowledged FDA's feedback and will provide the requested information in the advanced cancer BLA.*

11. FDA requests that, in addition to the CRFs discussed previously, Amgen provides case narratives for all patients who withdrew from the investigational product or the trials due to an adverse event, all patients who experienced SAEs, and all patients who died during the trials.

Discussion during meeting: *Reference slide 14. Amgen agreed to provide the case narratives for all patients who experienced SAEs and all patients who died during the trials. Amgen will provide listings for patients who withdrew from investigational product or the trials do to an AE. FDA requested Amgen provide case narratives for all patients who experience osteonecrosis events, including those cases evaluated by the adjudication process, but determined not to be SAEs.*

Additional Statistical Comments:

12. FDA reminds Amgen of advice regarding Protocol 20050244 previously conveyed in a letter to Amgen dated November 1, 2006:

> "We do not object to using a synthesis method for the primary analysis. However, the meta-analysis used to estimate the zoledronate effect uses patients having a wide variety of diseases. Direct and indirect comparisons were also used to determine the zoledronate effect. The patient population for which the estimate from the meta-analysis is unbiased and valid may not be the same as the patient population used for study 20050244. It is not clear that the estimate of the zoledronate effect from the meta-analysis is directly transferable to the current

trial. A quality assessment should be done of the transferability to this trial of the estimated pamidronate vs. placebo effect on the time to first skeletal-related event. Such an assessment cannot be made until after study 20050244 is complete. Also, the reproducibility of the effectiveness of Denosumab would need to be studied from the results of trials comparing Denosumab with zoledronate and studying the reproducibility of the zoledronate effect. The robustness of the results should also be evaluated in a determination of efficacy."

Discussion during meeting: *Reference Amgen's responses to FDA's comments; not discussed during the meeting. Amgen referenced previous submissions to the IND and agreed to perform assessments to evaluate the reproducibility of both the denosumab and zoledronic acid effect.*

13. FDA recommends that Amgen include in the BLA submission the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis.

Discussion during meeting: *Reference slide 15. Amgen agreed to provide the requested information for the SAS programs as well as the Summary of Clinical Efficacy (SCE) for all ADaM datasets and key efficacy endpoint tables. FDA found this proposal acceptable and had no additional comments.*

14. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will appear in the label.

Discussion during meeting: *Reference Amgen's responses to FDA's comments; not discussed during the meeting: Amgen will link the values in the label with the program and dataset used to derive those values.*

ADDITIONAL CLINICAL COMMENTS NOT CONVEYED DURING THE MEETING:

- SDTM datasets should be designed to follow all instructions in the SDTM Implementation Guide V3.1.2 (or later, as amended).
- ADaM datasets should be designed to follow all instructions in the ADaM Implementation Guide V1.0 (or later, as amended).
- All ADaM datasets must be based on the SDTM datasets provided and must support the concept, "same name, same meaning, same values" which requires that if an SDTM variable is placed into an ADaM dataset, then there must be no alteration in the content or meaning of the variable.

ISSUES REQUIRING FURTHER DISCUSSION
See action items below.

ACTION ITEMS

- *Amgen agreed to include the Summary of Clinical Safety in module 2; supporting documents and appendices will be included in module 5.*
- *Amgen and FDA will have follow-up conversations regarding the ability to cross-link common information in different applications.*
- *Amgen will provide the Integrated Summary datasets for all Phase 2 and 3 trials.*
- *Amgen will provide case narratives for all patients who experience osteonecrosis, including cases determined to not be SAEs.*
- *Amgen will provide SAS programs and SCE for all ADaM datasets.*

ATTACHMENTS AND HANDOUTS

- *Amgen's slide presentation*
- *Amgen's responses to FDA's comments.*
- *Attendees list*

AMGEN

Denosumab Type B Pre-BLA Meeting

January 30, 2009
White Oak CDER Office Building 22
10903 New Hampshire Avenue
Silver Spring, MD 20993

Meeting Objectives

1. Reach agreement on the proposed structure and format of the marketing application for denosumab in the treatment of patients with advanced malignancies involving bone, thereby ensuring that the proposed electronic data package meets the needs and expectations of the Agency.
2. Respond to FDA's comments received in response to Amgen's questions provided in the briefing document

Previous FDA Meetings

(b) (4)

- September 20, 2005 (FDA minutes included as Appendix 3)
  - Pre-Phase 3 meeting to discuss the proposed Phase 3 pivotal program

Bone Loss (PMO/HALT indications)

- February 5, 2008 (FDA minutes included as Appendix 8)
  - Type C teleconference to discuss Format and Structure of the Bone Loss BLA
- July 8, 2008
  - Type B Pre-BLA meeting to discuss CMC Module 3 (Quality)
- October 21, 2008 (FDA minutes included as Appendix 9)
  - Type B Pre-BLA meeting to discuss clinical and nonclinical aspects of the denosumab program

