CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125320Orig1s094

Trade Name:	XGEVA
Generic or Proper Name:	denosumab
Sponsor:	Amgen Inc.
Approval Date:	06/13/2013
Indication:	Xgeva is a RANK ligand (RANKL) inhibitor indicated for: • Prevention of skeletal-related events in patients with bone metastases from solid tumors • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity Limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma

CENTER FOR DRUG EVALUATION AND RESEARCH

BLA 125320Orig1s094

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/94

SUPPLEMENT APPROVAL

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), dated December 11, 2012, received December 12, 2012, submitted under section 351(a) of the Public Health Service Act for Xgeva (denosumab).

We acknowledge receipt of your amendments dated December 11, 2012, January 16, 2013, January 25, 2013, February 4, 2013, February 26, 2013, March 8, 2013, March 11, 2013, March 19, 2013, May 13, 2013, May 23, 2013, May 31, 2013, June 7, 1013, June 10, 2013 and June 12, 2013.

This 'Prior Approval" supplemental to your BLA provides for a new indication for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. 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/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 Xgeva (denosumab) was approved on November 18, 2010, we have become aware of risks (further described below) associated with long term use of Xgeva (denosumab) in adolescent and adult patients with giant cell tumor of bone (GCTB) from the clinical trial used to support the indication in GCTB. 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 longer duration of exposure to Xgeva (denosumab), and to assess signals of a serious risk of malignant transformation of GCTB with Xgeva (denosumab), secondary malignancies with Xgeva (denosumab), and embryo-fetal toxicity with Xgeva (denosumab), and to assess the known serious risk of osteonecrosis of the jaw with Xgeva (denosumab) and atypical fractures with Xgeva (denosumab).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess an unexpected serious risk of longer duration of exposure to Xgeva (denosumab); to assess signals of a serious risk of malignant transformation of GCTB with Xgeva (denosumab), secondary malignancies with Xgeva (denosumab), and embryo-fetal

toxicity with Xgeva (denosumab); and to assess the known serious risk of osteonecrosis of the jaw with Xgeva (denosumab) and atypical fractures with Xgeva (denosumab).

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

1. Submit a final report of follow-up safety data of Xgeva (denosumab) in patients with giant cell tumor of bone enrolled in the ongoing single arm trial through November 2012 for a minimum of five years or until death or lost to follow-up, whichever comes first. Comprehensively collect information regarding survival status, disease progression, serious adverse events, and adverse events of special interest including osteonecrosis of the jaw, pregnancy-related complications, atypical fractures, malignant transformation of giant cell tumor of bone, and secondary malignancies. Perform descriptive analyses of these safety data, including a subset analysis comparing the long-term safety of denosumab in adolescent and adult patients.

   The timetable you submitted on June 5, 2013, states that you will conduct this trial according to the following schedule:

   Final Report Submission: December 2019

Submit the protocol(s) to your IND 113617, 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 commitments:

2. Submit the final report including primary datasets, derived datasets, and analysis programs used to generate the safety and efficacy results for the ongoing single arm multicenter trial of denosumab in patients with giant cell tumor of bone. Include an analysis of radiographic response as determined by the local investigator in evaluable patients who received at least one dose of denosumab and underwent at least one post-baseline Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) tumor assessment during the trial. The primary analysis should be conducted after patients enrolled through November 2012 have had the opportunity to complete 12 months of treatment.

   The timetable you submitted on June 5, 2013, states that you will conduct this trial according to the following schedule:

   Final Report Submission: December 2019

3. Provide a detailed and thoughtful analysis of the risk factors associated with malignant transformation of GCTB and development of new sarcoma and the lifetime and annual incidences of these events in denosumab naïve patients. For this analysis, use data from a minimum of two representative databases in addition to information from published literature. Include subset analyses based on specific risk factors identified from the comprehensive investigation.

   The timetable you submitted on June 5, 2013, states that you will conduct this study according to the following schedule:

   Final Report Submission: December 2018

Submit clinical protocols to your IND 113617 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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
Office of Prescription Drug Promotion
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 Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above or by fax to 301-847-8444.

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) 795-1273.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, MD
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

PATRICIA KEEGAN
06/13/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

<u>LABELING</u>

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 U.S. Approval: 2010

----------RECENT MAJOR CHANGES----------

• Indications and Usage (1.2)	06/2013
• Dosage and Administration (2.1)	06/2013
• Warnings and Precautions (5.1)	02/2013
• Warnings and Precautions (5.2)	09/2012
• Warnings and Precautions (5.3)	06/2013

---------- 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)
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (1.2, 14.2)

Limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma

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

- Bone Metastasis from Solid Tumors: Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen (2.1)
- Giant Cell Tumor of Bone: Administer 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously 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

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

- Hypocalcemia: Xgeva can cause severe symptomatic hypocalcemia, and fatal cases have been reported. 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)#
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use highly effective contraception (5.3, 8.1, 8.7)#

#

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

- Bone Metastasis from Solid Tumors: Most common adverse reactions (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (6.1)
- Giant Cell Tumor of Bone: Most common adverse reactions (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity (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----------

- Nursing mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- Pediatric patients: Recommended only for treatment of skeletally mature adolescents with giant cell tumor of bone (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: 06/2013

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

Reference ID: 3324257

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.

Limitation of Use:
Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma *[see Clinical Trials (14.1)]*.

1.2 Giant Cell Tumor of Bone

Xgeva is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Bone Metastasis from Solid Tumors
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)]*.

Giant Cell Tumor of Bone
The recommended dose of Xgeva is 120 mg administered every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously 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 symptomatic hypocalcemia, and fatal cases have been reported. 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, 6.2) 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 in patients with osseous metastasis, 2.2% of patients receiving Xgeva developed ONJ after a median exposure of 13 doses; of these patients, 79% had a history of tooth extraction, poor oral hygiene, or use of a dental appliance *[see Adverse Reactions (6.1)]*. In a clinical trial conducted in patients with prostate cancer at high risk for osseous metastasis, a condition for which denosumab is not approved, 5.4% of patients developed ONJ after a median exposure of 20 doses.

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.

5.3 Embryo-Fetal Toxicity

Xgeva can cause fetal harm when administered to a pregnant woman. Based on findings in animals, Xgeva is expected to result in adverse reproductive effects. In utero denosumab exposure in cynomolgus

monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent peripheral lymph nodes, abnormal bone growth, and decreased neonatal growth *[see Use in Specific Populations (8.1) and (8.7)]*.

Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after with the last dose of Xgeva. Apprise the patient of the potential hazard to a fetus if Xgeva is used during pregnancy or if the patient becomes pregnant while patients are exposed to Xgeva. Advise patients to contact their healthcare provider if they become pregnant or a pregnancy is suspected during this time. *[see Use in Specific Populations (8.1) and (8.7)]*.

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

<u>Bone Metastasis from Solid Tumors</u>
The safety of Xgeva was evaluated in three randomized, double-blind, double-dummy trials *[see Clinical Trials (14.1)]* 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 (ONJ)

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).

Giant Cell Tumor of Bone
The safety of Xgeva was evaluated in two single arm trials (Trials 4 and 5) *[see Clinical Trials (14.2)]* in which a total of 304 adult or skeletally mature adolescent patients with giant cell tumor of bone received at least 1 dose of Xgeva. Patients received 120 mg Xgeva subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Patients receiving concurrent bisphosphonate therapy were excluded from enrollment in both studies. 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 were excluded from enrollment in Trial 5. During the trial, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

Of the 304 patients who received Xgeva, 145 patients were treated with Xgeva for ≥ 1 year, 44 patients for ≥ 2 years, and 15 patients for ≥ 3 years. The median number of doses received was 14 (range: 1 to 60 doses) and the median number of months on study was 11 (range: 0 to 54 months). Fifty-eight percent of the enrolled patients were women and 80% were White. The median age was 33 years (range: 13 to 83 years); a total of 10 patients were skeletally mature adolescents (13 to 17 years of age).

The adverse reaction profile of Xgeva in patients with giant cell tumor of bone was similar to that reported in Trials 1, 2, and 3. The most common adverse reactions in patients (per-patient incidence ≥ 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions were osteonecrosis of the jaw and osteomyelitis (per-patient incidence of 0.7%). The most common adverse reactions resulting in discontinuation of Xgeva were osteonecrosis of the jaw (per-patient incidence of 0.7%), and tooth abscess or tooth infection (per-patient incidence of 0.7%). The adverse reaction profile appeared similar in skeletally mature adolescents and adults.

Hypocalcemia and Hypophosphatemia
- Moderate hypocalcemia (corrected serum calcium less than 8 to 7 mg/dL or less than 2 to 1.75 mmol/L) occurred in 2.6% of patients treated with Xgeva.
- Severe hypophosphatemia (serum phosphorus less than 2 to 1 mg/dL or less than 0.6 to 0.3 mmol/L) occurred in 29 patients (9.5%).

Osteonecrosis of the Jaw (ONJ)
In Trials 4 and 5, ONJ was confirmed in 4 of 304 (1.3%) patients who received Xgeva. The median time to ONJ was 16 months (range: 13 to 20 months) *[see Warnings and Precautions (5.2)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xgeva. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypocalcemia: Severe symptomatic hypocalcemia, including fatal cases.

6.3 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 and none of the 304 patients with giant cell tumor of bone in Trials 4 and 5 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.

There was no evidence that various anticancer treatments affected denosumab systemic exposure and pharmacodynamic effect. 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 and were not altered by concomitant chemotherapy and/or hormone therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.3)]*

Risk Summary
Xgeva can cause fetal harm when administered to a pregnant woman based on findings in animals. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth, and decreased neonatal growth.

There are no adequate and well-controlled studies with Xgeva in pregnant women. Women should be advised not to become pregnant when taking Xgeva. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Women who become pregnant during Xgeva treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

Clinical Considerations
The effects of Xgeva are likely to be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

If the patient becomes pregnant during Xgeva therapy, consider the risks and benefits in continuing or discontinuing treatment with Xgeva.

Animal Data
The effects of denosumab on prenatal development have been studied in both cynomolgus monkeys and genetically engineered mice in which RANK ligand (RANKL) expression was turned off by gene

removal (a “knockout mouse”). In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy at a pharmacologically active dose, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia, and tooth malalignment; and decreased neonatal growth. At birth out to one month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels).

Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated.

In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.2)]*.

8.3 Nursing Mothers

It is not known whether Xgeva is excreted into human milk. Measurable concentrations of denosumab were present in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of denosumab (≤ 0.5% milk:serum ratio). 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. However, in cynomolgus monkeys treated with denosumab throughout pregnancy, maternal mammary gland development was normal, with no impaired lactation. Mammary gland histopathology at 6 months of age was normal in female offspring exposed to denosumab in utero; however, development and lactation have not been fully evaluated *[see Nonclinical Toxicology (13.2)]*.

8.4 Pediatric Use

The safety and efficacy of Xgeva have not been established in pediatric patients except in skeletally mature adolescents with giant cell tumor of bone. Xgeva is recommended only for treatment of skeletally mature adolescents with giant cell tumor of bone *[see Indications and Usage (1.2)]*.

Xgeva was studied in an open-label trial that enrolled a subset of 10 adolescent patients (aged 13-17 years) with giant cell tumor of bone who had reached skeletal maturity, defined by at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus), and had a body weight ≥ 45 kg *[see Indications and Usage (1.2) and Clinical Trials (14.2)]*. A total of two of six (33%) evaluable adolescent patients had an objective response by retrospective independent assessment of radiographic response according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. The adverse

reaction profile and efficacy results appeared to be similar in skeletally mature adolescents and adults *[see Adverse Reactions (6.1) and Clinical Trials (14.2)]*.

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 (the target of Xgeva therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 5 and 25 times (10 and 50 mg/kg dose) higher than the recommended human dose of 120 mg administered once every 4 weeks, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab.

Cynomolgus monkeys exposed in utero to denosumab exhibited bone abnormalities, reduced hematopoiesis, tooth malalignment, decreased neonatal growth, and an absence of axillary, inguinal, mandibular, and mesenteric lymph nodes. Some bone abnormalities recovered once exposure was ceased following birth; however, axillary and inguinal lymph nodes remained absent 6 months post-birth *[see Use in Specific Populations (8.1)]*.

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)]*.

8.7 Females and Males of Reproductive Potential

<u>Contraception</u>

Females

Counsel patients on pregnancy planning and prevention. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of Xgeva. Advise patients to contact their healthcare provider if they become pregnant, or a pregnancy is suspected, during treatment or within 5 months after the last dose of Xgeva *[see Use in Specific Populations (8.1) and Patient Counseling Information (17)]*.

Males

The extent to which denosumab is present in seminal fluid is unknown. There is potential for fetal exposure to denosumab when a male treated with Xgeva has unprotected sexual intercourse with a pregnant partner. Advise males of this potential risk.

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. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to osteolysis and tumor growth. Xgeva prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

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 once every 4 weeks, up to 2.8-fold accumulation in serum denosumab concentrations was observed and steady state was achieved by 6 months. A mean (± standard deviation) serum steady-state trough concentration of 20.5 (± 13.5) mcg/mL was achieved by 6 months.

With the administration of subcutaneous doses of 120 mg once every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy, mean (± standard deviation) serum trough concentrations on Day 8, 15, and one month after the first dose were 19.0 (± 24.1), 31.6 (± 27.3), 36.4 (± 20.6) mcg/mL, respectively. Steady-state was achieved in 3 months after initiation of treatment with a mean serum trough concentration of 23.4 (± 12.1) mcg/mL. The mean elimination half-life was 28 days.

<u>Special Populations</u>
Body Weight: 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.

Age, Gender and Race: The pharmacokinetics of denosumab was not affected by age, gender, and race.

Pediatrics: The pharmacokinetics of denosumab in pediatric patients has 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

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

Denosumab had no effect on female fertility or male reproductive organs in monkeys at doses that were 6.5- to 25-fold higher than the recommended 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.

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

14.1 Bone Metastasis from Solid Tumors

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.

14.2 Giant Cell Tumor of Bone

The safety and efficacy of Xgeva for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents were demonstrated in two open-label trials (Trial 4 and 5) that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity. Patients received 120 mg Xgeva subcutaneously every 4 weeks with additional doses on Days 8 and 15 of the first cycle of therapy.

Trial 4 was a single arm, pharmacodynamic, and proof of concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or magnetic resonance imaging (MRI) obtained within 28 days prior to study

enrollment. Patients enrolled in Trial 4 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly during Xgeva treatment.

Trial 5 was a parallel-cohort, proof of concept, and safety trial conducted in 282 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Trial 5 enrolled 10 patients who were 13 – 17 years of age *[see Use in Specific Populations (8.4)]*. Patients enrolled into one of three cohorts: Cohort 1 enrolled 170 patients with surgically unsalvageable disease (e.g., sacral or spinal sites of disease, or pulmonary metastases); Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy); Cohort 3 enrolled 11 patients who previously participated in Trial 4. Patients underwent imaging assessment of disease status at intervals determined by their treating physician.

An independent review committee evaluated objective response in 187 patients enrolled and treated in Trials 4 and 5 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Trial 4 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Trial 5). The primary efficacy outcome measure was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

The overall objective response rate (RECIST 1.1) was 25% (95% CI: 19, 32). All responses were partial responses. The estimated median time to response was 3 months. In the 47 patients with an objective response, the median duration of follow-up was 20 months (range: 2 to 44 months), and 51% (24/47) had a duration of response lasting at least 8 months. Three patients experienced disease progression following an objective response.

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 Warnings and Precautions (5.3) and 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
- The use of highly effective contraception during and for at least 5 months after treatment with Xgeva for females of reproductive potential.

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 U.S. Patents, including U.S. Patent Nos. 6,740,522; 7,411,050; 7,097,834; and 7,364,736, as well as other patents or patents pending.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

SUMMARY REVIEW

Division Director Summary Review

Date	June 13, 2013
From	Patricia Keegan
Subject	Division Director Summary Review
BLA Supplement #	BL STN 125320/94
Applicant Name	Amgen, Inc.
Date of Submission	December 12, 2012
PDUFA Goal Date	June 13, 2013
Proprietary Name / Established (USAN) Name	Xgeva/ Denosumab
Dosage Forms / Strength	Injection/ 120 mg in 1.7 mL (70 mg/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	Martha Donoghue
Statistical Review	Weishi (Vivian) Yuan
Clinical Pharmacology Review	Stacy Shord
Pharmacology Toxicology Review	Shawna Weis
CMC Review	Lixin Xu
OPDP/DPDP	Marybeth Toscano
OSE/DRISK	Suzanne Robottom
Pediatric and Maternal Health Staff Review	Jeanine Best
TB-EER Consult	Ranjani Prabhakara

OND=Office of New Drugs
CMC=Chemistry, Manufacturing and Controls
OPDP=Office of Prescription Drug Promotion
DPDP=Division of Professional Drug Promotion
OSE= Office of Surveillance and Epidemiology
DRISK=Division of Risk Management
TB-EER=Therapeutic Biological Establishment Evaluation Request

Reference ID: 3324237

Division Director Summary Review

1. Introduction

This is the third approval for Xgeva® (denosumab, Amgen Inc.) in patients with cancer and the first for treatment of malignancy. Denosumab was first approved under the proprietary name of Prolia for the treatment of post-menopausal osteoporosis at approximately one-twelfth the annual dose of denosumab used for the proposed indication. Denosumab is a human IgG2 monoclonal antibody that binds to human RANKL. RANKL is a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to osteolysis and tumor growth. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

Giant cell tumor of bone is an indolent, usually benign tumor that can be curatively treated with surgical resection or, if not resectable or having positive margins, with radiotherapy. There are an estimated 800 new cases in the U.S. each year. The recurrence rates identified in published literature are highly variable; across reports, approximately 50% of patients will recur and less than 5% will develop metastases or malignant transformation to osteosarcoma. There are no FDA approved drugs for GCTB, thus this represents an unmet need for patients who have recurred following radiotherapy, have unresectable disease or would require amputation or en bloc excisions for removal of disease.

Amgen's denosumab clinical program for denosumab for the treatment of giant cell tumor of bone (GCTB) consisted of two single-arm clinical trials, Study 20040215 and Study 20062004, which established the safety and efficacy of denosumab for this proposed indication. Patients in both studies received denosumab 120 mg subcutaneously every 4 weeks with additional doses on Days 8 and 15 of the first cycle of therapy.

Study 20040215 was a pharmacodynamic and proof -of-concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. The prespecified primary efficacy endpoint was elimination of at least 90% of giant cells, or complete elimination of giant cells in cases where giant cells represented <5% of tumor cells, or absence of radiographic progression of the target lesion up to week 25.Patients were required to have histologically-confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or magnetic resonance imaging (MRI) obtained within 28 days prior to study enrollment. Patients enrolled in Trial 4 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly while receiving denosumab.

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Study 20062004 was a parallel-cohort, proof-of-concept and safety trial conducted in 282 adults or skeletally mature adolescents with histologically confirmed giant cell tumor of bone and evidence of measurable active disease who had not previously received denosumab (Cohorts 1 and 2) or to collect additional safety data in patients who previously received denosumab (Cohort 3). A total of ten patients were enrolled who were 13-17 years of age. Cohort 1 enrolled 170 patients with surgically unsalvageable disease (e.g. sacral or spinal sites of disease, or pulmonary metastases) Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity (e.g. joint resection, limb amputation, or hemipelvectomy) and Cohort 3 enrolled 11 patients who previously participated in Study 20040215. Imaging and pathology reports were required at screening to confirm eligibility, and imaging was conducted at the physician's discretion as part of routine patient management. The pre-specified primary efficacy objective for Cohort 1 was time to disease progression while the pre-specified for Cohort was the proportion of patients without surgery at month 6. Additional pre-specified efficacy endpoints were the type and occurrence of surgery and tumor response.

Following an end-of-Phase 2 meeting with FDA, the analysis plans for both trials were revised to allow for an integrated analysis of efficacy using well-accepted measures, specifically evidence of durable objective tumor responses. An independent review committee evaluated objective response in 187 patients enrolled and treated in Studies 20040215 and 20062004 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Study 20040216 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Study 20062004). The primary efficacy outcome measure, as agreed-upon with FDA, was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

The overall objective response rate was 25% (95% CI: 19, 32). All responses were partial responses. The estimated median time to response was 3 months. In the 47 patients with an objective response, the median duration of follow-up was 20 months (range: 2 to 44 months), and 51% (24/47) had a duration of response lasting at least 8 months. Three patients experienced disease progression following an objective response.

The safety of denosumab was evaluated in 304 patients enrolled in Studies 20040215 and 20062004 with giant cell tumor of bone received at least one dose of denosumab. These data were supported by evaluation of safety from previous trials for other approved indications. The adverse reaction profile of denosumab in patients with giant cell tumor of bone was similar to that reported in 2841 denosumab-treated patients who received denosumab at a dose of 120 mg every four weeks for the treatment of solid tumors with osseous metastases for the prevention of skeletal-related events in three randomized, active-controlled trials. Among denosumab-treated patients with GCTB, the most common adverse reactions in patients (per-patient incidence ≥10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions were osteonecrosis of the jaw and osteomyelitis (per-patient incidence of less than 0.71%). The most common adverse reactions resulting in discontinuation of denosumab were osteonecrosis of the jaw (per-patient incidence of 0.7%) and tooth abscess or tooth infection (per-patient incidence of 0.7). Moderate hypocalcemia (corrected serum calcium less than 8 to 7 mg/dL or less than 2 to 1.75 mmol/L) occurred in 2.6% of patients and severe hypophosphatemia (serum phosphorus less than 2 to 1 mg/dL or less than 0.6 to 0.3 mmol/L)

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occurred in 29 patients (9.5%). Osteonecrosis of the jaw was confirmed in 4 of 304 (1.3%) denosumab-treated patients.

The major issues considered during this review was the method for determining tumor shrinkage, given the limitations of the commonly accepted response criteria (RECIST 1.1) when the disease may be underestimated by the extent of soft-tissue mass effect. Amgen's proposed alternate criteria were primarily measures of denosumab's pharmacologic effects on osteoclasts (modified EORTC criteria for metabolic activity by PET) or on new bone formation (density/size or Inverse Choi criteria). Both alternative response criteria yielded very high response rates but did not directly measure effects on the malignant component of GCTB, which is the stromal cell component rather than the giant cells. Additional issues considered were the adequacy of evaluation for late adverse reactions in this patient population, which is younger and has more indolent disease; therefore, these patients may experience longer exposure to denosumab than in previously approved indications. These issues are discussed in greater detail in Sections 7 and 8 of this review.

2. Background

Giant cell tumor of the bone and available therapy

As reported by the American Cancer Society[1], an estimated 3010 new cases of primary bone cancers and 1440 deaths from primary bone cancer are estimated to occur in the United States in 2013. Giant cell tumor of the bone (GCTB), which is locally destructive but generally benign in the majority of patients cancer (>95%), had the potential for malignant transformation and accounts for less than 4% of all primary bone cancers. The incidence of GCTB may be increased in patients with hyperparathyroidism and in those with Paget's disease. The incidence also appears to be higher in Asia and India than in the United States.

In a large case series[2] of 195 patients with giant-cell tumor of bone treated at the Mayo Clinic between 1910 and May 1969, the authors noted that the peak incidence was in the third decade of life, a slight female predominance (59%), and absence of tumors in younger patients with skeletally immature bones. Two of the 195 patients had multiple primary tumors (two patients with two primaries). Approximately three-quarters of the tumors occurred at or near the end of a major tubular bone of the extremities. In this series, 17 (8.7%) patients had malignant giant cell tumors of the bone; in 4 patients, evidence of malignancy was found at the initial diagnosis, 13 patients were diagnosed with sarcoma at the time of recurrence. Of these 13 patients, 11 had received prior radiotherapy.

The presence of multinucleated giant cells are not pathognomonic for GCTB, as giant cells can also be found in as benign chondroblastomas, nonosteogenic fibromas, aneurysmal bone cysts, simple bone cysts with a cellular lining, giant-cell reparative granulomas, bony lesions occurring with hyperparathyroidism, and osteogenic sarcomas. The histopathologic appearance is of

[1] http://www.cancer.org/cancer/bonecancer/detailedguide/bone-cancer-key-statistics accessed June 9, 2013
[2] Dahlin DC, Cupps RE. and Johnson Jr., EW. Giant-Cell Tumor: A Study of 195 Cases. Cancer 25:1061-1070, 1970.

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GCTB is of numerous giant cells distributed uniformly across spindle-like stromal cells and monocytes. The primary neoplastic component of GCTB is thought to arise from the spindle-like stromal cells, based on the ability of the stromal cells to proliferate in vitro and in tumor xenograft models[3]. The giant cells are primarily responses for the extensive bone resorption that is characteristic of GCTB, resulting in the lytic appearance on radiographs, however the stromal cells, promote giant cell formation. Multiple cytogenetic abnormalities have been identified with no single dominant cytogenetic abnormality in stromal cells from patients with GCTB; over-expression the p53 tumor suppressor has been suggested as an indicator of more aggressive disease.

There are no drugs which are approved for the treatment of GCTB. The primary treatment modalities are surgical resection (including resection of lung metastases) and radiation.

Regulatory History – denosumab

- June 1, 2010 denosumab was approved under the proprietary name, Prolia® 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. Evidence of efficacy was based on the results of a 3-year, randomized, double-blind, placebo-controlled trial of 7808 women in which treatment with denosumab 60 mg every 6 months resulted in a significant reduction in the incidence of new morphometric vertebral fractures at 1, 2, and 3 years, a significant reduction in the incidence of nonvertebral fractures at 3 years, and a significant increase in bone mineral density at all anatomic sites measured at 3 years.
- November 18, 2010, FDA approved an efficacy supplement for denosumab, under the proprietary name Xgeva™, for the prevention of skeletal-related events in patients with bone metastases from solid tumors. Denosumab was administered at a dose of 120 mg every 4 weeks. The safety and efficacy of Xgeva for this indication was demonstrated in three international, randomized (1:1), double-blind, active-controlled, noninferiority trials consisting of 2046 patients with advanced breast cancer and bone metastases, 1776 adults with solid tumors other than breast and castrate-resistant prostate cancer with bone metastasis and multiple myeloma, and 1901 men with castrate-resistant prostate cancer and bone metastases. The trials demonstrated that treatment with denosumab, as compared to zoledronic acid, resulted in a significantly lower incidence of skeletal-related events, a composite endpoint that included skeletal fractures, requirement for radiation or surgery to prevent impending fracture, or spinal cord compression.
- September 16, 2011, FDA approved two efficacy supplements for denosumab (Prolia) administered at a dose of 60 mg every 6 months for the treatment to increase bone mass. Safety and efficacy were demonstration in a 2-year, randomized (1:1), double-blind, placebo-controlled, multinational study two randomized, enrolling 252 women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer and in a 3-year, randomized (1:1), double-blind, placebo-controlled, multinational study enrolling 1468 men

[3] Cowan RW, Singh G. Giant Cell Tumor of the Bone: A Basic Science Perspective. Bone 52: 238-246, 2013.

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at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer. Treatment with denosumab at a dose of 60 mg every 6 months for four doses resulted in a significant increase in bone mineral density in the lumbar spine, total hip, and femoral neck at 2 years and significantly reduced the incidence of vertebral fractures in men and a significant increase in bone mineral density in the lumbar spine at one year in women.

- September 20, 2012, , supplemental approval was granted for Prolia for the treatment to increase bone mass in men 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. The efficacy and safety of denosumab were demonstrated in a 1-year, randomized, double-blind, placebo-controlled trial enrolling 242 men with osteoporosis. Treatment with denosumab at a dose of 60 mg every 6 months resulted in a significant increase in bone mineral density in the lumbar spine, total hip, and femoral neck at 1 year.

Regulatory history of denosumab for giant cell tumor of the bone

The clinical development program for denosumab for giant cell tumor of the bone was conducted under IND 9838.

December 20, 2010: Amgen received orphan drug designation for denosumab for "treatment of patients with giant cell tumor of bone."

April 5, 2011: A pre-sBLA meeting was held to discuss a proposed supplement for GCTB based on the results of Studies 20040215 and 20062004 based on demonstration of a "tumor response rate" of 86% of the 35 evaluable patients in 20040215. In this trial, "tumor response" was a composite endpoint of histologic response (≥90% elimination of giant cells relative to baseline or complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells) all 20 patients with sufficient baseline histological evaluation and lack of progression of the target lesion at week 25 by radiographic measurement in 10 of 15 patients where histopathology was not available. In Study 20062004, the primary endpoint was safety; Amgen presented the results of the secondary endpoints evaluating efficacy after the second interim analysis based on 77 patients in Cohort 1 and 23 subjects in Cohort 2 who had received at least one dose of denosumab and had been on study for at least 6 months. The second interim analysis demonstrated no evidence of disease progression in 72 patients in Cohort 1 based on investigator assessment and 22 of 23 patients in Cohort 2 who, by month 6, had not undergone the surgical procedure planned at baseline. In Cohort 2, 15 patients had not undergone surgery and five patients had a less morbid surgical procedure. Issues discussed during this meeting included"

- The definition of "tumor response" as used in Study 20040215 was not acceptable for demonstration of benefit. In the absence of a comparator arm, lack of radiographic progression does not provide meaningful information regarding clinical benefit and elimination of giant cells relative to baseline is of uncertain clinical significance.
- Amgen agreed to provide a proposal for characterizing tumor responses consistent with standard RECIST criteria for patients with measurable disease and to provide an alternate definition of tumor response for patients with bone only disease. FDA encouraged Amgen to identify additional criteria to measure responses in patients with GCTB confined to the bone or exhibiting tumor responses not well characterized by RECIST. PET imaging, pathologic

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examination of surgical specimens following tumor resection, objective determination of improvement in activities of daily living or reduction in opioid medication use may provide supportive evidence of responses to denosumab.

- Demonstration of durable objective responses using objective radiographic criteria determined by blinded independent review may be an acceptable endpoint for licensure, if of sufficient magnitude that the benefits are likely to outweigh the risks. FDA recommended that independent radiographic review be conducted to verify response for all patients that are identified as responders, as well as an equal number of a randomly selected subset of nonresponders.
- FDA stated that claims [redacted] (b) (4)

August 4, 2011: Type meeting held as a follow-up to the April 5, 2011 pre-sBLA meeting to discuss Amgen's draft proposal regarding radiographic image assessments for the proposed efficacy supplement for GCTB. Key agreements reached were

- Amgen agreed to characterize the duration of objective tumor responses using Kaplan Meier methodology.
- FDA stated that Amgen's proposal of using an imaging control group consisting of 20 patients with at least 3 radiographic images acquired prior to treatment with denosumab is reasonable if Amgen is not able to acquire 20 non-responders. FDA requested Amgen elevate the exploratory endpoint duration of response to a secondary endpoint
- FDA stated that efficacy data for studies 20040215 and 20062004 will be the subject of a future pre-sBLA meeting. Amgen will present the efficacy data separately and together in module 5 of an efficacy supplement.

IND 113617 submitted November 21, 2011, covering the pre-approval review for the clinical development program for giant cell tumor of the bone (GCTB) based on reorganization of the of the Office of Hematology and Oncology Products, in which the Division of Oncology Products 2 assumed responsibility for this development program. The new IND contained

- Protocol Amendment 1 and Statistical Analysis Plan (SAP) Version 4.0 for Study 20040215, "An open-label, multicenter, phase 2 safety and efficacy study of denosumab (AMG 162) in subjects with recurrent or unresectable giant cell tumor." These documents had been previously submitted to IND 9838.
- Clinical study report (CSR) for Study 20040215 dated April 2, 2009, using a data cut-off date of April 7, 2008.
- Protocol Version 6 for Study 20062004, "An open-label, multicenter, phase 2 study of denosumab in subjects with giant cell tumor of bone"; previously submitted to IND 9838.
- Version 6.0 of the statistical analysis plan (SAP) for Study 20062004, which superseded Version 5.0 of the SAP for Study 20062004 submitted on November 9, 2011 to IND 9838.
- Radiology charter for the independent radiology review of subjects enrolled in Study 20040215 and 20062004 to evaluate objective response. =

March 26, 2012: FDA issued an advice letter on the proposed radiologic review charter, stating "Your statistical analysis plan appears to be discordant with the agreements reached in the Type

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B meeting held on April 5, 2011 and the Independent Radiology Review Charter for Protocol 20062004 (dated August 30, 2011), submitted in response to this meeting. The Independent Radiology Review Charter for Study 20062004 and Study 20040215 describes the procedures for a retrospective review of radiographs to assess objective tumor response to denosumab treatment in patients with giant cell tumor of bone. (b) (4) (b) (4) . We also advised that durable objective response rate by blinded independent review may be an acceptable endpoint for licensure. (b) (4) and the methodologies for characterizing objective response contained in the independent radiology review charter."

September 11, 2012: A pre-sBLA meeting held to discuss whether proposed data and analyses of objective tumor response derived from Studies 20040215 and 20062004 would support an efficacy supplement for the proposed indication (b) (4) . A total of 190 patients had at least one evaluable time point assessment and were included in the objective tumor response analysis set. Among these patients, 187 were evaluable and included in modified RECIST evaluation (based on CT or MRI), 26 in modified EORTC criteria evaluation (based on PET and/or PET/CT), and 176 in modified inverse Choi criteria (density/size evaluation based on CT or MRI). Based on the best response using any tumor response criteria, 136 patients (72%) had an objective tumor response. As determined by the independent review committee (IRC), the response rates were 25% using modified RECIST, 96% using modified EORTC criteria, and 76% for modified inverse Choi criteria.

- Amgen proposes to include clinical study reports (CSRs) for the primary analysis and final analysis (including the 2-year safety follow-up period) of Study 20040215, and the third planned interim analysis (using a March 25, 2011 data cutoff date) of Study 20062004.
- Agreement was not reached on the primary method(s) for determination of objective response rate and response duration. FDA stated that objective tumor response as measured by modified RECIST should be the primary efficacy analysis for the sBLA with duration of response by RECIST criteria as a key secondary endpoint. Tumor response rates using the modified EORTC criteria and modified inverse Choi criteria could be used as supportive analyses to provide additional evidence of tumor response because the utility of these criteria in assessing GCTB response has not been well characterized. Amgen proposed that as criteria for determination of response are not well defined in this rare disease, Amgen proposed a comprehensive assessment of tumor response including RECIST, EORTC and inverse Choi criteria. During the meeting, FDA agreed to assess results by all three response criteria and that the best way to reflect the efficacy data for labeling would be decided during the review based on the evaluation of all of the results. Amgen agreed to provide separate efficacy datasets for each method of evaluating objective tumor response. In addition, Amgen agreed

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to provide a dataset that includes results for each method of evaluating tumor response and best overall response by any measurement criteria.

- FDA requested that Amgen include sensitivity analyses exploring the correlation of the three response criteria in the sBLA.
- Due to the uniqueness of the endpoints used in the proposed sBLA and the rarity of GCTB, FDA noted that it was likely that the application would be referred to an advisory committee.
- Agreement was not reached on the final wording of proposed indication, however FDA stated that the proposed indication (b) (4) (b) (4) patients with patients with GCTB that is not amenable to curative surgical resection or who require surgery for GCTB associated with significant morbidity,

December 12, 2012: Efficacy supplement STN BL 125320/94 was submitted. The application was designated as priority review.

3. CMC/Device

I concur with the conclusions reached by the Office of Biotechnology Products reviewer that there are no outstanding quality issues that preclude approval. No new CMC data were provided in this supplement and the request for waiver of environmental assessment was granted. There are no pending or ongoing compliance actions that prevent approval of this supplement.

The quality reviewer evaluated the data provided on immunogenicity of denosumab in patients with GCTB. These data were derived from =304 patients who received at least one dose of denosumab in Studies 20040215 and 20062004, of whom 147 patients received denosumab for ≥ 1 year, 46 patients for ≥ 2 years, and 15 patients for ≥ 3 years. No patient developed evidence of an anti-product antibody response as determined by a validated electrochemiluminescent bridging immunoassay.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval. No new nonclinical studies were submitted to support this supplement, however nonclinical pharmacology/toxicology was consulted by the clinical reviewer to determine if a nonclinical study could assess for the potential increased risk of malignant transformation to sarcoma in GCTB resulting from denosumab. This potential risk could not be adequately assessed in the clinic due to the lack of internal controls in the clinical trials and the relatively high (as compared to healthy subjects) high background rate of sarcoma in GCTB. Based on the nonclinical reviewer determination that conventional carcinogenicity studies would not be useful for the goal of investigating an increased risk of malignant transformation in this population, Amgen was asked to investigate the availability of *in vitro* or *in vivo* pharmacology models for further

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exploration of this potential risk. Amgen was unable to identify an appropriate model; therefore this potential risk will be evaluated under a clinical PMR.

5. Clinical Pharmacology

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

Amgen's proposed rationale for the dose and schedule used in the GTCB clinical development program is similar to the currently approved regimen for prevention of skeletal-related events in patients with solid tumors and osseous metastases, which results in steady-state levels able to maintain maximal reductions in bone turnover over the entire dosing interval in more than 95% of treated patients. Amgen stated that two additional doses of denosumab (120 mg administered on days 8 and 15 during the first 4-week cycle of treatment) were included in the regimen for the GTCB program (b) (4)

The supplement contained the results of optimal sparse pharmacokinetic (PK) sampling conducted in Study 20040215. (b) (4) The reviewer noted that the highest denosumab trough concentration was reached on day 29 after weekly dosing during the first 3 weeks of the first treatment cycle, (b) (4) steady-state concentrations similar to the concentrations described in approved labeling for approved indications (20 ± 14 mcg/mL) were achieved at 3 months (day 85).

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The number of trials and scope of the clinical development program is limited by the orphan status of the disease. It is further limited by study design of Protocol 20062004 in which periodic tumor imaging was not required and the retrospective nature of the analysis, in which data were available for only a subset of the patients enrolled. However, the endpoint utilized in the retrospective analysis is the most appropriate and commonly used criteria for measuring tumor shrinkage and is an accepted surrogate endpoint for clinical benefit in patients with metastatic cancer. In rare diseases, where controlled trials may not be feasible and there is no acceptable alternative therapy, demonstration of durable tumor responses has also been accepted as a direct measure of clinical benefit. The extensive safety experience and evidence of

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effectiveness in other cancer settings provided supportive information for this new proposed indication.

The major issues relating to this efficacy supplement was consideration of alternative criteria for measurement of tumor shrinkage using novel criteria (Modified EORTC and Inverse Choi criteria) as well as proposed claims [redacted] (b) (4) The rationale for FDA's decision not to include such claims in product labeling is discussed in Section 1 and in greater detail in this Section of the Summary Review.

Trial Design

Study 20040215 "An Open-Label, Multicenter, Phase 2 Safety and Efficacy Study of Denosumab (AMG 162) in Subjects With Recurrent or Unresectable Giant Cell Tumor (GCT) of Bone. The original protocol was dated December 2, 2005 and was amended on January 11, 2007 and July 31, 2007. The protocol was conducted under IND 9838.

The trial was an open-label, single-arm, pharmacodynamic and safety trial of denosumab 120 mg/kg subcutaneously on days 1, 8, and 15 of the first 28 day-cycle, then on day 1 of each subsequent 28-day cycle in patients with primary or recurrent, unresectable GCTB.