Introduction to Amgen Responses

- Ensure Amgen's understanding of FDA's comments is consistent with expectations
- Ensure Amgen's planned [redacted] (b) (4) BLA meets the needs of the Agency to facilitate an efficient and smooth BLA review
- Address items that require further clarification or confirmation
  - For all other items, we refer you to Amgen's written response

Question 1c

- **Amgen is exploring the inclusion of a "pilot" quantitative statistical analysis plan (QSAP) as part of the Advanced Cancer BLA. Is the FDA receptive to discussion on a potential "pilot" QSAP as part of the Advanced Cancer BLA during subsequent pre-submission meetings?**
- ***FDA Response:*** *The Division of Biologic Oncology Products (DBOP) in conjunction with the Division of Biometrics VI is agreeable to discussions regarding the optimal presentation of safety data as a Quantitative Safety Analysis Plan at the pre-BLA meeting and additional meetings as necessary.*

Question 1c

- ***Amgen Response:*** *Amgen acknowledges the Agency's feedback and looks forward to sharing the proposed pilot QSAP for the denosumab Advanced Cancer BLA. As an overview, this document will provide a centralized index of all components of the safety analysis and hyperlinks to documents that comprise the safety analysis, e.g., SAPs, charters, adjudication procedures and the risk management plan. The content of this document will be directly taken from existing documents and no new analyses are planned. Amgen intends to submit a draft table of contents for the pilot QSAP to the IND shortly to solicit further FDA input.*
- *Does the Agency have any comments to this approach?*
- *Could the Agency provide a point of contact for further discussion?*

Question 1d

- **Does the Agency agree with Amgen's proposal for inclusion of the Summary of Clinical Safety from the Bone Loss BLA in Module 5 of the [redacted] (b) (4) BLA?**
- ***FDA Response:*** *No, Amgen's proposal to include the Summary of Clinical Safety from the bone loss BLA in Module 5 of the [redacted] (b) (4) BLA is not acceptable. In general, summaries should be included in Module 2. However, if feasible, Amgen should cross reference BLA STN 125320 in the [redacted] (b) (4) BLA and provide hyperlinks to the relevant data.*

Question 1d

- ***Amgen Response:*** *Amgen will provide the Summary of Clinical Safety of the Bone Loss BLA in Module 2. In addition, supportive appendices and datasets of the Bone Loss BLA will be located in Module 5 as appropriate. Hyperlinks within the* (b) (4) *BLA will be provided as needed. Does the Agency have any comments to this approach?*

Question 6

- **Does the Agency agree with Amgen's proposal for management of the CMC Module 2.3 and Module 3 information contained in the [redacted](b) (4) BLA?**
- ***FDA Response:*** *Yes. Please include only the drug substance and drug product information that would be required for registration of the 70 mg/ml vial presentation. Please clearly delineate in the BLA the information that is unique to the [redacted](b) (4) BLA, as well as identifying sections that are unchanged from what was submitted under STN 125320 as such.*

Question 6

- ***Amgen Response:*** *Amgen acknowledges the Agency's feedback. In order to gain further clarity regarding the identical sections of both filings, Amgen would welcome further advice from the Agency regarding the circumstances under which it may be appropriate to provide information in the SRE BLA by cross-referencing to the Bone Loss BLA STN 125320. Specifically, if the Bone Loss BLA were to be granted approval prior to submission of the* (b) (4) *BLA, would cross-referencing the entire drug substance section be appropriate?*