Key eligibility criteria were at least 18 years of age, histologically confirmed giant cell tumor, measurable disease defined as being at least 10 millimeters in the greatest dimension, recurrent GCT confirmed by radiology or unresectable GCT, ECOG performance status of 0, 1, or 2

The prespecified primary efficacy endpoint was elimination of at least 90% of giant cells, or complete elimination of giant cells in cases where giant cells represented <5% of tumor cells, or absence of radiographic progression of the target lesion up to week 25. Imaging and pathology reports were required at screening to confirm eligibility and radiographic measurements via spiral CT scan or MRI were obtained quarterly during treatment.

Protocol 20062004 "An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone." The original version of the protocol was dated April 22, 2008. The protocol was amended six times between December 2008 and August 2011, to specify the sample size at 100 and to increase the sample size in subsequent amendments from 100 to 250 to 375 to 500 patients. In addition, the trial was modified to add cohort 3 (patients previously treated in Protocol 20040215. The statistical analysis plan was finalized on October 31, 2011. The trial was conducted under IND 9838.

The trial was designed as an open-label, two-cohort trial of denosumab 120 mg/kg subcutaneously on days 1, 8, and 15 of the first 28 day-cycle, then on day 1 of each subsequent 28-day cycle. As originally planned, the total duration of study participation in this study will be approximately 18 months (approximately 12 months in the treatment phase and 6 months in the follow-up phase). An additional cohort was subsequently added to allow patients enrolled in Protocol 20040215 who were deemed to be benefitting from denosumab treatment to continue to receive denosumab at the time of closure of Protocol 20040215.

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Key eligibility criteria were pathologically confirmed giant cell tumor of bone within the 1 year prior to study enrollment; measurable evidence of active disease within the 1 year prior to study enrollment; Karnofsky performance status at least 50% (i.e., ECOG status 0, 1, or 2); adults or skeletally mature adolescents (i.e., radiographic evidence of at least one mature long bone, e.g., humerus with closed growth epiphyseal plate), at least 12 years of age, and mass of at least 45 kg. Additional criteria for Cohort 1 was the presence of surgically unsalvageable disease (e.g., sacral, spinal GCT, or multiple lesions including pulmonary metastases) and for Cohort 2 was the presence of surgically salvageable disease whose planned initial on-study surgery is associated with severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy). Imaging and pathology reports were required at screening to confirm eligibility, however imaging evaluation for tumor status during treatment were obtained at the investigator's discretion.

The primary objective of Protocol 20062004 was to evaluate the safety profile of denosumab in patients with GCTB by characterizing the type, frequency, and severity of adverse events and laboratory abnormalities for each cohort. The secondary objectives were evaluation of time to disease progression in subjects with unsalvageable GCT treated with denosumab (Cohort 1) and evaluation of the proportion of subjects able to undergo limb or joint sparing (e.g., curettage) surgical procedures in denosumab treated subjects with salvageable GCT who would have otherwise required *en bloc* excision (Cohort 2). The protocol also contained exploratory objectives of time to disease progression for all subjects, time to disease recurrence for subjects with complete clinical response or complete resection, evaluation of pathologic response to denosumab treatment for those subjects that undergo complete/partial resection or biopsy, radiographic changes over time (e.g., PET, CT, MRI, x-ray) for all subjects, and change in pain score from baseline as measured by the Brief Pain Inventory (BPISF).

At initiation, there was no pre-specified sample size for the trial, overall, or for each cohort. Amgen stated that the number of subjects to be enrolled would be governed by the number of patients with GCT who qualified for the study. The statistical analysis was to be descriptive in nature and no hypothesis testing will be performed. Interim analyses would be performed after each increment of 50 patients enrolled into the trial, however there were no prespecified plans for termination of the trial for either safety or efficacy based on the interim analyses.

Integrated Analysis Plan: As discussed in Section 2 of this review, based on FDA's advice given at the April 2011 pre-sBLA meeting, Amgen submitted an amendment to the statistical analysis plans for Protocols 20040214 and 20062004 on March 23, 2012, describing the plan to conduct a retrospective independent review of radiographic imaging data for all patients enrolled in these trials for whom a baseline and at least one post-treatment assessment by computed tomography [CT], magnetic resonance imaging [MRI], or whole body fluorodeoxyglucose positron emission tomography [^{18}FDG-PET] could be obtained. Plain X-ray film, bone scans, or ultrasounds were not evaluated in the radiographic imaging assessment. The acceptability of various criteria to support labeling claims based on tumor response were discussed during the pre-sBLA meeting of April 2011, August 2011, September 2012, and FDA's advice letter of March 2012 (see Section 2 of this review).

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Since there are no well-established tumor response criteria for subjects with giant cell tumor of the bone, and given the limitations of RECIST in measuring change in bony lesions, FDA agreed that Amgen could propose additional criteria for assessment of tumor response. The additional response criteria proposed were based tumor response on change in metabolic activity using the Modified EORTC Evaluation Criteria and based on a composite of change in lesion size on CT or MRI and change in lesion density based on CT Hounsfield units, using a modification of the Choi criteria. A summary of these criteria and key response definitions are provided below.

Modified RECIST 1.1 Evaluation Criteria

Response	Target Lesion	Non-target Lesion
Complete response (CR)	Disappearance of all target lesions. All target lymph nodes are < 10 mm in the short axis	Disappearance of all nontarget lesions. All nontarget lymph nodes are < 10 mm in the short axis
Partial response (PR)	At least a 30% decrease in SLD using baseline SLD as reference	
Stable disease (SD)	Neither sufficient shrinkage of target lesions to qualify for PR not sufficient increase to qualify for PD, taking as reference the nadir SLD	The persistence of one or more nontarget lesions not qualifying for CR or PD
Progressive disease (PD)	At least a 20% increase in the SLD of target lesions, taking as reference the nadir SLD. In addition to the relative increase of 20% in SLD, the SLD must also demonstrate an absolute increase of ≥ 5 mm	The unequivocal progression of existing nontarget lesion(s)
Unevaluable (UE)	A target lesion present at baseline which subsequently became unevaluable	Any nontarget lesion present at baseline, which subsequently became unevaluable

SLD = sum of the longest diameter

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Modified EORTC Evaluation Criteria

Response	PET Target Lesion
CMR	Complete metabolic response defined as resolution of abnormal FDG-uptake within the tumor volume of all target lesions to a level which is indistinguishable from surrounding normal tissue
PMR	Partial metabolic response defined as percent change of the sum of the SUV_{max} ($\%\Delta\sum SUV_{max}$) decrease of ≥25% compared with baseline
SMD	Stable metabolic disease defined as the $\%\Delta\sum SUV_{max}$ increased by < 25% or decreased by < 25% compared with baseline
PMD	Progressive metabolic disease defines as the $\%\Delta\sum SUV_{max}$ increased by ≥ 25% compared to baseline
*UE**	*FDG-PET exam was unavailable or, if received, deemed unevaluable. If one of the target lesions is deemed unevaluable, and the rules for PD do not a apply, a response of CR, PR, or SD cannot be assigned for the time point and the response will be UE, unless unequivocal progression is determine on the basis of the evaluable target lesion*

CR = complete response; FDG-PET = fluorodeoxyglucose positron emission tomography; PD = progressive disease; PR = partial response; SD = stable disease; SUV_{max} = maximum Standardized Uptake Value; UE = unevaluable

* The term "unevaluable" was not a response criterion described in the original EORTC criteria (Young et al, 1999)

Amgen references the paper by Young[4] (Young, 1999) as the basis for these criteria. The paper describes the purpose for generating these criteria as follows "([^{18}F]-fluorodeoxyglucose (^{18}F-FDG) uptake is enhanced in most malignant tumours which in turn can be measured using positron emission tomography (PET). A number of small clinical trials have indicated that quantification of the change in tumour [^{18}F]-FDG uptake may provide an early, sensitive, pharmacodynamic marker of the tumoricidal effect of anticancer drugs. *This may allow for the introduction of subclinical response for anticancer drug evaluation in early clinical trials* (emphasis added) and improvements in patient management." The article further states "These recommendations, based on presently available data, are not intended to have implications for regulatory authorities but rather to provide a common framework for data comparison. These recommendations will be subject to review on a three yearly cycle as these data mature." These original criteria do not appear to have been updated nor could a 3-yearly review be located in the published literature. New criteria (PERCIST[5]) based on PET imaging have emerged which purport to have greater standardization and clearer definitions of metabolic response or progression.

[4] Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammerrsma AA, Pruim J, and Price P. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: Review and 1999 EORTC recommendations - European Organization for Research and Treatment of Cancer (EORTC) PET Study Group.. Eur J Cancer 33: 1773-1782, 1999.

[5] Wahl RL, Jacene H, Kasamon Y, and Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med 50 (Suppl 1): 122S-150S, 2009.

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In addition, the independent review committee assessed response using the modification of the Choi[6] criteria developed for the assessment of gastrointestinal stromal tumors (GIST). These "response" criteria also referred to as the density/size evaluation, uses a modification of the Choi criteria (Choi et al, 2007). These criteria were modified specifically for the GCTB radiographic image assessment because denosumab inhibits osteoclastic activity; denosumab treatment is expected to result in ossification and calcification of the GCTB lesion. Therefore, the Choi criteria were modified to define response based on an increase in lesion density (as measured by a percent change in Hounsfield Units). This is the inverse of the density response as defined by the Choi criteria (in which decrease in metabolic activity on ^{18}FDG-PET correlated with a decrease in CT Hounsfield units). Changes in lesion size were also evaluated according to the Choi criteria. The "response" criteria using density/size evaluation of target lesions are provided in the table immediately below.

Density/Size Evaluation (Modified Inverse Choi) Criteria

Response	Target Lesion
CR	Disappearance of all disease
PR	A decrease in size (%Δ Choi SLD) ≥ 10% or an increase in CT density (%ΔHU_{mean}) ≥ 15% compared with baseline
SD	Does not meet the criteria for CR, PR, or PD
PD	An increase in unideminsional tumor size (Choi SLD) of > 10% and does not meet the criteria for PR using CT density The identification of any new lesions identified by CT/MRI
UE	The CT/MRI exam is unavailable or, if received, is deemed unevaluable. If a target lesion is deemed unevaluable by density and size measurement, and the rules for PD do not apply, a response of CR, PR, or SD cannot be assigned for the time point and the response will be UE

CR = complete response; CT = computed tomography; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; SD = stable disease; SLD = sum of the longest diameter; UE = unevaluable
* The term "unevaluable" was not a response criterion described in the original article (Choi et al, 2007)

Results

The application was based on data obtained in 305 unique patients who were enrolled in Studies 20040215 or 20062004. Efficacy data for patients in Cohort 3 who received prior denosumab in Protocol 20040215 were analyzed with the 20040215 population. There were 11 patients who were enrolled in Cohort 3 directly from Protocol 20040215 and 3 additional patients from Protocol 20040215 who completed treatment in that protocol and were subsequently enrolled in Cohort 1 of Protocol 20062004 at a later data. All such patients are identified only once in the

[6] Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA, and Benjamin RS. Correlation of Computed Tomography and Positron Emission Tomography in Patients With Metastatic Gastrointestinal Stromal Tumor Treated at a Single Institution With Imatinib Mesylate: Proposal of New Computed Tomography Response Criteria. J Clin Oncol 25:1753-1759. 2007

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integrated analyses as Protocol 20040215 participants, with duration of participation measured from entry onto Protocol 20040215 through the data cut-off date for Protocol 20062004.

Efficacy analyses were conducted in an integrated population consistent of all patients from Study 20040215 and all patients from Cohorts 1 and 2 of Study 20062004 for whom a baseline and at least one post-baseline set of radiographic images could be obtained for independent radiologic review.

Demographics and Baseline Tumor Characteristics By Protocol or Cohort and for the Integrated RECIST-Evaluable Population

Baseline Variable	20040215 (n=27)	20062004 Cohorts 1 & 2 (n=160)	Integrated Population (n=187)
Male	44%	45%	45%
White	78%	79%	79%
Age < 65 yrs	100%	97%	97%
Region			
North America	52%	37%	39%
Europe	4%	57%	50%
Australia	44%	6%	11%
ECOG PS			
0	33%	60%	56%
1	59%	36%	40%
2	0	4%	3%
Missing	7%	0	1%
GCT "stage"			
Primary resectable	0	15%	13%
Primary unresectable	33%	21%	23%
Recurrent resectable	22%	14%	15%
Recurrent unresectable	44%	49%	49%

In contrast to advice provided by FDA during meetings and in the March 26, 2012 advice letter, Amgen did not consider the primary analysis of response rate and duration to be that based on RECIST v 1.1 with the Modified EORTC metabolic response criteria and the Density/Size (Inverse Choi) criteria as supportive. Instead, Amgen used the "Integrated Best Response" based on best response as determined by independent review in 190 patients who were evaluable by any of the three response criteria systems. As discussed by the statistical reviewer, FDA considered the independently determined response rate and duration by RECIST 1.1 as the primary efficacy analyses in the overall population. The rationale for FDA's selection of this population is discussed later in this section. The results for IRC-determined response rate for all response criteria and as an integrated "best response" are summarized in the following table.

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Response Rate and Duration by IRC Review by Response Criteria in the Pooled Analyses of All IRC-Evaluable Patients in Protocols 20040215 and 20062004 (Cohorts 1 and 2)

	RECIST 1.1	EORTC	Density/size	Integrated Best Response
IRC Evaluable	N=187	N=26	N=176	N=190
Responders	47	25	134	136
Response Rate	25%	96%	76%	72%
95% CI	(19.1, 32.0)	(80.4, 99.9)	(69.1, 82.2)	(64.6, 77.9)
Median duration of follow-up	13.4 mos	13.8 mos	13.4 mos	13.4 mos
Median DoR	8.1 mos	3.9 mos	8.1 mos	8.1 mos
DoR Min-Max	0-41	0-40.5 mos	0-45.3 mos	0-45.3 mos

DoR= duration of response
Min-Max= Minimum and maximum observed duration of response

During discussions with Amgen regarding re-evaluation of the data using acceptable endpoints to support a request for approval, FDA advised that the RECIST criteria were acceptable based on the experience with these criteria in many types of cancer. FDA also indicated a willingness to consider other assessments as supportive. In response, Amgen provided two novel criteria which have not been accepted by FDA for labeling claims in any cancer. It is notable that the Density/Size (Inverse Choi) criteria, which is a composite endpoint incorporating both size and change in density on CT, provides a much higher response rate as compared to RECIST. Based on the analyses provided in the statistical review, it is clear that both RECIST and the "size" component from the similar results as displayed in the two waterfall plots reproduced from the statistical review, below. The similarity of these two curves supports the objective response rates using RECIST 1.1.

The difference between these two criteria is driven by the change in density (as displayed in the third waterfall plot), where nearly all patients had an increase in density however the effects were variable, with dramatic increases (500 to >7500% increases) identified in a minority of the patients. The basis for the 10% increase in density selected for the Inverse Choi criteria has not been justified based on clinical relevance. Instead, it was selected based on the known pharmacologic effect of denosumab on bone turn-over. As such, it appears to confirm the pharmacologic effects of denosumab in this population and indicates that there is bone deposition. Since no data were provided in the application which correlates the 10% increase in density with reduction in tumor pathologically or with a specific amount of normal bone formation at tumor sites, the relevance of this finding is uncertain. (b) (4)

(b) (4)

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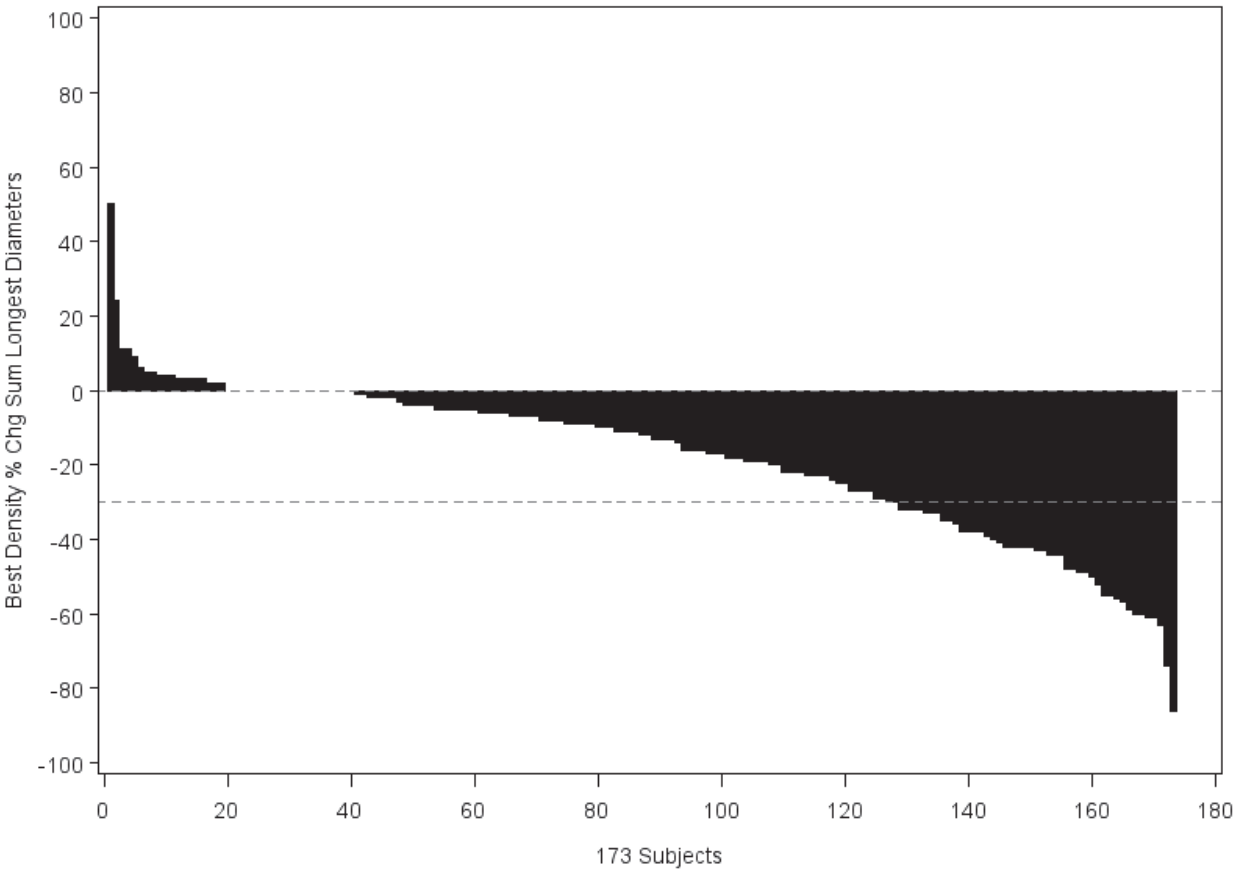
Figure 2. Best Percentage Change in Sum of Longest Diameters in RECIST-Evaluable Population



Reference ID: 3324237

Figure 3. Best Percent Change in Sum of Lesion Diameters in Density/Size Evaluable Population

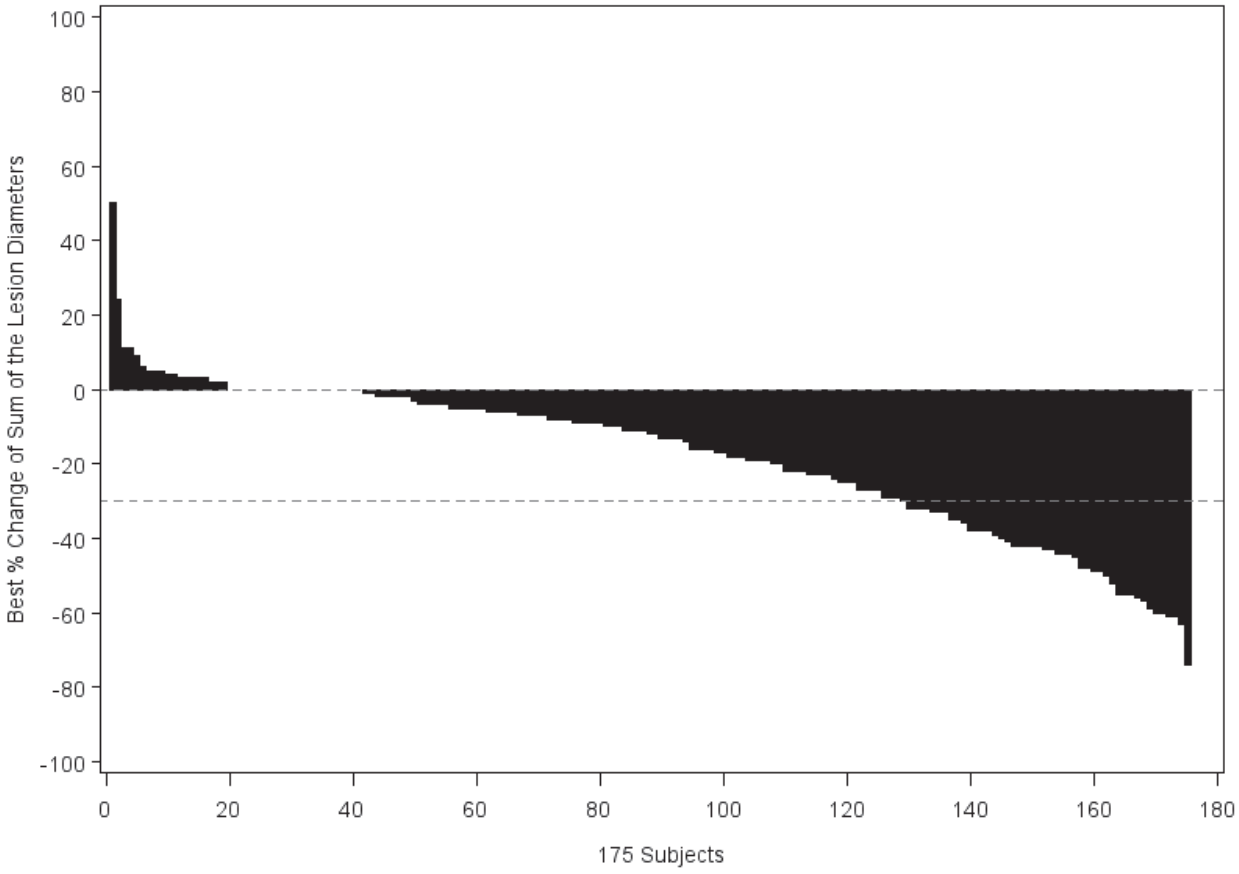


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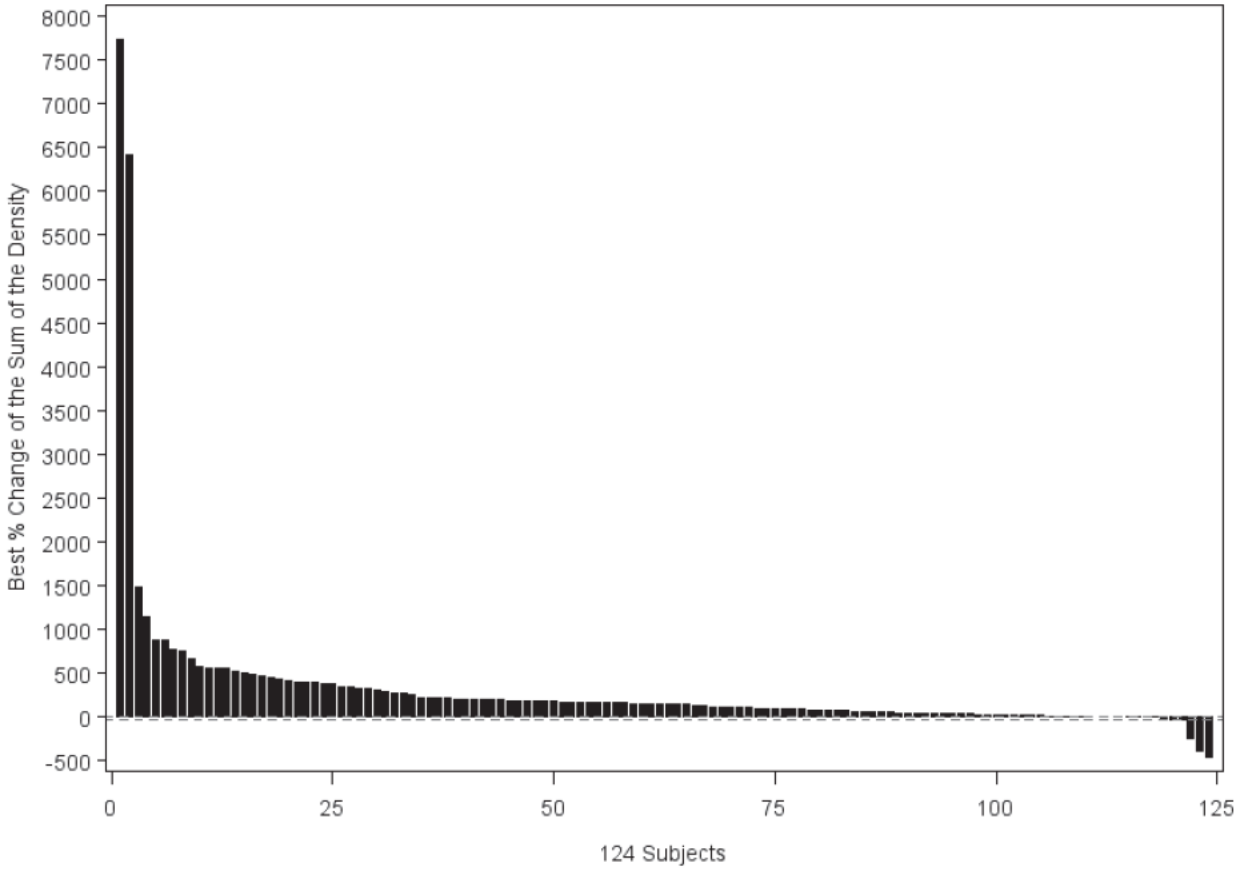
Figure 4. Best Percent Change of the Sum of the Density for Target Lesions in Density/Size (Inverse Choi) Evaluable Population



The other tumor response evaluation system proposed by Amgen was the modified EORTC criteria, which is a measure of metabolic activity. It is notable that, even in the original publication of these criteria, the authors caution that the intent is to identify drugs of interest for further development and not for regulatory intent. It is notable that, unlike other primary tumors of the bone, GTCB is PET-avid as a result of the high metabolic activity of the giant cells within the tumor. The finding that denosumab decreased metabolic activity in these cells is consistent with previously described pharmacologic effects on osteoclasts. However such effects are not evidence of anti-tumor activity, since the malignant component of GCTB are the stromal cells rather than the giant cells. (b) (4) (b) (4) .

Amgen originally proposed and conducted numerous exploratory analyses as well as planned analyses on change in planned surgery post-treatment as compared to pre-treatment. Although summarized in the clinical review, none of these analyses provide substantial evidence of effectiveness; (b) (4) . Additionally, for both patient-reported outcomes and physician-

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predictions for change in management, open-label clinical trials, where patients and investigators are aware of assigned therapy, [redacted] (b) (4) Notably, improvement in pain was identified as an exploratory analysis, with no prespecified hypothesis for testing or justification of the validity of the instrument in this patient population or of the change in effect size which was clinically meaningful.

The clinical reviewer also evaluated the results of the key secondary efficacy endpoint for Cohort 2 of Protocol 20062004, i.e., evaluation of the proportion of subjects able to undergo limb or joint sparing (e.g., curettage) surgical procedures in denosumab treated subjects with salvageable GCT who would have otherwise required *en bloc* excision Prior to submission of the supplement, FDA raised concerns regarding the ability to evaluate this endpoint in an open-label trial, particularly where there are no objective criteria for determine when to perform an *en* bloc excision rather than a less morbid surgery.

The analyses presented by Amgen provide data for all patients in Cohort 2; however this precluded an ability to correlate the proposed change in surgical management with changes in tumor size. The clinical reviewer also evaluated the planned and actual surgery performed in the 47 patients in Cohort 2 with IRC assessment for response by RECIST criteria. In this subset, there was no little evidence that change in tumor size correlated with change in surgical management. Only 11 of these 47 patients underwent surgery. Of those eleven, one patient with a 24% increase in SLD underwent a more aggressive surgical procedure, while five patients with decreases in tumor SLD of 4%, 5%, 6%, 16%, and 55% underwent the same surgical procedure as originally planned and the remaining five patients with a similar treatment effect (decrease in tumor SLD of 2%, 5%, 7%, 13% or 17%) underwent a less morbid surgical procedure. In addition, patients with prolonged stable disease (2% reduction in tumor SLD for up to 851 days and 4% increase in tumor SLD for up to 532 days in two patients with a planned *en bloc* excision or 0% change for 395 days and 0% change for 555 days in two patients with planned amputation) did not undergo any surgical procedure. Based on this lack of correlation between planned procedures with change in tumor measurement, it is difficult to put any credence on this outcome.

I concur with the clinical reviewer's assessment that these trials have demonstrated substantial evidence of clinical benefit, i.e., durable objective tumor responses of more than 6 months, in a segment of the GCTB population who have serious and life-threatening disease and no effective alternative therapy. Regular approval was granted based on the durability of the responses in a population subgroup who would otherwise experience substantial morbidity from their disease or surgical treatment. Since the durability of the responses has not been fully characterized, the clinical reviewer requested the following post-marketing commitment under 506(B) to further characterize long-term clinical outcomes:

- Submit the final report including primary datasets, derived datasets, and analysis programs used to generate the safety and efficacy results for the ongoing single arm multicenter trial of denosumab in patients with giant cell tumor of bone. Include an analysis of radiographic response as determined by the local investigator in evaluable patients who received at least one dose of denosumab and underwent at least one post-baseline Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) tumor assessment during the trial. The primary

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analysis should be conducted after patients enrolled through November 2012 have had the opportunity to complete 12 months of treatment.

8. Safety

Size of the database
A total of 2841 patients with solid tumors and have received denosumab at a dose of 120 mg every 4 weeks in randomized, active-controlled trials supporting the first approval of denosumab under the proprietary name Xgeva in 2010.

The safety of Xgeva was evaluated in 304 patients enrolled in Studies 4 and 5 with giant cell tumor of bone received at least 1 dose of Xgeva. Patients receiving concurrent bisphosphonate therapy not eligible for either study and those 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 were ineligible for Study 5.

Of the 304 patients who received Xgeva, 145 patients were treated with Xgeva for ≥ 1 year, 44 patients for ≥ 2 years, and 15 patients for ≥ 3 years. The median number of doses received was 14 (range: 1 to 60 doses) and the median number of months on study was 11 (range: 0 to 54 months). Fifty-eight percent of the enrolled subjects were women and 80% were White. The median age was 33 years (range: 13 to 83 years); a total of 10 subjects were skeletally mature adolescents (13 to 17 years of age).

The adverse reaction profile of denosumab in patients with giant cell tumor of bone is similar to that reported in patients with solid tumors metastatic to bone who received denosumab for the prevention of skeletal-related events. The most common adverse reactions occurring in Protocols 20040215 and 20062004, with a per-patient incidence of ≥ 10% were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions were osteonecrosis of the jaw and osteomyelitis (per-patient incidence of 0.7%). The most common adverse reactions resulting in discontinuation of denosumab were osteonecrosis of the jaw (per-patient incidence of 0.7%), and tooth abscess or tooth infection (per-patient incidence of 0.7%).

Major safety concerns related to labeling
There were no new serious adverse reactions identified in the giant cell tumor population and no new Contraindications or Warnings were added to product labeling based on data provided in this efficacy supplement. As noted by Dr. Donoghue, the incidence of secondary malignancy (osteosarcoma) or malignant transformation of giant cell tumor was 2.3% (7 of 304 patients). While this incidence is within the range reported in published literature which includes small case series and variable follow-up, in the absence of a control group, it is not possible to rule out a modest increase in the risk of secondary malignancies. Therefore, the clinical reviewer has requested long-term follow-up in Protocol 20062004, which will enroll a total of 500 patients, to obtained additional information on the observed risk of secondary malignancies.

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In addition, Dr. Donoghue noted a higher rate of exposure to denosumab during pregnancy which likely reflects the younger age and premenopausal status of patients with GCTB as compared to the previously approved indications and the chronic use in this indication. Product labeling has been updated to include specific recommendations on contraceptive use and counseling. In addition, this risk will continued to be monitored under the proposed PMR (below), in order to determine whether additional steps may be needed to further mitigate this risk.

REMS
The DRISK consultant and clinical reviewer agreed =that a REMS is not required for denosumab for the new indication for treatment of GCTB. Information on potential risks will be further evaluated under the PMRs and PMC described below.

PMRs and PMCs
The clinical reviewer has proposed the following post-marketing requirements to further evaluate the long-term risks of denosumab in this patient population, for both known risks (ONJ, embryofetal toxicity) and for unknown but potential risks (malignant transformation of giant cell tumor or of secondary osteogenic sarcoma).

- Submit a final report of follow-up safety data of Xgeva (denosumab) in patients with giant cell tumor of bone enrolled in the ongoing single arm trial through November 2012 for a minimum of five years or until death or lost to follow-up, whichever comes first. Comprehensively collect information regarding survival status, disease progression, serious adverse events, and adverse events of special interest including osteonecrosis of the jaw, pregnancy-related complications, atypical fractures, malignant transformation of giant cell tumor of bone, and secondary malignancies. Perform descriptive analyses of these safety data, including a subset analysis comparing the long-term safety of denosumab in adolescent and adult patients.

In addition, because the incidence of osteosarcoma is not clearly different from the reported background incidence, which is limited to case series, the clinical reviewer has asked for a post-marketing commitment to better characterize this background rate of malignant transformation in the following post-marketing commitment under 506(B)

- Provide a detailed and thoughtful analysis of the risk factors associated with malignant transformation of GCTB and development of new sarcoma and the lifetime and annual incidences of these events in denosumab naïve patients. For this analysis, use data from a minimum of two representative databases in addition to information from published literature. Include subset analyses based on specific risk factors identified from the comprehensive investigation.

9. Advisory Committee Meeting

This is an efficacy supplement for a new indication. Although the application was not referred to the Oncologic Drugs Advisory Committee (ODAC), the advice of two Special Government

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Employees were sought regarding whether the objective response rate and durability of responses observed were evidence of clinical benefit and whether the clinical benefits outweighed the risks. Both SGEs stated that observed response rate and durability of responses were clinically meaningful in this patient population and that benefits outweighed the risks. Both considered the duration of exposure to be prolonged and agreed that additional data should be obtained on long-term risks including characterization of the incidence of malignant transformation (to sarcoma).

The decision not to refer take this supplement to the ODAC considered the following: the safety profile is acceptable for treatment of giant cell tumor of the bone, the application did not raise significant safety or efficacy issues that were unexpected in the intended population, and there were no individuals on the ODAC with specific expertise in this rare cancer.

10. Pediatrics

Amgen received orphan drug designation for the treatment of giant cell tumor of the bone and therefore is exempt from the requirements of the Pediatric Research Equity Act (PREA). GCTB does not develop in individuals with immature bone development. Ten adolescents (aged 13-17 years) with giant cell tumor of bone who had reached skeletal maturity were enrolled in clinical studies of denosumab. Skeletal maturity was defined as having at least one mature long bone (e.g. closed epiphyseal growth plate of the humerus) and body weight ≥ 45 kg. The adverse reaction profile and efficacy results appeared to be similar in skeletally mature adolescents and adults.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: No new safety issues were identified during the review of this efficacy supplement regarding the approved proprietary name. =

- Physician labeling

  - Indications and Usage: FDA requested that Amgen [redacted] (b) (4) [redacted] (b) (4) "that is unresectable or where surgical resection is likely to result in severe morbidity", since surgical resection is the treatment of choice where possible and morbidity is acceptable. In addition, FDA placed the previous limitation of use with the previously approved indication for bone metastases from solid tumors (1.1) as it pertains more closely to that indication.
  - Dosage and Administration: added recommendation for supplementation with calcium and vitamin D under the recommended dosing for each indication.

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- Warnings and Precautions: Added information on patient counseling, including recommendations for contraception to this section and retitled section 5.3 from "Pregnancy" to "Embryofetal Toxicity" to ensure clarity on the risk being described in this section.
- Adverse Reactions: Added information on adverse reactions in Studies 20040215 and 20062004; included information on key eligibility criteria that might influence adverse reaction rates for context (e.g. no concurrent bisphosphonates), and demographic information on safety population, in accordance with FDA Guidances for Adverse Reactions section of product labeling. Also included results of immunogenicity testing in Studies 20040215 and 20062004.
- Drug Interactions: edited for brevity.
- Use in Specific Populations: Added efficacy information on adolescents enrolled in Protocol 20062004. Added new subsection on Males and Females of Reproductive Potential as recommended by the Maternal Health Team consultant.
- Clinical Pharmacology: Edited new information on possible mechanism of action of denosumab for treatment of GCTB but deleted new information on pharmacodynamics as it is not clear that this relates to its anti-tumor activity in GCTB. Edited information on time to reach steady-state with new regimen for GCTB as recommended by the Clinical Pharmacology reviewer (reasons discussed in section of this summary review).
- Clinical Studies: Edited trial description to remove (b) (4) (b) (4)

- Carton and immediate container labels: No new safety issues were identified during the review of this efficacy supplement regarding the approved carton and container labeling.

- Patient labeling/Medication guide: Not applicable

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I concur with the recommendations of all review team members and also recommend approval of this efficacy supplement.

- Risk Benefit Assessment: Giant cell tumor of the bone is an orphan disease with an estimated 800 new cases in the United States annually. The only effective curative treatment is surgical resection, which can result in significant morbidity depending on the location of the tumor and number of recurrences. GCTB is responsive to radiation therapy, which is employed for tumors located in the pelvis or spine. For patients who are able to undergo surgical resection of tumor this is the preferred treatment and denosumab is not indicated for these patients.

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However, recurrences are reported following both surgery and radiotherapy; there are no effective therapies for such patients. Persistent unresectable tumor can have an indolent course complicated by pathologic fractures, infection, and in a minority, malignant transformation. Given the lack of satisfactory alternative therapy, the independently documented response rate of 25%, many of which were durable for more than 8 months, provides a substantial evidence of clinical for these patients. In general, tumor reduction is considered a surrogate for clinical benefit (longer or better quality of life) in patients with metastatic cancer, however in this setting, reduction in tumor size offers the only potential for tumor control and avoidance of morbid surgical procedures. In addition, the toxicity profile of denosumab is tolerable, with the most common adverse reactions being fatigue/asthenia, hypophosphatemia, and nausea in patients with solid tumors (more than 2500 patients) and the most common adverse reaction observed in 10% or more of patients with GCTB being The most common adverse reactions in patients with giant cell tumor of bone receiving Xgeva (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, fatigue, back pain, and pain in extremity. The most serious adverse reactions of denosumab were ONJ, occurring in 1.3% of patients with GCTB and hypocalcemia and hypophosphatemia, which were clinically asymptomatic in the 304 denosumab-treated patients. This level of risk is acceptable to patients who may undergo extensive surgical resection or amputation or who have received radiotherapy for treatment of their disease. I concur with the clinical reviewer that the benefits of tumor reduction outweigh these risks.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendations of the clinical reviewer and DRISK consultant that a REMS is not required for denosumab in this indication population in order to ensure safe use through mitigation of risks.