Additional Clinical Comments – 10a

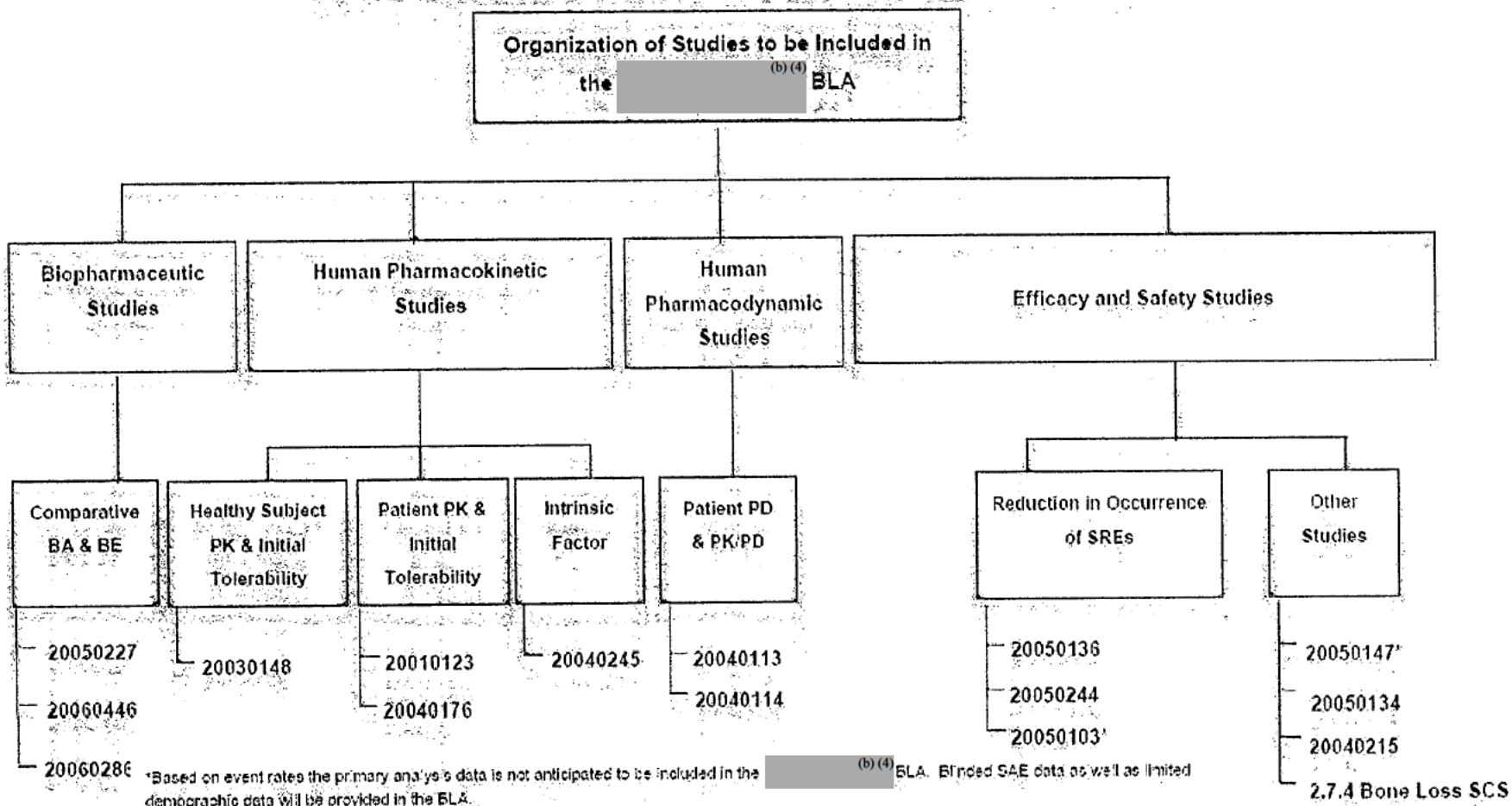
- FDA requests that all submitted datasets include the following information. Please note that some of the information may have been discussed above in FDA's responses to Amgen's questions.
  - 10a. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration. The integrated safety dataset should include the following fields/variables:
    - A unique patient identifier
    - Study/protocol number
    - Patient's treatment assignment
    - Demographic characteristics, including gender, chronological age (not date of birth), and race
    - Dosing at time of adverse event
    - Dosing prior to event (if different)
    - Duration of event (or start and stop dates)
    - Days on study drug at time of event
    - Outcome of event (e.g. ongoing, resolved, led to discontinuation)
    - Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
    - Marker for serious adverse events
    - Verbatim term

Additional Clinical Comments – 10a

- ***Amgen Response:*** *Amgen will provide the requested dataset for the Phase 2 and Phase 3 studies which will include data from Studies 20040113, 20040114, 20050136, and 20050244 (data from 20050103 will be included if available). Please refer to Figure 2 (page 38) from the pre-BLA briefing document for the studies planned to be included in the* (b) (4) *BLA. Does the Agency agree with this proposal?*

Additional Clinical Comments – 10a

Figure 2. Organization of Clinical Studies in the Planned (b) (4) BLA



*Based on event rates the primary analyses data is not anticipated to be included in the (b) (4) BLA. Blinded SAE data as well as limited demographic data will be provided in the BLA.

BA = bioavailability; BE = bioequivalence; SCS = Summary of Clinical Safety; PD = pharmacodynamics; PK = pharmacokinetics; SRE = skeletal-related

Additional Clinical Comments – 11

- FDA requests that, in addition to the CRFs discussed previously, Amgen provides case narratives for all patients who withdrew from the investigational product or the trials due to an adverse event, all patients who experienced SAEs, and all patients who died during the trials.
- ***Amgen Response***: *Amgen confirms that case narratives will be provided for all patients who experienced SAEs, and all patients who died during the trials. For patients who withdrew from investigational product or the trials due to an adverse event (including serious and non-serious AEs), Amgen proposes to provide listings which will capture all relevant information from the case report forms. Does the Agency agree with this approach?*

Additional Statistical Comments – 13

- FDA recommends that Amgen include in the BLA submission the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis.
- ***Amgen Response***: Amgen will provide these programs as requested for Studies 20050136 and 20050244 and the Summary of Clinical Efficacy (SCE) for all ADaM datasets as well as key efficacy endpoint tables displaying inferential statistics (i.e., primary and secondary endpoints of the individual studies and corresponding endpoints in the SCE). Does the Agency agree with this proposal?

Wrap-up

FDA's Preliminary Responses to Questions Included in Amgen's Briefing Document Submitted on 19 December 2008 (BB-IND 9838, Serial No. 0497)

AMGEN'S RESPONSES TO THE AGENCY'S COMMENTS ARE PROVIDED IN RED TEXT

Clinical/Statistical:

1. As defined in the protocols for the pivotal Phase 3 studies (20050136 and 20050244), the primary analysis is to occur on the anticipated date when approximately 745 subjects have experienced an initial on-study skeletal related event. As detailed in Appendix 1, full clinical study reports (CSRs) for these primary analyses will be prepared and included in the BLA. In addition, full CSRs will be provided for non-pivotal, Phase 2 advanced cancer clinical studies 20040113 and 20040114.

   Within Module 2 sections 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety, analyses will be presented for each individual study together with an integrated analysis of efficacy and safety for pivotal Phase 3 studies 20050136 and 20050244 to provide insight beyond the individual clinical studies. Section 6.3 describes the general plan for preparation of these clinical summaries, including the integrated analyses.

   To provide transparency on the safety profile of denosumab in placebo-controlled clinical studies in approximately 10,000 subjects in the PMO and HLT populations, Amgen Proposes to include the Summary of Clinical Safety (Module 2, Section 2.7.4) from the Bone Loss BLA (submitted to FDA on 19 December 2008 under STN 12532o/o/o) in Module 5 of the (b) (4) BLA. Therefore, Amgen proposes to not include PMO/HALT CSRs from the Bone Loss BLA in the Advanced Cancer BLA.

   1a. **Does the Agency agree with Amgen's proposal for provision of CSRs for advanced cancer pivotal studies 20050136 and 20050244 and non-pivotal studies 20040113 and 20040114 as the clinical basis of the (b) (4) (b) (4) BLA?**

   FDA Response: Yes, Amgen's proposal to submit CSRs for the pivotal and non-pivotal studies is acceptable.

   Amgen Response: Amgen acknowledges the Agency's feedback.

   1b. **Does the Agency agree with Amgen's proposal for integration and analysis of efficacy and safety data from the pivotal Phase 3 studies as described in Sections 6.3.1 and 6.3.2, in particular, does the FDA have comments on the SAPs for the Clinical Summaries of Efficacy and Safety provided in Appendix 3 and Appendix 4, and the SAPs for Studies 20050136 and 20050244 included in Appendix 6 and Appendix 7?**

   FDA Response: The SAP pertaining to the Clinical Summary of Safety appears acceptable. However, in addition to pooled safety data, safety data from each individual study should be submitted. Defer to Statistics Reviewer for efficacy summary.

The proposed primary analysis is not acceptable to support a broad labeling claim for the [redacted] (b) (4) For each study, substantial evidence should be provided on the efficacy of denosumab. Each comparison may be supportive of each other. Integrated analyses may be supportive.

Amgen Response: Amgen confirms that the safety analysis from each study will be provided in the BLA. Amgen agrees that substantial evidence of efficacy should be provided by each of the 2 studies and the proposed analysis using the primary efficacy set for the combined data will be considered supportive.

Once the data are available from the pivotal Phase 3 studies, Amgen looks forward to further discussions with the Agency in a subsequent pre-BLA meeting.

1c. **Amgen is exploring the inclusion of a "pilot" quantitative statistical analysis plan (QSAP) as part of the Advanced Cancer BLA. Is the FDA receptive to discussion on a potential "pilot" QSAP as part of the Advanced Cancer BLA during subsequent pre-submission meetings?**

FDA Response: The Division of Biologic Oncology Products (DBOP) in conjunction with the Division of Biometrics VI is agreeable to discussions regarding the optimal presentation of safety data as a Quantitative Safety Analysis Plan at the pre-BLA meeting and additional meetings as necessary.

Amgen Response: Amgen acknowledges the Agency's feedback and looks forward to sharing the proposed pilot QSAP for the denosumab [redacted] (b) (4) BLA. As an overview, this document will provide a centralized index of all components of the safety analysis and hyperlinks to documents that comprise the safety analysis, e.g., SAPs, charters, adjudication procedures and the risk management plan. The content of this document will be directly taken from existing documents and no new analyses are planned. Amgen intends to submit a draft table of contents for the pilot QSAP to the IND shortly to solicit further FDA input.

- Does the Agency have any comments to this approach?
- Could the Agency provide a point of contact for further discussion?