- Recommendation for other Postmarketing Requirements and Commitments
  I concur with the recommendation by the clinical reviewer that Post-Marketing Trials under 505(o) be required to obtained longer follow-up of serious adverse reactions and adverse reactions of interest to evaluate for potential increases over time in the incidence or severity of the labeled serious risks of denosumab.

  I also concur with the request for agreed-upon post-marketing commitments under 506(B) to further characterize clinical outcomes in a larger population (500 patients) with longer follow-up and to further characterize the background rate of second malignancies in this population.

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/s/

PATRICIA KEEGAN
06/13/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: 125320/94

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

Best, Jeanine
Demko, Suzanne
Donoghue, Martha
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Sridhara, Rajeshwari
Toscano, Marybeth
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125320/94
Priority or Standard	Priority
Submit Date(s)	December 11, 2012
Received Date(s)	December 12, 2012
PDUFA Goal Date	June 13, 2013
Division / Office	DOP2/OHOP
Reviewer Name(s)	Martha Donoghue, MD
Review Completion Date	May 20, 2013
Established Name	Denosumab
(Proposed) Trade Name	Xgeva
Therapeutic Class	Biologic
Applicant	Amgen
Formulation(s)	subcutaneous injection
Dosing Regimen	120 mg every 4 weeks, with additional doses on Days 8 and 15 of the first cycle
Indication(s)	Treatment of giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
Intended Population(s)	Adults and skeletally mature adolescents

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends accelerated approval of Supplemental Biologics Application (sBLA) 125320/94 for the following indication:

> *Xgeva is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.*

1.2 Risk Benefit Assessment

Giant cell tumor of bone (GCTB) is an osteolytic bone tumor that can cause pathologic fractures, joint destruction, physical deformity, and loss of function through rapid and extensive local destruction of bone. GCTB is a rare tumor that affects roughly one of every million people per year[1]. If GCTB is resectable, surgery can be curative. However, in some cases curative resection requires extensive surgery, such as limb amputation, joint resection, or hemi-pelvectomy, that can result in severe morbidity and impair quality of life. There are currently no approved therapies for GCTB.

To support the approval of Xgeva (denosumab) for the treatment of patients with GCTB, the Applicant submitted results of two multicenter single arm trials conducted in adult and skeletally mature adolescent patients with histologically-confirmed giant cell tumor of bone that was either recurrent, unresectable, or for which curative surgery would be associated with severe morbidity (Trial 20040215 and Trial 20062004).

This sBLA included data from the final analysis of Trial 20040215. Trial 20040215 enrolled and treated 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically-confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a CT or MRI obtained within 28 days prior to trial enrollment. Patients enrolled in Trial 20040215 underwent Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) assessment of giant cell tumor of bone at baseline and quarterly during Xgeva treatment.

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This sBLA also included data from the third interim analysis of Trial 20062004 (using a data cut-off March 25, 2011). The third interim analysis of Trial 20062004 included data from 267 adult or skeletally mature adolescent patients GCTB treated with denosumab who had not previously enrolled in Trial 20040215. A total of 10 patients were 13-17 years of age. Patients were required to have histologically-confirmed giant cell tumor of bone and evidence of measurable active disease confirmed by a report from an imaging study obtained within one year prior to trial enrollment. A total of 167 patients had surgically unsalvageable disease (e.g. sacral, spinal, or multiple lesions, including pulmonary metastases) and 100 patients had surgically salvageable disease and a planned surgery likely to result in severe morbidity (e.g. joint resection, limb amputation, or hemipelvectomy). Patients enrolled in Trial 20062004 underwent imaging assessment of disease status at the discretion of their treating physician.

During a Type B pre-sBLA meeting held on April 5, 2011, FDA advised the Applicant that the pre-specified efficacy endpoints for Trial 20040215 and Trial 20062004, which included demonstration of elimination of giant cells from biopsy specimens and lack of radiographic progression (without a comparator), were of unclear clinical significance and would therefore not provide sufficient evidence of efficacy to support licensure. FDA advised the Applicant that demonstration of durable objective response, as determined by blinded independent review of images obtained in Trial 20040215 and Trial 20062004, may support licensure if the magnitude and duration of objective response are sufficient such that the benefits outweigh the risks of Xgeva therapy.

Based upon this advice, the Applicant performed a retrospective independent review of radiographic imaging data obtained in patients enrolled in Trials 20040215 and 20062004. Of the 304 patients enrolled and treated in Trial 20040215 and Trial 20062004, 187 (61%) had at least one post-baseline radiographic assessment available for evaluation of objective response according to Modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1). An objective response by modified RECIST 1.1 was observed in 47 of 187 (25%) evaluable patients (95% CI: 19, 32). All responses were partial responses. The median time to response was 3 months (range: 1 to 21 months). With a median follow-up duration of 13 months, disease progression occurred following an objective response in three patients and the median duration of ongoing responses was 8 months (range: 0 to 41 months). Efficacy results in skeletally mature adolescents appeared to be similar to those observed in adults.

As discussed in a pre-sBLA meeting held on September 11, 2012, FDA considers objective response using modified RECIST 1.1 the primary endpoint supporting the efficacy of denosumab in the treatment of GCTB. The sBLA included additional efficacy analyses, including analyses of radiographic response using Density/Size and modified European Organization for Research

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and Treatment of Cancer (EORTC) criteria, analyses of requirements for surgical resection of GCTB after initiation of denosumab, and changes in analgesic use. These analyses were generally supportive of analyses of the primary regulatory endpoints of objective response rate and duration of response according to modified RECIST 1.1.

Overall, the adverse reaction profile of denosumab in patients with giant cell tumor of bone was similar to that observed in the 2,841 patients with bone metastases from solid tumors treated with denosumab in the placebo-controlled trials supporting the original approval of Xgeva. The median number of doses received by the 304 patients treated in Trial 20040215 and Trial 20062004 was 14 (range: 1 to 60 doses) and the median number of months on study was 11 (range: 0 to 54 months). The most common adverse reactions in patients enrolled in Trial 20040215 and Trial 20062004 combined (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions (per-patient incidence of 1%) were osteonecrosis of the jaw and osteomyelitis. The most common adverse reactions (per-patient incidence of 1%) resulting in discontinuation of Xgeva were osteonecrosis of the jaw, tooth abscess or infection, and development of sarcoma or malignant transformation of GCTB. Grade 3 or 4 hypocalcemia was not observed, and Grade 3 hyophosphatemia occurred in 29 (10%) patients. A single death, attributable to disease progression, occurred during or within 30 days of study therapy. At the time of the third interim analysis of Trial 20062004, 238 of 304 (78%) of patients continued to receive denosumab therapy. The most common reason for discontinuing denosumab was complete resection of GCTB (23 of 304, or 7% of patients).

The clinical review team recommends granting Subpart E (accelerated) approval to this sBLA under 21 CFR 601.41. This subpart applies to “certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).” These regulations also state that “*Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit….”*

There are limitations inherent in relying on results from single arm trials enrolling small numbers of patients to support approval. However, the Food and Drug Administration’s procedures outlined in Subpart E of 21 CFR part 312 state that the Food and Drug Administration (FDA) should apply an appropriate degree of flexibility in applying statutory standards when evaluating new therapies designed to treat individuals with life threatening and severely debilitating diseases,

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especially when no satisfactory alternative therapy exists. Subpart E of 21 CFR part 312 also acknowledges that FDA must make a medical risk-benefit judgment when deciding whether to approve a new therapy. As part of this risk-benefit analysis, the FDA considers "whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy" (21 CFR 312.84).

The clinical review team has determined that the clinical benefits of denosumab treatment, as evidenced by achievement of durable objective response in approximately one quarter of patients treated with denosumab in Trial 20040215 and 20062004 who had images available for assessment, outweigh the known and potential risks of denosumab in patients with GCTB that is unresectable or in cases where curative resection is likely to result in severe morbidity. Due to the rarity of GCTB, it is not feasible to conduct randomized controlled trials to establish the efficacy of potential treatments for this disease. Additionally, there are no approved therapies for giant cell tumor of bone. Furthermore, although surgical en-bloc resection or curettage can be curative, GCTB can recur following surgery and GCTB often occurs in locations that are not amenable to curative surgery without incurring the risk of substantial morbidity. Therefore, taking into consideration the challenges of studying treatments for rare diseases such as GCTB, the serious nature of GCTB, the absence of satisfactory, approved therapeutic alternatives to surgery, and the existing safety database for denosumab, the clinical review team concluded that the totality of data included in this submission provides sufficient evidence of safety and efficacy to grant accelerated approval to Xgeva (denosumab) for the treatment of skeletally mature adolescent and adult patients with GCTB that is unresectable or where surgical resection is likely to cause substantial morbidity.

The clinical team recommends three postmarketing requirements (PMRs) to confirm clinical benefit for this indication and to gather more comprehensive safety data to better inform patients and healthcare providers of the risks and benefits of denosumab therapy for GCTB. Section 1.4 provides details of these proposed PMRs.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The clinical reviewer does not recommend a postmarket risk evaluation and mitigation strategy (REMS) for this sBLA because the risks of Xgeva are well characterized and monitorable.

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1.4 Recommendations for Postmarket Requirements and Commitments

This clinical reviewer proposes to seek the following postmarketing requirement (PMR) to confirm the clinical benefit of denosumab in the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

- Submit a final study report for Trial 20062004, "An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone." The final report should also include the primary and derived datasets and analysis programs used to generate the safety and efficacy results for this study. The primary analysis will be conducted after all enrolled patients have had the opportunity to complete 12 months of treatment, and will include an analysis of radiographic response in patients who have images obtained on study.

This PMR is necessary to confirm clinical benefit in the proposed patient population for several reasons. First, accelerated approval of this sBLA is based upon data derived from a small number of patients with GCTB treated for a limited period of time. According to an email received by the Applicant on March 6, 2013, the final analysis of Trial 20062004 will include clinical data from at least 500 patients, which will reflect clinical experience with denosumab treatment in approximately 200 additional patients with GCTB. Secondly, GCTB is not immediately life threatening in the majority of patients and it is therefore likely that a substantial proportion of patients will receive denosumab treatment for an extended period of time. Thus, the clinical review team considers it important to further characterize the risk:benefit relationship of denosumab in patients with GCTB through analysis of data reflecting a longer duration of treatment prior to granting full approval for this indication.

The following additional PMRs are proposed under FDAA under Section 505(o)(3) of Federal Food, Drug and Cosmetic Act (FDCA) to further characterize the safety of long term use of denosumab in patients with GCTB:

- Provide descriptive analyses of the long term safety of Xgeva using data collected from all patients enrolled in Trial 20062004 through November 2012 for a minimum of 5 years, or until death or lost to follow-up, whichever comes first. In addition, use available safety data from patients enrolled after November 2012 for the safety analyses. Systematically collect information regarding survival status, disease progression, and serious adverse events, including adverse events of special interest such as osteonecrosis of the jaw, pregnancy-related complications, skeletal fractures, malignant transformation of giant cell

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tumor of bone, and secondary malignancies. Perform descriptive analyses of these safety data, including a subset analysis comparing the long-term safety of denosumab in adolescent and adult patients.

- Conduct a retrospective cohort study using multiple existing available databases and published sources to systematically investigate the lifetime and yearly per-patient incidence and the risk factors associated with malignant transformation of GCTB and development of new sarcoma in patients who have not received treatment with denosumab. Provide thoughtful analyses of the results of this study in comparison with the incidence of malignant transformation of GCTB or development of new sarcoma derived from the long term safety data accumulated in the second PMR described above.

At the time of this review, negotiation of postmarket requirements and committments is ongoing and milestone dates have not been established.

2 Introduction and Regulatory Background

Giant cell tumor of bone (GCTB) is an osteolytic bone tumor that accounts for 4 to 5% of all primary bone tumors and approximately 20% of benign bone tumors[2]. GCTB is a rare tumor that affects roughly one of every million people per year[1]. Although the peak incidence of GCTB is in the third decade of life, GCTB also occurs rarely in pediatric patients[3,4].

Although GCTB is generally considered a benign tumor, it can cause pathologic fractures, joint destruction, physical deformity, and loss of function through rapid and extensive local destruction of bone. Additionally, up to approximately 6% of cases of GCTB metastasize to the lungs and approximately 1 to 5% of cases undergo malignant transformation[5,6,7,8].

Giant cell tumors consists of stromal cells that express receptor activator of nuclear factor kappa B ligand (RANKL) and receptor activator of nuclear factor kappa B (RANK)-expressing giant cells and giant cell precursors Growth of giant cell tumors is dependent upon RANKL[8,9].

If GCTB is resectable, surgery, either in the form of en-block resection or curettage, can be curative. However, curative resection can require extensive surgery, such as limb amputation, joint resection, or hemi-pelvectomy, that is likely to cause severe morbidity and adversely impact quality of life. Additionally, GCTB recurs in approximately 10-20% of patients following surgical resection and 40% of patients following curettage[10].

Multiple therapies, including embolization, radiation therapy, cytotoxic chemotherapy, and bisphosphonates, have been employed to treat patients for whom surgical resection is not a feasible option. However, none of these therapies have been demonstrated to confer a durable treatment benefit in controlled clinical trials. There are currently no approved therapies to treat patients with GCTB that is unresectable or for whom resection would pose a risk of unacceptable morbidity.

2.1 Product Information

Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human receptor activator of nuclear factor kappa B ligand (RANKL), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Denosumab prevents RANKL from activating its receptor, receptor activator of nuclear factor kappa B (RANK), on the surface of osteoclasts and their precursors. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Xgeva (denosumab) is a sterile, preservative-free, clear colorless to pale yellow solution supplied as an injection for subcutaneous use in 120 mg/1.7mL (70 mg/mL) single-use vials. 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.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no FDA-approved products for the treatment of patients with Giant Cell Tumor of Bone (GCTB).

2.3 Availability of Proposed Active Ingredient in the United States

Xgeva (denosumab) injection for subcutaneous use is currently marketed and available in the United States. Xgeva is currently approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

Denosumab is also marketed under the trade name Prolia

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2.4 Important Safety Issues With Consideration to Related Drugs

Section 5 (WARNINGS AND PRECAUTIONS) of the Xgeva (denosumab) package insert conveys the risks of hypocalcemia, osteonecrosis of the jaw (ONJ), and fetal harm with use of Xgeva during pregnancy at the approved dose and schedule (120 mg administered subcutaneously every 4 weeks). The XGEVA package insert also includes instructions for routine monitoring of calcium levels and adequate supplementation of all patients with calcium and vitamin D. The package instructs prescribers to perform an oral examination prior to starting Xgeva, and avoid invasive dental procedures in patients treated with Xgeva in order to reduce the risk of ONJ.

Denosumab is marketed as Prolia for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture, treatment of men at high risk for fracture who are receiving androgen deprivation therapy for nonmetastatic prostate cancer, and treatment of women who are at high risk for fracture who are receiving adjuvant aromatase inhibitor therapy for breast cancer. The approved dose of Prolia is 60 mg administered subcutaneously every 6 months. Section 5 (WARNINGS AND PRECAUTIONS) of the Prolia® (denosumab) package insert conveys the risks of hypocalcemia, serious infections including skin infections, dermatologic reactions, ONJ, atypical femoral fractures, and suppression of bone turnover.

Labeled risks of bisphosphonates include hypocalcemia, renal toxicity, fetal harm, bone pain, atypical femur fractures, and osteonecrosis of the jaw (ONJ). Nephrotoxicity associated with bisphosphonate therapy is dose and infusion-time dependent.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1 summarizes the key regulatory activities for denosumab that are not specifically related to the proposed GCTB indication (BLA 125320/94).

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Table 1: Key regulatory activities unrelated to the proposed GCTB indication

Date	Nature of Regulatory Activity	Issues
7/17/2001	IND application	• May proceed letter issued for IND 9838.
6/1/2010	Initial approval of denosumab BLA 125320 (Prolia)	• Prolia approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture.
11/18/2010	Approval of denosumab sBLA (Xgeva)	• Xgeva approved for prevention of skeletal-related events in patients with bone metastases from solid tumors.
9/16/2011	Approval of denosumab sBLA (Prolia)	• Prolia approved as a treatment to increase bone mass in men receiving androgen deprivation therapy for nonmetastatic prostate cancer and women receiving adjuvant aromatase inhibitor therapy for breast cancer who are at high risk for fracture.
9/20/2012	Approval of denosumab sBLA (Prolia)	• Prolia approved as a treatment to increase bone mass in men with osteoporosis at high risk for fracture.

Table 2 summarizes the key regulatory activities for denosumab that are related to this sBLA.

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Table 2: Key regulatory activities for sBLA 125320/94 (GCTB indication)

Date	Nature of Regulatory Activity	Issues
12/20/2010	Orphan Designation	• FDA grants orphan designation for denosumab for the treatment of patients with giant cell tumor of bone.
4/5/2011	Type B pre-sBLA meeting	• Amgen proposed to submit sBLA relying on results from Trials 20040215 and 20062004 to demonstrate safety and efficacy of denosumab for the treatment of GCTB. • FDA stated that the proposed definition of treatment response, which included elimination of giant cells and lack of radiographic progression (in a single arm trial) was not an acceptable endpoint for licensure. • Amgen agreed to provide a proposal for characterizing objective tumor response that is consistent with RECIST for patients with measurable disease and provide an alternate definition of tumor response for patients with bone-only disease or atypical responses to denosumab therapy. • FDA stated that durable objective tumor response rate, defined as the proportion of patients that exhibit partial or complete responses to denosumab therapy using objective radiographic criteria by blinded independent review, may be an acceptable endpoint for licensure if the magnitude is sufficient such that benefits are likely to outweigh risks. • FDA stated that demonstration of improvement in patients' pain indices, elimination of requirement for narcotics, histologic response, or reduction in morbidity may provide supportive evidence to strengthen the sBLA for a GCTB indication. • (b) (4)

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Date	Nature of Regulatory Activity	Issues
		(b) (4) [redacted]
8/4/2011	Type C Meeting (Teleconference)	• FDA held a teleconference to discuss Amgen's proposal for use of retrospective evaluation of objective response rate based on an independent review of radiographic image assessments. • FDA agreed that assessment of objective radiographic response in evaluable patients using modified RECIST, modified EORTC criteria, and inverse Choi (density/size) criteria was acceptable to provide the basis for an sBLA submission. • Amgen agreed to characterize the duration of objective tumor response using Kaplan Meier methodology. • FDA stated that Amgen's proposal to use an imaging control group consisting of 20 patients with at least 3 radiographic images acquired prior to treatment with denosumab was acceptable. • FDA requested Amgen to elevate the exploratory endpoint of duration of response to a secondary endpoint. • FDA stated that Amgen should include narratives for each patient who is not evaluable for objective radiographic response that explains why they were not evaluable.
11/21/2011	Administrative split of IND 9838	• Amgen submits original application for new IND 113617 to administratively split GCTB indication from existing IND 9838.
12/7/2011	30-day waiver for IND 113617	• FDA acknowledged IND application to administrative split of IND 9838. FDA grants 30-day waiver for IND 113617 for the study of denosumab for the treatment of GCTB.

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Date	Nature of Regulatory Activity	Issues
9/11/2012	Type B pre-sBLA meeting	• FDA stated that based upon the information provided in the meeting package, the retrospective analysis of radiographic images from Studies 20040215 and 20062004 (including 190 evaluable patients in the objective response analysis set) appears to provide an adequate basis for a sBLA submission, but that filability would be determined after the sBLA is submitted. • FDA recommended that objective tumor response using modified RECIST be used for the primary efficacy analysis with duration of response by modified RECIST as a key secondary endpoint. • FDA recommended that modified EORTC criteria and inverse Choi criteria be used for supportive analyses only because the utility of these criteria in assessing GCTB response has not been well characterized. • FDA agreed that the sBLA should contain results for each method of evaluating objective tumor response separately, in addition to analyses of objective tumor response by best overall response, but that the best way to reflect the efficacy data in product labeling will be decided during the review based on the evaluation of all of the results. • FDA stated that the GCTB indication [redacted] (b) (4) adult and skeletally mature adolescent patients with GCTB that is either unresectable or for whom curative resection would pose a risk of substantial morbidity (such as limb or joint amputation). • FDA requested that a detailed justification of the proposed dosage regimen be included in the sBLA.

Date	Nature of Regulatory Activity	Issues
11/30/2012	Written Request Issued	• FDA issued Original Written Request (WR) for pediatric studies of denosumab. WR includes the following studies: (b) (4) [redacted] (b) (4)

2.6 Other Relevant Background Information

For Prolia, the following post marketing requirements (PMRs) under Section 505(o) of the Federal Food, Drug and Cosmetic Act (FDCA) are outstanding:

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. Inclusion of a new target population, men with osteoporosis, in the required postmarketing study entitled, “The Denosumab Global Postmarketing Safety Observational Study (Trial 20090522), designated above as PMR #2.

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5. Inclusion of a new target population, men with osteoporosis, in the required postmarketing study entitled "The Prolia Postmarketing Active Safety Surveillance Program (Trial 20090601), designated above as PMR #3.
6. A clinical trial to investigate the levels of denosumab in semen of men treated with Prolia.

Prolia was approved in conjunction with a Risk Evaluation and Mitigation Strategy (REMS) 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 current REMS for Prolia includes a Medication Guide for health care providers to dispense to each patient who receives Prolia, a communication plan, and a timetable for submission of assessments of the REMS. The REMS assessment plan was to include the following elements:

- 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.
- 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.
- An evaluation of whether patients receive the Medication Guide and actions taken to ensure that patients receive the Medication Guide.
- 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.

For Xgeva, the following post marketing requirement (PMR) under Section 505(o)(3) of Federal Food, Drug and Cosmetic Act (FDCA) is outstanding:

- 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

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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 using the CDISC and ADaM data models and the analysis programs used to generate the safety and laboratory analyses. *Reviewer note: the status of this PMR is delayed.*

Amgen also agreed to the following post marketing commitment for Xgeva:

- 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.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Amgen submitted tabulated datasets in Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) format and analysis datasets based on the CDISC Analysis Data Model (ADaM). Adverse events from a subset of case report forms for Trial 20042015 and Trial 20062004 were reviewed and compared to the adverse event datasets in order to confirm accuracy of the data transfer. Verbatim terms for all treatment-emergent adverse events (TEAE) of Grade 3 or greater severity for both trials were compared to the corresponding MedDRA lower level terms; based upon this comparison, adverse event coding appeared to be accurate.

The submission was of adequate quality and integrity to permit review of the supplemental biological license application (sBLA).

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3.2 Compliance with Good Clinical Practices

Module 2, Section 2.5 (Clinical Overview, page 11) of this submission contained a statement indicating that the GCTB clinical trials were conducted according to Good Clinical Practices (GCP), as described in International Conference on Harmonization (ICH) E6 guidelines, under the principles of the Declaration of Helsinki, and in accordance with local and regional regulations.

The study protocol, patient information, and informed consent documents for Trial 20040215 and Trial 20062004 were reviewed and approved by the independent ethics committee or institutional review board for each study center. A safety/data monitoring committee was used during the conduct of either study.

Notable deviations from protocol-specified procedures occurred in 3 of 37 (8%) patients enrolled in Trial 20040215 (Table 3). Two patients did not meet the eligibility criteria for enrollment; however, one patient was enrolled after Amgen waived the eligibility criteria requiring measurable disease.

Table 3: Major protocol deviations in Trial 20040215

Patient Number	Country of Enrollment	Description of Protocol Deviation
(b) (6)	United States	This patient enrolled in violation of exclusion criteria prohibiting enrollment of patients with known diagnosis of osteosarcoma. This patient was diagnosed with “benign GCTB” of the left femur in 1996 and with “malignant GCTB” in March 2000 (pathology report indicated that pathology was consistent with diagnosis of osteosarcoma). The first dose of denosumab was administered in April 2007. An incisional biopsy performed on Week 13 of therapy stated that material was “reminiscent” of osteosarcoma. This patient discontinued trial participation on October 31, 2008 due to disease progression.
	Australia	This patient did not meet eligibility criteria for measurable disease; however, a waiver was granted by Amgen prior to enrollment
	France	Missing imaging data

None of the patients listed in Table 3 were considered responders according to modified RECIST 1.1.

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A review of Trial 20062004 conducted by Amgen uncovered major protocol deviations in 7 of 282 (2%) patients (Table 4). Two patients, shaded in light gray, achieved a partial response by modified RECIST 1.1 according to the Independent Review Committee; however, the protocol deviations for these patients are unlikely to impact the ability to interpret the efficacy data for this trial.

Table 4: Major protocol deviations in Trial 20062004

Patient Number	Country of Enrollment	Cohort	Description of Protocol Deviation
(b) (6)	The Netherlands	Cohort 2	Screening procedures performed prior obtaining informed consent. Informed consent ultimately obtained and patient continued treatment and participation in the trial.
	US	Cohort 1	Pregnancy; continued participation in the trial after pregnancy termination
	US	Cohort 1	Pregnancy; continued participation in the trial after pregnancy termination
	France	Cohort 1	Pregnancy; continued participation in the trial after pregnancy termination
	US	Cohort 1	Pregnancy; discontinued study therapy.
	US	Cohort 1	Cycle 1 Day 15 dose missed due to pre-planned vacation
	Italy	Cohort 1	Receipt of denosumab prior to enrollment approval. First dose administered on 12/23/08 and site received eligibility confirmation on 1/12/09.
			Receipt of wrong denosumab dose

3.3 Financial Disclosures

The Applicant submitted financial disclosure information for all primary investigators who participated in Trial 20040215 and Trial 20062004 and for members of the Independent Radiology Committee (IRC). None of the primary investigators for either trial or IRC radiologists disclosed financial interests. Disclosure information was not provided for one US subinvestigator who was incorrectly listed on the 1572 form and five Australian subinvestigators who were no longer at the study site for Trial 20040215. Additionally, disclosure information was not provided for eight Australian subinvestigators who were no longer at the study site for Trial 20062004.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no new chemistry manufacturing and controls information included in this efficacy supplement. The dosage form used for the proposed indication is the same dosage form used for the original Xgeva indication.

4.2 Clinical Microbiology

There was no new clinical microbiology information included in this efficacy supplement.

4.3 Preclinical Pharmacology/Toxicology

There was no new preclinical pharmacology/toxicology information included in this efficacy supplement.

4.4 Clinical Pharmacology

Please see the review by FDA clinical pharmacology reviewer Stacy Shord, PharmD for a detailed discussion of the clinical pharmacology issues related to this sBLA.

This application investigated a single dosage regimen for denosumab in patients with GCTB. Patients enrolled in Trial 20040215 and Trial 20062004 received denosumab at a dose of 120 mg subcutaneously, administered on Days 1, 8, and 15 of the first cycle of therapy, then every four weeks starting on Day 29 (Day 1 of Cycle 2). This dosage regimen was based upon pharmacokinetic, safety, and efficacy data that was included in the sBLA supporting the 2010 approval of Xgeva. The approved dose of Xgeva for the prevention of skeletal related events in patients with bone metastases from solid tumors is 120 mg, administered subcutaneously every 4 weeks. Hypothesizing that more rapid achievement of steady state was desirable to achieve optimal treatment of GCTB, the Applicant chose to incorporate additional doses of denosumab on Day 8 and 15 of the first cycle.

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Reviewer note: Because only one dosage regimen was explored, it is unknown whether the additional doses on Days 8 and 15 of Cycle 1 result in improved effectiveness in the treatment of GCTB. However, the adverse reaction profile in the GCTB studies appears acceptable for the proposed indication and is comparable to the adverse reaction profile observed in the studies supporting the sBLA supporting the 2010 approval of Xgeva.

4.4.1 Mechanism of Action

Denosumab binds receptor activator of nuclear factor kappa B ligand (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, resulting in inhibition of formation, activation, and survival of osteoclasts. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing the RANK receptor and signaling through the RANK receptor contributes to tumor growth. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, or osteoclast-like giant cells.

4.4.2 Pharmacodynamics

The Applicant provided analyses of reduction in two markers of bone turnover, urinary N-telopeptide of type 1 collagen corrected for urine creatinine (uNTx/Cr) and serum C-terminus peptide of type 1 collagen (sCTx). According to the Applicant, median reductions of uNTx/Cr and sCTx of approximately 80% were observed by Week 9 in patients enrolled in Trial 20040215. With continued dosing of denosumab every four weeks, median reductions of 56% to 77% for uNTx/Cr and 79% to 83% for sCTx from weeks 5 to 25 of were observed.

(b) (4)

[redacted]

4.4.3 Pharmacokinetics

With the administration of subcutaneous doses of 120 mg once weekly for the first three weeks of the first 28 days, then once every 4 weeks, mean (± standard deviation) serum steady-state trough concentrations of 23.3 (± 12.4) mcg/mL were achieved by 3 months. The mean elimination half-life was 28 days.

5 Sources of Clinical Data

Tables of Studies/Clinical Trials

The primary safety and efficacy analyses in this review center on results from two single arm trials of denosumab conducted in patients with giant cell tumor of bone (GCTB), Trial 20040215 and Trial 20062004 (Table 5). Table 6 provides a listing of the human biopharmaceutic, pharmacokinetic (PK), and pharmacodynamic (PD) studies of denosumab that were included in this application. Table 7 provides a listing of the efficacy and safety studies of denosumab unrelated to the GCTB application that were included in this application. During the review of this supplemental application, summary-level data provided for the trials listed in Table 6 and Table 7 was used to compare the adverse event profile of denosumab in patients with GCTB with the safety database accumulated from clinical trials of denosumab in healthy volunteers and patients with diseases other than GCTB.

Table 5: Trials used for the primary analyses in sBLA 125320/94

Trial	Study Population	Study Design	Primary Efficacy Objective	Regimen*	Patients Enrolled/ Treated	Status
20040215	Adults with recurrent or unresectable GCTB	Single arm	Response rate based upon histopathologic or radiographic measurement	denosumab 120 mg SC on Days 1, 8, 15, 29 and Q4w thereafter	37/37	Complete; Finals study report submitted to sBLA; treatment and survival follow-up ongoing.
20062004	Adults or skeletally mature adolescents with unresectable GCTB (Cohort 1), GCTB for which planned surgical resection would cause substantial morbidity (Cohort 2), or recurrent or unresectable GCTB and previously enrolled in 20050215 (Cohort 3)	Single arm	Time to disease progression (Cohort 1); Proportion of patients not requiring surgery by Month 6 (Cohort 2)	denosumab 120 mg Q4w with 120-mg loading doses on days 8 and 15	286/281	Ongoing; Full study report for third interim analysis submitted to sBLA

*SC = subcutaneous; IV = intravenous

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Table 6: Human biopharmaceutic, PK, and PD studies of denosumab

Study	Study population	Study Design	Primary Objective	Number of Patients Exposed to Denosumab	Status
Biopharmaceutic Studies Comparative Bioavailability and Bioequivalency Study Reports					
20050227	Healthy adult volunteer BE Study	randomized, open label, single-dose	comparative PK of denosumab drug substances produced at Amgen Colorado vs. Amgen Thousand Oaks	122	Complete
20060286	Healthy adult volunteers	randomized, open label, single-dose	comparative PK of denosumab drug substances produced at Amgen Thousand Oaks vs. Boehringer Ingelheim Pharma	116	Complete
20060446	Healthy volunteers	randomized, open label, single-dose	comparative PK of denosumab 60 and 70 mg/mL formulations	116	Complete
PK and Initial Tolerability Studies in Healthy Subjects					
20010124	Healthy postmenopausal women	randomized, double-blind, placebo-controlled single- and multiple- dose	safety, tolerability, PK	79	Complete
20030148	Healthy men	randomized, double-blind, placebo-controlled single-dose	PK, PD, safety, tolerability	32	Complete
20030164	Postmenopausal Japanese Women	randomized, double-blind, placebo-controlled single-dose	Safety, tolerability, PK, PD	30	Complete
20030180	Healthy postmenopausal women	randomized, double-blind, placebo-controlled single-dose	PK, PD, safety, tolerability	35	Complete
20010123	Adults with multiple myeloma or breast cancer with bone lesions/	randomized, double-blind, active-controlled (vs. pamidronate), double dummy, single-dose	safety, tolerability, PD compared with pamidronate; PK; antibody response	54	Complete

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Study	Study population	Study Design	Primary Objective	Number of Patients Exposed to Denosumab	Status
	metastases				
PK Studies in Patients with Advanced Cancer					
20040176	Japanese women with confirmed metastatic breast cancer with bone metastasis	open-label ascending dose single and multiple-dose	safety, PK, antibody response, PD	18	Complete
Intrinsic Factor PK Studies					
20040245	Adults with normal renal function and varying degrees of renal impairment	open-label, single dose	PK, safety, tolerability	55	Complete
PD and PK/PD Studies in Patients with Advanced Cancer					
20040113	Women with breast cancer with bone metastasis without prior bisphosphonate therapy	randomized, active control (bisphosphonate) parallel group	efficacy (urinary N-telopeptide), safety, PD, PK, dose selection	211	Complete
20040114	Adults with non-lung cancer solid tumors or multiple myeloma receiving bisphosphonates for bone metastasis	randomized, open-label, active control (bisphosphonate)	efficacy (urinary N-telopeptide), safety, PD, PK	73	Complete

Reference ID: 3311616

Table 7: Non-GCTB efficacy and safety studies of denosumab

Trial	Study Population	Study Design	Primary Efficacy Objective	Regimen*	Patients Enrolled	Status
20050103	Men with 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 120 mg SC and zoledronic acid placebo IV Q4W, or zoledronic acid IV and denosumab placebo SC Q4w	1901	Open-Label treatment phase ongoing
20050136	Women and men with breast cancer and at least 1 bone metastasis				2046	
20050244	Men or women with solid tumors (excluding breast and prostate cancer), multiple myeloma, and lymphoma with at least 1 bone metastasis or lytic bone lesion				1776	Survival follow-up ongoing
20050134	Men and women with relapsed or plateau-phase multiple myeloma	Open-label	To assess objective response rate, and survival	denosumab 120 mg SC on Days 1,8, 15, of Cycle 1 and Day 1 of every 28-day cycle thereafter	96	Treatment and survival follow-up ongoing
20050147	Men with castrate-resistant prostate cancer considered at high risk for bone metastasis	Randomized, double-blind, placebo-controlled	To assess whether denosumab prolongs bone-metastasis-free survival	denosumab or placebo 120 mg SC Q4W	1435	Open-label treatment phase ongoing

The studies listed in Table 7 enrolled patients with non-GCTB tumors. However, these studies utilized the same dose of denosumab with a schedule that is identical to the schedule used in the GCTB Trials after Cycle 1.

5.2 Review Strategy

The clinical review of the safety and efficacy of denosumab for the treatment of patients with GCTB focused on the review of data from Trial 20040215 and Trial 20062004. The key review activities are outlined below:

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- Comprehensive review of the raw data, case report forms (CRFs), and clinical study reports for Trial 20040215 and Trial 20062004 contained in the December 11, 2012 sBLA submission.
- Review of the Applicant's subsequent electronic submissions in response to FDA information inquiries.
- The major efficacy and safety analyses contained in proposed labeling and clinical study reports were reproduced or audited using the raw datasets and JReview or JMP programming.
- The data and study reports contained in the 120-day safety update submitted by the Applicant on March 8, 2013 were reviewed, analyzed, and incorporated into the safety review. This safety update included approximately 17 months of additional safety data from Trial 20062004 that were not included in the original sBLA submission.
- Additionally, safety data included in the integrated summary of safety were examined to look for additional safety signals relevant to the GCTB population that were not evident from analyses of data from Trial 20040215 and Trial 20062004.
- Review of relevant published literature.

A comprehensive review of clinical study reports, CRFs, and electronic datasets for Trial 20040215 and Trial 20062004 was conducted during review of this sBLA. Data from studies of denosumab listed in Table 6 and Table 7, which were conducted in either healthy volunteers or patients with cancers other than GCTB, were also reviewed as part of the integrated analysis of safety.

During the safety review, adverse event reporting in a subset of case report forms and case narratives for Trial 20040215 and Trial 20062004 was reviewed and compared to the datasets in order to confirm accuracy of the data transfer. Additional case report forms and case narratives were examined as needed during the safety review. The safety review included review of Trial 20040215 and Trial 20062004 both individually and via pooled analysis of the two 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. The safety review also included separate investigations for submission-specific safety concerns.

Section 5.3 contains a description of the Trial 20040215 and Trial 20062004.

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5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial 20040215

Trial 20040215, entitled "An Open-Label, Multicenter, Phase 2 Safety and Efficacy Study of Denosumab (AMG 162) in Subjects with Recurrent or Unresectable Giant Cell Tumor (GCT) of Bone," is an industry-sponsored trial conducted under IND 9838. This clinical trial enrolled patients from five sites in the United States, two sites in Australia, and one site in France. The applicant submitted the study report for the primary analysis of Trial 20040215 (dated April 2, 2009) and the final study report for Trial 20040215 (dated June 19, 2011) to the sBLA. The primary analysis of Trial 20040215 reflects data collected from the date the first patient was enrolled, July 10, 2006, until the date of final data cut-off on April 07, 2008. The final study report includes additional data collected after the cut-off date for the primary analysis through the end of the 2 year safety follow-up period or until patient rollover to Trial 20062004, whichever occurred first. After November 16, 2010, all patients either remaining on study therapy or undergoing safety follow-up were enrolled on Trial 20062004.

Amgen submitted the original protocol for Trial 20040215 on December 15, 2005 and a single protocol amendment for this trial was submitted on August 16, 2007. The primary purpose of the protocol amendment was to enroll 10 additional patients into the trial, increasing the sample size from 25 to 35 patients. Additionally, the definition of progressive disease was changed from a ≥ 25% increase in the volumetric measurement of the largest GCTB lesion to a ≥ 20% increase (change in the longest dimension) of the target lesion by CT or MRI compared to baseline.

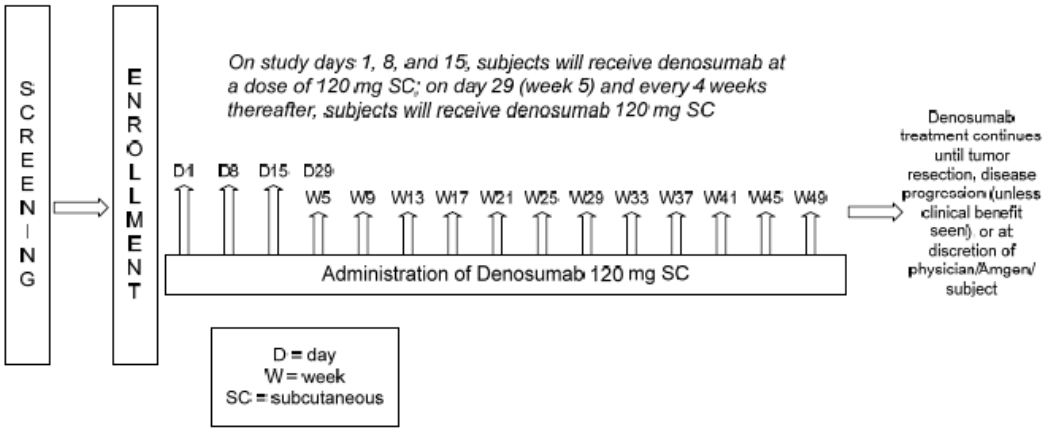
5.3.1.1 Study Design

Trial 20040215 is an open label, single arm trial evaluating the activity of denosumab monotherapy in 37 adult patients with recurrent or unresectable giant cell tumor of bone. All patients received denosumab at a dose of 120 mg SC administered subcutaneously in 28-day cycles. During Cycle 1, patients received denosumab on Days 1, 8, and 15. Patients continued to receive denosumab on Day 1 of subsequent cycles until tumor resection, disease progression, or the patient or investigator decided to withdraw study therapy due to toxicity or other reasons.