1d. **Does the Agency agree with Amgen's proposal for inclusion of the Summary of Clinical Safety from the Bone Loss BLA in Module 5 of the [redacted] (b) (4) BLA?**

FDA Response: No, Amgen's proposal to include the Summary of Clinical Safety from the bone loss BLA in Module 5 of the [redacted] (b) (4) BLA is not acceptable. In general, summaries should be included in Module 2. However, if feasible, Amgen should cross reference BLA STN 125320 in the advanced cancer BLA and provide hyperlinks to the relevant data.

Amgen Response: Amgen will provide the Summary of Clinical Safety of the Bone Loss BLA in Module 2. In addition, supportive appendices and datasets of the Bone Loss BLA will be located in Module 5 as appropriate. Hyperlinks within

the [redacted] (b) (4) BLA will be provided as needed. Does the Agency have any comments to this approach?

2. Amgen plans to submit safety data from the ongoing advanced cancer Phase 2 and 3 studies in the 120-day safety update. Section 6.4 describes Amgen's proposal for the 120-day safety update.

Does the Agency agree with the proposed content, structure, analysis, and estimated data cut off date for the 120-day safety update?

FDA Response: Yes, Amgen's overall approach for the 120-day safety update is acceptable.

Amgen Response: Amgen acknowledges the Agency's feedback.

3. Amgen plans to provide case report forms (CRFs) from Phase 2 and Phase 3 advanced cancer studies (Phase 2 studies 20040113, Phase 3 studies 20050136 and 20050244) for all subjects who died on study, for all subjects who withdrew from the investigational product or the study due to an adverse event and for all subjects who experienced a serious adverse event. In accordance with the approach agreed to by the FDA for the bone loss BLA, the CRFs will be hyperlinked within the common technical document (CTD) at the page level with any changes in the CRF documentation hyperlinked to the query or documentation from which the change resulted.

Does the Agency agree with Amgen's proposal for inclusion of CRFs?

FDA Response: Yes, Amgen's proposal for inclusion of CRFs is acceptable.

Amgen Response: Amgen acknowledges the Agency's feedback.

4. Amgen used [redacted] (b) (4) as the independent imaging vendor for the pivotal Phase 3 studies. Data from these images were used in the analysis of key components of the efficacy endpoints (i.e., identification of confirmation of fracture or spinal cord compression as skeletal related events). The imaging charters will be submitted in the BLA. In addition, the datasets included in the BLA for each study will contain the event results from each independent reader and the final decision, thereby providing each radiologists review of each assessment. Amgen does not plan to include individual radiographic images for each patient in the BLA unless otherwise requested by the FDA.

Does the Agency agree with this proposal?

FDA Response: Yes, Amgen's proposal with regard to imaging data is acceptable.

Amgen Response: Amgen acknowledges the Agency's feedback.

5. Consistent with Amgen's structure of the Bone Loss BLA, [redacted] (b) (4) BLA will be compliant with the CDISC SDTM Implementation Guide 3.1.1 for tabulation data and observe the CDISC ADaM 1.0 for analysis data. Therefore, Amgen proposes to follow the proposals and FDA feedback on the CDISC SDTM implementation as agreed during

the Bone Loss meetings in February and October 2008 (FDA minutes provided in Appendix 5 and Appendix 6).

5a. Does the Agency agree with Amgen's proposal for inclusion of datasets in the [redacted] (b) (4) BLA?

FDA Response: a. Yes, Amgen's dataset plan appears adequate.

5b. Does the Agency agree with the proposed dataset structure for the [redacted] (b) (4) BLA which will be provided in accordance with the agreements reached for the Bone Loss BLA?

FDA Response: Yes

5c. Can the agency provide a point of contact within the Office of Business Process Support that Amgen can liaise with to follow-up on questions prior to submission of the BLA?

FDA Response: Amgen may contact Connie Robinson-Kuiperi in OBPS with any general eCTD questions via email at constance.robinson-kuiperi@fda.hhs.gov. Questions regarding datasets should be directed to Zei-Pao Huang, email: zeipao.huang@fda.hhs.gov.

5d. Amgen expects most submission data files to be less than 400 Mb in size. In line with previous guidance, no large SDTM (tabulation) datasets will be split. At least 6 ADaM (analysis) submission datasets are expected to be 1 to 3 Gb. Amgen proposes not to split these datasets into multiple smaller component datasets in the BLA. Does the Agency agree with this proposal? If splitting is desired, please provide specific guidance to Amgen on the desired method of splitting such large ADaM datasets.

FDA Response: This is correct, if less than 400 MB, no splitting is required. Specific guidance on splitting analysis datasets that are 1-3 GB can be obtained in consultation with Zei-Pao Huang from OBP and the review team who will be examining the data.

5e. Amgen proposes to supply numeric preferred term codes in addition to the decodes in the ACM ADaM datasets for the pivotal Phase 3 studies (20050136 and 20050244). In addition, Amgen proposes to supply Chemical Therapeutic Subgroup (Code and Decode) variables for each concomitant medication in the ACM datasets for these two studies. This presents the most granular level within the ATC hierarchy (level 4); and allows for the Therapeutic Subgroup (ATC level 3); Therapeutic Main Group (ATC level 2); and Anatomical Main Group (ATC level 1) to be derived. In accordance with FDA feedback from the Bone Loss pre-BLA meeting in October 2008 (Appendix 6), Amgen will supply all possible level 4 ATC codes/decodes associated with each medication record, however, these will not be used for analyses conducted by Amgen.

Does the Agency agree with this proposal?

FDA Response: Yes.

5f. Aside from AB, PC, and PP, Amgen plans to include 7 custom SDTM domains in one or more studies in the BLA:

- CE (Clinical Events; this domain is intended to contain additional information about deaths.)
- DF (Disorder Findings; this domain is intended to contain additional information about bone metastases, malignancies, lesions along with details of specific treatments.)
- HE (Healthcare Event; this domain is intended to contain additional information about hospitalizations, out-patient visits or other healthcare utilization.)
- LS (Lesion Findings; this domain is intended to contain additional information about specifics of lesions.)
- NF (Non-vertebral Fracture Assessment; this domain is intended to contain non-vertebral fracture confirmation data from facture confirmation performed by a third-party vendor. This data is qualitative in nature.)
- SX (Surgery Events; this domain is intended to contain additional information about surgical events, basic information such as the type of surgery and date performed)
- VF (Vertebral Fracture Assessment; this domain is intended to contain vertebral fracture assessment data that produced a semi-quantitative score as a result. The assessments were provided by a third-party vendor.)

All custom domains are designed in strict adherence to the guidance for creating new domains found in the SDTM-IF 3.1.1 (Section 2.6) and as such are considered SDTM compliant. Custom domains will follow the same validation procedures as used for published domains, based on the rules for the SDTM General Observation Class on which the custom domain was based.

Does the Agency agree with this proposal?

FDA Response: Yes.

5g. Amgen intends to remap MedDRA terms from studies that were coded in different versions to a single, consistent version in the CSS datasets and analysis. Amgen proposes to retain both the original and remapped MedDRA hierarchy in the CSS adverse events ADaM datasets, to provide transparency to the Agency on which events changed preferred term or hierarchy mapping when the data was converted from one MedDRA version to another.

Does the Agency agree with this proposal?

FDA Response: Yes. Amgen should also note that the MedDRA version utilized for the final remapping should be indicated in your submission.

Amgen Response to 5a through 5g: Amgen acknowledges the Agency's feedback and will provide the information in the [redacted] (b) (4) BLA as requested.

Chemistry, Manufacturing and Controls:

6. A freestanding BLA is proposed for the [redacted] (b) (4) indication and may be submitted to the FDA prior to approval of the Bone Loss BLA. Therefore, Amgen intends to provide complete Modules 2.3, and 3 in the [redacted] (b) (4) BLA. As the majority of the Chemistry, Manufacturing, and Controls (CMC) information will be identical to that submitted in the Bone Loss BLA, Section 6.1 details Amgen's proposal for identification of information that is new in the [redacted] (b) (4) BLA, and information that is updated compared to that included in the Bone Loss BLA.

Does the Agency agree with Amgen's proposal for management of the CMC Module 2.3 and Module 3 information contained in the [redacted] (b) (4) BLA?

FDA Response: Yes. Please include only the drug substance and drug product information that would be required for registration of the 70 mg/ml vial presentation. Please clearly delineate in the BLA the information that is unique to the [redacted] (b) (4) BLA, as well as identifying sections that are unchanged from what was submitted under STN 125320 as such.

Amgen Response: Amgen acknowledges the Agency's feedback. In order to gain further clarity regarding the identical sections of both filings, Amgen would welcome further advice from the Agency regarding the circumstances under which it may be appropriate to provide information in the SRE BLA by cross-referencing to the Bone Loss BLA STN 125320. Specifically, if the Bone Loss BLA were to be granted approval prior to submission of the [redacted] (b) (4) BLA, would cross-referencing the entire drug substance section be appropriate?

Nonclinical:

7. Amgen intends to provide complete Modules 2.4, 2.6, and 4 in the [redacted] (b) (4) BLA. As for the CMC information, the majority of the nonclinical information will be identical to that submitted in the Bone Loss BLSA. Section 6.2 details Amgen's proposal for identification of information that is new in the [redacted] (b) (4) BLA, and information that is updated compared to that included in the Bone Loss BLA.

Does the Agency agree with Amgen's proposal for management of the nonclinical information in Modules 2.4, 2.6, and 4 contained in the Advanced Cancer BLA?