Figure 1, copied from the Applicant's sBLA submission, summarizes the design of Trial 20040215.

Reference ID: 3311616

Figure 1: Trial 20040215 study schema



Source: Amgen submission to sBLA 125320/94

5.3.1.2 Study Objectives and Endpoints

The primary objective of Trial 20040215 was to evaluate the response to treatment achieved by denosumab in patients with recurrent or unresectable giant cell tumor. The protocol definition of response consisted of the following conditions:

- elimination of at least 90% of giant cells present at baseline <u>or</u>
- in cases in which giant cells represented less than 5% of tumor cells, complete elimination of giant cells, <u>or</u>
- if histopathology was not available, a lack of progression of the target lesion at week 25 by radiographic measurement.

The protocol specified that all biopsy samples obtained during denosumab treatment would undergo histopathologic analysis, and that tissue samples would be obtained on all patients undergoing palliative resection at the time of resection. The protocol also specified that local and blinded central histologic assessment of tissue samples and core biopsies would be obtained.

Secondary objectives included evaluation of the following parameters:

- serum trough levels of denosumab
- degree of suppression of bone turnover
- safety profile of denosumab
- incidence of serum antidenosumab antibody formation.

There were multiple exploratory objectives, including evaluation of radiographic changes in measurable lesions in patients unable to undergo palliative resection; qualitative characterization of bone lesions; evaluation of changes in

pharmacodynamic parameters such as bone specific alkaline phosphatase and osteocalcitonin; and proteomic evaluation of pre-and post-treatment samples.

The primary analysis for Trial 20040215 was performed using all data up to the data cut-off date (April 07, 2008). The pre-specified primary endpoint for Trial 20040215 was response rate, determined after 25 weeks of denosumab exposure. Patients meeting one of the following conditions were considered to have achieved a response to denosumab:

- at least 90% elimination of giant cells compared to baseline or
- in cases in which giant cells represented less than 5% of tumor cells, complete elimination of giant cells, or
- when histopathology was not available, a lack of progression of the target lesion at week 25 by radiographic measurement

Reviewer note: stable disease is not generally considered evidence of an objective response in clinical trials investigating the activity of drugs for cancer indications.

The efficacy analysis set consisted of patients who remained on study for at least 28 days following the first dose of denosumab and who either had a baseline histology assessment and at least one post dose histology assessment between weeks 5 and 25 of denosumab treatment or had a baseline radiology assessment and at least one post dose radiology assessment between weeks 5 and 25.

5.3.1.3 Eligibility Criteria

The target population consisted of patients 18 years of age or older with histologically-confirmed giant cell tumor of bone (GCTB) and measurable recurrent or unresectable disease. Measurable disease was defined as at least one lesion measuring at least 10 millimeters in its greatest dimension. Patients with recurrent GCTB were required to have radiologic confirmation of disease recurrence. Patients were also required to have an Eastern Cooperative Group (ECOG) performance status of 2 or better.

Patients meeting one or more of the following criteria were excluded from enrollment in Trial 20040215:

- Planned surgical intervention of the affected limb or area within 27 days following administration of the first dose of denosumab
- Radiation to the affected region within 28 days prior to trial enrollment
- Diagnosis of osteosarcoma or brown tumor of bone (osteitis fibrosa cystica)

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- Secondary malignancy within 5 years of enrollment, except for basal cell carcinoma or cervical carcinoma in situ
- Prior denosumab treatment
- Concurrent treatment with bisphosphonates, calcitonin, or interferon alpha-2a
- Pregnancy or lactation
- For women of child-bearing potential and men, lack of willingness to use adequate contraceptive methods during and for at least one year following completion of study therapy
- Receipt of investigational therapy or participation in a clinical trial (other than for long term safety or survival follow up) within 30 days of enrollment.

5.3.1.4 Treatment Plan

Amgen provided an investigational formulation of denosumab for use in this trial. Denosumab was supplied as a sterile, clear, colorless, preservative-free liquid in single use 1.0 mL glass vials in a concentration of 60 mg/mL.

Patients received denosumab at a dose of 120 mg subcutaneously (SC) on Days 1, 8, and 15 of the first 28-day cycle, then on Day 1 of each 28-day cycle thereafter.

During Cycle 1, if a scheduled weekly dose was delayed by more than 3 days, it was considered a missed dose and the next dose was given at the next scheduled visit date. An interval of at least 96 hours in between the first three doses was required. After Cycle 1, doses delayed by more than 7 calendar days were considered to be missed doses and the next dose was given at the next scheduled visit date. No dose adjustments were permitted during the trial.

Patients received 120 mg denosumab SC every 4 weeks after Cycle 1 until undergoing complete resection of their tumor, disease progression, determination by the investigator or Amgen that the patient should discontinue study therapy, patient decision to discontinue study therapy, or administration of bisphosphonates, calcitonin, or interferon alpha-2a. Patients were eligible to continue receiving denosumab beyond 25 weeks until the end of the trial.

Patients were evaluated for safety every 6 months up to 2 years after the date of receipt of the last dose of denosumab.

5.3.1.5 Concomitant Therapies

Patients enrolled in Trial 20040215 were permitted to receive any concomitant medication or treatment except for intravenous or oral bisphosphonates, calcitonin, or interferon alpha-2a.

The protocol also recommended that patients without pre-existing hypercalcemia receive daily oral supplementation of calcium (500 mg minimum) and Vitamin D (400 IU).

5.3.1.6 Protocol-Specified Discontinuation Criteria

The Trial 20040215 protocol indicated that patients could discontinue study treatment for any of the following reasons: palliative tumor resection, withdrawal of consent, administrative decision by the investigator or Amgen, pregnancy, ineligibility, significant protocol deviation, patient noncompliance, adverse event, disease progression (unless clinical benefit is observed), administration of bisphosphonates, calcitonin, or interferon alpha-2a. The protocol also indicated that patients could withdraw from the trial at any time.

Disease progression was defined as a ≥ 20% increase in the longest dimension of the target lesion by CT or MRI compared with baseline.

5.3.1.7 Schedule of Assessments for Trial 20040215

The schedule of assessments for Trial 20040215 is provided in Table 8 (copied from Applicant's submission)

Table 8: Schedule of assessments for Trial 20040215

	Prior To Day 1 Week 1		Treatment Period[1]: (in weeks)																	
Protocol Activities	≤ 28 days	≤ 14 days	First 4-week period (days 1 to 28)			Day 29 (Week [W] 5) and every 4 weeks thereafter														
			Day 1	Day 8	Day 15	(Day 29) W5	W 9	W 13	W 17	W 21	W 25	W 29	W 33	W 37	W 41	W 45	W 49	W 53	End of Study[14]	Safety Follow-Up[15]
Informed Consent	X																			
Medical history	X																			
Histopathology[2]	X						Biopsy obtained anytime between weeks 9 and 25 if palliative resection not performed													
Additional tissue/biopsies[3]	←←←←←←To be submitted if obtained during study →→→→→→																			
Spiral CT scan/MRI[4]	X							X			X			X			X		X	
PET scan[5]	X							X			X			X			X		X	
Physical exam[6]		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Source: Amgen submission to sBLA 125320/94

Schedule of assessments for Trial 20040215 (continued)

	Prior To Day 1 Week 1		Treatment Period[1]: (in weeks)																	
Protocol Activities	≤ 28 days	≤ 14 days	First 4-week period (days 1 to 28)			Day 29 (Week [W] 5) and every 4 weeks thereafter														
			Day 1	Day 8	Day 15	(Day 29) W5	W 9	W 13	W 17	W 21	W 25	W 29	W 33	W 37	W 41	W 45	W 49	W 53	End of Study[14]	Safety Follow-Up[15]
Pregnancy test[7]		X						X			X			X			X		X	
ECOG PS, weight		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	
Serum chemistries[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum and urine bone turnover markers[10]		X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Denosumab antibody assay[11]		X									X						X		X	X
Serum denosumab trough levels			X	X	X	X	X	X			X						X		X	
Denosumab Administration[1, 12]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Source: Amgen submission to sBLA 125320/94

Schedule of Assessments for Trial 20040215 (continued)

	Prior To Day 1 Week 1		Treatment Period[1]: (in weeks)																	
Protocol Activities	≤ 28 days	≤ 14 days	First 4-week period (days 1 to 28)			Day 29 (Week [W] 5) and every 4 weeks thereafter														
			Day 1	Day 8	Day 15	(Day 29) W5	W 9	W 13	W 17	W 21	W 25	W 29	W 33	W 37	W 41	W 45	W 49	W 53	End of Study[14]	Safety Follow-Up[15]
Calcium and Vitamin D			←←←←←←←←Strongly recommended to be taken daily→→→→→→→→																	
Adverse Event Assessment[13]			←←←←←←←←←←←←Documented throughout the study→→→→→→→→→→→→																	X

1. Subjects will continue to receive AMG-162 until **complete** tumor resection (if applicable), disease progression (unless clinical benefit is seen) physician's or subject's decision, or Amgen's decision to discontinue for any reason, or administration of any of the proscribed therapies listed in Section 6.6. **Re-treatment may be possible as described in Section 3.1.**
2. Histopathology samples are to be obtained from fresh or embedded paraffin blocks (or unstained, **unsealed** slides if institutional practice) prior to administration of the 1st dose of denosumab; **at least one post-dose histology assessment between study weeks 9 and 25, and during re-treatment.**
3. In addition to resection and core biopsy samples, fresh or archived paraffin-embedded tumor tissue and corresponding pathology reports for tissue biomarkers analyses by IHC. This may include RANK, RANKL, OPG, TRAP-5b, OC, and others.
4. **Radiographic** measurements via spiral CT scan or MRI **will be conducted at baseline and quarterly during the treatment period (including re-treatment).** Scans may be obtained on the day of, or up to 10 calendar days after the scheduled dose of denosumab is given, but not before. There should be consistent use of imaging machines, contrast, and cut size throughout the study.
5. PET scan to be obtained prior to resection or guided core biopsy or at anytime during the study **that CT/MRI is performed**.
6. Physical exam: Includes pulse, blood pressure, respiratory rate, temperature, and height (height only required at baseline). After the subject has signed the informed consent, the investigator should describe abnormal findings at baseline on the Medical and Surgical History CRF. During study treatment, any new or worsened conditions since baseline should be reported on the Adverse Event CRFs.
7. Pregnancy test (urine): For women of childbearing potential

Source: Amgen submission to sBLA 125320/94

Reference ID: 3311616

Schedule of Assessments for Trial 20040215 (continued)

8. Red blood cells, white blood cells, hemoglobin, hematocrit, differential, and platelet.
9. Glucose, blood urea nitrogen (BUN), creatinine, albumin, total protein, alkaline phosphatase, lactic dehydrogenase (LDH) total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) calcium, phosphorus, magnesium , sodium , potassium , chloride , bicarbonate.
10. Serum CTx (sCTx), urine NTx (uNTx), urine creatinine, RANKL, BSAP, TRAP 5b, and OC samples. Samples are to be obtained prior to administration of denosumab.
11. Serum samples to detect the presence of denosumab antibodies are to be obtained at baseline, Week 25, Week 49 (if the subject is still on study treatment), and at the end of study. **Samples will also be collected at each safety follow up visit and at the end of safety follow-up visit.**
12. Denosumab given by SC injection.
13. Adverse event assessment should be documented and recorded at each visit. **Subjects must be followed for adverse events until all denosumab treatment-related toxicities have resolved**.
14. End of Study (EOS-**Treatment Phase**): Obtain all noted procedures/assessments if not completed within the last week (or in the last 8 weeks for CT scan)
15. **Safety** Follow-Up: **Safety data including AEs and concomitant medications will be collected approximately every 6 months for up to 2 years after the end of study date. Serum samples will also be collected and tested for presence of denosumab antibodies.**

Source: Amgen submission to sBLA 125320/94

Reference ID: 3311616

The protocol required PET imaging, spiral CT scan or MRI imaging of the tumor, and a paraffin-embedded tumor tissue sample (or unstained, unsealed slides from fresh or paraffin-embedded tumor tissue) be obtained within 28 days prior to administration of the first dose of denosumab. A target bone lesion was identified, measured, and recorded at baseline. Target lesions were selected on the basis of size (greater than 10 mm in the longest diameter) and suitability for accurate imaging measurement by CT or MRI.

Spiral CT scans or MRI imaging was performed at baseline, Week 13, Week 25, every 12 weeks thereafter during study treatment, and at the end of study therapy. Scans could be obtained on the day of or up to 10 calendar days after the scheduled dose of denosumab. PET scans were scheduled to be obtained prior to resection or guided core biopsy and at any time during the trial that CT/MRI imaging was obtained.

Patients who did not undergo palliative resection were required to undergo biopsy after administration of the 5th dose of denosumab but prior to administration of the 9th dose (between weeks 9 and 25) for histopathologic assessment of response.

Adverse events were graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Safety data was collected throughout study therapy, at the end of treatment visit, and approximately every 6 months for up to 2 years after the end of study date. Serious adverse events were collected throughout the study period, beginning with the signing of the informed consent document through 30 days after the last dose of investigational product or the end of the trial (including the follow-up period), whichever was longer.

Serum samples for assessment of anti-denosumab antibodies were obtained at baseline, Week 25, Week 49, and at the end of study. Samples were also collected at each safety follow-up visit and at the end of safety follow-up visit.

5.3.1.7 Statistical Analysis of Trial 20040215

The planned sample size for Trial 20040215 was 35 patients, and a total of 37 patients enrolled. After November 16, 2010, all patients who continued to participate in the trial were enrolled in Trial 20062004.

5.3.2 Trial 200062004

Trial 200062004, entitled “An Open-Label, Multicenter, Phase 2 Study of Denosumab in Patients with Giant Cell Tumor of Bone,” is an Amgen-sponsored trial that was initiated under IND 9838 and then transferred to IND 113617 after the administrative split of IND 9838 . This clinical trial enrolled patients from 29 sites in North America, Europe, and Australia. The clinical study report for Trial 20062004 submitted to the sBLA (dated February 29, 2012) represents the third interim analysis of this trial, reflecting data

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collected from September 9, 2009 (the date the first patient was enrolled) through March 25, 2011. Trial 2006204 remains ongoing.

Table 9 provides a summary of the protocol amendments submitted to the FDA. Sections 5.3.2.1 through Sections 5.3.2.7 summarize the final design of Trial 20062004.

Table 9: Submission of protocol and protocol amendments for Trial 20062004

Protocol or Amendment	Submission Date	Summary of Key Changes
Original Protocol	7/8/2008	N/A
Amendment 1	1/12/2009	• Included skeletally mature adolescents as eligible patients • Added eligibility criterion to exclude women of childbearing potential who are pregnant or breastfeeding. • Extended follow-up from 6 months to 12 months
Amendment 2	10/28/2009	• Increased the sample size from 100 to 200 patients • Added exploratory endpoints • Added interim analyses corresponding with the increased sample size
Amendment 3	6/15/2010	• Permitted enrollment of patients from Trial 20040215 • Exploratory objectives and endpoints were updated to include the proportion of patients who were able to undergo a less morbid surgical procedure compared with the planned surgical procedure at baseline and disease status changes over time for all patients.
Amendment 4	12/7/2010	• Increased the sample size from 250 patients to 375 patients
Amendment 5	6/13/2011	• Modified the exclusion criterion for contraception to include two methods of highly effective contraception during treatment and for 7 months after the end of treatment. • Added provision for historical and on-study imaging that was performed as part of standard of care be sent to a

Reference ID: 3311616

Protocol or Amendment	Submission Date	Summary of Key Changes
		central imaging vendor for evaluation of objective response. • The frequency of interim analyses was modified so that subsequent interim analyses may be performed after every 100 patients have an opportunity to complete 6 months of treatment.
Amendment 6	11/9/2011	• The sample size was increased from 375 to 500 patients.

5.3.2.1 Study Design

Trial 20062004 is an open label, multicenter single arm trial evaluating the activity and safety of denosumab monotherapy in adult and skeletally mature adolescent patients aged 12 and older with giant cell tumor of bone. This trial remains ongoing. Trial 20062004 enrolled patients into one of the following 3 cohorts:

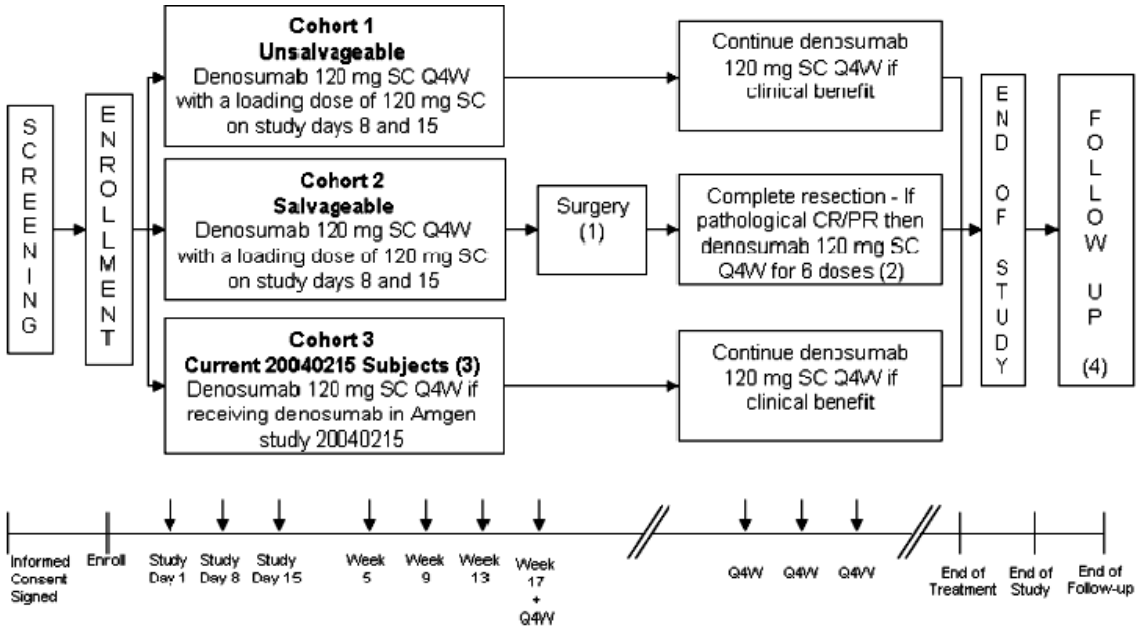
- Patients with surgically unsalvageable GCTB (Cohort 1)
- Patients with surgically salvageable disease whose planned resection was associated with substantial morbidity, such as joint resection, limb amputation, or hemipelvectomy (Cohort 2)
- Patients initially enrolled in Trial 20040215 who wanted to continue denosumab treatment or who were in the safety follow-up phase at the time of completion of Trial 20040215 (Cohort 3).

The denosumab dosage regimen used in Trial 20062004 is identical to the dosage regimen used in Trial 20040215. All patients received denosumab at a dose of 120 mg SC administered subcutaneously in 28-day cycles. Patients in Cohorts 1 and 2 received denosumab on Day 1, 8, and 15 of Cycle 1 and then on Day 1 of each subsequent cycle. Patients in Cohort 3 received denosumab on Day 1 of each 28-day cycle. Patients who underwent a complete tumor resection during the trial received six additional doses of denosumab following pathological confirmation of partial or complete response. For all other patients, denosumab treatment continued until disease progression, or the patient, investigator, or Amgen decided to withdraw study therapy due to toxicity or for other reasons.

Figure 2, copied from the Applicant's sBLA submission, summarizes the design of Trial 20062004.

Reference ID: 3311616

Figure 2: Trial 20062004 schema



1. Surgical resection may occur at any time during the study based on the clinical judgment of the investigator
2. Subjects not achieving a complete resection post surgery may continue to receive denosumab at a dose of 120 mg SC Q4W if clinical benefit is determined
3. Subjects participating in the 20040215 study will enroll and receive denosumab at a dose of 120 mg Q4W (subjects will not receive the day 8 and 15 dose).
4. Subjects currently in the long-term follow-up in study 20040215 will continue on the safety follow-up in this study for up to 2 years after their end of study visit on study 20040215. The total length of safety follow-up on this study for patients enrolling from the safety follow-up phase of Amgen study 20040215 will be 2 years less the time spent in long term follow-up on study 20040215.

Source: Amgen submission to sBLA 125320/94

5.3.2.2 Study Objectives and Endpoints

The primary objective of Trial 20062004 is to evaluate the safety profile of denosumab in patients with GCTB. Secondary objectives of Trial 20062004 include evaluation of the time to disease progression in patients with unsalvageable GCTB (Cohort 1) and the proportion of patients with surgically salvageable disease who do not require surgery after treatment with denosumab (Cohort 2).

There are multiple exploratory objectives, including assessment of the following parameters:

- Time to disease progression, progression free survival, radiographic changes over time, and change in pain score from baseline, as measured by the Brief Pain Inventory – Short Form (BPI-SF) (all patients)
- Time to disease recurrence (for patients with complete clinical response)

- Time to surgery and the proportion of patients able to undergo a less morbid surgical procedure compared to the surgical procedure planned prior to enrollment (Cohort 2 only)
- Pathologic response to denosumab treatment and proportion of patients without tumor post baseline (for patients undergoing histopathologic procedures only).

The pre-specified efficacy assessments were based upon the investigator assessments of tumor response and disease progression. These assessments could be based upon histopathologic findings, radiographic changes in the tumor over time, the occurrence and type of surgery performed in Cohort 2, patient-reported pain, and analgesic use.

Reviewer note: in the clinical study report submitted to this sBLA, Amgen acknowledges that "the efficacy assessments….were largely based on the investigator's subjective evaluations."

Disease status, including tumor response, progression of disease, and disease recurrence, was recorded by the investigator on the case report form at each visit. When histopathology was obtained as part of the patient's standard of care, investigators provided these reports to Amgen. Similarly, when radiologic studies were obtained as deemed necessary by the investigator, the imaging reports were submitted to Amgen. The change in pain score from baseline was measured using the BPI-SF, which is a questionnaire completed by patients that captures information relating to the severity of pain and the degree to which pain effects patient function. Concomitant use of analgesics was documented in the case report form pages at each study visit. Patients received an analgesic score at each visit based upon their analgesic requirement, with scores ranging from 0 (no analgesic used) to 7 (strong opioid use equivalent to > 600 mg of oral morphine per day) was

The safety analysis set included all enrolled patients who received at least one dose of denosumab. The efficacy analysis set included all patients in the safety analysis set who were eligible for the trial.

Retreatment was permitted for patients who had previously discontinued denosumab after achieving a protocol-defined response. Data collected during the re-treatment period were not included in efficacy analyses. If the retreated patient was originally enrolled in Trial 20062004, all safety data accumulated during the initial and retreatment periods were included in the safety analyses; if the patient originally enrolled in Trial 20040215, the patient was considered to be a new patient and safety data collected

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after receipt of the first dose of denosumab in Trial 20062004 were included in the safety analyses.

The protocol indicated that all statistical analyses for Trial 20062004 would be descriptive in nature, and the pre-specified endpoints of Trial 20062004 mirrored the objectives for this trial. The expected sample size for this trial is 500 subjects. The protocol indicated that a minimum of 1 interim analysis would be conducted in order to monitor the safety of denosumab and make decisions regarding further study of denosumab in patients with GCTB. The first interim analysis occurred after a total of 50 subjects had the opportunity to complete 6 months of denosumab treatment. A second, planned interim analysis with a data cutoff date of May 21, 2010 occurred after 100 subjects had the opportunity to receive treatment for six months. The third interim analysis, which provides the results for this sBLA, used a data cutoff date of March 25, 2011.

The primary analysis of Trial 20062004 is scheduled to be performed after all subjects have the opportunity to complete 12 months of treatment.

The trial consists of three periods: The screening period (the time from informed consent to the date of enrollment), the on-study period (the time from the date of enrollment to the end of study date, inclusive), and the safety follow-up period (time from the end of the study date until lost to follow-up, patient death, or up to 12 months, whichever occurs first).

5.3.2.3 Eligibility Criteria

The target population consisted of adult or skeletally mature adolescent patients (12 years of age and older) with histologically-confirmed giant cell tumor of bone (GCTB) who have measurable disease that was either unresectable or resectable only with a surgical procedure that would result in substantial morbidity. The key inclusion criteria are summarized below (adapted from Applicant's Clinical Study Report):

- GCTB confirmed by pathology within 1 year prior to enrollment
- Evidence of measurable active disease within 1 year prior to enrollment
- Surgically unsalvageable disease (such as GCTB of the sacrum or spine, or multiple lesions including pulmonary metastases) (Cohort 1) <u>or</u> disease for which surgical resection would involve join resection, limb amputation, hemipelvectomy or other severe morbidity (Cohort 2) <u>or</u> current enrollment in Trial 20040215 (Cohort 3)
- Either ≥ 18 years of age or ≥ 12 years of age with evidence of skeletal maturity (radiologic evidence of at least 1 mature long bone)
- If less than 18 years of age, minimum weight of 45 kg
- Karnofsky performance status of at least 50%
- Written informed consent.

Reviewer note: the protocol for Trial 20062004 did not include a definition of measurable disease.

Patients meeting one or more of the following criteria were excluded from enrollment in Trial 20062004:

- Current treatment with other GCTB specific therapies (such as radiation, chemotherapy, or embolization)
- Concurrent bisphosphonate treatment
- Known or suspected diagnosis of underlying malignancy including high-grade sarcoma, osteosarcoma, fibrosarcoma, malignant giant cell sarcoma
- Known or suspected diagnosis of non-GCTB giant cell-rich tumors, brown cell tumor of bone, or Paget's disease
- Diagnosis of secondary malignancy within 5 years of enrollment
- Presence of one or more risk factors for development of osteonecrosis of the jaw:
  - history or current evidence of ONJ
  - active dental or jaw condition requiring oral surgery
  - non-healed dental/oral surgery
  - planned invasive dental procedure during the course of the trial
- Receipt of investigational therapy or participation in a clinical trial (other than for long term safety or survival follow up) within 30 days of enrollment
- Unstable systemic disease including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, or myocardial infarction within 6 months prior to enrollment
- Pregnancy, planning to become pregnant within 7 months after the end of treatment, or lactation
- For women of child-bearing potential, lack of willingness to use two methods of highly effective contraception during and for at least 7 months following completion of denosumab.

5.3.2.4 Treatment Plan

Amgen provided an investigational formulation of denosumab for use in this trial. Denosumab was supplied as a sterile, clear, colorless, preservative-free liquid in single use 3.0 mL glass vials containing 1.7 mL of denosumab at a concentration of 70 mg/mL.

Patients in Cohorts 1 and 2 received 120 mg of denosumab subcutaneously on Days 1, 8, and 15 of the first 28-day cycle, then on Day 1 of each 28-day cycle thereafter. Patients enrolled in Cohort 3, all of whom had initiated therapy in Trial 20040215, continued to receive denosumab according to their current schedule every 28-days.

During cycle 1, if a scheduled weekly dose was delayed by more than 8 calendar days, it was considered a missed dose and the next dose was given at the next scheduled visit date. An interval of at least 96 hours in between the first three doses was required. After Cycle 1, doses delayed by more than 7 calendar days were considered to be missed doses and the next dose was given at the next scheduled visit date. No dose adjustments were permitted during the trial.

Patients continued to receive denosumab for six cycles after pathological confirmation of partial response or complete response following a complete resection of their tumor (Cohort 2 patients only) or until disease progression, determination by the investigator or Amgen that the subject should discontinue study therapy, subject decision to discontinue study therapy, or administration of prohibited concomitant treatments. Retreatment of patients who had discontinued study therapy after having achieved a response to denosumab was permitted on a case-by-case basis, with prior authorization from Amgen.

For patients enrolled in Cohorts 1 and 2, safety assessments occured throughout therapy, at the end of study visit approximately one month after discontinuation of denosumab, and then six and twelve months after the end of study visit. Patients enrolled into Cohort 3 were followed for safety for up to 2 years after their end of study visit.

5.3.2.5 Concomitant Therapies

Patients enrolled in Trial 20062004 were permitted to receive any concomitant medication or treatment except for intravenous or oral bisphosphonates, calcitonin, or interferon alpha-2a.

The protocol also recommended that patients without pre-existing hypercalcemia receive daily oral supplementation of calcium (500 mg minimum) and Vitamin D (400 IU).

The following concomitant treatments were prohibited during study therapy:

- bisphosphonates
- other active therapy for GCTB, such as chemotherapy, embolization, and radiation therapy
- use of other unapproved investigational products or devices.

The protocol also contained instructions for avoidance of invasive dental procedures, if possible. In cases where invasive dental procedures were required, investigators had to document a clinical decision to continue study therapy.

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5.3.2.6 Protocol-Specified Discontinuation Criteria

The Trial 20062004 protocol indicated that patients could discontinue trial participation or denosumab treatment for any of the following reasons: palliative tumor resection, withdrawal of consent, administrative decision by the investigator or Amgen, pregnancy, ineligibility, significant protocol deviation, patient noncompliance, adverse event, disease progression, or administration of bisphosphonates or other prohibited therapies. The protocol also indicated that patients could withdraw from the trial at any time.

Disease progression was defined as a ≥ 20% increase in the longest dimension of the target lesion by CT or MRI compared with baseline.

5.3.2.7 Schedule of Assessments for Trial 20062004

The schedule of assessments for Trial 20062004 is provided in Table 10 (copied from the Applicant's submission). After completion of study therapy, safety data, including serious adverse events, adverse events, concomitant medications, and serum samples for anti-denosumab testing, were collected approximately every six months for up to 12 months (or, for patients who enrolled into Cohort 3, for a total of up to 24 months after the end of study visit in the Trial 20040215).

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Table 10: Schedule of assessments for Trial 20062004

	Prior To Day 1 Wk 1		Treatment Period [1]: (Weeks)															
Protocol Activities	≤ 28 days	≤ 7 days	First 4-wk period (days 1 to 28)															
			Day 1	Day 8	Day 15	Day 29 W5	W9	W13	W17	W21	W25	W29	W33	W37	W41	W45	End of Study	Safety Follow Up [2]
Informed Consent [12]	X																	
Medical history	X																	
Pathology sample [4]			←←←←←←To be submitted if performed as standard of care→→→→→→→→														X	
Pathology reports [3]	X		←←←←←←To be submitted if performed as standard of care →→→→→→→														X	
Imaging reports [5]	X		←←←←←←To be submitted if performed as standard of care→→→→→→→→															
Serum chemistries [6, 14]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PE, Disease Status, Karnofsky [7, 14]	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [8, 14]		X	X					X			X			X			X	X
Antibody assay [10]			X														X	X
Denosumab Administration [1]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Patient Reported Outcomes [9,13]			X	X	X	X	X	X	X	X	X			X			X	
Calcium / Vitamin D			←←←←←←←←←Strongly recommended to be taken daily→→→→→→→→															
AE Assessment [11]	X	X	←←←←←←←←←←Documented throughout the study→→→→→→→→→→														X	X
Con Med Review	X	X	←←←←←←←←←←Documented throughout the study→→→→→→→→→→														X	X

Source: Amgen submission to sBLA 125320/94

Table 10: Schedule of Assessments for Trial 20062004 (cont.)

Protocol Activities	Treatment Period [1]: (Weeks)														
	W49	W53	W57	W61	W65	W69	W73	W77	W81	W85	W89	W93 and Q4W	Additional Tests at W97 and Q12W	End of Study	Safety Follow Up [2]
Pathology sample [4]	←To be submitted if performed as standard of care→													X	
Pathology reports [3]	←To be submitted if performed as standard of care →													X	
Imaging reports [5]	←To be submitted if performed as standard of care→														
Serum chemistries [6, 14]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
PE, Disease Status, Karnofsky [7, 14]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pregnancy test [8, 14]	X			X			X			X			X	X	X
Antibody assay [10]														X	X
Denosumab Administration [1]	X	X	X	X	X	X	X	X	X	X	X	X			
Patient Reported Outcomes [9,13]	X			X			X			X			X	X	
Calcium / Vitamin D	←Strongly recommended to be taken daily→														
AE Assessment [11]	←Documented throughout the study→													X	X
Con Med Review	←Documented throughout the study→													X	X

Source: Amgen submission to sBLA 125320/94

Table 10: Schedule of Assessments for Trial 20062004 (cont.)

Footnote	Explaination
1	Subjects will continue to receive denosumab until complete tumor resection (if applicable), disease progression, physician's or subject's decision, or Amgen's or Daiichi Sankyo Co., Ltd's. decision to discontinue for any reason, or administration of any of the proscribed therapies listed in Section 6.5. Denosumab 120 mg is given by SC injection as a 1.7 mL injection of denosumab 70 mg/mL.
2	Safety Follow-Up: Safety data will be collected approximately every 6 months for up to 12 months after the end of study date. For subjects who were in the safety follow-up of study 20040215 and are enrolling in this study, safety data will be collected approximately every 6 months for up to 24 months after the end of study visit in the 20040215 study.
3	Histopathology reports confirming the diagnosis of GCT of bone and demonstrating active disease are to be obtained to determine eligibility at screening (not required for 20040215 subjects). All on-study reports will be collected if performed as standard of care except at end of study where this may be required.
4	Histopathology samples may be requested at end of study.
5	Imaging report will be required at screening to confirm eligibility (not required for 20040215 subjects). All on-study imaging reports will be collected if performed as standard of care. Select historical and select on-study imaging performed as standard of care will be required to be sent to a central imaging vendor for evaluation of disease response.
6	Serum chemistries performed by local lab must include serum creatinine, calcium, albumin, magnesium and phosphorus.
7	Physical exam: The screening PE includes medical history, Karnofsky performance status, disease status, blood pressure, respiratory rate, temperature, weight and height. (After the subject has signed the informed consent and the medical history is recorded on the Medical and Surgical History eCRF, any new or worsening conditions should be reported on the Adverse Event eCRF, including any reported during the screening period.) Thereafter, only a disease status and Karnofsky performance status will be collected during the treatment phase of the study and at safety follow up.
8	Pregnancy test for women of childbearing potential is to be conducted at screening, on study (approximately every 12 weeks while receiving denosumab treatment) and during safety follow up. A urine/serum pregnancy test must be done at baseline prior to first dose of denosumab if study day 1 is greater than 7 days from the pregnancy confirmation done at screening.
9	Patient Reported Outcomes (PRO): Consist of BPI-SF. The BPI-SF will be administered prior to each administration of investigational product at baseline, study days 8 and 15, then every 4 weeks (Q4W) from weeks 5 – 25, then every 12 weeks (Q12W) to end of study.
10	Serum for anti-denosumab antibody assay will be collected at baseline and as outlined on the schedule of assessments, including 2 samples during follow up (approximately 6 and 12 months after the end of study visit). For subjects who were in the safety follow-up of study 20040215 and are enrolling in this study, serum samples for anti-denosumab antibody assay will be collected approximately every 6 months for up to 24 months after the end of study visit in the 20040215 study. These samples may also be used for future biomarker development testing.
11	Adverse event assessment should be documented and recorded at each visit upon signing informed consent. Subjects must be followed for adverse events until all denosumab treatment-related toxicities have resolved.
12	Informed consent may be obtained more than 28 days before Day 1 week 1.
13	Cohort 3 subjects will enroll at their next Q4W visit (based on their 20040215 schedule). Informed consent will be obtained prior to any protocol specific procedures; PRO s will be collected at their next Q12W assessment visit.
14	For subjects who were in the safety follow-up of study 20040215 and are enrolling in this study, serum chemistries, physical examination, disease status, Karnofsky performance status, and pregnancy testing are not required during the safety follow-up

Source: Amgen submission to sBLA 125320/94

Reference ID: 3311616

5.3.3 Retrospective Analysis of Objective Tumor Response

During the pre-sBLA meetings held on April 5, 2011 and September 11, 2012, FDA and Amgen agreed that the key regulatory endpoint for this sBLA would be based upon retrospective assessment of objective tumor response as determined by blinded independent radiology review of radiographs collected from patients enrolled in Trials 20040215 and 20062004.

Patients enrolled in Trial 20040215 underwent computer tomography (CT) or magnetic resonance imaging of their tumor at baseline and quarterly during the treatment period. Patients enrolled in Trial 20062004 were not required to undergo periodic radiographic imaging of their tumor; imaging reports were required at screening to confirm eligibility for patients enrolled in Cohort 1 and Cohort 2, and reports of on-study images performed as part of standard of care were also collected. Amendment 5 to the protocol (instituted on May 5, 2011) provided for collection of historical and on-treatment images performed as part of standard of care and submission of these images to a central imaging facility to enable the retrospective radiographic evaluation of objective tumor response. The informed consent documents for subjects enrolled in Trial 20040215 and 20062004 were amended and approved by the institutional review board (IRB) or independent ethics committee (IEC) at the investigational sites. Available pre-treatment and on-study CT, MRI, and whole body fluorodeoxyglucose positron emission tomography (18FDG-PET) images were collected from patients that provided informed consent for collection of these images.

Blinded independent central radiologic review was performed by (b) (4) (b) (4). Amgen contracted (b) (4) to provide a retrospective independent radiology review of subjects enrolled in Trial 20040215 and Trial 200620004. The following radiological evaluations were performed, depending upon available imaging and presence of bone and soft tissue components of GCTB:

- For patients with soft tissue lesions (with or without a bone component), evaluation of objective response using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines was performed on available CT or MRI images. Target lesion response, non-target lesion response, presence or absence of a new lesion, and the overall time point RECIST response for all evaluable subjects were assessed for each time point.

- For patients with soft tissue lesions or bone lesions who had available PET imaging, evaluation of response was performed using modified European Organization for Research on the Treatment of Cancer) guidelines. Target lesion response, presence or absence of a non-target or new lesions, and the overall EORTC time point response for all evaluable subjects were assessed for each time point.

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- For patients with soft tissue or bone lesions, evaluation of response was performed on available and evaluable digital CT images through evaluation of tissue density (using Hounsfield units) and lesion size ("Density/Size Evaluation" or "Inverse Choi" criteria) using Choi criteria (Choi, 2007) which were modified for the assessment of GCTB. The Applicant considers an increase in lesion density (as measured by a percent increase in Hounsfield units) indicative of new bone growth and evidence of a "desirable outcome" in patients with GCTB. The target lesion response, presence or absence of new lesions, and the overall response using the specified density/size criteria were assessed for each time point.

A two-reader paradigm was used for evaluation of objective response using the modified RECIST 1.1 and Density/Size criteria. Each radiologist was blinded to subject demographic data, site assessment of response, site choice of target and non-target lesions, and the identification of new lesions, clinical history (with the exception of information regarding benign radiographic abnormalities that could mimic neoplastic disease and clinical listing of on-study surgical procedures performed on patients), and results of the other independent radiology reviewer's assessment. If the RECIST time point responses and the Density/Size time point responses were identical between the two radiology reviewers, then no adjudication was required. If there was discordance, an adjudicator performed an additional evaluation to determine the final assessment. A single radiologist read the applicable time points for the EORTC evaluation of response.

The integrated analysis of efficacy included evaluation of objective response using modified RECIST 1.1 (Table 11). For each radiographic imaging time point, responses were assessed based upon evaluation of the longest diameters of target and non-target lesions (except for nodal lesions, which were measured bidimensionally) and presence or absence of new lesions. Responses at each time point were assessed with reference to baseline for the determination of response, and with reference to the nadir tumor size for evaluation of progressive disease. Identification of a new lesion resulted in an assessment of progressive disease.

Table 11: Summary of Modified RECIST 1.1

Response Category	Target Lesion	Non-target Lesion[a]	Comment
Complete Response (CR)	Disappearance of all target lesions and all target lymph nodes <10mm in the short axis	Disappearance of all non-target lesions and all non-target lymph nodes < 10mm in the sort axis.	CR requires CR of non-target and target lesions, and no new lesions

Response Category	Target Lesion	Non-target Lesion[a]	Comment
Partial response (PR)	≥ 30% decrease in the sum of the lesion diameter(s) (SLD) compared to baseline SLD		PR requires absence of new lesions and absence of PD in non-target lesions.
Stable disease (SD)	Insufficient tumor shrinkage to qualify for PR or insufficient increase in size to qualify as PD.		SD requires absence of new lesions and absence of PD in non-target lesions.
Progressive disease (PD)	≥ 20% increase in SLD of target lesions (compared to the nadir SLD) with an absolute increase in SLD of ≥ 5 mm	Unequivocal progression of existing nontarget lesions.	Overall response is PD if there is a new lesion or PD is observed in target lesions, irrespective of status of non-target lesions. If there is PD in non-target lesions, overall response is categorized as PD irrespective of status of target lesions.
Unevaluable (UE)	Target lesion present at baseline subsequently becomes unevaluable	Any non target lesion present at baseline become unevaluable.	

[a] The worst response of any non-target lesion was used to categorize the overall response of the non-target lesions.
SLD = sum of lesion diameters. SLD consists of the sum of the longest diameters (LD) of non-nodal lesions in the axial plane, and the short axis diameters of nodal lesions.

The integrated analysis of efficacy also included evaluation of objective response using Density/Size criteria (Table 12). For evaluation of objective response using Density/Size criteria, a partial response required a decrease in the Choi longest

diameter (LD) of at least 10% (using the sum of the measurements of LD of each target lesion measuring at least 10 mm) or an increase in CT density [%Δ Hounsfield Units $(HU)_{mean}$] of at least 15% compared to baseline. For bone lesions without a soft tissue component, the Choi LD included the bone component of the lesion. For bone lesion with a soft tissue component, the Choi LD included both the bone and soft tissue components. The Choi LD of each target lesion were added together to determine the Choi SLD and the percent change in Choi SLD contributed to the determination of response or progression.

For the target lesions identified by CT, density evaluation was performed and the mean of the attenuation coefficient in Hounsfield Units (HU_{mean}) was determined and provided at each of the time points for which there was CT imaging available (including bone lesions with and without target lesions). The percent [%Δ Hounsfield Units $(HU)_{mean}$] was calculated using the sum of the differences between the HU mean for each target lesion compared to baseline.

Progressive disease was considered an increase in unidimensional tumor size of at least 10% without meeting the criteria for PR using CT density. The identification of any new lesion identified on CT/MRI also resulted in a determination of progressive disease.

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Table 12: Density/Size Criteria Used for Evaluation of Objective Response

Target Lesions		New Lesions[1]	TPR
Density (%ΔHU_{mean})	Size (%Δ Choi SLD)		
Any	Resolved	No	CR
≥ 15% increase	Any (except fully resolved)	No	PR
< 15% increase	≥ 10% decrease[5]	No	PR
< 15% increase	< 10% decrease or ≤ 10% increase	No	SD
< 15% increase	> 10% increase	No	PD
UE[2]	≥ 10% decrease[5]	No	PR
UE[2]	< 10% decrease or ≤ 10% increase	No	SD
UE[2]	> 10% increase	No	PD
UE[2] or NA[3]	UE[4]	No	UE
NA[3]	≥ 10% decrease[5]	No	PR
NA[3]	< 10% decrease or ≤ 10% increase	No	SD
NA[3]	> 10% increase	No	PD
NA[6]	NA[6]	No	UE
Any	Any	Yes	PD

1: Identification of new lesions at a post-Baseline time point will result in a TPR of PD. If an identified new lesion subsequently becomes UE, the TPR will be recorded as PD unless the new lesion has proven to have resolved.

2: If a change in imaging technique (e.g. a switch between contrast and non-contrast, etc.) does not allow an accurate HU measurement comparison, the density portion of the TPR will be UE.

3: In the event a density measurement cannot be obtained at Baseline, a designation of NA will be applied to the density portion of the TPR at all on-study time points.

4: If a change in imaging technique (e.g. a switch in modality between CT and MRI, etc.) does not allow an accurate Choi LD measurement comparison, the size assessment will be UE.

5: But not fully resolved.

6: No target lesion(s) selected at Baseline.

Source: (copied from sBLA submission)

6 Review of Efficacy

Efficacy Summary

The safety and efficacy of denosumab for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents was demonstrated in two open-label, single arm trials, Trial 20040215 and Trial 20062004. These trials enrolled patients with histologically-confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity. Patients received 120 mg denosumab subcutaneously every 4 weeks with additional doses on Days 8 and 15 of the first cycle of therapy.

Trial 20040215 enrolled and treated 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically-confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a CT or MRI obtained within 28 days prior to trial enrollment. Patients enrolled in Trial 20040215 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly during Xgeva treatment.

Trial 20062004 enrolled and treated 267 adults or skeletally mature adolescents with giant cell tumor of bone, not including 14 patients who previously enrolled in Trial 20040215. A total of 10 patients were 13-17 years of age. Patients were required to have histologically-confirmed giant cell tumor of bone and evidence of measurable active disease confirmed by a report from an imaging study obtained within one year prior to trial enrollment. A total of 167 patients had surgically unsalvageable disease (e.g. sacral, spinal, or multiple lesions, including pulmonary metastases) and 100 patients had surgically salvageable disease and a planned surgery likely to result in severe morbidity (e.g. joint resection, limb amputation, or hemipelvectomy). Patients enrolled in Trial 20062004 underwent imaging assessment of disease status at the discretion of their physician.

A retrospective independent review of radiographic imaging data was performed for patients enrolled in Trial 20040215 and Trial 20062004. Of the 304 patients enrolled and treated in Trial 20040215 and Trial 20062004, 187 (61%) had at least one post-baseline radiographic assessment for evaluation of objective response according to Modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1). An objective response by RECIST 1.1 was observed in 47 of 187 (25%) evaluable patients (95% CI: 19, 32). All responses were partial responses. The median time to response was 3 months (range: 1 to 21 months). Disease progression occurred following an objective response in three patients and the median duration of response was not estimable. A total of 24 patients had a duration of response lasting at least 8 months. The median follow-up duration for evaluable patients was 13 months (range: 2 to 49 months). Efficacy results in skeletally mature adolescents appeared to be similar to those observed in adults.

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Overall, of the100 patients enrolled in Trial 20062004 who planned to undergo a surgical resection likely to result in severe morbidity, 74 patients (74%) had no surgery performed and 16 patients (16%) underwent a less morbid surgical procedure compared to the surgical procedure planned at baseline. The surgical procedures were performed a median of 9 months (range: 0 to 28 months) following initiation of denosumab.

6.1 Indication

The Applicant proposed the following indication for Xgeva:

(b) (4)

6.1.1 Methods

This sBLA included data and analyses from the final analysis of Trial 20040215 and the third interim analysis of Trial 20062004 to support the efficacy of denosumab in patients with giant cell tumor of bone.

Trial 20050215 began on July 10, 2006 and ended on November 16, 2010. After November 16, 2010, all patients who wished to continue denosumab therapy (n=11) enrolled into Cohort 3 of Trial 20062004, and patients no longer receiving denosumab who remained in the safety follow-up phase of Trial 20040215 (n=4) entered directly into the safety follow-up phase of Trial 20062004. The primary endpoint was tumor response, defined as elimination of at least 90% of giant cells or complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells, or no radiographic progression of the target lesion up to week 25. Secondary endpoints included serum trough levels of denosumab, the degree of suppression of bone turnover and safety measurements.

Trial 20062004 is underway at 29 sites in North America, Europe, and Australia. This submission contains data and results with cut-off date March 25, 2011, which is also the third planned interim analysis of the trial. The primary objective of the trial was to evaluate the safety of denosumab in patients with GCTB. Secondary endpoints included time to disease progression in subjects with unsalvageable GCTB (Cohort 1) and proportion of subjects who do not require surgery in subjects with salvageable GCTB (Cohort 2).

As described in Section 1.2, Section 2.5, and Section 5.3.3 of this review, prior to submission of this sBLA, FDA advised the Applicant that achievement of the pre-specified endpoints for Trial 20040215 and 20062004 would not provide substantial evidence of efficacy in the proposed patient population. FDA advised the Applicant that demonstration of durable objective response, as determined by blinded independent review of images obtained in Trial 20040215 and Trial 20062004, may support licensure if the magnitude and duration of objective response are sufficient such that the benefits outweigh the risks of Xgeva therapy. As discussed in a pre-sBLA meeting held on September 11, 2012, FDA considers objective response using modified RECIST 1.1 the primary regulatory efficacy endpoint and duration of response a key secondary endpoint to support the efficacy of denosumab in the treatment of GCTB. Therefore, the clinical review of this sBLA focused primarily upon the analyses of objective response rate according to modified RECIST 1.1 and duration of response, based upon blinded independent radiographic review of images retrospectively collected from Trial 20040215 and 20062004.

The sBLA included analyses of other efficacy endpoints, including reduction or elimination of giant cells by histological examination of biopsy specimens, radiographic response using Density/Size (modified Choi) and Modified EORTC criteria, and changes in requirements for surgery or analgesic use. Because the clinical significance of these endpoints is either uncertain (e.g., analyses of radiographic response using Density/Size or Modified EORTC criteria) or difficult to interpret when derived from unblinded single arm trials (e.g., analyses of changes in surgical or analgesic requirements) analyses of these endpoints are considered supportive.

6.1.2 Demographics

Table 13 provides a summary of the baseline demographic characteristics of patients enrolled in Trial 20040215 and Trial 20062004. Trial 20040215 was conducted at 8 sites: 5 in the United States, 2 in Australia, and 1 in France. A total of 37 subjects were enrolled in the trial.

At the time of the third interim analysis, a total of 286 subjects had enrolled in Trial 20062004, including 4 patients from Trial 20040215 no longer receiving denosumab treatment who entered directly into the safety follow-up phase of Trial 20062004.

Table 13: Demographic characteristics at baseline

Demographic Characteristic	Trial 20040215 N = 37	Trial 20062004				Overall[a]
		Cohort 1 N = 170	Cohort 2 N=101	Cohort 3 N=11	All N =282	N = 305
Gender n (%)						
Female	20 (54)	135 (79)	85 (84)	10 (91)	164 (58)	178 (58)

Demographic Characteristic	Trial 20040215 N = 37	Trial 20062004				Overall[a]
		Cohort 1 N = 170	Cohort 2 N=101	Cohort 3 N=11	All N =282	N = 305
Male	17 (46)	68 (40)	44 (43)	6 (55)	118 (42)	127 (42)
Age yrs						
Median (range)	30 (19, 63)	33 (13, 83)	34 (16, 69)	30 (22, 63)	33 (13, 83)	33 (13,83)
< 18 n (%)	0 (0)	8 (5)	2 (2)	0 (0)	10 (4)	10 (3)
> 65 n (%)	0 (0)	9 (5)	1 (1)	0 (0)	10 (4)	10 (3)
Ethnicity n(%)						
White or Caucasian	27 (73)	135 (79)	85 (84)	10 (91)	230 (82)	245 (80)
Black or African American	2 (5)	10 (6)	6 (6)	0 (0)	16 (6)	18 (6)
Hispanic or Latino	5 (14)	11 (7)	3 (3)	1 (9)	15 (5)	19 (6)
Asian	3 (8)	8 (5)	4 (4)	0 (0)	12 (4)	15 (5)
Other	0 (0)	6 (4)	3 (3)	0 (0)	9 (3)	8 (3)
Enrollment Country n(%)						
United States	21 (57)	78 (46)	15 (15)	6 (55)	99 (35)	113 (37)
Non-United States						
Australia	12 (32)	7 (4)	19 (19)	1 (9)	27 (10)	36 (12)
France	4 (11)	15 (9)	14 (14)	4 (36)	33 (12)	33 (11)
Italy	0 (0)	22 (13)	21 (21)	0 (0)	43 (15)	43 (14)
Sweden	0 (0)	5 (3)	3 (3)	0 (0)	8 (3)	8 (3)
Poland	0 (0)	6 (4)	15 (15)	0 (0)	21 (7)	21 (7)
The Netherlands	0 (0)	2 (1)	6 (6)	0 (0)	8 (3)	8 (3)
Great Britain	0 (0)	6 (4)	1 (1)	0 (0)	7 (2)	7 (2)
Spain	0 (0)	7 (4)	6 (6)	0 (0)	13 (5)	13 (4)
Germany	0 (0)	16 (9)	1 (1)	0 (0)	17 (6)	17 (6)
Canada	0 (0)	2 (1)	0 (0)	0 (0)	2 (1)	2 (1)
Austria	0 (0)	4 (2)	0 (0)	0 (0)	4 (1)	4 (1)

[a] Patients who rolled over from 20040215 to 20062004 or who discontinued 2050215 and later enrolled into Trial 20062004 are counted only once in the overall column.

Overall, the demographic characteristics of patients enrolled in the GCTB studies appear to be representative of the overall population of patients with GCTB in the United States. Fifty-eight percent of the enrolled subjects were women and 80% were White. The median age was 33 years (range: 13 to 83 years). A total of 113 (37%) patients were enrolled in the United States.

Reference ID: 3311616

A total of 10 subjects were skeletally mature adolescents 13 to 17 years of age The adolescent patients were predominantly female (80%), and Caucasian (60%), with either primary unresectable GCTB (30%) or recurrent unresectable (50%) disease.

Table 14 provides a summary of the GCTB characteristics of patients enrolled in both studies. Consistent with the eligibility criteria for each trial, Trial 20062004 enrolled some patients with primary resectable GCTB (63 patients who enrolled into Cohort 2), whereas all patients who enrolled in Trial 20040215 had either recurrent GCTB or primary unresectable GCTB. For both studies, the most common location of the target lesion in both studies was the pelvis, followed by the lower extremity. The median size of the target GCTB lesion was 5.8 cm (range, 0.6 to 30.8 cm).

Table 14: GCTB characteristics at baseline

Disease Characteristics	Trial 20040215 N = 37	Trial 20062004				Overall[a]
		Cohort 1 N = 170	Cohort 2 N=101	Cohort 3 N=11	All N =282	N = 305
GCTB Category						
Primary resectable	0 (0)	0 (0)	63 (62)	0 (0)	63 (22)	63 (21)
Primary unresectable	13 (35)	48 (28)	0 (0)	2 (18)	50 (18)	61 (20)
Recurrent resectable	6 (16)	0 (0)	38 (38)	0 (0)	38 (14)	44 (14)
Recurrent unresectable	18 (49)	122 (72)	0 (0)	9 (82)	131 (47)	137 (45)
Target Lesion Longest Diameter (mm)						
Mean (standard deviation)	56 (38)	65 (49)	71 (39)	38 (29)	66 (45)	66 (44)
Median (range)	47 (6, 170)	54 (7, 308)	64 (7, 221)	29 (3, 88)	59 (3, 308)	58 (6,308)
Target Lesion Location n (%)						
Pelvis[b]	10 (37)	67 (39)	16 (16)	2 (18)	85 (30)	90 (30)
Pelvic bone		23 (14)	12 (12)	0 (0)	35 (12)	
Sacrum		42 (25)	4 (4)	2 (18)	48 (17)	
Pelvis (soft tissue only)		2 (1)	0 (0)	0 (0)	2 (1)	
Lower Extremity[b]	8 (22)	14 (8)	57 (56)	1 (9)	72 (26)	79 (26)
Tibia		9 (5)	34 (34)	0 (0)	43 (15)	
Femur		3 (2)	21 (21)	0 (0)	24 (9)	
Fibula		1 (1)	2 (2)	1 (9)	4 (1)	
Patella/knee		1	0	0	1 (0.4)	

Disease Characteristics	Trial 20040215 N = 37	Trial 20062004				Overall[a]
		Cohort 1 N = 170	Cohort 2 N=101	Cohort 3 N=11	All N =282	N = 305
Lung/other[b]	9 (26)	50 (29)	8 (8)	4 (36)	62 (22)	69 (23)
Upper Extremity[b]	5 (14)	11 (6)	17 (17)	1 (9)	29 (10)	32 (11)
Radius		6 (4)	10 (10)	0 (0)	16 (6)	
Humerus		3 (2)	6 (6)	0 (0)	9 (3)	
Metacarpus		2 (1)	1 (1)	0 (0)	3 (1)	
Ulna		0 (0)	0 (0)	1 (9)	1 (0)	
Spine[b]	4 (9)	21 (12)	3 (3)	3 (27)	27 (10)	27 (9)
Cervical vertebrae		11 (7)	0 (0)	0 (0)	11 (4)	
Thoracic vertebrae		9 (5)	2 (2)	2 (18)	13 (5)	
Lumbar vertebrae		1 (1)	1 (1)	1 (9)	3 (1)	
Skull/Neck	0 (0)	7 (4)	0 (0)	0 (0)	7 (3)	7 (2)
Missing location	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)

[a] Patients who rolled over from 20040215 to 20062004 or who discontinued 2050215 and later enrolled into Trial 20062004 are counted only once in the overall column.
[b] Trial 20040215 categorized the location of target lesions as "Pelvis", "Lower extremity", "Lung", "Upper extremity", or "Other."

Table 15 lists the types of surgeries that were planned at baseline for patients with resectable GCTB that enrolled in Cohort 2. En-bloc resections were the most common surgery planned at baseline (37%), followed by amputation (17%) and joint resection (15%).

Table 15: Surgery planned at baseline for patients with resectable GCTB

Planned Surgery	Cohort 2 N = 101 n (%)
En bloc resection	37 (37)
Amputation	17 (17)
Joint resection	15 (15)
Curettage[a]	13 (13)
Joint/prosthesis replacement	9 (9)
En bloc excision	4 (4)
Hemipelvectomy	4 (4)
Marginal excision[b]	1 (1)
Pneumonectomy	1 (1)

[a] Curettage planned for lesions located in the humerus (2 patients, one with a 2.7 cm lesion and the other with a 10.6 cm lesion), pelvic bone (1 subject with an 8.4 cm lesion), radius (2 patients, one with a 5.2

cm lesion and the other with a 6.7 cm lesion) thoracic vertebrae (2 patients, one with a 4.6 cm lesion and the other with a 6.0 cm lesion), tibia (5 patients with lesions ranging from 3.5 to 4.9 cm), lung (1 patient with 12.7 cm lesion), and "other" (1 patient with a 7.8 cm lesion).

b. one patient with a 12.7 cm target lesion in the lung.

6.1.3 Subject Disposition

Table 16 summarizes the disposition of patients enrolled in Trial 20040215 and Trial 20062004.

Table 16: Patient disposition for Trial 20042015 and Trial 20062004

Patient Disposition	Trial 20040215 n (%)	Trial 20062004			
		Cohort 1 n (%)	Cohort 2 n (%)	Cohort 3 n (%)	All Cohorts[a] n (%)
Number enrolled	37	170	101	11	282
No. Who did not received denosumab	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Number of patients Who Received Denosumab	37 (100)	169 (99)	101 (100)	11 (100)	281 (100)
Ongoing	0 (0)	149 (88)[b]	81 (80)[b]	11 (100)	241 (86)
Discontinued trial	37 (100)	21 (12)	20 (20)	0 (0)	41 (15)
Rollover to Trial 20062004	12[c] (32)	0 (0)	0 (0)	0 (0)	0 (0)
Protocol-specified criteria[d]	10 (27)	2 (1)	10 (10)[e]	0 (0)	12 (4)
Administrative decision	1 (3)	4 (2)	4 (4)	0 (0)	8 (3)
Adverse event	2 (5)	7 (4)	1 (1)[f]	0 (0)	8 (3)
Consent withdrawn	2 (5)	1 (1)	2 (2)	0 (0)	3 (1)
Disease progression	3 (8)	1 (1)	2 (2)	0 (0)	3 (1)
Lost to follow-up	0 (0)	2 (1)	1 (1)	0 (0)	3 (1)
Requirement for alternative therapy	1 (3)	2 (1)	0 (0)	0 (0)	2 (1)
Noncompliance	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Other[g]	4 (11)	1 (1)	0 (0)	0 (0)	1 (0)
Pregnancy	0 (0)	1 (1)	0 (0)	0 (0)	1 (0)

[a] Does not include the following four patients from Trial 20040215 who discontinued denosumab and enrolled directly into the safety follow-up phase of Trial 20062004: ID number [redacted] (b) (6) (Trial 20062004 ID number. [redacted] (b) (6); ID number [redacted] (b) (6) (Trial 20062004 ID number

(b) (6); Trial 20040215 ID number (b) (6) (Trial 20062004 ID number (b) (6)); and ID number (b) (6) (Trial 20062004 ID number (b) (6).
[b] A total of 148 patients in Cohort 1 remain on study therapy; one patient discontinued study therapy but remains on the trial. A total of 79 patients in Cohort 2 remain on study therapy – one patient remains on the trial but discontinued denosumab following complete resection of GCTB, and one patient remains on the trial but discontinued study therapy due to an adverse event.
[c.] A total of 11 patients enrolled into Cohort 3, and 1 (Patient (b) (6)) enrolled into the safety follow-up phase of Trial 20062004.
[d] Complete resection of GCTB
[e] One additional patient remains on study but discontinued denosumab following complete resection of GCTB
[f]One additional patient remains on the trial but discontinued study therapy due to an adverse event.
[g] Other includes "investigator decision", "investigator discretion" "stable disease and "PI decision", "partial withdrawal of informed consent".

In Trial 20040215, two patients discontinued due to adverse events. Patient (b) (6) discontinued due to lung metastases and Patient (b) (6) discontinued study therapy due to osteonecrosis of the jaw. Of the two patients who withdrew consent, one patient (Patient (b) (6)) discontinued following a diagnosis of disease progression. Review of the case report forms for Patient (b) (6) did not reveal a reason for withdrawal of consent, but there was no evidence that an adverse event was a factor in the decision to withdraw from study therapy.

In Trial 20040215, four patients discontinued due to a reason classified as "Other." These patients, who enrolled at the same site, discontinued study therapy at the discretion of the investigator. Review of subject narratives and case report forms did not reveal a specific reason for the investigator's decision to withdraw study therapy for these subjects. None of the subjects had an adverse event that was temporally related to the date of therapy discontinuation.

In Trial 20062004, 8 (3%) subjects discontinued due to adverse events according to the disposition classification; however, the adverse event database included 14 (5%) patients classified as having adverse events leading to investigational product discontinuation (Table 17). Three of the adverse events (shaded in light gray) were related to disease progression, and therefore do not represent true adverse reactions to denosumab.

Table 17: Patients who experienced adverse events leading to discontinuation of denosumab in Trial 20062004

Patient Number	Cohort	Age	Disposition Reason	Adverse event
(b) (6)	Cohort 1	22	Adverse Event	Osteonecrosis of the jaw (considered related)
	Cohort 1	44	Adverse Event	Sarcoma
	Cohort 1	44	Adverse Event	Spindle cell sarcoma
	Cohort 1	24	Adverse Event	Grade 2 Intratumoral bleeding
	Cohort 2	45	Adverse Event	Grade 3 Tooth infection
	Cohort 1	31	Adverse Event	Grade 4 Respiratory failure
	Cohort 1	40	Adverse Event	Grade 3 Extremity pain
	Cohort 1	48	Adverse Event	Bone neoplasm (tumor progression involving right sacrum), *Reviewer note: this should not be considered an adverse event leading to discontinuation of denosumab.*
	Cohort 1	29	Ongoing in the trial at the time of data cut-off, but last dose received on March 2, 2011.	Grade 2 hip arthralgia (considered related)
	Cohort 2	43	Ongoing in the trial at the time of data cut-off, but last dose received 2/24/2011 and trial participation on September 22, 2011	Grade 3 post procedural infection
	Cohort 2	21	Disease progression	Grade 3 anemia (started on the same date progression was diagnosed)
	Cohort 2	45	Adverse event	Grade 1 tooth abscess

Patient Number	Cohort	Age	Disposition Reason	Adverse event
(b) (6)	Cohort 1	62	Disease Progression	Grade 3 metastatic GCTB to lung. *Reviewer note: this should not be considered an adverse event leading to discontinuation of denosumab.*
	Cohort 2	41	Disease Progression	Neoplasm progression; *Reviewer note: This patient ultimately was diagnosed with a high grade sarcoma.*

Table 18 lists the eight (3%) patients who discontinued from Trial 20062004 due to "Administrative decision." Based upon review of the case report forms in two cases (shaded in grey), it appears that the primary cause of discontinuation of study therapy was either disease progression or an adverse event.

Table 18: Listing of patients categorized as discontinuing denosumab due to "administrative decision" in Trial 20062004

Patient ID	Cohort	Age	Best objective response by IRC review using any criteria.	Reviewer Notes
(b) (6)	Cohort 2	32	CR	SD by RECIST, CR by EORTC, PR by Density/Size criteria. The patient discontinued study therapy on (b) (6), underwent embolization on (b) (6) and enrolled for retreatment with denosumab on (b) (6).
	Cohort 1	36	CR	PR by RECIST, CR by EORTC, PR by Density/Size criteria. Discontinued Trial (b) (6), at the time of discontinuation, patient had no complaints.

Patient ID	Cohort	Age	Best objective response by IRC review using any criteria.	Reviewer Notes
(b) (6)	Cohort 2	42	NE	Ended trial participation on (b) (6) (b) (6) Case report form indicates that the clinician determined that the patient had a compete response by imaging and discontinued denosumab.
	Cohort 2	50	PR	PR by RECIST and Inverse Choi. Discontinued (b) (6); On the CRF, the investigator noted that the subject had stable disease and decided to see how the patient fared off therapy.
	Cohort 1	44	NE	Discontinued (b) (6) due to ONJ and osteomyelitis of the jaw that was diagnosed (b) (6)
	Cohort 1	28	NE	Discontinued from study participation on (b) (6). Patient diagnosed with ONJ on (b) (6). Investigator diagnosed progression beginning (b) (6)
	Cohort 1	26	NE	Ended treatment (b) (6) Investigator considered the subject to have achieved a PR.
	Cohort 2	32	NE	Screening pathology diagnosed GCTB of the humerus. Patient began treatment on November 11, 2010 and discontinued treatment (b) (6). The CRF indicates that repeat pathological analysis of the tumor performed (b) (6) identified the lesion as a malignant fibrous histiocytoma instead of a giant cell tumor of the bone. *Reviewer note: the investigator considered the patient to have been misdiagnosed as GCTB initially.*

Abbreviations: CR: complete response; NE: images not available for assessment of objective response; PR: partial response; SD: stable disease.

Table 19 provides a summary of the disposition of subjects for the analysis of objective tumor response. Overall, 303 subjects could potentially have provided imaging data for the retrospective analysis of objective response: 37 subjects enrolled in Trial 20040215 at trial completion and 266 subjects in Trial 20062004 at the time of data cut-off for the preplanned third interim analysis. Two patients enrolled in Trial 20062004 were not included in the efficacy analysis set: Patient [redacted] (b) (6) and Patient [redacted] (b) (6) Patient [redacted] (b) (6) enrolled in Cohort 1 but did not receive denosumab treatment. Patient [redacted] (b) (6) did not provide informed consent prior to receiving denosumab treatment, but subsequently provided informed consent and continued to receive study therapy at the time of data cut-off. *Reviewer note: Patient* [redacted] (b) (6) *had a best response of progressive disease according to modified RECIST 1.1.* In order to avoid double counting subjects originally enrolled in Trial 20040215 who either subsequently rolled over to Trial 20062004 (n=11) or entered Trial 20062004 after discontinuing from Trial 20040215 (n = 3) analysis of objective response for these patients was based on images collected under Trial 20040215 only.

Approximately one third of patients were not included in the analysis of objective response. The most common reasons were lack of informed consent for imaging collection [40 (13%) subjects], lack of on-study images [32 (11%) subjects], inability to obtain images that were performed [20 (7%) subjects], and lack of baseline images [10 (3%) subjects]. On-study imaging was required for Trial 20040215 but was not required for subjects enrolled in Trial 20042006.

Reference ID: 3311616

Table 19: Patient disposition for retrospective radiologic assessment of objective tumor response

Category	Trial 20040215	Trial 20062004			Overall
		Cohort 1	Cohort 2	Cohorts 1&2 Combined	
	n (%)	n (%)			n (%)
Potential subjects available for retrospective collection of images for determination of radiographic response	**37**	**166**	**100**	**266**	**303**
With At least one evaluable time point assessment	**27 (73)**	**114 (69)**	**49 (49)**	**163 (61)**	**190 (63)**
Without an evaluable time point assessment	**10 (27)**	**52 (31)**	**51 (51)**	**103 (39)**	**113 (37)**
Unable to obtain informed consent	7 (19)	13(8)	20 (20)	33 (12)	40 (13)
No on-study images	0	16 (10)	16 (16)	32 (12)	32 (11)
Unable to obtain images	0 (0)	12 (7)	8 (8)	20 (8)	20 (7)
No baseline images	3 (8)	3 (2)	4 (4)	7 (3)	10 (3)
Only X-ray images available (not CT or MRI)	0 (0)	4 (2)	2 (2)	6 (2)	6 (2)
Images received but not evaluable[a]	0 (0)	4 (2)	1 (1)	5 (2)	5 (2)

[a.] Not evaluable due to image quality or because the subject had surgical resection prior to the time point assessment.

Noting that informed consent was not obtained or images were not able to be obtained for a large proportion of patients, FDA requested the Applicant to provide a description of the procedures used to obtain informed consent and explanations for the inability to obtain images that were performed in some subjects.

The Applicant submitted a response to clarify the procedures that were used to obtain informed consent. For Trial 20040215, the Applicant issued an initial communication on May 24, 2011 to notify investigators that FDA requested independent review of images obtained for subjects participating in this trial, along with an addendum to the informed consent document requesting permission for collection and transmission of copies of images. For Trial 20062004, Amgen issued a communication on June 17, 2011 notifying investigators of FDA's request for independent radiographic review of images obtained for subjects participating in the trial. Amendments to the Trial 20062004 protocol and informed consent document (Amendment Number 5, Dated May 5, 2011) were submitted to IND 9838 to incorporate image collection and analysis. Sites were requested to submit the amended informed consent document to the site IRB or independent ethics committees and reconsent all subjects immediately following IRB/IRC approval.

For Trial 20040215, the Applicant provided specific instructions for provision of informed consent for collection of images from deceased subjects through legal representatives or through alternative mechanisms, as dictated by the local IRB or IEC. Investigators of both studies were instructed to document that informed consent could not be obtained in the patient chart, if efforts to obtain informed consent were unsuccessful. Additionally, the Applicant sent follow-up communications on August 17, 2011, October 3, 2011, and January 12, 2012 to remind sites of the deadline for submission of images and to provide clarification of the process for submitting images.

In response to a follow-up inquiry by FDA regarding the reasons that informed consent was not obtained for some subjects, the Applicant provided the following listing (Table 20, copied from the Applicant's submission)

Reference ID: 3311616

Table 20: Listing of patients who did not provide informed consent for collection of images for retrospective analysis of objective response.

PI Name (Site No.)	Subject Number	Reasons for Lack of Images
Dr. Robert Henshaw (Site 105)	(b) (6)	Lost to follow up
		Lost to follow up
		Lost to follow up
Dr. William Tap (Site 106)		Site closure
Dr. Sant Chawla (Site 108)		Consent withdrawn
		Consent withdrawn
Dr. Arthur Staddon (Site 110)		Consent withdrawn
Dr. Keith Skubitz (Site 101)		Lost to follow-up
Dr. Edwin Choy (Site 104)		Site could not obtain consent prior to imaging submission deadline
Dr. Robert Henshaw (Site 105)		Consent withdrawn
Dr. Scott Schuetze (Site 109)		IRB submission/review/approval delays
		Subject ended study- could not be re-consented
		Consent withdrawn
Dr. Arthur Staddon (Site 110)		Deceased; could not consent next of kin
		Subject ended study- could not be re-consented
		Consent withdrawn
		Deceased; could not consent next of kin
Dr. Ronald Blum (Site 111)		Lost to follow-up
		Deceased; could not consent next of kin
Dr. Charles Gibbs (Site 112)		IRB submission/review/approval delays
		IRB submission/review/approval delays
Dr. Thomas David (Site 201)		Consent withdrawn
		Site could not obtain consent prior to imaging submission deadline
Dr. Andre Gelderblom (Site 303)		Inability to consent subject
Dr. Paolo Casali (Site 305)		Subject ended study (phone consent cannot be used in Italy)
		Deceased; could not consent next of kin
		Subject ended study (phone consent cannot be used in Italy)

PI Name (Site No.)	Subject Number (b) (6)	Reasons for Lack of Images
Dr. Stefano Ferrari (Site 306)		Lost to follow-up
		Subject ended study (phone consent cannot be used in Italy)
		Subject ended study (phone consent cannot be used in Italy)
		Subject ended study (phone consent cannot be used in Italy)
		Subject ended study (phone consent cannot be used in Italy)
		Subject ended study (phone consent cannot be used in Italy)
		Subject ended study (phone consent cannot be used in Italy)
Dr. Peter Reichardt (Site 307)		Deceased; could not consent next of kin
Dr. Martin Dominkus (Site 308)		Consent withdrawn
Dr. Antonio Lopez Pousa (Site 309)		Subject ended study- site not able to consent as subject now in Brazil
Dr. Javier Martin Broto (Site 310)		Subject could not be consented by site due to administrative reasons
Dr. Rutkowski Piotr (Site 314)		Subject ended study, phone consent not allowed
		Subject ended study, phone consent not allowed
		Subject ended study, subject unable to make clinic visit for consenting process

Source: Amgen submission to sBLA 125320/94

A total of 10 of the 40 patients (25%) from whom informed consent was not obtained enrolled in countries where telephone consent was not permitted (Italy: Site 305 and Site 306; and Poland: Site 314). Additionally, 7 patients withdrew consent, 6 patients were lost to follow-up, 3 patients died, 1 patient moved out of the country, and 1 patient was enrolled in a site that subsequently closed.

In response to an inquiry by FDA, the Applicant also clarified that subjects not included in the retrospective imaging review due to the category “unable to obtain images” had images performed that were not included in the analysis for the following reasons:

- Media could not be obtained from the site (N = 2)

- Images not submitted or no media received due to oversight by personnel at the study site (N = 5)
- Media sent to the central lab after the deadline for submission (N = 8)
- Inability at the site to obtain images prior to the deadline for submission (N = 3)
- Images performed at a site external to the site (N = 1)
- Digital images not available (N = 1).

In response to a follow-up inquiry by FDA, the Applicant provided the following site-level details to explain why images could not be obtained (Table 21, copied from the Applicant's submission).

Table 21: Listing of patients who underwent imaging that Amgen was unable to obtain for central radiologic assessment of objective response

PI Name (Number of subjects without images collected)	Subject Number	Reasons for Lack of Images
Dr. Keith Skubitz (1 subject) (Site 108)	(b) (6)	Transfer subject to site 305; could not obtain media from subject
Dr. Arthur Staddon (3 subjects) (Site 110)		Transfer subject to site 105; could not obtain media from subject
		Transfer subject to site 104; site did not submit images due to site oversight
		Transfer subject to site 105; no media received due to oversight
Dr. Ronald Blum (3 subjects) (Site 110)		Oversight by site staff in sending images prior to submission deadline
		Oversight by site staff in sending images prior to submission deadline
		Oversight by site staff in sending images prior to submission deadline
Dr. Alex Powell (8 subjects) (Site 202)		Media sent after imaging deadline
		Media sent after imaging deadline
		Media sent after imaging deadline
		Site unable to obtain images prior to imaging deadline
		Media sent after imaging deadline
		Media sent after imaging deadline
		Site unable to obtain images prior to imaging deadline
		Site unable to obtain images prior to imaging deadline
Dr. Paolo Casali (4 subjects) (Site 305)		Digital images not available only films
		Media sent after imaging deadline
		Media sent after imaging deadline
		Media sent after imaging deadline
Dr. Antonio Lopez Pousa (1 subject) (Site 309)		Subject EOS, images all performed at external facility and site unable to obtain

Source: Amgen submission to sBLA 125320/94

Reviewer note: it appears that inability to acquire images and submit them in a timely manner was primarily clustered at four sites. This implies that the sites did not have adequate motivation or infrastructure to support imaging collection. It does not appear that Amgen provided additional financial compensation for the collection of images.

Overall, the baseline demographic characteristics of patients included in the evaluation of objective response was reflective of the overall population enrolled in Trial 20062004 and Trial 20040215. A total of 105 (55%) of patients were female, and 150 (79%) were White. The median age of patients in the imaging analysis set was 33 years (range: 13, 76). A total of 6 patients were skeletally mature adolescents.

The majority of patients (48%) with evaluable images for the analysis of objective response had recurrent unresectable disease. The median diameter of the target lesions was 56 cm (range: 6 to 240 cm), and the most common location of GCTB was the pelvis (32%).

Of the 190 patients included in the analysis of objective tumor response, 152 (80%) remained on study therapy at the time of data cut-off for the third interim analysis of Trial 20062004 (Table 22).

Table 22: Disposition of patients with imaging available for central radiological assessment of objective response

Category	Trial 20040215	Trial 20062004			Overall
		Cohort 1	Cohort 2	Cohorts 1&2 Combined	
	n (%)	n (%)			n (%)
Patients with at least one evaluable time point assessment	27	114	49	163	190
Ongoing	0 (0)	108 (95)	44 (90)	152 (93)	152 (80)
Discontinued	27 (100)	6 (5)	5 (10)	11 (7)	38 (20)
Protocol-specified criteria[a]	8 (29)	2(2)	3 (6)	5 (3)	13 (6.8)
Rollover to Trial 20062004	9 (33)	0 (0)	0 (0)	0 (0)	9 (5)
Other[b]	4 (15)	0 (0)	0 (0)	0 (0)	4 (2)
Administrative decision	1 (4)	1 (1)	2 (4)	3 (2)	4 (2)
Disease progression	2 (7)	1 (1)	0 (0)	1 (1)	3 (2)
Adverse event	1 (4)	2 (2)	0 (0)	2 (1)	3 (2)
Consent withdrawn	1 (4)	0 (0)	0 (0)	0 (0)	1 (1)
Noncompliance	1 (4)	0 (0)	0 (0)	0 (0)	1 (1)

[a.] Complete resection
[b.] Discontinued from the trial at the investigator's discretion.

A total of 190 subjects had a baseline assessment and at least 1 on-study assessment that was evaluable for central blinded independent radiologic review. Among these 190 subjects, a total of 187, 176, and 26 subjects were evaluable according to modified RECIST, (density/size), Density/Size (inverse Choi), and modified EORTC criteria, respectively. Non-target lesions were evaluable by modified RECIST 1.1 but not by Density/Size criteria; therefore, 11 subjects were evaluable by modified RECIST 1.1 but not by Density/Size criteria.