FDA Response: FDA disagrees with the proposal to omit the following studies from Module 4.2.1.1 of the [redacted] (b) (4) BLA:

- R2004321 Effects of denosumab (AMG 162) on bone mass and bone resorption in aged human rank ligand knock-in mice
- R2004430 Effect of denosumab (AMG 162) on bone mass and resorption in human rank ligand knock-in mice
- 103981 AMG 162: A monthly subcutaneous injection osteoporosis prevention study for 16 months in the cynomolgus monkey
- 106564 A 12-month osteoporosis "switch" study in cynomolgus monkey
- R2006458 Comparison of two anti-resorptive therapies (alendronate vs AMG 162 monoclonal anti-RANKL antibody) on murine fracture healing

For the advanced cancer BLA, FDA requires a complete dossier of the available nonclinical data; therefore, Amgen will need to include all final study reports in Module 4.2.1.1 including the studies listed above, as this information is essential for reviewing the nonclinical pharmacologic activity of denosumab. Furthermore, while updates to the nonclinical sections of the (b) (4) indication BLA are reasonable, module 2.6.2.2 will need to include all the information relevant for any of the proposed indications. FDA requests that all changes relative to the previously submitted PMO and HALT bone loss BLA applications are clearly indicated in the dossier.

Amgen Response: Amgen acknowledges the Agency's feedback and will provide the information in the (b) (4) BLA as requested.

Regulatory:

8. Amgen intends to market denosumab with proprietary names for different indications. On 30 July 2008, Amgen submitted to BB-IND 9837, Serial 0507 (cross referenced to BB-IND 9838, Serial 0431) a request for FDA review of the following proposed proprietary names:

   - PROLIA™ for the indications related to PMO and HALT (being studied under BB INDs 9837 and 11709, respectively, and subject to the Bone Loss BLSA submitted on 19 December 2008)
   - (b) (4) for the indications related to (b) (4) (being studied under BB IND 9838 and subject to the (b) (4) BLA that is anticipated to be submitted in December 2009)

   Does the Agency have a status update regarding the review of Amgen's proposed proprietary name request?

   FDA Response: No. Amgen's proposed request for two proprietary names remains under FDA review.

   Amgen Response: Amgen acknowledges the Agency's feedback and looks forward to the Agency's decision.

Additional Clinical Comments:

9. The BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: http://www.fda.gov/cder/mapp/6010.3.pdf.

   a) To facilitate the review, FDA requests Amgen provide analyses, where applicable, that will address the items in the template, including:

   - Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
   - Exposure-Response Relationships - important exposure-response assessments.
   - Less common adverse events (between 0.1% and 1%).
   - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
   - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
   - Marked outliers and dropouts for laboratory abnormalities.
   - Analysis of vital signs focused on measures of central tendencies.
   - Analysis of vital signs focused on outliers or shifts from normal to abnormal.
   - Marked outliers for vital signs and dropouts for vital sign abnormalities.
   - Overview of ECG testing in the development program, including a brief review of the nonclinical results.
   - Overdose experience.
   - Explorations for dose dependency for adverse findings.
   - Explorations for time dependency for adverse findings.
   - Explorations for drug-demographic interactions.
   - Explorations for drug-disease interactions.
   - Explorations for drug-drug interactions.
   - Dosing considerations for important drug-drug interactions.
   - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Amgen Response: Amgen confirms that the requested analyses and supportive information will be included in the BLA, as applicable.

10. FDA requests that all submitted datasets include the following information. Please note that some of the information may have been discussed above in FDA's responses to Amgen's questions.

a. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration. The integrated safety dataset should include the following fields/variables:

- A unique patient identifier
- Study/protocol number
- Patient's treatment assignment
- Demographic characteristics, including gender, chronological age (not date of birth), and race
- Dosing at time of adverse event
- Dosing prior to event (if different)
- Duration of event (or start and stop dates)
- Days on study drug at time of event
- Outcome of event (e.g. ongoing, resolved, led to discontinuation)
- Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
- Marker for serious adverse events
- Verbatim term

Amgen Response: Amgen will provide the requested dataset for the Phase 2 and Phase 3 studies which will include data from Studies 20040113, 20040114, 20050136, and 20050244 (data from 20050103 will be included if available). Please refer to Figure 2 (page 38) from the pre-BLA briefing document for the studies planned to be included in the [redacted] (b) (4) BLA. Does the Agency agree with this proposal?

b. The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form.

c. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.

d. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider.

document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

e. The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.

f. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.

g. In every dataset, all dates should be formatted as ISO date format.

Amgen Response to 10b through 10g: Amgen will provide the information, dataset, or analyses as requested.

h. Provide a comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities. Also, provide a list of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The BLA analyses of the frequency of abnormalities across treatment groups are not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

Amgen Response: Amgen confirms that data from patients with potentially clinically significant laboratory or vital sign abnormalities will be provided in the Summary of Clinical Safety ADaM datasets. Amgen confirms that patients reporting adverse events involving abnormalities of laboratory values or vital signs will be tabulated. Analyses of laboratory values will include assessments of changes from baseline to worst values.

i. For patients listed as discontinued due to "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

Amgen Response: Amgen reviews reasons for discontinuation to confirm that the appropriate reason for discontinuation has been selected by the investigator. Amgen tabulates the study disposition table according to the reason for discontinuation provided by the investigator.

j. If Amgen and/or FDA believes that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you

are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

Amgen Response: Amgen acknowledges the Agency's comment and will engage in these discussions as necessary.