6.1.4 Analysis of Primary Endpoint(s)

During the April 5, 2011 and September 11, 2012 pre-sBLA meetings, FDA and Amgen agreed that retrospective analyses of objective response rate and duration of response, as determined by retrospective independent radiographic review of available images from subjects enrolled in studies 20040215 and 2006204, would be the primary efficacy endpoints in the sBLA. Additionally, at the September 11, 2012 meeting, FDA stated that objective response according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria would be the primary regulatory endpoint for the sBLA (Table 2). A follow-up assessment was not required to confirm tumor response. See Section 5.3.3 of this review for a summary of the procedures used for assessment of objective response by independent radiology review.

<u>Analysis of Objective Tumor Response in the Control Group</u>

As requested by FDA, Amgen conducted an analysis of objective tumor response in a control group consisting of a subset of subjects who had at least 3 images obtained prior to denosumab treatment that were available for blinded central radiologic review. A total of 26 subjects with at least 3 pretreatment images were included in the imaging control group. Pretreatment images for the subjects included in the control group were assessed using the same imaging criteria used to evaluate tumor response following treatment with denosumab.

Table 23 summarizes the Independent Radiology Committee (IRC) assessments of objective response for the subjects in the control group. Images used for the control group were obtained between 782 days to 65 days prior to enrollment into Trial 20040215 or 20062004. The IRC determined that 9 of the 26 control group subjects (34.6%) achieved a partial response according to least one of the three tumor response criteria (modified RECIST, modified EORTC or inverse Choi (density/size) criteria). According to IRC review, two of 26 subjects (8%) exhibited a partial response using modified RECIST 1.1; in contrast, all nine control group "responders" were considered to have achieved a PR using density/size (inverse Choi) criteria. None of the control

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subjects had pre-treatment PET images available for evaluation using modified EORTC criteria.

Table 23: Listing of radiographic assessment of objective response in the control group by retrospective independent radiologic review

Patient ID No.	Cohort	Location of Target Lesion	Best Response	Reviewer Comment
(b) (6)	Cohort 1	Sacrum	PD	
	Cohort 1	Sacrum	PD	
	Cohort 2	Hyoid Bone	PD	
	Cohort 1	Cervical Vertebrae	PD	
	Cohort 1	Lung	PD	
	Cohort 1	Skull	PD	
	Cohort 1	Tibia	SD	
	Cohort 1	Humerus	SD	
	Cohort 1	Sacrum	SD	
	Cohort 1	Lung	SD	
	Cohort 1	Lung	SD	
	Cohort 1	Tibia	SD	
	Cohort 2	Tibia	SD	
	Cohort 2	Tibia	SD	
	Cohort 1	Cervical Vertebrae	SD	
	Cohort 1	Radius	SD	
	Cohort 1	Lung	SD	
	Cohort 1	Retro-peritoneum	PR	Patient underwent XRT from Day -216 through Day -164. Baseline image acquired on Day -151. The next pre-denosumab image obtained on Day -112 was assessed as stable disease. Day -44 imaging assessed as PR by RECIST and density/size criteria. Best IRC determined post-treatment response of PR on Study Day 54 that was sustained through Day 419 by IRC based on density/size criteria (stable RECIST).
	Cohort 1	Sacrum	PR	PR by density/size criteria only.

Patient ID No.	Cohort	Location of Target Lesion	Best Response	Reviewer Comment
				Patient underwent sacral laminectomy of tumor on Day -470 (39 days after the first pre-treatment image).
(b) (6)	Cohort 1	Skull	PR	PR by RECIST (57% decrease from baseline) based on Day -151 image and PR by density/size criteria based on Day -403, Day -259, and Day -151 images). Patient underwent tumor resection on Day -469 (51 days prior to the baseline image). Patient underwent another tumor resection on Day -398 followed by radiation therapy, and a repeat tumor resection approximately two months prior to trial enrollment. Patient also received interferon from Day -489 through approximately Day -60. Patient had best post-treatment response of SD by RECIST and density/size criteria.
	Cohort 1	Metacarpus	PR	Transient PR by density/size criteria only from Day -171 until Day -105. The subject had multiple local excisions from the time of the baseline image to the time of the transient PR.
	Cohort 1	Lung	PR	Transient PR by density/size criteria only from Day -85 until Day -21.
	Cohort 1	Lung	PR	Transient PR by density/size criteria only from day -167(pretreatment image 2) until Day -41 (pretreatment image 3, determined to be stable disease by IRC).
	Cohort 1	Sacrum	PR	Transient PR by density size criteria from Day -120 to Day -100; On Day -12, progressive disease

Patient ID No.	Cohort	Location of Target Lesion	Best Response	Reviewer Comment
				by RECIST and stable disease by density/size criteria.
(b) (6)	Cohort 1	Pelvic Bone	PR	Stable disease by RECIST on multiple time points between Day -611 to Day -150 ; PR from Day -611 to Day -150 using density/size criteria. The subject underwent surgical interventions on Day -700 and Day -321 (approximately). These interventions occurred after the first baseline image.
	Cohort 1	Pelvic Bone	PR	PR by density/size criteria from day -36 through Day -72; SD by RECIST.
	Cohort 1	Cervical Vertebrae	UE	Pretreatment images available, but not evaluable
	Cohort 1	Sacrum	UE	Pretreatment images available
	Cohort 1	Femur	UE	Pretreatment images available

[1]No pre-treatment images evaluable by RECIST
Abbreviations: PD = progressive disease; SD = stable disease; PR = partial response; UE = unevaluable.

Four of the nine subjects assessed as having a response received therapy during the pre-treatment period that could account for radiographic changes consistent with tumor response. However, for five of the nine subjects (shaded in gray), there was either no clear explanation to account for the determination of radiographic objective response (b) (6)) or for which the temporal relationship between the therapy and response introduced uncertainty that the response was attributable to the therapeutic intervention. For three subjects, Patient (b) (6) Patient (b) (6), and Patient (b) (6), there was a single pre-treatment image that was considered a PR by density/size criteria and an assessment of stable disease by density/size criteria at the next pre-treatment imaging time point.

Patient (b) (6) was assessed by the independent radiology review committee as having achieved a PR by RECIST and density/size criteria on Day -44. The Applicant asserted that the assessment of response for this subject was due to surgery and embolization that took place over a year earlier. However, there were prior post-intervention images on Day -151 (approximately 4 months after the therapeutic interventions) and Day -112 that presumably would have reflected the impact of these interventions. After FDA requested clarification about this case, Amgen provided

additional information about this subject. According to Amgen, this subject underwent radiation therapy from Day -216 through Day -164. Compared to the baseline image obtained in Day -151, the pre-denosumab images obtained on Day -112 and Day -44 were assessed as stable disease and partial response according to modified RECIST 1.1.

If the four subjects who received therapeutic intervention during the pre-denosumab imaging period are removed from the control group, a total of five of 20 (25%) evaluable control subjects were assessed as having an objective response by Density/Size criteria and a total of one of 19 (5%) RECIST-evaluable subjects had an objective response by modified RECIST prior to receiving denosumab. In general, the responses by Density/Size criteria were assessed as response in a single pre-treatment image, with a subsequent pre-treatment image read as stable disease.

Reviewer note: The increased percentage of responses according to Density/Size criteria in the control group is likely to be at least partially due to the fact that the threshold for response based upon reduction in size of the target lesion(s) is lower in the Density/Size criteria (which requires ≥10% decrease in the sum of the measurement of the longest diameter of each target lesion) compared to Modified RECIST 1.1 [which required ≥ 30% decrease in the sum of the diameter of the target lesion(s)]. Additionally, a response by Density/Size criteria did not require both a reduction in target lesion size and an increase in density of the lesion; achievement of only one criterion was required. Please see Section 5.3.3 of this review for details regarding assessment of objective response according to Modified RECIST 1.1 and Density/Size criteria. Although the responses by Density/Size criteria tended to be transient, the high percentage of pre-treatment responses using these criteria calls into question whether demonstration of a radiographic response using these criteria reflects a true antitumor response.

Retrospective Analysis of Objective Response: Treatment Group

Table 24 provides a summary of the results of the retrospective analysis of objective tumor response, according to blinded independent central review. A total of 190 patients had images that were evaluable using at least one of the sets of radiographic criteria used to assess response.

A total of 187 patients were evaluable for objective response using modified RECIST 1.1. A total of 47 of 187 (25.1%) patients evaluable by RECIST exhibited a partial response. No complete responses were observed.

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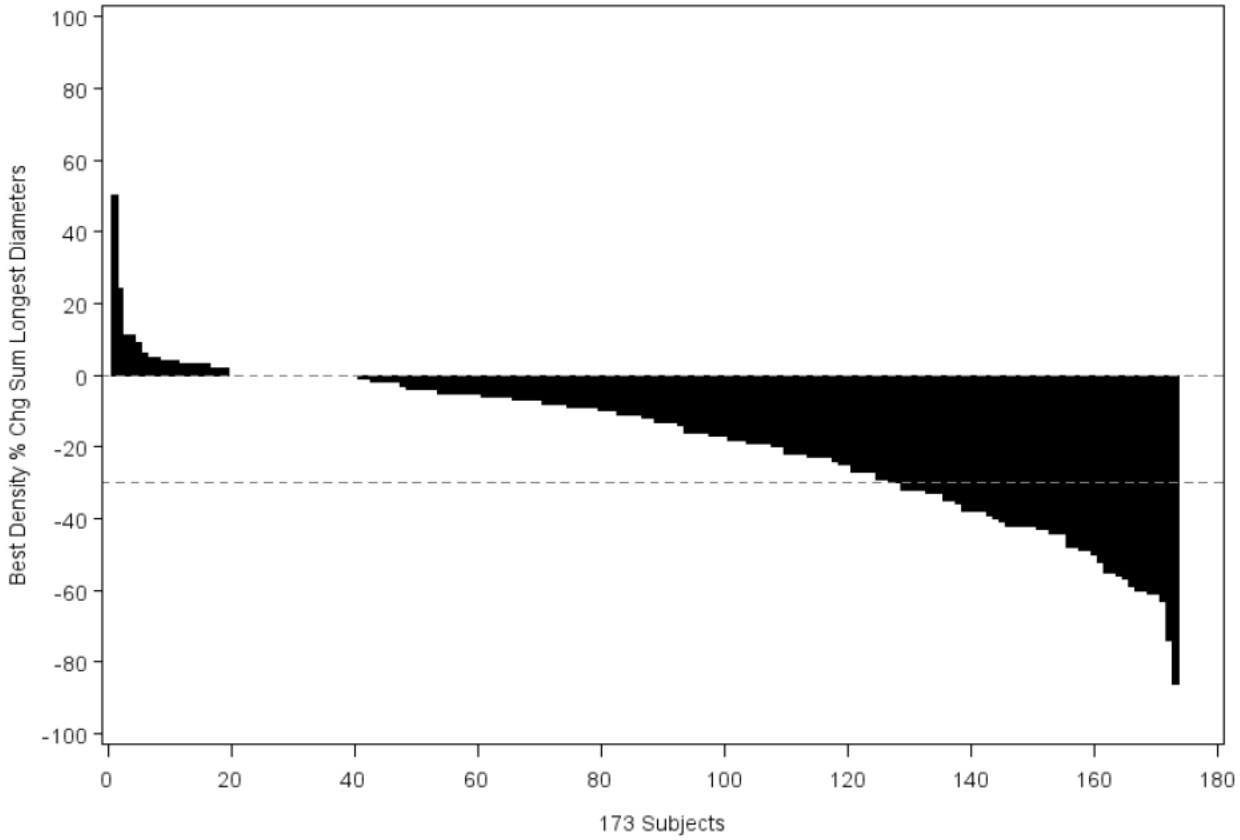
Table 24: Analysis of objective response according to blinded independent central radiology review

Response Parameter	Number of Responders	Number of Evaluable Patients	Percent Response	95% Exact CI
RECIST 1.1	47	187	25.1	(19.1, 32.0)
EORTC	25	26	96.2	(80.4, 99.9)
Density/Size	134	176	76.1	(69.1, 82.2)
Best Response	136	190	71.6	(64.6, 77.9)

A waterfall plot of the best percentage change in the sum of the lesion diameters of target lesions in RECIST-evaluable patients is provided in Figure 3.

Figure 3: Best percentage change in the sum of the target lesion diameters in RECIST-evaluable patients



Source: Provided by FDA Statistical Reviewer Weishi Yuan

6.1.5 Analysis of Secondary Endpoints(s)

Duration of Response

Table 25 provides a summary of the duration of objective response according to blinded independent central radiology review. The statistical analysis plan defined the duration of response as the time interval in days between the date of the first objective tumor response to the date of progressive disease. If progressive disease was not documented following an objective tumor response by the analysis cut-off date, duration was censored the last evaluable time point response date, the end of study date, or the analysis cut-off date, whichever came first.

The median duration of response could not be estimated because only three patients experienced disease progression within a median follow-up of 13.4 months.

Table 25: Duration of objective response according to retrospective independent radiology review

Response Parameter	Number of patients evaluable for the endpoint	Number of patients with disease progression after response	Proportion (%) (95% CI) [a]	Median duration of observed responses at the time of data cut-off (months)
RECIST 1.1	47	3	6.4	8.1
EORTC	25	0	0.0	3.9
Density/Size	134	1	0.7	8.1
Based on best response[b]	136	1	0.7	8.1

[a] Exact Confidence Interval
[b] Using any of the three sets of criteria for evaluation of objective tumor response (Modified RECIST, EORTC, or Density Size criteria)

Table 26 provides a summary of the minimum response duration among RECIST responders observed at the time of data cut-off. The minimum duration of objective response required confirmation of sustained objective response at least 4, 8, 12, and 24 weeks after the initial objective tumor response

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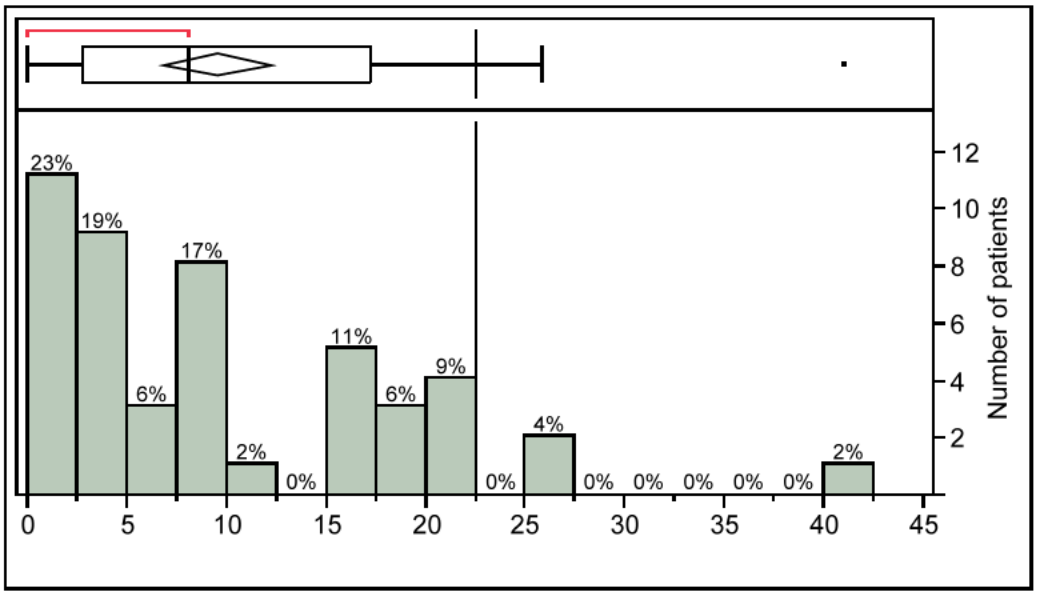
Table 26: Duration of objective tumor response by modified RECIST 1.1 at the time of data cut-off

Minimum Response Duration	N	No. Responders	% Response
4 weeks	150	32	21
8 weeks	144	32	22
12 weeks	141	32	23
24 weeks	109	26	24

Figure 4 provides an analysis of the distribution of the duration of response in months at the time of data cut-off for the 47 patients who achieved a response by RECIST.

Figure 4: Duration of RECIST response (in months) at the time of data cut-off



Quantiles

100.0%	maximum	40.9692
99.5%		40.9692
97.5%		37.9466
90.0%		21.8612
75.0%	quartile	17.2813
50.0%	median	8.08214
25.0%	quartile	2.79261
10.0%		0.03285
2.5%		0.03285
0.5%		0.03285
0.0%	minimum	0.03285

Time to Objective Response

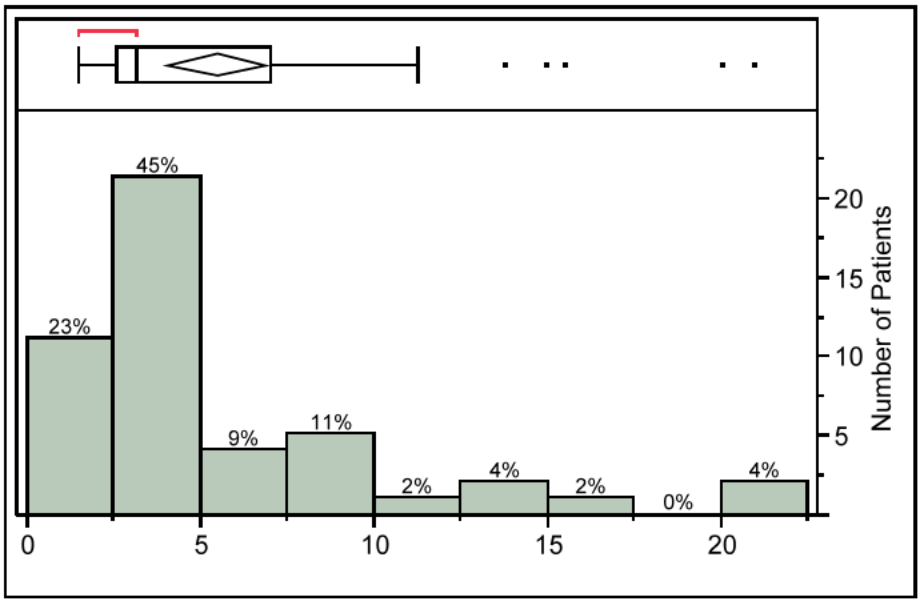
The time to objective tumor response was defined as the time interval from the date of patient receipt of the first dose of denosumab to the date of the first objective tumor response. If a subject did not exhibit an objective tumor response by the analysis data cut-off date, the time to first objective tumor response was censored at the last evaluable imaging time point, the end of study date, or the analysis data cut-off date, whichever came first. Table 27 provides a summary of the time to first objective response according to blinded independent central radiology review. The median time to response based on best response using any of the three radiological criteria for assessment of response was 2.8 months.

Table 27:Time to first objective response according to retrospective independent radiology review

Response Parameter	Number of Responders	Median Time to Objective Response (Months)	95% CI of Median (Months)	Range of Time to Objective Response (Months)
RECIST 1.1	47	3.2	(2.8, 4.6)	(1.5, 20.9)
EORTC	25	2.7	(1.6, 2.8)	(0.9, 9.7)
Density/Size	134	2.8	(2.8, 3.0)	(0.5, 23.4)
Based on best response[b]	136	2.8	(2.8, 2.9)	(0.5, 23.4)

Figure 5 provides an analysis of the distribution of the time to RECIST response in months at the time of data cut-off for the 47 patients who achieved a response by RECIST. Among the responding patients, the median time to objective response using modified RECIST 1.1 was 3.2 months.

Figure 5: Time to RECIST response (in months) among responding patients



Quantiles

100.0%	maximum	20.9281
99.5%		20.9281
97.5%		20.7507
90.0%		13.9762
75.0%	quartile	6.99795
50.0%	median	3.154
25.0%	quartile	2.59548
10.0%		1.80041
2.5%		1.53758
0.5%		1.51129
0.0%	minimum	1.51129

6.1.6 Other Endpoints

Additional Supportive Efficacy Results – Trial 20040215

In Trial 20040215, at least 90% elimination of giant cells relative to baseline (or complete elimination of giant cells in cases where giant cells represented < 5% of tumor cells) or a lack of progression of the target lesion by radiographic measurements (in cases where histopathology was not available) was observed in 30 of the 35 (85.7%) evaluable patients.

Additional Supportive Efficacy Results – Trial 20062004

In Cohort 2 (patients enrolled who had resectable GCTB but whose planned surgery was anticipated to cause severe morbidity), 64 of the 71 (90.1%; 95% CI: 80.7%,

95.9%) evaluable patients treated with denosumab had not undergone surgery by month 6. Overall, of 100 patients for whom surgery was planned, 74 patients (74%) had no surgery performed, and 16 patients (16%) underwent a less morbid surgical procedure from that planned at baseline (Table 28).

Table 28: Comparison of planned versus actual surgery for patients enrolled in Cohort 2

Surgical Procedure	Baseline Planned (n) [a]	Actual Total (n) [a]
Total number of surgeries	100	26
Major surgeries	44	3
Hemipelvectomy	4	0
Amputation	17	0
Joint/prosthesis replacement	9	1
Joint resection	14	2
Marginal excision, en bloc excision, or en bloc resection	42	6
Curettage	13	16
Other	1	1
No surgery	0	74

[a] n = number of patients

Table 29, copied from Amgen's submission, provides a summary of symptom improvement by patient report:

Table 29: Summary of change in patient symptoms for Trial 20062004

	N1 (%)	Pain Reduction n (%)	Improved Mobility n (%)	Improved Function n (%)	Other n (%)
Cohort 1 (N = 169)	67 (39.6)	48 (28.4)	38 (22.5)	32 (18.9)	6 (3.6)
Cohort 2 (N = 100)	61 (61.0)	50 (50.0)	33 (33.0)	23 (23.0)	10 (10.0)
Cohort 3 (N = 11)	3 (27.3)	3 (27.3)	2 (18.2)	2 (18.2)	1 (9.1)
Cohorts 1 and 2 (N = 269)	128 (47.6)	98 (36.4)	71 (26.4)	55 (20.4)	16 (5.9)

N = number of enrolled subjects who were eligible for the study and received at least one dose of denosumab
N1 = Number of subjects who reported clinical benefit
For an individual subject, within each category, if multiple responses are present in the same time frame, the best response is presented.
Percentages based on N

Program: /stat/amg162/therapeutic/20062004/analysis/interim_3/tables/program/t-clinical.sas
Output: t14-04-003-006-clinical.rtf (Date Generated: 14NOV2011:10:26:58) Source Data: adam.adfcb

Source: Amgen submission to sBLA 125320/94

At baseline, 25% of patients reported strong opioid use (i.e., an analgesic score ≥ 3). During the trial, the proportion of patients who shifted from strong opioid use to no/low analgesic use at any study visit ranged from 4.2% to 38.5%. The proportion of patients who shifted from no/low analgesic use to strong opioid use at any study visit was ≤ 4.7%.

6.1.7 Subpopulations

Table 30 provides a comparison of objective tumor response according to Modified RECIST 1.1 by gender, age, and race.

Table 30: Subgroup analysis of objective response by Modified RECIST 1.1

Demographic Parameter	Number of Responders	Number of Patients	Percent
Gender			
Male	25	84	29.8
Female	22	103	21.4
Age			
< 18 years	2	6	33.3
≥ 18 years	45	181	24.9
< 65 years	46	182	25.3
≥ 65 years	1	5	20.0
Race			
Caucasian	32	147	21.8
Non-Caucasian	15	40	37.5

Efficacy results in skeletally mature adolescents appeared to be similar to those observed in adults. Six of the 10 adolescent patients enrolled in Trial 20062004 had at least one evaluable time point assessment available for the retrospective assessment of objective tumor response. As of the data cut-off for the third interim analysis, all six subjects remained on study and were continuing to receive denosumab. Among the adolescent subjects in the objective response analysis set, the median time on study was 6.3 months. The median number of denosumab doses received was 9.5 and the maximum number was 21. An objective response by modified RECIST was observed in a total of two of six (33.3%) evaluable adolescent patients and an objective response by density/size criteria was observed in four of six (66.7%) evaluable adolescent patients.

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6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A single dosage regimen was used in Trial 20040215 and Trial 20062004. Please refer to the clinical pharmacology review of this sBLA by Stacy Shord, PharmD for additional information related to pharmacokinetic analyses relevant to this application.

The Written Request for denosumab issued by FDA on November 30, 2012 (b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please see Section 6.1.5 for a discussion regarding the duration of objective response observed in the retrospective analysis of radiographic response by modified RECIST.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues or analyses pertinent to this application. Please refer to the statistical review of this sBLA by Weishi Yuan for additional information regarding the statistical issues relevant to this application.

7 Review of Safety

Safety Summary

Overall, the adverse reaction profile of denosumab in patients with giant cell tumor of bone was similar to that observed in the 2,841 patients with bone metastases from solid tumors treated with denosumab in the placebo-controlled trials supporting the original approval of Xgeva. The median number of doses received by the 304 patients treated in Trial 20040215 and Trial 20062004 was 14 (range: 1 to 60 doses) and the median number of months on study was 11 (range: 0 to 54 months). The most common adverse reactions in patients enrolled in Trial 20040215 and Trial 20062004 combined (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions (per-patient incidence of 1%) were osteonecrosis of the jaw and osteomyelitis. The most common adverse reactions (per-patient incidence of 1%) resulting in discontinuation of Xgeva were osteonecrosis of the jaw, tooth abscess or infection, and development of sarcoma or malignant transformation of GCTB. Grade 3 or 4 hypocalcemia was not observed, and Grade 3 hyophosphatemia occurred in 29 (10%) patients. A single death, attributable to disease progression, occurred during or within 30 days of study therapy. At the time of the third interim analysis of Trial 20062004, 238 of 304 (78%) of patients continued to receive denosumab therapy. The most common reason for discontinuing denosumab was complete resection of GCTB (23 of 304, or 7% of patients).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review focused primarily on the safety database compiled from the treatment of 304 subjects with GCTB treated in Trials 20040215 and 20062004. In addition, summary data from the studies supporting approval of XGEVA for the prevention of skeletal related events, current labeling, the denosumab Annual Report covering the period of March 24, 2011 to March 26, 2012, and the Periodic Safety Update Report for the period of May 27, 2012 to November 26, 2012 were also reviewed.

7.1.2 Categorization of Adverse Events

Trial 20040215 and 20062004 used the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 and 14.1, respectively, to code adverse events. The adverse event database for Trial 20040215 and 20062004 contained 385 and 1,753 individual adverse event listings, respectively.

Review of verbatim terms in the adverse event dataset to determine whether MedDRA preferred terms were appropriately coded revealed no instances of inaccurate coding. In addition, based on review of case report forms (CRFs) for a subset of subjects enrolled in each trial, the adverse event databases appeared to be accurate and complete.

Adverse events were assessed using the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse events version 3.0.

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

Because the patient populations treated were similar and the dosage regimen used was identical in Trials 20040215 and 20062004, the majority of safety analyses conducted during the course of clinical review of this application pooled safety data across both trials. Comparison of per-patient incidence of adverse events between the two trials would not yield meaningful information due to the disproportionately small number of patients enrolled in Trial 200420015.

7.2 Adequacy of Safety Assessments

Overall, the safety assessments performed in Trial 20040215 and Trial 20062004 were of adequate breadth and quality to permit an appropriate assessment of safety of the use of denosumab in subjects with GCTB. Data required to fulfill the proposed postmarketing requirements related to the GCTB indication for XGEVA will enable a

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more complete assessment of the safety of long term use of denosumab in adult and skeletally mature adolescent patients at the proposed dose and schedule.

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

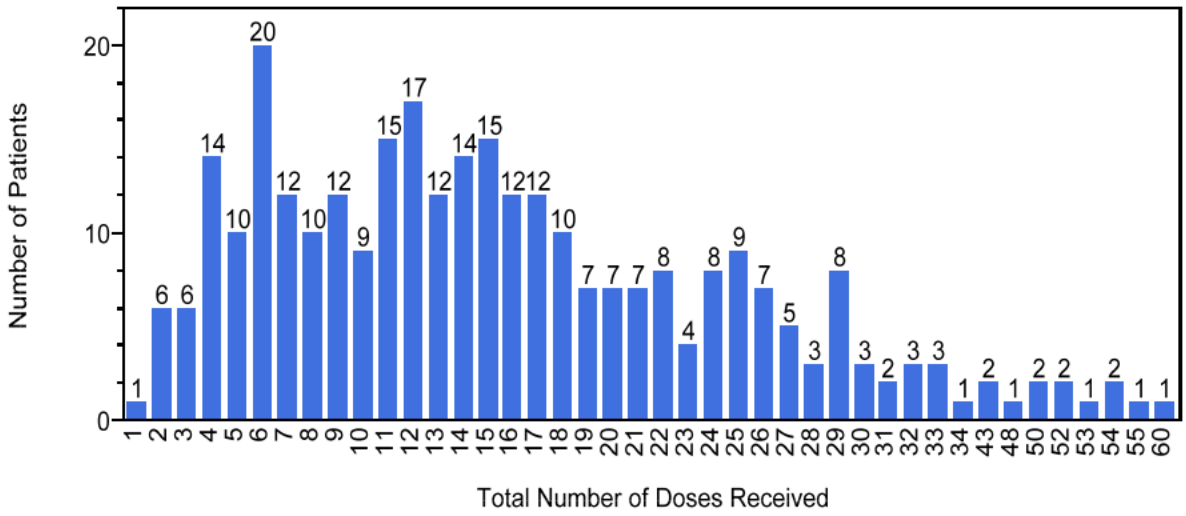
Overall, exposure to denosumab was sufficient to permit an adequate assessment of safety in the target population of subjects (Table 31 and Figure 6). The number and demographic composition of subjects studied in Trial 20040215 and Trial 20062004 were appropriate given the given epidemiology of giant cell tumor of bone.

Table 31: Summary of exposure to denosumab in Trial 20040215 and Trial 20062004

Category	Trial 20040215	Trial 20062004	Overall[a]
Number of subjects enrolled	37	282	305[a]
Number of months on study			
Mean (standard deviation)	22 (16)	11 (8)	13 (11)
Median (min, max)	19 (2,49)	10 (0,29)	11 (0,54)
Number of subjects receiving at least 1 dose	37	281	304[a]
Number of doses received			
Mean (standard deviation)	24 (17)	14 (8)	16 (11)
Median (min, max)	21 (9, 42)	13 (1,33)	14 (1, 60)

[a.] The 11 subjects who entered Cohort 3 from Trial 20040215 and 3 subjects who discontinued Trial 20040215 and later enrolled in Cohort 1 are counted only once and their analysis period starts from Trial 20040215 and ends at Trial 20062004.

Figure 6: Summary of total number of doses received – overall study population



7.2.2 Explorations for Dose Response

Only one dose of denosumab was explored in Trial 20040215 and Trial 20062004. This dose was chosen to achieve at least 95% occupancy of RANKL at steady state over the dosing interval, as demonstrated in the sBLA resulting in the 2010 approval of Xgeva.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed to support his supplemental BLA.

7.2.4 Routine Clinical Testing

Overall, routine clinical and laboratory evaluations were adequate to assess the safety of denosumab in Trial 20040215 and 20062004. Refer to Table 8 and Table 10, which describe the laboratory schedule of assessments for Trial 20040215 and Trial 20062004, respectively.

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal analyses to examine the effect of drug interactions on exposure or safety were conducted to support this sBLA.

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

Refer to Section 7.3.5 for details regarding submission-specific primary safety concerns.

7.3 Major Safety Results

7.3.1 Deaths

Trial 20040215

No patients enrolled in Trial 20040215 died within 30 days of receiving denosumab. Six patients died during the follow-up period, which began 30-days after receipt of the last dose of denosumab (Table 32).

Table 32: Deaths occurring during the follow-up phase of Trial 20040215

Patient ID	Age (yrs)	Duration of Therapy (days)	Cause of Death	Time From Last Dose (days)	Comments
(b) (6)	63	134	GCTB progression	644	Developed disease progression of GCTB of the cervical spine approximately 3.5 months after starting denosumab.
	65	634	Congestive heart failure	146	Patient had discontinued study therapy due to a submental abscess that later was diagnosed as osteonecrosis.
	34	130	Metastasis/ Secondary malignancy	437	Malignant component of original tumor (right distal femur) diagnosed during curettage resection of tumor two months after initiation of denosumab treatment. Approximately 6 months later, needle biopsy revealed high grade pleomorphic sarcoma without giant cells from soft tissue mass distal right femur. Narrative states that the original GCT had a malignant element not detected on original core biopsy." The investigator considered that there was a reasonable possibility that the adverse event was related to study therapy.

Reference ID: 3311616

Patient ID	Age (yrs)	Duration of Therapy (days)	Cause of Death	Time From Last Dose (days)	Comments
(b) (6)	47	95	Disease progression	285	
	36	94	Progressive lung metastases	263	Patient had lung metastases prior to treatment.
	28	337	Ventricular tachycardia	87	Developed post-pelvic tumor resection.

Trial 20062004

One subject died during the treatment phase of the trial, and three of 38 subjects who entered the safety follow-up phase (which began after the end of study visit, 30-days after the last denosumab dose) died (Table 33).

Table 33: Deaths occurring during the treatment or follow-up phase of Trial 20062004

Patient ID	Age (yrs)	Duration of Therapy (days)	Cause of Death	Time From Last Dose (days)	Comments
(b) (6)	32	273	Respiratory insufficiency and disease progression	20	Patient enrolled with GCT lung metastases. Hospitalized for Grade 4 respiratory failure on Study Day 266, 15 days following last denosumab dose. Respiratory insufficiency was due to cardiac and pulmonary tumor compression.
	24	86	Progressive GCTB	63	This patient had recurrent unresectable GCTB at baseline, and discontinued study therapy on approximately Study Day 85 secondary to intratumoral hemorrhage (requiring transfusion) and progressive GCTB.

Patient ID	Age (yrs)	Duration of Therapy (days)	Cause of Death	Time From Last Dose (days)	Comments
(b) (6)	45	139	Bone sarcoma	191	Metastatic pleomorphic sarcoma diagnosed approximately four months after starting investigational therapy. Pleomorphic sarcoma in same location (sacrum) as the GCT prior to therapy. Unclear if this tumor evolved from GCT or represents a new primary malignancy.
	62	175	Lung metastases	89	

7.3.2 Nonfatal Serious Adverse Events

Table 34 provides the per-patient incidence of serious adverse events by preferred term for patients enrolled in Trial 20040215 and Trial 20062004 combined. Serious adverse events occurred in 9 of 37 subjects (24%) enrolled in Trial 20040215 and in 25 of 281 subjects (9%) treated in Trial 20062004. Osteomyelitis and osteonecrosis of the jaw were the only serious adverse events that occurred in more than 1 patient (shaded in grey below).

Table 34: Per-patient incidence of serious adverse events in GCTB studies

System Organ Class	Overall GCTB Program N = 304		
	Preferred Term	No. of Patients	Percent
Blood and lymphatic system disorders	Anemia	1	0%
Endocrine disorders	Hyperparathyroidism	1	0%
	Toxic nodular goiter	1	0%
Gastrointestinal disorders	Nausea	1	0%
General disorders and administration site conditions	Device extrusion	1	0%
	Device failure	1	0%
Hepatobiliary disorders	Cholelithiasis	1	0%

System Organ Class	Overall GCTB Program N = 304		
	Preferred Term	No. of Patients	Percent
Infections and infestations	Appendicitis	1	0%
	Device related infection	1	0%
	Gastroenteritis	1	0%
	Lobar pneumonia	1	0%
	Lower respiratory tract infection	1	0%
	Osteomyelitis	2	1%
	Pneumonia	1	0%
	Urinary tract infection	1	0%
Injury, poisoning and procedural complications	Ankle fracture	1	0%
	Endotracheal intubation complication	1	0%
	Gun shot wound	1	0%
	Open wound	1	0%
	Patella fracture	1	0%
	Spinal compression fracture	1	0%
	Tibia fracture	1	0%
	Vena cava injury	1	0%
	Wound	1	0%
	Wound dehiscence	1	0%
Musculoskeletal and connective tissue disorders	Arthralgia	1	0%
	Back pain	1	0%
	Musculoskeletal pain	1	0%
	Osteonecrosis	1	0%
	Osteonecrosis of jaw	2	1%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bone giant cell tumor	1	0%
	Ganglioneuroma	1	0%
	Neoplasm malignant	1	0%
	Spindle cell sarcoma	1	0%
	Tumor pain	1	0%
Nervous system disorders	Central nervous system lesion	1	0%
	Intracranial hypotension	1	0%
	Nerve compression	1	0%
	Peripheral sensory neuropathy	1	0%
	Presyncope	1	0%
Psychiatric disorders	Depression	1	0%
Renal and urinary disorders	Hydronephrosis	1	0%
	Nephrolithiasis	1	0%

System Organ Class	Overall GCTB Program N = 304		
	Preferred Term	No. of Patients	Percent
Respiratory, thoracic and mediastinal disorders	Dyspnea	1	0%
	Respiratory failure	1	0%

Two serious adverse events led to patient death: Neoplasm malignant (Patient [redacted] (b) (6) and Respiratory failure (Patient [redacted] (b) (6)). These cases, which appear to be related to underlying GCTB, are summarized in Section 7.3.1, Table 32and Table 33.

As summarized in Table 35, the per-patient incidence of serious adverse events was highest in the *infections and infestations and injury, poisoning and procedural complications*, *musculoskeletal and connective tissue disorders*, *neoplasms benign, malignant and unspecified (incl cysts and polyps)*, and *nervous systems disorders* MedDRA Systems Organs Classes (SOC).

Table 35: Per-patient incidence of serious adverse events by MedDRA system organ class (SOC)

System Organ Class	Overall GCTB Program N = 304	
	No. of Patients	Percent
Infections and infestations	9	3%
Injury, poisoning and procedural complications	9	3%
Musculoskeletal and connective tissue disorders	6	2%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	2%
Nervous system disorders	5	2%
Endocrine disorders	2	1%
General disorders and administration site conditions	2	1%
Renal and urinary disorders	2	1%
Respiratory, thoracic and mediastinal disorders	2	1%
Blood and lymphatic system disorders	1	0%
Gastrointestinal disorders	1	0%
Hepatobiliary disorders	1	0%

System Organ Class	Overall GCTB Program N = 304	
	No. of Patients	Percent
Psychiatric disorders	1	0%

Review of the case narratives and case report forms did not uncover a pattern implicating denosumab as a causal agent in the development of the serious adverse events that occurred within the following SOCs:

- Injury, poisoning, and procedural complications
- Nervous systems disorders
- Endocrine disorders
- General disorders and administration site conditions
- Renal and urinary disorders
- Respiratory thoracic and mediastinal disorders
- Blood and lymphatic system disorders
- Gastrointestinal disorders
- Hepatobiliary disorders
- Psychiatric disorders.

The serious adverse events within *the Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)* SOC included GCTB progression in 2 patients, increased tumor pain from underlying GCTB in one patient, a benign ganglioneuroma in one patient, and malignant transformation to spindle cell carcinoma in another patient. (Patient number [redacted] (b) (6); this patient is subsequently discussed in Section 7.3.5, Submission Specific Primary Safety Concerns, of this review).