11. FDA requests that, in addition to the CRFs discussed previously, Amgen provides case narratives for all patients who withdrew from the investigational product or the trials due to an adverse event, all patients who experienced SAEs, and all patients who died during the trials.

Amgen Response: Amgen confirms that case narratives will be provided for all patients who experienced SAEs, and all patients who died during the trials. For patients who withdrew from investigational product or the trials due to an adverse event (including serious and non-serious AEs), Amgen proposes to provide listings which will capture all relevant information from the case report forms. Does the Agency agree with this approach?

Additional Statistical Comments:

12. FDA reminds Amgen of advice regarding Protocol 20050244 previously conveyed in a letter to Amgen dated November 1, 2006:

"We do not object to using a synthesis method for the primary analysis. However, the meta-analysis used to estimate the zoledronate effect uses patients having a wide variety of diseases. Direct and indirect comparisons were also used to determine the zoledronate effect. The patient population for which the estimate from the meta-analysis is unbiased and valid may not be the same as the patient population used for study 20050244. It is not clear that the estimate of the zoledronate effect from the meta-analysis is directly transferable to the current trial. A quality assessment should be done of the transferability to this trial of the estimated pamidronate vs. placebo effect on the time to first skeletal-related event. Such an assessment cannot be made until after study 20050244 is complete. Also, the reproducibility of the effectiveness of Denosumab would need to be studied from the results of trials comparing Denosumab with zoledronate and studying the reproducibility of the zoledronate effect. The robustness of the results should also be evaluated in a determination of efficacy."

Amgen Response: Amgen acknowledges this comment, and references our submission dated 14 August 2007 sent to BB-IND 9838 (serial no. 0241). As previously stated in the 14 August 2007 response and as detailed in version 2.0 of the SAP for Study 20050244 submitted to BB-IND 9838 on 18 December 2008, (serial no. 0496), assessments will be performed to evaluate the reproducibility of both the denosumab and the zoledronic acid effect.

13. FDA recommends that Amgen include in the BLA submission the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis.

Amgen Response: Amgen will provide these programs as requested for Studies 20050136 and 20050244 and the Summary of Clinical Efficacy (SCE) for all ADaM

datasets as well as key efficacy endpoint tables displaying inferential statistics (i.e., primary and secondary endpoints of the individual studies and corresponding endpoints in the SCE). Does the Agency agree with this proposal?

14. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will appear in the label.

Amgen Response: Amgen will create a document that will link each value appearing in the label with the program and source dataset(s) that were used to derive the value.

MEETING ATTENDANCE LIST

Meeting between Amgen, Inc. and the Center for Drug Evaluation and Research.

DATE: 01/30/2009 TIME: 10:00 - 11:00 a.m. ROOM: 1309

NAME - Please print	AFFILIATION
Norma S. Griffin	FDA/CDER/DBOP
Steven Swadiuk	Amgen
LAURA BLOSS	Amgen
ROGER DANSEY	AMGEN
Brad Glasscock	Amgen
Randy Steiner	Amgen
DAVID FEIGAL	AMGEN
MAKAN SARKESHIK	AMGEN
BILL DOUGALL	AMGEN
SUSIE JUN	AMGEN
Mike Abernathy	Amgen
Qi Jiang	Amgen
ANDRÉ DANIEL	Amgen
ROY BAYNES	AMGEN
JAVIER SAN MARTIN	AMGEN
BARBIE NELSON	AMGEN
Michelle Fan	Amgen
Zei Paul Huang	FDA/OBPS
Constance Robinson-Kuiper	FDA/OBPS
Kyung Yul Lee	FDA/OTS/DB/DBV
Suzanne Demko	FDA/OODP/DBOP
Jeff Summers	" "
PATRICIA KEEGAN	FDA/CDER/OODP/DBOP
Anne Pilaro	FDA/CDER/OODP/DBOP
Sarah Schriebe	FDA/CDER/OTS/OCP/DCRS
Vaishali Sopal, MD MPH	FDA/CDER/DRUG
Melanie Pierce	FDA/CDER/DBOP
Michael Orr	FDA/CDER/DBOP

Linked Applications	Sponsor Name	Drug Name / Subject
IND 9838	AMGEN INC	Denosumab {Human Monoclonal Antibody (AMG 162) to the Osteoprotegerin Ligand (RANKL)] and Chemotherapy

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

/s/

MELANIE B PIERCE
02/26/2009