A single patient (Patient [redacted] (b) (6)) developed a serious adverse event within the *Blood and Lymphatic System Disorders* SOC. This patient developed Grade 3 anemia requiring transfusion secondary to intratumoral bleeding. This adverse event occurred in the context of disease progression approximately 85 days after initiation of denosumab therapy. This patient withdrew from the trial and subsequently died due to disease progression.

Within the *Infections and Infestations* SOC, Patient [redacted] (b) (6) developed a fistula at the buccal gum level and subsequently developed Grade 3 osteomyelitis/mandibular abscess on Study Day 405 following tooth extraction that required surgical debridement of the mandible and a biopsy. Denosumab was temporarily interrupted and then restarted in this subject. *(Reviewer note: it is unclear why this was not considered to be*

osteonecrosis of the jaw). Patient [redacted] (b) (6) developed Grade 3 osteomyelitis of the jaw on Day 436 of study therapy; this adverse event was later positively adjudicated as osteonecrosis of the jaw (ONJ). This patient, who is described as having several risk factors for ONJ including poor dental hygiene with most teeth missing, required several surgical procedures including open dissection of the sinuses, open reconstruction of the alveolar rest, extraction of multiple teeth, and oral-antral fistula closure. Denosumab was interrupted for 103 days and the adverse event remained ongoing at the time of the 120-day safety up date.

A total of 6 patients experienced serious adverse events within the M*usculoskeletal and Connective Tissue Disorders* SOC. The preferred terms included *arthralgia*, *musculoskeletal pain*, *back pain*, *osteonecrosis*, and *osteonecrosis of the jaw* (2 patients). Based upon review of the case report forms and narratives, the isolated serious adverse events either appeared to be primarily related to underlying GCTB (*arthralgia, musculoskeletal pain*) or were transient despite continuation of denosumab (*back pain*). Patient [redacted] (b) (6) experienced avascular necrosis of the femoral head (preferred term: *osteonecrosis*) approximately three months following initiation of denosumab for GCTB involving the right sacral area. Denosumab was temporarily interrupted and then restarted approximately one month later. This patient received concomitant dexamethasone, which may have contributed to the adverse event. Patients [redacted] (b) (6) experienced osteonecrosis of the jaw, which was positively adjudicated by Amgen. Both patients had risk factors for the development of osteonecrosis of the jaw (such as smoking, gingivitis or dental caries, tooth and extraction).

Analysis of Serious Adverse Events by MedDRA High Level Term (HLT)

Table 36 provides a summary of the per-patient incidence of serious adverse events grouped by MedDRA high level term (HLT)

Table 36: Per-patient incidence of serious adverse events by HLT (per-patient Incidence of ≥ 1%):

HLT	Overall GCTB Program N = 304		Reviewer Comment
	No. of Patients	Percent	
Bone disorders NEC	3	1%	Includes preferred terms *avascular necrosis of femoral head*, *osteonecrosis of the jaw* (discussed in the analysis of SAEs by SOC, above)

HLT	Overall GCTB Program N = 304		Reviewer Comment
	No. of Patients	Percent	
Lower limb fractures and dislocations	3	1%	See discussion in Table 37, below.
Lower respiratory tract and lung infections	3	1%	Includes preferred terms *lobar lower respiratory tract infection, and pneumonia.* All patients had GCTB metastatic to lungs. One patient developed pneumonia two weeks following thoracotomy with resection of three nodules. Study drug was continued in all cases.
Non-site specific injuries NEC	3	1%	Includes preferred terms *gun shot wound*, *open wound* (due to extrusion of a surgical screw from a prior surgery) and *wound (this patient,* (b) (6) *later developed osteonecrosis of the jaw).*
Abdominal and gastrointestinal infections	2	1%	Includes preferred terms *appendicitis* and *gastroenteritis*
Bone and joint infections	2	1%	Includes preferred term *osteomyelitis*
Device issues NEC	2	1%	Includes preferred terms *device extrusion* and *device failure*
Musculoskeletal and connective tissue pain and discomfort	2	1%	Includes preferred terms *back pain and musculoskeletal pain.*
Neurological signs and symptoms NEC	2	1%	Includes preferred terms *intracranial hypotension* (this patient developed cerebrospinal fluid leakage two months status post decompression laminectomy for spinal GCTB) and *presyncope.*

Three patients experienced adverse events within the *Lower limb fractures and dislocations* HLT (Table 37). Based upon review of the case narratives, it appears that two fractures were related to trauma, and one was related to giant cell tumor of bone.

Reference ID: 3311616

Table 37: Adverse events occurring within the *Lower Limb Fractures and Dislocations* HLT

Patient ID	Patient Age (years)	Preferred Term	GCTB location	Reviewer Comment
(b) (6)	20	Tibia fracture	Left proximal tibia	Hairline fracture left tibia six weeks following initiation of study treatment. Patient continued study treatment.
	63	Patella fracture	Sacrum	Prior history of amputation below the right knee. Patient fell while putting on prosthetic device
	59	Ankle fracture	Spine	Case report form indicates that fracture was caused by trauma

7.3.3 Dropouts and/or Discontinuations

A total of 17 of 304 (5.6%) patients experienced an adverse event leading to treatment discontinuation or trial withdrawal (Table 38).

Table 38: Per-patient incidence of adverse events leading to treatment discontinuation or trial withdrawal.

Preferred term	Total	%	Toxicity Grade	Reviewer Comment
Metastases to lung[a]	2	1%	3	These cases appear to represent disease progression
Osteonecrosis of jaw	2	1%	2	
Anemia	1	0%	3	Caused trial withdrawal but not treatment discontinuation
Arthralgia	1	0%	2	
Bone neoplasm	1	0%	1	This represented GCTB progression of the right sacral bone
Neoplasm progression	1	0%	1	
Pain in extremity	1	0%	3	This adverse event was temporally related to disease progression of

Preferred term	Total	%	Toxicity Grade	Reviewer Comment
				GCTB in the sacrum
Pathological fracture	1	0%	3	This represented disease progression
Post procedural infection	1	0%	3	
Respiratory failure	1	0%	4	This adverse event was related to disease progression of metastatic disease in the lung that was present at baseline.
Sarcoma	1	0%	4	
Spindle cell sarcoma	1	0%	4	
Tooth abscess	1	0%	1	
Tooth infection	1	0%	3	
Tumor hemorrhage	1	0%	2	

[a] Datasets indicate that one patient withdrew from the trial without discontinuing study therapy, but the CRF indicated that this patient discontinued study therapy.

7.3.4 Significant Adverse Events

7.3.5 Submission Specific Primary Safety Concerns

The application contained focused analyses of the following adverse events, which are either currently included in denosumab labeling, or are of special interest in the GCTB patient population: hypocalcemia, osteonecrosis of the jaw, hypersensitivity reactions, infections, malignancy, cardiac disorders, and vascular disorders.

<u>Hypocalcemia</u>

Hypocalcemia is a known risk associated with denosumab treatment and is currently described in Section 5 of approved Xgeva labeling. Prophylactic treatment with supplemental calcium and Vitamin D was recommended, but not required, in patients enrolled in Trial 20040215 and Trial 20062004. No adverse events of hypocalcemia were reported for Trial 20040215, and hypocalcemia was reported as an adverse event in 15 subjects (5%) enrolled in Trial 20062004. None of the adverse events of hypocalcemia was considered serious, and one adverse event was severe (patient [redacted] (b) (6). One patient [redacted] (b) (6) reported symptoms associated with hypocalcemia (concurrent muscle spasms). Most patients reported a single event and no patient discontinued denosumab due to hypocalcemia. Based upon laboratory analyses across both studies, mild to moderate hypocalcemia (corrected serum calcium

less than 7 mg/dL or less than 1.75 mmol/L) occurred in 2.6% of patients treated with Xgeva. CTCAE Grade 3 or 4 hypocalcemia was not observed.

Reviewer note: The incidence of hypocalcemia as an adverse event and hypocalcemia as a laboratory abnormality was lower in the GCTB population, compared to the incidence observed in patients with metastatic solid tumors enrolled in registration studies supporting approval of Xgeva for the prevention of skeletal-related events. In the 120-day safety update, no cases of hypocalcemia of Grade 3 or greater severity were reported, and no patient discontinued study therapy due to hypocalcemia.

Osteonecrosis of the Jaw

The 120-day safety update reported three additional positively adjudicated cases of osteonecrosis of the jaw in patients enrolled across the two GCTB studies. Thus, the cumulative incidence of osteonecrosis of the jaw in patients with GCTB through August 31, 2012 is 1.5% (or 7 of 472 patients). The cases of osteonecrosis of the jaw occurred following exposure to denosumab ranging from 13 to 33 months. Surgical treatment was required in 5 of the 7 subjects, and all but two of the cases are unresolved.

Reviewer note: The incidence of osteonecrosis of the jaw was 1.8% in patients receiving Xgeva and 1.3% in the zoledronic acid group during the primary treatment phases of the three trials supporting the initial approval of Xgeva for the prevention of skeletal related events in patients with bone metastases from solid tumors. The median exposure to Xgeva was 12.0 months in these studies. Thus, the incidence of ONJ in patients with GCTB receiving Xgeva appears to be comparable to slightly lower than the incidence in patients with metastatic solid tumors.

A labeling supplement is currently under review by the Division of Oncology Products 1 to include additional information regarding the incidence of osteonecrosis of the jaw in patients receiving Xgeva for patients with metastatic solid tumors for the prevention of skeletal related events. The supplement includes an additional sentence describing increased incidence of ONJ in this patient population with increased duration of exposure. Therefore, patients and physicians should consider the increased risk of ONJ with longer duration of exposure to Xgeva when making treatment decisions, particularly in cases where GCTB is resectable.

Malignancies

Table 39 provides a summary of adverse events of sarcoma or malignant transformation of GCTB.

Reference ID: 3311616

Table 39: Summary of adverse events of bone malignancies and events of disease progression

Patient	Lesion location	Duration of treatment	Description
(b) (6) 44 year old female	Lung	124 Days	First Dose (b) (6) Last Dose (b) (6) This patient was diagnosed with GCTB proximal tibia in (b) (6) with lung metastasis. This patient underwent resection of GCTB at the proximal tibia with positive margins. Spindle cell sarcoma reported (b) (6), resulting in discontinuation of study therapy. Investigator considered this event to be malignant transformation of the tumor (considered unrelated by investigator).
(b) (6) 24 year old female	Humerus	95 days	First dose (b) (6) Last dose: (b) (6) Enrolled with primary unresectable GCTB. Discontinued trial on 4 (b) (6) due to pathological fracture. Resection of right humerus (b) (6) pathology showed high-grade osteosarcoma with possible residual GCTB.
(b) (6) 33 year old male	Femur	38 days	First dose (b) (6) Last dose (b) (6) Enrolled with primary unresectable GCTB. Two months after discontinuation of study drug, resection curettage showed malignant component of original tumor. Approximately 6 months later, needle biopsy showed high grade sarcoma without giant cells, diagnosed as secondary sarcoma (reported as SAE of secondary malignancy on (b) (6) 287 days after the last dose of denosumab)
(b) (6) 40 year old female	Tibia	29 days	First dose (b) (6) Last dose: (b) (6) Neoplasm progression reported on Study Day 57. Patient had recurrent resectable (limb amputation planned) GCTB of right tibia. High grade osteosarcoma was reported in the lesion (patient had prior XRT).

Patient	Lesion location	Duration of treatment	Description
(b) (6) 21 year old female	Pelvis	257 days	Patient enrolled with primary GCTB of the pelvis. First dose: (b) (6) Last dose: (b) (6) Discontinued trial due to disease progression on (b) (6) Excision of lesion on (b) (4) revealed sarcoma. Investigator stated that it is likely that the subject was misdiagnosed as GCTB originally, but there is no histologic evidence to support this.
(b) (6) 46 year old female	Pelvis	86 Days	First dose (b) (6) Last dose (b) (6) Discontinued trial on (b) (6) due to disease progression. Biopsy on (b) (6) revealed spindle cell tumor of the right pubic region (patient had metastatic osteosarcoma of the lung at baseline).
(b) (6) 44 year old female	Sacrum	120 days	First dose: (b) (6) Last dose: (b) (6) Biopsy performed prior to initiation of denosumab documented giant cells intermixed with sheets of cells with atypical features (cytologic atypia and brisk mitotic activity, including atypical mitoses at baseline). Pleomorphic Sarcoma reported on (b) (6), resulting in discontinuation of denosumab. Investigator considered this to be a new malignancy, likely present at baseline. Disease progressed and resulted in death (b) (6)
(b) (6) 42 year old male	Femur	533 days	Ended the trial on (b) (6) due to disease progression. Patient was diagnosed with fibroblastic osteosarcoma at baseline (on (b) (6) and had undergone multiple chemotherapy regimens from (b) (6) to (b) (6).

Patient	Lesion location	Duration of treatment	Description
(b) (6) 30 year old male	Humerus	30 days	This patient appears to have been misdiagnosed initially. Discontinued from the trial due to "administrative decision." Local hospital pathology diagnosed GCTB, but repeat assessment by investigator pathology lab diagnosed malignant fibrous histiocytoma.

A total of 7 patients (shaded in light grey, above) appear to have developed malignant transformation or a new sarcoma. In one case (Patient (b) (6), the patient had received prior radiotherapy, which is a known risk factor for malignant transformation. Two cases (Patients (b) (6)) appear to be confounded by prior malignancy or evidence of potentially aggressive giant cell tumor of bone.

Two cases do not appear to represent development of malignant transformation or a new sarcoma following receipt of denosumab. One patient appears to have been misdiagnosed originally (Patient (b) (6), and another patient discontinued due to disease progression but had a baseline history of fibroblastic osteosarcoma (Patient (b) (6).

A single patient ((b) (6) developed a non-sarcoma malignancy, thyroid papillary microcarcinoma, on Study Day 148.

If the four cases of malignant transformation or new sarcoma that occurred in patients with a prior diagnosis of sarcoma or evidence of atypical GCTB prior to initiation of denosumab are eliminated (Patient (b) (6), Patient (b) (6), Patient (b) (6), and Patient (b) (6) a total of five of 304 (1.6%) denosumab-treated patients (Patients (b) (6)) developed either malignant transformation or a new sarcoma.. The median duration of exposure for these patients is 95 days (range: 29 to 257).

Six of 438 (1.4%) of patients who were treated with denosumab during the reporting period for the 120-day safety update (March 26, 2011 through August 31, 2012) reported events consistent with new sarcoma or malignant transformation of GCTB.

- Patient (b) (6) was diagnosed with high grade sarcoma approximately 9 months after starting denosumab for recurrent unresectable GCTB (denosumab exposure 258 days); the patient ultimately died due to progressive high-grade sarcoma.

- Patient [redacted] (b) (6) died due to transformation into high-grade sarcoma (metastatic germ cell tumor) approximately 23 months after starting denosumab for recurrent unresectable GCTB of the pelvis (denosumab exposure: 620 days).

- Patient [redacted] (b) (6) was diagnosed with a high-grade sarcoma approximately 4 months after the first dose of denosumab, and it is unclear whether this represents a misdiagnosis of the original lesion or malignant transformation (denosumab exposure: 85 days).

- A histopathology specimen obtained approximately eight months after starting denosumab was consistent with malignant transformation of GCTB in the following patients:

  - Patient [redacted] (b) (6) (exposure 239 days)

  - Patient [redacted] (b) (6) (exposure 449 days)

  - Patient [redacted] (b) (6) (exposure 169 days for recurrent resectable GCTB of the femur; patient had prior radiation therapy). This patient ultimately died due to lung metastases.

Taking into account the five cases of malignant transformation in patients without prior evidence of malignancy or malignant features of GCTB at baseline that were reported in the integrated analysis of safety for Studies 20062004 and 20040215, the cumulative incidence of malignant transformation or new sarcoma among denosumab-treated patients through August 31, 2012 (N=472), is 2.3%. The incidence of new sarcoma or malignant transformation of GCTB is not well characterized, and ranges from 1 to 5% across published GCTB studies [5,6,7,8]. Some sources indicate that the incidence of malignant transformation is more common in patients with recurrent giant cell tumors[8,10]. Because these adverse events occurred in trials that lack a comparator arm, it is difficult to determine whether denosumab exposure played a role in the development of malignant tumors in these patients. However, in light of the fact that some of the cases occurred in patients that had known or potential risk factors for malignant transformation of GCTB (such as recurrent GCTB or prior radiation therapy) or occurred after relatively short exposure (< 100 days) to denosumab (e.g. patients [redacted] (b) (6), [redacted] (b) (6)), the observed incidence of malignant transformation or development of new sarcoma does not appear to be unusually high. However, the information that will be obtained from the studies outlined in the postmarketing requirements recommended by the clinical review team will assist in elucidating whether the incidence of malignant transformation in patients treated with denosumab is substantially higher than the expected background rate for this patient population (see Section 1.4 for details regarding proposed postmarketing requirements).

Hypersensitivity Reactions

The incidence of adverse events potentially related to hypersensitivity was 10% overall across Trial 20040215 and 20062004. The most common adverse events associated with potential hypersensitivity were rash, facial edema, and eczema. One adverse event (localized edema) was of Grade 3 severity, but did not result in discontinuation of denosumab. No cases of anaphylaxis were reported. In the 120-day safety update, the incidence of adverse events associated with hypersensitivity was similar (8.4% in Trial 20062004). A serious adverse event of dermatitis psoriasiform was reported, but the event resolved despite continuation of denosumab.

Reviewer note: A Changes Being Effected (CBE) labeling supplement submitted by Amgen is currently under review by the Division of Oncology Products 1 to include the risk of hypersensitivity (including anaphylaxis) in the postmarketing adverse reactions section and add clinically significant hypersensitivity to any component of denosumab as a contraindication to denosumab. In this supplement, the Applicant described two cases of anaphylactic reaction temporally related to the first dose of Xgeva in patients with metastatic solid tumors. In both cases, there was a positive rechallenge and subsequent discontinuation of Xgeva.

Infections

The per-patient incidence of adverse events in the MedDRA infections and infestations system organ class was 35.9% overall. The most common (≥ 3%) infections reported were nasopharyngitis, upper respiratory infection, urinary tract infection, influenza, and gastroenteritis. The majority of infections were mild to moderate in severity (Table 40). The only serious adverse event of infection reported by more than one subject was osteomyelitis, which was reported in two subjects (Table 34); one case was positively adjudicated as osteonecrosis of the jaw.

Table 40: Common or Severe adverse events under the Infections and Infestations SOC (PPI of ≥ 3% All Grades and all ≥ Grade 3 severity)

Preferred Term N = 304	All Grades		Grade 3 and above	
	n	%	n	%
Nasopharyngitis	24	8%	0	0%
Upper respiratory tract infection	23	8%	0	0%
Urinary tract infection	11	4%	1	0%
Influenza	9	3%	0	0%
Gastroenteritis	8	3%	0	0%
Sinusitis	7	2%	0	0%

Preferred Term N = 304	All Grades		Grade 3 and above	
	n	%	n	%
Cystitis	6	2%	0	0%
Bronchitis	5	2%	0	0%
Tooth abscess	5	2%	0	0%
Tooth infection	4	1%	1	0%
Lower respiratory tract infection	3	1%	1	0%
Cellulitis	2	1%	1	0%
Osteomyelitis	2	1%	2	1%
Appendicitis	1	0%	1	0%
Device related infection	1	0%	1	0%
Lobar pneumonia	1	0%	1	0%
Post procedural infection	1	0%	1	0%
Postoperative wound infection	1	0%	1	0%

In the 120-day safety update, the incidence of adverse events of infection was similar.

Cardiovascular Events

Adverse events in the Cardiac Disorders MedDRA system organ class occurred in a total of 12 subjects (4%) enrolled in the GCTB studies. Cardiac adverse events occurring in two or more subjects included palpitations (2%), tachycardia (1%), angina pectoris (1%), and sinus tachycardia (1%). All cardiac adverse events were of Grade 2 or lesser severity, and none were considered serious. The 120-day safety reported two patients who experienced cardiac adverse events that were considered serious. One patient experienced supraventricular tachycardia and another developed coronary artery disease; denosumab was not discontinued following these adverse events.

Adverse events in the Vascular Disorders MedDRA system organ class occurred in 18 subjects (6%) enrolled in the GCTB studies. The adverse events included hot flush (4%), hypertension (1%), flushing (< 1%), and lymphedema (< 1%). All adverse vascular adverse events were mild to moderate in severity and none were serious. The 120-day safety update included one serious adverse event in this SOC (superficial thrombophlebitis); denosumab was continued and the adverse event resolved.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Trial 20040215

Table 43 shows adverse events that occurred in at least 10% of patients during the treatment phase of Trial 20040215. A total of 33 of 37 (89%) patients experienced a

treatment emergent adverse event. By preferred term, the most common (≥ 20%) treatment emergent adverse events were arthralgia, back pain, and extremity pain. Adverse events of grade 3 or greater severity did not occur in more than a single patient for any preferred term.

Table 41:Common adverse events occurring during the treatment phase of Trial 20040215

Preferred Term N = 37	All Grades		≥ Grade 3	
	n	%	n	%
Arthralgia	11	30%	0	0%
Back pain	11	30%	1	3%
Pain in extremity	9	24%	1	3%
Nausea	7	19%	1	3%
Constipation	6	16%	0	0%
Cough	6	16%	0	0%
Fatigue	6	16%	0	0%
Headache	6	16%	0	0%
Musculoskeletal pain	5	14%	1	3%
Dyspnea	4	11%	0	0%
Muscle spasms	4	11%	0	0%
Muscular weakness	4	11%	0	0%
Nasopharyngitis	4	11%	0	0%
Non-cardiac chest pain	4	11%	0	0%
Upper respiratory tract infection	4	11%	0	0%

An adverse event occurred in 12 of 21 (57%) patients following entry into the safety follow-up phase of the trial, which began after the end of study visit (30 days after the last dose of denosumab). Muscular weakness, anemia, arthralgia and nausea were the only adverse events that occurred in more than one subject (Table 42).

Table 42: Adverse events occurring in two or more patients during the safety follow-up phase of Trial 20040215

Preferred Term N = 38	All Grades		≥ Grade 3	
	n	%	n	%
Muscular weakness	3	14%	1	5%
Anemia	2	10%	2	10%
Arthralgia	2	10%	0	0%
Nausea	2	10%	1	5%

Trial 20062004

Table 43 lists adverse events that occurred in at least 5% of patients during the treatment phase of Trial 20062004. A total of 236 of 281 treated patients experienced a treatment emergent adverse event. By preferred term, the most common (≥ 15%) treatment emergent adverse events were arthralgia, headache, nausea, back pain, and pain in extremity. Adverse events of Grade 3 or greater severity occurring in more than two patients included hypophosphatemia (9 patients), anemia, back pain, and pain in the extremity (3 patients each).

Table 43: Common adverse events occurring during the treatment phase of Trial 20062004

Preferred Term N = 281	All Grades		≥ Grade 3	
	n	%	n	%
Arthralgia	55	20%	2	1%
Headache	51	18%	2	1%
Nausea	48	17%	0	0%
Fatigue	45	16%	0	0%
Back pain	42	15%	3	1%
Pain in extremity	41	15%	3	1%
Vomiting	25	9%	0	0%
Edema peripheral	24	9%	0	0%
Musculoskeletal pain	21	7%	2	1%
Nasopharyngitis	20	7%	0	0%
Diarrhea	19	7%	0	0%
Upper respiratory tract	19	7%	0	0%

Preferred Term N = 281	All Grades		≥ Grade 3	
	n	%	n	%
infection				
Weight increased	18	6%	2	1%
Hypophosphatemia	17	6%	9	3%
Toothache	17	6%	0	0%
Constipation	16	6%	0	0%
Myalgia	16	6%	0	0%
Bone pain	15	5%	1	0%
Insomnia	15	5%	0	0%
Abdominal pain	14	5%	0	0%
Paresthesia	14	5%	0	0%
Cough	14	5%	0	0%

A total of 8 of 38 (21%) subjects reported adverse events during the follow-up phase of the trial, which began after the end of study visit (30 days after the last dose of denosumab). Abdominal pain was the only adverse event that occurred in more than one subject (Table 44).

Table 44: Adverse events occurring during the safety follow-up phase of Trial 20062004

Preferred Term N = 38	All Grades		≥ Grade 3	
	n	%	n	%
Abdominal pain	2	5%	0	0%
Asthenia	1	3%	1	3%
Bone giant cell tumor	1	3%	1	3%
Bone sarcoma	1	3%	1	3%
Decreased appetite	1	3%	1	3%
Diarrhea	1	3%	1	3%
Febrile neutropenia	1	3%	1	3%
Metastases to lung	1	3%	1	3%
Mucosal inflammation	1	3%	1	3%
Toxicity to various agents	1	3%	1	3%
Constipation	1	3%	0	0%
Facial pain	1	3%	0	0%
Gastritis	1	3%	0	0%
Nausea	1	3%	0	0%
Pain in extremity	1	3%	0	0%
Pain in jaw	1	3%	0	0%

Preferred Term N = 38	All Grades		≥ Grade 3	
	n	%	n	%
Procedural pain	1	3%	0	0%
Productive cough	1	3%	0	0%
Pruritus	1	3%	0	0%
Rash pustular	1	3%	0	0%
Weight decreased	1	3%	0	0%
Weight increased	1	3%	0	0%

Common Adverse Events Overall GCTB Program

A total of 259 of 304 patients treated in Trials 20040215 and 20062004 combined experienced at least one adverse event. The most frequently occurring (per-patient incidence ≥ 15%) adverse events across both trials were arthralgia, headache, nausea, back pain, fatigue, and pain in the extremity (Table 45). The incidence of adverse events appeared similar across both trials, with any differences in incidence likely to be attributed to the small number of patients enrolled in Trial 20040215.

A total of 59 of 304 (19%) patients experienced at least one severe (≥ Grade 3) adverse event. The preferred term with the highest incidence of severe adverse events was hypophosphatemia (per-patient incidence of 3%).

Table 45: Adverse events with PPI of ≥ 5% All Grades or ≥ 1% Grade 3 and above

Preferred Term N = 304	All Grades		Grade 3 and above	
	n	%	n	%
Arthralgia	64	21.1	2	0.7
Headache	56	18.4	2	0.7
Nausea	54	17.8	1	0.3
Back pain	53	17.4	4	1.3
Fatigue	51	16.8	0	0.0
Pain in extremity	49	16.1	4	1.3
Vomiting	28	9.2	0	0.0
Musculoskeletal pain	26	8.6	3	1.0
Nasopharyngitis	24	7.9	0	0.0
Edema peripheral	24	7.9	0	0.0
Upper respiratory tract infection	23	7.6	0	0.0
Constipation	22	7.2	0	0.0
Diarrhea	21	6.9	0	0.0

Preferred Term N = 304	All Grades		Grade 3 and above	
	n	%	n	%
Cough	20	6.6	0	0.0
Weight increased	19	6.3	2	0.7
Hypophosphatemia	17	5.6	9	3.0
Muscle spasms	17	5.6	0	0.0
Toothache	17	5.6	0	0.0
Abdominal pain	16	5.3	0	0.0
Bone pain	16	5.3	1	0.3
Insomnia	16	5.3	0	0.0
Myalgia	16	5.3	0	0.0
Non-cardiac chest pain	16	5.3	0	0.0
Paresthesia	16	5.3	0	0.0
Depression	14	4.6	3	1.0
Anemia	12	3.9	3	1.0

7.4.2 Laboratory Findings

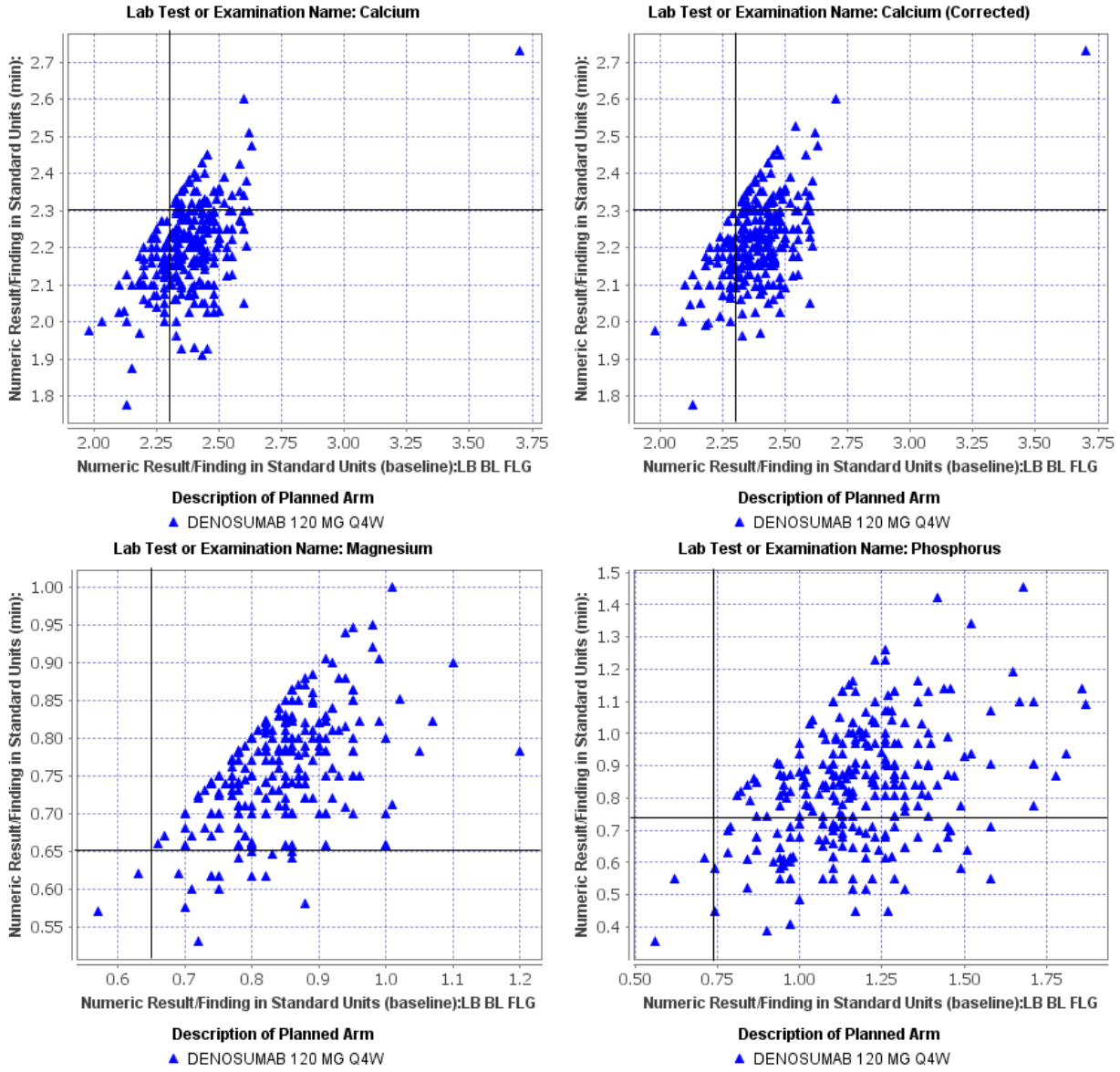
In Trial 20040215, comprehensive assessment of hematologic and chemistry parameters was performed at baseline, every four weeks during study therapy, and at the end of study visit. Analysis of laboratory data obtained during the course of Trial 20040215 did not uncover any clinically relevant hematologic safety signals. No Hy's Law cases occurred. Aside from decreases in serum calcium and serum phosphorus, no changes in serum chemistry parameters suggestive of a treatment-related effect were reported.

In Trial 20062004, laboratory assessments were performed at baseline, on Day 1 and Day 15 of Cycle 1, Day 29, every four-weeks thereafter during study therapy, and at the end of study visit. The only laboratory parameters that were systematically assessed during this trial were serum creatinine, calcium, albumin, and phosphorus.

Figure 7 depicts the baseline levels of serum calcium, magnesium, and phosphorus versus the minimum levels of these parameters observed during denosumab treatment for patients enrolled in Trial 20062004.

Reference ID: 3311616

Figure 7: Scatter plots of baseline versus minimum electrolyte levels during denosumab therapy in Trial 20062004



Consistent with current Xgeva labeling, hypocalcemia and hypophosphatemia were the primary laboratory-related adverse effects related to denosumab therapy in patients enrolled in Trials 20040215 and 20062004. NCI CTCAE Grade 2 hypocalcemia (corrected serum calcium less than 8 to 7 mg/dL or less than 2 to 1.75 mmol/L) occurred in 2.6% of patients treated with Xgeva. NCI CTCAE Grade 3 hypophosphatemia (serum phosphorus less than 2 to 1 mg/dL or less than 0.6 to 0.3 mmol/L) occurred in 29 patients (9.5%).

7.4.3 Vital Signs

No clinically relevant changes in weight, pulse, blood pressure, or body temperature were observed in patients treated with denosumab in Trial 20040215.

Trial 20062004 did not collect vital signs after the screening visit. *Reviewer note: Given the large existing safety database, this is acceptable.*

7.4.4 Electrocardiograms (ECGs).

Electrocardiograms were not routinely performed during Trials 20040215 and 20062004.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

In Trial 20040215, testing for anti-denosumab antibodies was performed from serum samples obtained at baseline, Week 25, Week 49, and at the end of study. Samples were also collected at each safety follow up visit and at the end of the safety follow-up visit. In Trial 20062004, anti-denosumab antibody testing was performed on serum collected at baseline, at the end of study therapy, and approximately 6 and 12 months after the end of study visit. For patients enrolled in Cohort 3, serum samples for anti-denosumab antibody testing were collected approximately every six months for up to 24 months after the end of the study visit for Trial 20040215. Anti-denosumab antibodies were not detected in any patient enrolled in Trials 20040215 or 20062004, through the third interim analysis.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Trial 20040215 and Trial 20062004 employed a fixed dose of denosumab. The sBLA did not contain formal analyses evaluating the relationship between pharmacokinetic parameters and the risk of adverse events.

7.5.2 Time Dependency for Adverse Events

With the exception of osteonecrosis of the jaw (ONJ), there did not to appear to be a relationship between the risk of development of serious adverse events and duration of denosumab exposure. As described in the 120-day safety update, a total of 7 cases of positively adjudicated osteonecrosis of the jaw have been observed in the GCTB

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program to date (per-patient incidence of 1.5%). The duration of treatment was over 12 months prior to onset of ONJ in all cases.

Reviewer note: A labeling supplement is currently under review by the Division of Oncology Products 1 to include additional information regarding the incidence of osteonecrosis of the jaw in patients receiving Xgeva for patients with metastatic solid tumors for the prevention of skeletal related events. The supplement includes an additional sentence describing increased incidence of ONJ in this patient population with increased duration of exposure. Therefore, patients and physicians should consider the increased risk of ONJ with longer duration of exposure to Xgeva when making treatment decisions, particularly in cases where GCTB is resectable.

The risk of hypophosphatemia appeared to be greatest during the first few months of denosumab treatment. Hypophosphatemia occurred within the first two months of initiation of denosumab treatment in 12 of 17 (71%) patients who experienced an adverse event of hypophosphatemia.

7.5.3 Drug-Demographic Interactions

No consistent trends were evident that conveyed an increase risk of adverse events in any particular patient subgroup. However, there were only 10 adolescents and 10 patients ≥ 65 years of age enrolled in the GCTB studies, so the ability to analyze interactions between variations in age and risk of adverse events is limited. Of the patients who received denosumab in the trials supporting the original approval of Xgeva, 1260 (44%) were 65 years of age and older. No overall differences in safety or efficacy were observed between these patients and younger patients.

The overall incidence and pattern of adverse events were similar between men and women. Analyses by race were limited by the small number of patients in non-White subgroups.

7.5.4 Drug-Disease Interactions

There was no new information regarding drug-disease interactions in this supplement. Current Xgeva labeling includes a description of a trial of 55 patients without cancer and with varying degrees of renal function who received a single dose of 60 mg of denosumab. Among these patients, there was a greater risk of severe hypocalcemia in patients with a creatinine clearance of less than 30 mL/min and in patients receiving dialysis compared to patients with normal renal function. The risk of hypocalcemia at the recommended dosage regimen has not been evaluated in patients with a creatinine clearance of less than 30 mL/min or in patients receiving dialysis.

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7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were submitted in this supplement.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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

7.6.2 Human Reproduction and Pregnancy Data

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

Current Xgeva labeling describes nonclinical studies of the effects of denosumab on prenatal development in cynomolgus monkeys and in knockout mice in which RANK ligand (RANKL) expression was turned off. In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy at a pharmacologically active dose, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia and tooth malalignment; and decreased neonatal growth. At birth out to one month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels). Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated. In RANKL knockout mice, absence of RANKL also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation

7.6.3 Pediatrics and Assessment of Effects on Growth

The *Pediatric Use* section of current Xgeva labeling includes a statement to describing the potential risk of impaired bone growth in children with open growth plates and

inhibition of eruption of dentition based upon findings in nonclinical studies. In neonatal rats, inhibition of RANKL with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 5 and 25 times (10 and 50 mg/kg dose) higher than the recommended human dose of 120 mg administered once every 4 weeks, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab.

All pediatric subjects enrolled in Trial 20052004 were skeletally mature and the proposed patient population for approval excludes pediatric patients who are not skeletally mature. Thus, there are no anticipated safety issues related to potential effects of denosumab on pediatric growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no experience with overdosage of denosumab. Based upon its mechanism of action, side effect profile, and approved indications, it is unlikely that denosumab will be intentionally misused or abused.

This application did not include any new data regarding the risks of withdrawal or rebound effects with the use of denosumab.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120-day safety update on March 8, 2013. The safety update provided data from 472 subjects who enrolled and received denosumab cumulatively through August 31, 2012. No additional data was submitted from Trial 20040215 because this trial was complete at the time of the sBLA submission.

The amendment consisted of materials previously agreed upon by FDA, including new and updated case narratives and CRFs. Also included were updated integrated analyses of adverse events of interest.

Overall, the results from the safety update were consistent with the findings presented in the sBLA.

<u>Denosumab Exposure During Pregnancy</u>

Xgeva is designated as Pregnancy Category D. Subsection 8.1 of the *Use in Specific Populations* section of labeling includes the following sentences

> *Women who become pregnant during Xgeva treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.*

As of November 26, 2012, a total of 18 pregnancies have been reported, including 4 paternal exposure cases. A total of 17 pregnancies occurred in clinical trials of denosumab, and one postmarketing case occurred outside of a clinical trial. Fifteen of the 17 (88%) pregnancies reported in a clinical trial involved patients enrolled in Trial 20040215 or Trial 20062004. In a May 13, 2013 submission to the sBLA, the Applicant reported the following outcomes from the 18 pregnancies:

- Four pregnancies resulted in healthy, full-term births without complications; 2 of these cases were from paternal exposure to denosumab
- Five pregnancies were electively terminated
- Spontaneous abortions occurred in two pregnancies
- The outcome of four pregnancies is unknown at this time
- Three pregnancies, including two paternal exposure cases, were lost to follow-up.

The applicant provided narratives describing the first 7 to 13 months of life of three infants born to mothers who became pregnant while receiving denosumab or who had potential paternal exposure to denosumab. According to these narratives, no unusual health issues have occurred, and the infants appear to be following a normal course of growth and development.

A safety report submitted to IND 113617 on April 5, 2013 described a termination of a hydatidiform mole that occurred in the partner of a male patient receiving denosumab for GTCTB.

Reviewer comment: There is insufficient information to make an assessment regarding whether denosumab exposure had a causal role in the development of the hydatidiform mole. It is unknown whether denosumab is present in the semen of male patients receiving denosumab. There is an outstanding PMR for Prolia requiring the applicant to conduct a clinical trial to investigate the levels of denosumab in the semen of men treated with Prolia. The final report for this study is due December 2014.

The Warnings and Precautions section of Xgeva labeling includes the risk of fetal harm if Xgeva is used during pregnancy but does not include a recommendation for use of contraception in females of reproductive potential. Because many patients with GCTB who are candidates for treatment with Xgeva will be of reproductive potential, incorporation of language instructing patients with GCTB to use highly effective contraception during Xgeva therapy is recommended.

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8 Postmarket Experience

The most recent periodic safety update report (PSUR) for Xgeva, which covered the reporting period from May 27, 2012 through November 26, 2012, was reviewed. As of November 26, 2012, denosumab is marketed under the trade name Xgeva in the United States, Europe, and in 18 other countries for the prevention of skeletal related events in patients with bone metastases from solid tumors. Xgeva is marketed in Switzerland for bone metastases from solid tumors, and denosumab is marketed under the trade name Ranmark in Japan for the treatment of multiple myeloma and bone metastases of solid tumors. The Applicant estimates that (b) (4) patient years of postmarketing exposure to Xgeva have occurred cumulatively through November 26, 2012.

During the most recent PSUR reporting period, the Applicant identified atypical femoral fracture and hypersensitivity reactions, including anaphylaxis, as new risks associated with Xgeva. Additionally, the Applicant identified a pattern of increased risk of osteonecrosis of the jaw with longer exposure to Xgeva. *Reviewer note: The Applicant submitted a CBE labeling supplement on December 20, 2012 to update the Xgeva label to communicate the risks of atypical subtrochanteric and diaphyseal fracture and hypersensitivity. The Applicant submitted a PAS supplement on March 5, 2013 to communicate the increased risk of ONJ with longer exposure to Xgeva. This labeling supplement is currently under review by the Division of Oncology Products 1.*

9 Appendices

9.1 Literature Review/References

1. "Giant Cell Tumor of Bone" at http://orthoinfo.aaos.org/topic.cfm?topic=a00080 accessed on May 15, 2013.
2. Gamberi G, Serra M, Ragazzini P, Magagnoli G, Pazzaglia L, Ponticelli F, Ferrari C, Zanasi M, Bertoni F, Picci P, Benassi M (2003). "Identification of markers of possible prognostic value in 57 giant-cell tumors of bone". *Oncol Rep* 10 (2): 351–6.
3. Zheng MH, Robbins,P, Xu J, Juang L, Wood DJ, Papadimitriou JM. The histogenesis of giant cell tumour of bone: a model of interaction between neoplastic cells and osteoclasts. *Histol Histopathol*. 2001;16:297-307.
4. Puri A, Agarwal MG, Shah M, Jambhekar NA, Anchan C, Behle SB. Giant cell tumor of bone in children and adolescents. *J Pediatr Orthop*. 2007;27:635-639.
5. Werner, M. (2006). Giant cell tumour of bone: morphological, biological and histogenetical aspects. Springer-Verlag , 30, 484-489
6. Thomas, D. M., & Skubitz, T. (2009). Giant-cell tumour of bone. Current Opinion in Oncology , 21, 338-344
7. Dickson, B. C., Li, S.-Q., Wunder, J. S., Ferguson, P. C., Eslami, B., Werier, J. A., et al. (2008). Giant-cell tumor of bone express p63. Modern Pathology , 21, 369-375
8. Szendröi M. Giant-cell tumour of bone [Review]. *J Bone Joint Surg* (British Volume). 2004;86B(1):5-12.
9. Szendröi M, Kiss J, Antal I. Surgical treatment and prognostic factors in giant cell tumor of bone. *Acta Chir Orthop Traumatol Cech*. 2003;70(3):142-50.
10. Malawer M, Helman L, and Brian O' Sullivan. In: Cancer: Principles & Practice of Oncology, 7th Edition. Sarcomas of the Soft Tissues and Bone - Chapter 35. Lippincott Williams & Wilkins. 2005.

9.2 Labeling Recommendations

Please refer to the FDA approved labeling for Xgeva.

At the time of completion of this review, labeling negotiations are ongoing. Proposed wording for the key clinical sections of the label that are impacted by this sBLA are listed below in italics. This wording is subject to change:

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

(b) (4)

9.3 Advisory Committee Meeting

The Division of Oncology Products 2 of the Office of Hematology and Oncology Products decided that advice from the Oncology Drugs Advisory Committee (ODAC) was not needed in order to render a regulatory decision for this sBLA. The clinical review team plans to seek opinions from two consultants (Special Government Employees) who have been cleared for conflict of interest by the Division of Advisory Committee and Consultant Management at the Center for Drug Evaluation and Research. At the time of completion of this review, teleconferences with these consultants are being scheduled.

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

/s/

MARTHA B DONOGHUE
05/20/2013

SUZANNE G DEMKO
05/20/2013
I have discussed the contents and conclusions of this review and am in full agreement with the decision to approve this supplement.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: sBLA 125320/94 **Applicant:** Amgen **Stamp Date: December 12, 2012**

Drug Name: Xgeva (denosumab) **NDA/BLA Type:** BLA supplement

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 sequence number 0255
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			
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?				This is a 505(b)1 application.
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: Study Title: Sample Size: Arms: Location in submission:		X		Dose ranging studies not performed, however, proposed dosage regimen targets achievement of >95% occupancy of RANKL at steady state over the dosing interval, as demonstrated in original BLA for Xgeva.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and	X			The single arm study

Reference ID: 3255768

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 Study 20040125 Indication: Giant cell tumor of bone (GCTB) Pivotal Study #2 Study 20062004 Indication: Giant cell tumor of bone				design and number of patients enrolled appears appropriate given the rarity of giant cell tumor of bone and lack of available therapy.
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		Could not find this in the submission. However, in Study 20062004, 98 (35%) of 282 patients were enrolled in the US. In Study 20040215, 21 (57%) of 37 patients were enrolled in the US. Based upon literature review, treatment approaches and patient characteristics appear similar in the US and foreign sites.
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			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Previously addressed in other applications
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
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			Given the existing safety database for Xgeva and Prolia and the rarity of Giant Cell Tumor of bone, it appears that an

[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.

	Content Parameter	Yes	No	NA	Comment
					adequate number of patients have been exposed at the proposed dosage.
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			Sponsor provided "MedDRA Term Selection: Points to Consider" document. Adverse event analyses for the summary of safety and clinical study report for Study 20062004 used MedDRA v. 14.1. Adverse event analyses in the clinical study report for Study 20040215 used MedDRA version 11.0.
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			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
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			Indication includes skeletally mature adolescents. This orphan indication is not covered by PREA. WR for pediatric studies has been issued.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to			X	

[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
	assess the abuse liability of the product?				
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		Could not find this in the submission. However, in Study 20062004, 98 (35%) of 282 patients were enrolled in the US. In Study 20040215, 21 (57%) of 37 patients were enrolled in the US. Based upon literature review, treatment approaches and patient characteristics appear similar in the US and foreign sites.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
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			
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			Disclosure information was provided for all primary investigators for both studies and for the IRC panel. None of the investigators or radiologists disclosed financial interests. Disclosure information was not provided for one US subinvestigator who was incorrectly listed on the 1572 form and 5 Australian subinvestigators no

Reference ID: 3255768

	Content Parameter	Yes	No	NA	Comment
					longer at the study site for Study 20040215; Disclosure information was not provided for 8 Australian subinvestigators who were no longer at the study site for Study 20062004.
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			

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.

No additional issues identified at this time. Information inquiries identified during the filing review have already been sent to the Application Holder.

Reviewing Medical Officer Date

Clinical Team Leader Date

Reference ID: 3255768

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/s/

MARTHA B DONOGHUE
02/05/2013

SUZANNE G DEMKO
02/05/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

<u>CHEMISTRY REVIEW(S)</u>

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Monoclonal Antibodies
Rockville, MD 20852
Tel. 301-827-0850

Memorandum of Review

Date: May 16, 2013
To: File for STN125320/94
From: Lixin Xu, M.D., Ph.D., Product Quality Reviewer, DMA/OBP/OPS/CDER, HFD-123
Through: Chana Fuchs, Ph.D., Team Leader, HFD-123
Subject: Supplemental Biologics License Application 125320/94 : to apply for the [redacted] (b) (4) in addition to the approved application for prevention of skeleton-related events in patients with bone metastases from solid tumors for XGEVA® (denosumab).
Applicant: Amgen Inc., One Amgen Center Dr., Thousand Oaks, CA 91320-1799.
Contact: Thomas M. DeMelfi Jr, MS, Sr. Manager, Regulatory affairs. Tel: (805) 447-2753. Email: tdemelfi@amgen.com
Product: XGEVA® (denosumab)
Submission Date: December 11, 2012
Received Date: December 12, 2012

Link: \\cbsap58\m\eCTD_Submissions\STN125320\125320.enx

Summary:
Xgeva (denosumab) is a human IgG_2 kappa monoclonal antibody against Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), and produced in CHO cells. Xgeva is supplied in a 70 mg/ml vial and is formulated in (b) (4) mM acetate, (b) (4)% sorbitol, pH 5.2. In November 2010, denosumab as Xgeva was approved for the prevention of skeleton-related events in patients with bone metastases from solid tumors. This supplement is a Supplemental Biologics License Application (sBLA) to apply for [redacted] (b) (4) in addition to the approved application. This review covers both the immunogenicity section and the environmental assessment section.

Review of immunogenicity:
For the proposed indication for GCTB, the safety of Xgeva was evaluated in two Phase 2 open-label, single arm trials in which a total of 304 patients with GCTB received at least 1 dose of Xgeva. Patients received 120 mg Xgeva subcutaneously every 4 weeks with a loading dose of 120 mg on days 8 and 15. Of the 304 patients who received Xgeva, 147 patients were treated with Xgeva for ≥ 1 year, 46 patients for ≥ 2 years, and 15 patients for ≥ 3 years. No patient was detected positive for immunogenicity by the validated assay used for the approved indication, which is the electrochemiluminescent bridging immunoassay.

The following is the current immunogenicity description, which is also the proposed description used by the Sponsor for the GCTB indication.

6.3 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.

Reviewer's Comment: The immunogenicity ratio is below 1%. With the new data from the clinical trials for the proposed indication GCTB, the ratio would be even lower. The overall ratio basically will remain unchanged, therefore, it is considered adequate to keep the most of the current description for the proposed description. However the data listed above of less than 1% (7/2758) were only from the patients with osseous metastases treated with denosumab. The 304 patients of GCTB were not included in the data set. Therefore, we will discuss with clinical team with the new data generated from the patient population form GCTB. The Labeling meeting scheduled is on-going, which will pass the GRMP deadline. This review will not cover this proposed labeling section in order to meet the GRMP deadline.

Review of environmental assessment:
Environmental assessment section has been provided in the submission. In Section 1.12.14, the Sponsor requested a categorical exclusion under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31(c), based on consideration of its lack of effects when exposed to the environment.
The Sponsor further explained as follow "*Action on this submission will not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Amgen is in compliance with the categorical exclusion criteria listed in 21 CFR § 25.31(a) and no extraordinary circumstances exist. 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.*" It is considered adequate.

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/s/

LIXIN XU
05/20/2013

CHANA FUCHS
05/20/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: 21 May 2013
From: Shawna L. Weis, Ph.D.
Pharmacologist
Division of Hematology Oncology Toxicology (DHOT) for Division of Oncology Products 2 (DOP2)
Through: Whitney S. Helms, Ph.D.
Pharmacology Supervisor, DHOT-DOP2
To: File for sBLA #125320
Xgeva for Giant Cell Tumor of Bone
Re: Approvability of Pharmacology and Toxicology

Amgen Inc. submitted a supplemental BLA for the use of denosumab in the [redacted] (b) (4)
Xgeva® (denosumab) is currently marketed for the treatment of bone metastases, and denosumab is also marketed as Prolia®, which is indicated for the treatment or prevention of postmenopausal osteoporosis and for the treatment or prevention of bone loss in breast or prostate cancer patients undergoing hormone ablation.
No new nonclinical studies were submitted to support this application. An issue that arose in the context of the medical review is the concern that denosumab (RankL inhibition) may promote malignant transformation of GCTB, which has a low, spontaneous background rate of occurrence in this patient population.
Whereas this concern would be most appropriately addressed in the treatment population, the low incidence of this tumor and the unknown baseline rate of malignant transformation make such studies difficult to conduct. As a result, the medical officer discussed options with the pharmacology/toxicology team for nonclinical studies that could serve to better characterize this risk. The pharmacology/toxicology team advised that conventional carcinogenicity studies would not be useful for the goal of investigating an increased risk of malignant transformation in this population, but suggested that additional *in vitro* or *in vivo* pharmacology models may be available for further exploration of the potential risk. As a result, the team has requested that the Sponsor evaluate the possibility of performing additional nonclinical pharmacology studies as a postmarketing commitment to evaluate the potential of RankL inhibition by denosumab to promote GCTB malignant transformation in an animal model. The Division is awaiting the Sponsor's response to this request.

Recommendations: The application is approvable from a nonclinical perspective. A postmarketing commitment may be requested if appropriate animal or *in vitro* studies are proposed that could potentially provide useful information in understanding the risk of malignant transformation of GCTB.

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/s/

SHAWNA L WEIS
05/22/2013

WHITNEY S HELMS
05/22/2013

I concur with Dr. Weis's conclusion that the supplemental BLA for the treatment of patients with GCTB with Xgeva is approvable from a pharmacology/toxicology perspective. All nonclinical data required to support the approval of this supplement was submitted during the review of this product for other previously approved indications.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125320/94 Applicant: Amgen **Stamp Date:**

Drug Name: Denosumab **NDA/BLA Type: sBLA** **12 December 2012**

On **initial** overview of the NDA/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?			N/A
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A
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)?			N/A
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).			N/A
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?			N/A
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?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES_____

If the NDA/BLA is not fileable from the pharmacology/toxicology 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 Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

SHAWNA L WEIS
02/07/2013

WHITNEY S HELMS
02/07/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125320
Supplement #:	94
Drug Name:	Xgeva® (Denosumab)
Indication:	Giant Cell Tumor of Bone
Applicant:	Amgen
Submission Date:	December 11, 2012
PDUFA Date:	June 13, 2013
Review Priority:	Priority
Biometrics Division:	DBV
Statistical Reviewer:	Weishi Yuan
Concurring Reviewers:	Kun He, Team Leader
	Rajeshwari Sridhara, Division Director
Medical Division:	Oncology Products 2
Clinical Team:	Martha Donoghue, Clinical Reviewer
	Suzanne Demko, Team Leader
	Patricia Keegan, Division Director
Project Manager:	Melanie Pierce

Keywords:

Giant Cell Tumor of Bone (GCTB), Objective Tumor Response Rate, RECIST 1.1

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Reference ID: 3309912

1 EXECUTIVE SUMMARY

The applicant submitted data and final study reports of two studies to support approval for denosumab indicated for the [redacted] (b) (4)

This application was based on combined data of two studies: Study 20040215 (Study 0215) and Study 20062004 (Study 2004). Study 0215 was a phase 2, open-label, single-arm study in adult subjects with unresectable or recurrent GCTB. The primary objective was tumor response and safety. A total of 37 subjects were enrolled and this study is completed. Study 2004 is an on-going, phase 2, single arm study in adult and skeletally mature adolescent subjects in surgically salvageable or unsalvageable GCTB. The primary objective was safety. A total of 500 subjects were planned for this study and as of data cut-off date for this application 286 subjects were enrolled in the study.

The efficacy analysis for this application is based on a retrospective integrated analysis of objective tumor response by independent evaluation which included 190 evaluable subjects who participated in or are currently participating in the two Studies 0215 and 2004. Among these subjects, 187 were evaluable and included in the analysis based on RECIST 1.1 criteria.

The data and analyses from current submission showed that the objective tumor response by RECIST 1.1 was 25.1% (47 of 187 subjects) with 95% Confidence Interval (CI): (19.1%, 32.0%). The median time to first objective tumor response is 3.2 months with 95% CI (2.8 months, 4.4 months). All responses were partial responses. Three of 47 responders reported progressive disease following objective tumor response. The median duration of objective tumor response was not estimable.

Based on the data and analyses, the results showed objective tumor response with denosumab treatment in 25.1% of subjects. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

Reference ID: 3309912

2 INTRODUCTION

The applicant submitted data and final study reports of two Phase II studies to seek a new indication in giant cell tumor of bone (GCTB) for denosumab. This application was based a retrospective integrated analysis of data based on Study 20040215 and Study 20062004, two Phase 2, open-label, single arm studies that enrolled a total of 305 subjects.

2.1 Overview

GCTB is a relatively uncommon tumor of the bone. For patients with unresectable or metastatic GCTB, no therapy has been approved.

2.1.1. Class and Indication

Denosumab is a fully human monoclonal IgG2 antibody to RANKL that binds to the soluble and transmembrane forms of human RANK ligand (RANKL). Giant cell tumors of bone produce and are dependent upon RANKL for growth. This binding of denosumab to RANKL prevents RANK activation and inhibits the formation, activation, and survival of osteoclasts. The indication sought was the (b) (4) (b) (4)

2.1.2. Regulatory History

Denosumab was approved as Prolia for treatment of postmenopausal women with osteoporosis at high risk for fracture in June 2010, as Prolia as a treatment to increase bone mass in men receiving androgen deprivation therapy for nonmetastatic prostate cancer and women receiving adjuvant aromatase inhibitor therapy for breast cancer who are at high risk for fracture in September 2011, as Prolia as a treatment to increase bone mass in men with osteoporosis at high risk for fracture, and approved as Xgeva for prevention of skeletal-related events in patients with bone metastases from solid tumors.

In December 2010, FDA granted orphan designation for denosumab for the treatment of patients with giant cell tumor of bone. In the meeting in August, 2011, FDA discussed with Amgen on their proposal for use of retrospective evaluation of objective response rate based on an independent review of radiographic image assessments. FDA agreed that assessment of objective radiographic response in evaluable patients using modified RECIST, modified EORTC criteria, and modified inverse Choi criteria was acceptable to provide the basis for an sBLA submission. A pre-sBLA meeting was held in September 2012, FDA recommended that objective tumor response using modified RECIST criteria be used for the primary efficacy analysis with duration of response by RECIST criteria as a key secondary endpoint.

The s-BLA was submitted in December, 2012.

Reference ID: 3309912

2.1.3. Studies Reviewed

Study 0215 was an open-label, multicenter, single-arm, Phase 2 safety and efficacy study of denosumab in 37 subjects with recurrent or unresectable giant cell tumor of bone (GCTB). The study was initiated on July 10, 2006 and completed on November 16, 2010. The data cut-off date for this submission was March 02, 2011.

Subjects received denosumab 120 mg SC Q4W, with additional 120-mg loading doses administered on study days 8 and 15. The primary objective of this study was to evaluate tumor response and the safety of denosumab in adult subjects with GCTB. The primary endpoint was tumor response defined as elimination of at least 90% of giant cells, or complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells or no radiographic progression of the target lesion up to week 25.

Study 2004 is an on-going, open-label, single arm, Phase 2 study in adult and skeletally mature adolescents. The study is planned to enroll 500 subjects, and 286 subjects have been enrolled as of March 25, 2011. Subjects were enrolled into one of the three cohorts:

- Cohort 1: Subjects with surgically unsalvageable disease;
- Cohort 2: Subjects with surgically salvageable disease whose planned on-study surgery was associated with severe morbidity; and
- Cohort 3: Subjects who rolled over from Study 20040215.

Subjects received denosumab 120 mg SC Q4W, with additional 120-mg loading doses administered on study days 8 and 15. The study objective was to evaluate safety of denosumab treatment.

Overall, 187 subjects from the two studies had at least one evaluable time point assessment by RECIST 1.1 and were included in the integrated analysis for objective response rate.

2.2 Data Sources

Data used for review is from the electronic submission received on December 11, 2012. The network path is: \\cbsap58\m\eCTD_Submissions\STN125320\0255.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data for both studies as well as the related SAS programs for analysis.

The reviewer was able to perform the analyses using the submitted data.

Reference ID: 3309912

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 0215 was an open-label, multicenter, single-arm, Phase 2 safety and efficacy study of denosumab in 37 subjects with recurrent or unresectable GCTB.

All eligible subjects received 120 mg denosumab subcutaneously (SC) every 4 weeks (Q4W) starting with study day 1, with additional doses on study days 8 and 15, until complete tumor resection; disease progression; investigator's or Amgen's recommendation for discontinuation; the subject's decision to discontinue; administration of bisphosphonates, calcitonin, or interferon alfa-2a; or rollover to study 20062004. After the last dose of denosumab, safety data were collected every 6 months for up to 2 years. After 16 November 2010, all subjects on study or in the follow-up were enrolled to Amgen study 20062004.

The primary objective of this study was to evaluate tumor response and the safety of denosumab in adult subjects with GCTB. The primary endpoint was tumor response defined as elimination of at least 90% of giant cells, or complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells or no radiographic progression of the target lesion up to week 25. Secondary endpoints included serum trough levels of denosumab, the degree of suppression of bone turnover and safety measurements.

Study 2004 is an on-going, open-label, single arm, Phase 2 study in adult and skeletally mature adolescents. Subjects were enrolled into one of the three cohorts:

- Cohort 1: subjects with surgically unsalvageable disease (e.g., sacral, spinal giant cell tumor of bone, or multiple lesions including pulmonary metastases)
- Cohort 2: subjects with surgically salvageable disease whose planned initial on study surgery was associated with severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy)
- Cohort 3: subjects who participated in Study 0215 and were eligible to enroll in Study 2004 for continuation of treatment or safety follow-up.

Subjects received denosumab 120 mg SC Q4W, with additional 120-mg loading doses administered on study days 8 and 15. The study objective was to evaluate safety of denosumab treatment. Secondary endpoints included time to disease progression in subjects with unsalvageable GCTB (Cohort 1) and proportion of subjects who do not require surgery in subjects with salvageable GCTB (Cohort 2).

3.2.2 Efficacy Measures

A retrospective independent radiographic review of objective tumor response was performed by a central imaging vendor for subjects enrolled in Studies 0215 and 2004.

Reference ID: 3309912

An objective tumor response was defined as either a CR or PR, determined using the best response evaluated by any of the following response criteria:

- RECIST 1.1: modified Response Evaluation Criteria in Solid Tumors version 1.1 evaluated tumor burden based on computed tomography (CT)/magnetic resonance imaging (MRI),
- EORTC: modified European Organisation for Research and Treatment of Cancer criteria evaluated metabolic response using fluorodeoxyglucose positron emission tomography (18FDG-PET), and
- density/size: modified inverse Choi criteria evaluated tumor size by CT/MRI and density using Hounsfield units on CT.

These 3 response criteria were used to collectively define and characterize objective tumor response in subjects with GCTB. In addition, best response based on any criteria was also reported.

An objective tumor response by modified RECIST 1.1 was determined by evaluation of target and non-target lesions according to the following response criteria in Table 1. A follow-up assessment was not required to confirm tumor response; a two-reader paradigm was used for assessments using modified RECIST. Identification of a new lesion resulted in an assessment of PD by the modified RECIST.

Table 1. Modified RECIST 1.1 Evaluation Criteria

Response	Target Lesion	Nontarget Lesion
Complete response (CR)	Disappearance of all target lesions. All target lymph nodes are < 10 mm in the short axis	Disappearance of all nontarget lesions. All nontarget lymph nodes are < 10 mm in the short axis
Partial response (PR)	At least a 30% decrease in SLD using baseline SLD as reference	-
Stable disease (SD)	Neither sufficient shrinkage of target lesions to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the nadir SLD	The persistence of one or more nontarget lesions not qualifying for CR or PD
Progressive disease (PD)	At least a 20% increase in the SLD of target lesions, taking as reference the nadir SLD. In addition to the relative increase of 20% in SLD, the SLD must also demonstrate an absolute increase of ≥ 5 mm	The unequivocal progression of existing nontarget lesion(s)
Unevaluable (UE)	A target lesion present at baseline, which subsequently became unevaluable	Any nontarget lesion present at baseline, which subsequently became unevaluable

SLD = sum of the longest diameter

(Adapted from the applicant's Summary of Clinical Efficacy)

Reference ID: 3309912

Reviewer's Comments:

This applicant reported objective tumor response based on three different criteria: modified RECIST 1.1, modified EORTC, and density/size. This reviewer considers the results based on modified RECIST 1.1 as the primary analysis. However, results for each criterion are all reported.

3.2.3 Sample Size Consideration

Study 0215 was planned to have a sample size of 35 and enrolled 37 subjects upon completion of the study.

Study 2004 is planned to enroll 500 subjects, and 286 subjects have been enrolled as of March 25, 2011. Four subjects were enrolled directly into the safety follow-up phase, and 282 subjects were included in the treatment phase.

There were 11 subjects rolled over from Study 0215 to Study 2004. In addition, 3 subjects enrolled in Study 0215 and then re-enrolled in Study 2004. Therefore a total of 305 subjects were enrolled in the two studies, among which 304 received treatments. Overall, 190 subjects had a baseline assessment and at least 1 evaluable, on-study time point assessment and were included in the best response evaluation using any tumor response criteria. These 190 subjects formed the objective tumor response analysis set. Among these subjects, 187, 26, and 176 subjects were evaluable and were included in the modified RECIST, the modified EORTC criteria, and the density/size evaluations, respectively.

Reviewer's Comments:

This reviewer considers the 187 subjects that were evaluable in the modified RECIST criteria as the primary analysis population.

3.2.4 Statistical Methodologies

The statistical analysis for the evaluation of objective tumor response is descriptive in nature with no hypothesis testing. The primary endpoint was calculated as the proportion of subjects with objective tumor response with 2-sided exact 95% CI. For the secondary endpoints, time to first tumor response and duration of objective tumor response were estimated using the Kaplan-Meier estimates.

3.2.5 Patient Disposition, Demographic and Baseline Characteristics

Study 0215 was conducted at 8 study centers: 5 in the United States, 2 in Australia, and 1 in France. The study was initiated on July 10, 2006 and completed on November 16, 2010. This submission included data with cut-off date March 02, 2011. A total of 37 subjects were enrolled in the study. Twenty seven subjects were included in the integrated objective tumor response

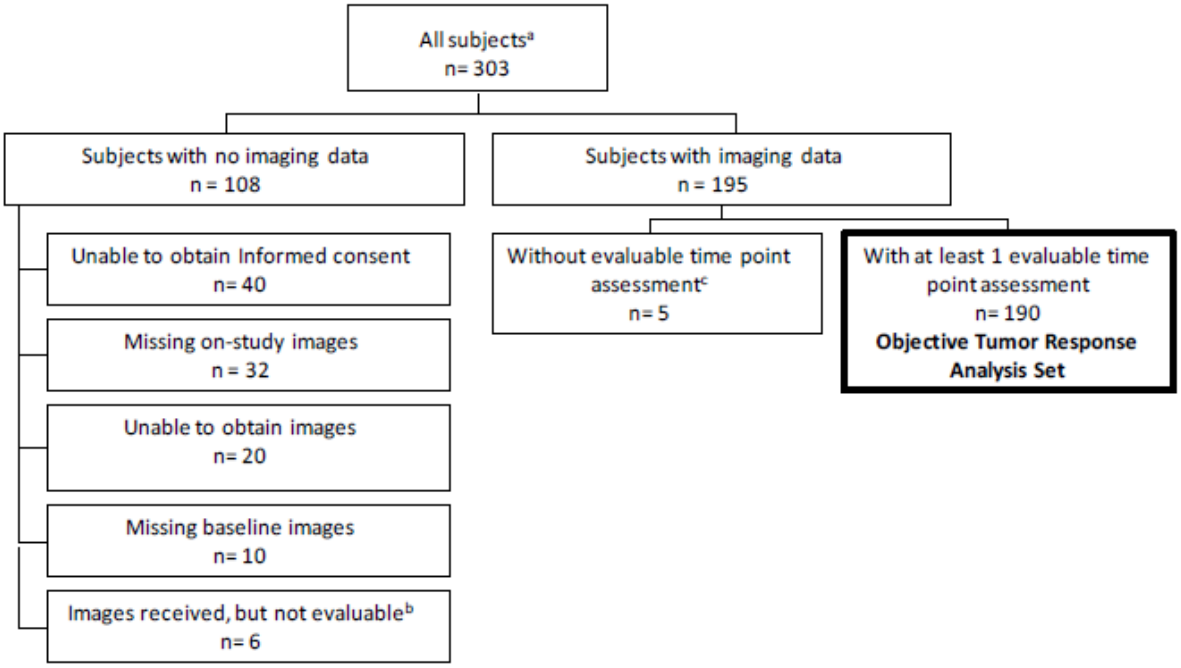
Reference ID: 3309912

analysis set and the median time (range) on study for these subjects were 20.8 (2.0, 48.9) months.

Study 2004 is still on-going and being conducted at 29 study centers in North America, Europe, and Australia. This submission contains data and results with cut-off date March 25, 2011, which is also the third planned interim analysis of the study. A total of 286 subjects have been enrolled in the study at cut-off date. From Cohort 1 and Cohort 2, 163 subjects were included in the integrated objective tumor response analysis set and the median time (range) on study for these subjects were 13.0 (1.7, 29.1) months.

The disposition of the subject imaging data is presented in the following figure.

Figure 1. Disposition of Imaging Data



[a] Rollover or re-entry subjects from Study 20040215 who were enrolled in Study 20062004 were included only once in the imaging analysis.
[b] X-ray only
[c] Lesions unevaluable due to image quality or determination that subject had surgical resection prior to the time point assessment.

(Adapted from the applicant's Summary of Clinical Efficacy)

Reference ID: 3309912

As of the analysis cut-off date, 38 subjects (20.0%) discontinued treatment. The reasons for discontinuation are summarized in the following table.

Table 2. Reasons for Study Discontinuation

	Study 0215 n(%)	Study 2004 Cohort 1 & 2 n(%)	Overall n(%)
Objective Tumor Response Analysis Set	27 (100)	160 (100)	187 (100)
Ongoing	0	149 (93.1)	149 (79.7)
Discontinued	27 (100)	11 (6.9)	38 (20.3)
Complete resection	8 (29.6)	5 (3.1)	13 (7.0)
Rollover to other study	9 (33.3)	0	9 (4.8)
Admisnistrative decision	1 (3.7)	3 (1.9)	4 (2.1)
Investigator's descretion	4 (14.8)	0	4 (2.1)
Adverse event	1 (3.7)	2 (1.2)	3 (1.6)
Disease progrssion	2 (7.4)	1 (0.6)	3 (1.6)
Consent withdrawn	1 (3.7)	0	1 (0.5)
Noncompliance	1 (3.7)	0	1 (0.5)

Demographic characteristics at baseline are summarized in the following table.

Table 3. Baseline Demographics

	Study 0215 n (%)	Study 2004 n (%)	Overall n (%)
Objective Tumor Response Analysis Set	27 (100)	160 (100)	187 (100)
Gender			
Male	12 (44.4)	72 (45)	84 (44.9)
Female	15 (55.6)	88 (55)	103 (55.1)
Race			
Caucasian	21 (77.8)	34 (22.3)	147 (78.6)
Non-Caucasian	6 (22.2)	126 (78.8)	40 (21.4)
Age			
< 65	27 (100)	155 (96.9)	182 (97.3)
≥ 65	0	5 (3.1)	5 (2.7)
Region			
North America	14 (51.9)	59 (36.9)	73 (39.0)
Europe	1 (3.7)	92 (57.5)	93 (49.7)
Australia	12 (44.4)	9 (5.6)	21 (11.2)

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Baseline characteristics are summarized in the following table.

Table 4. Baseline Characteristics

	Study 0215 n (%)	Study 2004 n (%)	Overall n (%)
Objective Tumor Response Analysis Set	27 (100)	160 (100)	187 (100)
ECOG Status at Baseline			
0	9 (33.3)	96 (60)	105 (56.1)
1	16 (59.3)	58 (36.3)	74 (39.6)
2	0	6 (3.8)	6 (3.2)
Missing	2 (7.4)	0	2 (1.1)
GCT Disease Type			
Primary Resectable	0	24 (15)	24 (12.8)
Primary Unresectable	9 (33.3)	34 (21.3)	43 (23.0)
Recurrent Resectable	6 (22.2)	23 (14.4)	29 (15.5)
Recurrent Unresectable	12 (44.4)	79 (49.4)	91 (48.7)

Reviewer's comments:

The demographic and baseline characteristics are from the 187 subjects that is evaluable based on RECIST criteria.

The majority of the subjects in Study 0215 are Caucasians while the majority of subjects in Study 2004 are non-Caucasians. About 33% of the subjects in Study 0215, compared with 60% of the subjects in Study 2004, had ECOG status 0. Most of the subjects in Study 0215 were enrolled in Australia and North American, while more than half of the subjects in Study 2004 were enrolled in Europe.

3.2.6 Results and Conclusions

Primary Endpoint: Objective Tumor Response

A total of 190 subjects had a baseline assessment and at least one evaluable, on-study time point assessment and were included in the best response evaluation using any tumor response criteria. Among these subjects, 187, 26, and 176 subjects were evaluable and were included in the modified RECIST, the modified EORTC criteria, and the density/size evaluations, respectively. Subjects could be evaluated according to more than one response criteria.

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The following table summarizes the results of the objective tumor response.

Table 5. Summary of Tumor Response Rate

	Number of Responders	Number of Subjects	Percent	95% Exact CI
RECIST 1.1	47	187	25.1	(19.1, 32.0)
EORTC	25	26	96.2	(80.4, 99.9)
Density/Size	134	176	76.1	(69.1, 82.2)
Best Response	136	190	71.6	(64.6, 77.9)

Secondary Endpoints and Supportive Analyses

The following table summarized the results of duration of response. Since few subjects had disease progression (DP) after objective tumor response, the median of duration of response is not estimable. The median reported in the following table is the median of the observed duration of response, which does not account for censored observations,

Table 6. Summary of Duration of Response in Months

	Number of Responders	Number of DP after response	Median of Observed DoR	Range of Observed DoR
RECIST 1.1	47	3	8.1	(0.0, 41.0)
EORTC	25	0	3.9	(0.0, 40.5)
Density/Size	134	1	8.1	(0.0, 45.3)
Best Response	136	1	8.1	(0.0, 45.3)

The following table summarizes the results of time to objective tumor response.

Table 7. Summary of Time to Response in Months

	Number of Responders	Median	95% CI of Median	Range of Time to Response
RECIST 1.1	47	3.2	(2.8, 4.6)	(1.5, 20.9)
EORTC	25	2.7	(1.6, 2.8)	(0.9, 9.7)
Density/Size	134	2.8	(2.8, 3.0)	(0.5, 23.4)
Best Response	136	2.8	(2.8, 2.9)	(0.5, 23.4)

Reference ID: 3309912

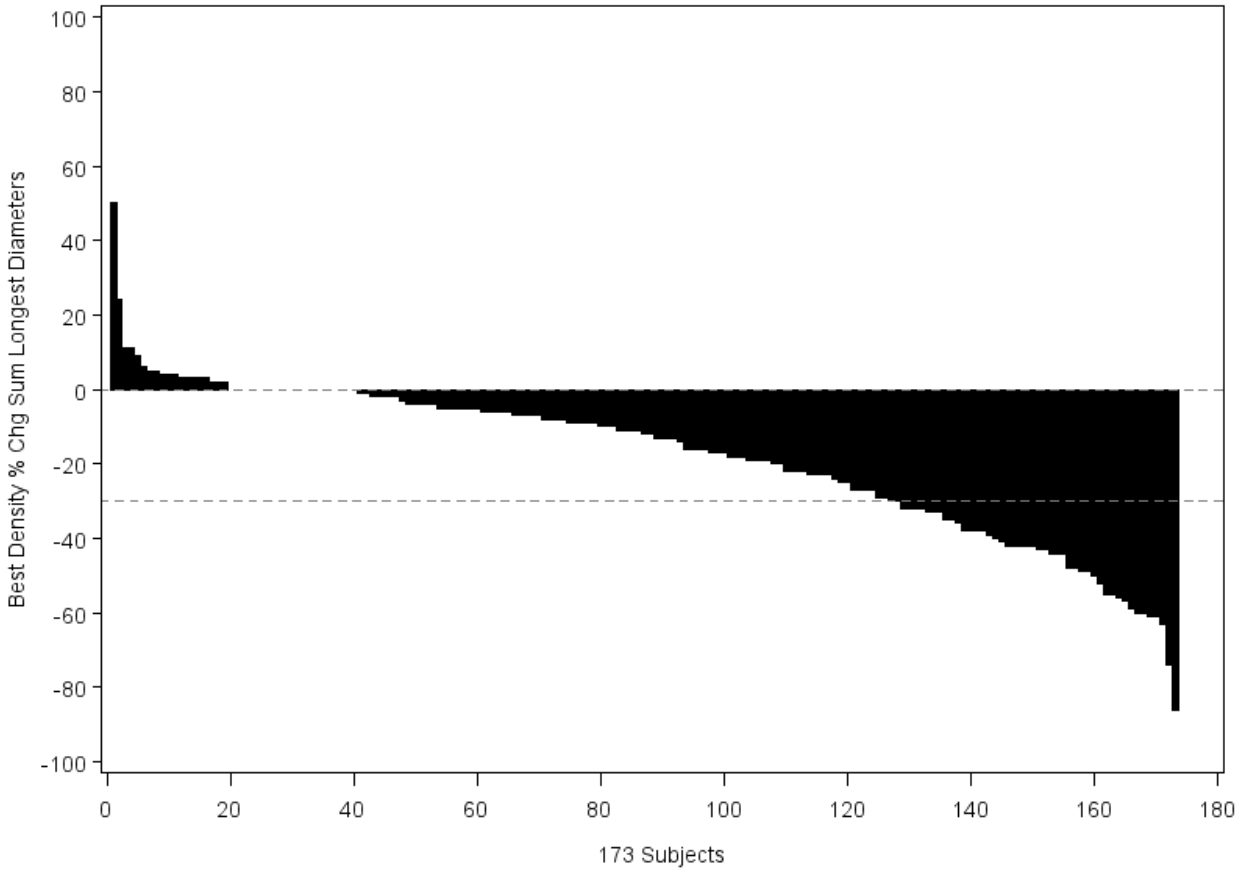
The following table summarizes the results of duration of follow-up.

Table 8. Summary of Duration of Follow-up in Months

	Number of Subjects	median duration on study	95% CI of Median	Range on Study
RECIST 1.1	187	13.4	(11.3, 14.8)	(1.7, 48.9)
EORTC	26	13.8	(8.1, 28.1)	(2.0, 47.1)
Density/Size	176	13.4	(11.3, 14.6)	(1.7, 47.1)
Best Response	190	13.4	(11.3, 14.6)	(1.7, 48.9)

The following figure presents the waterfall plot of best percent change in the sum of the longest diameter of target lesions compared to baseline in RECIST-evaluable population.

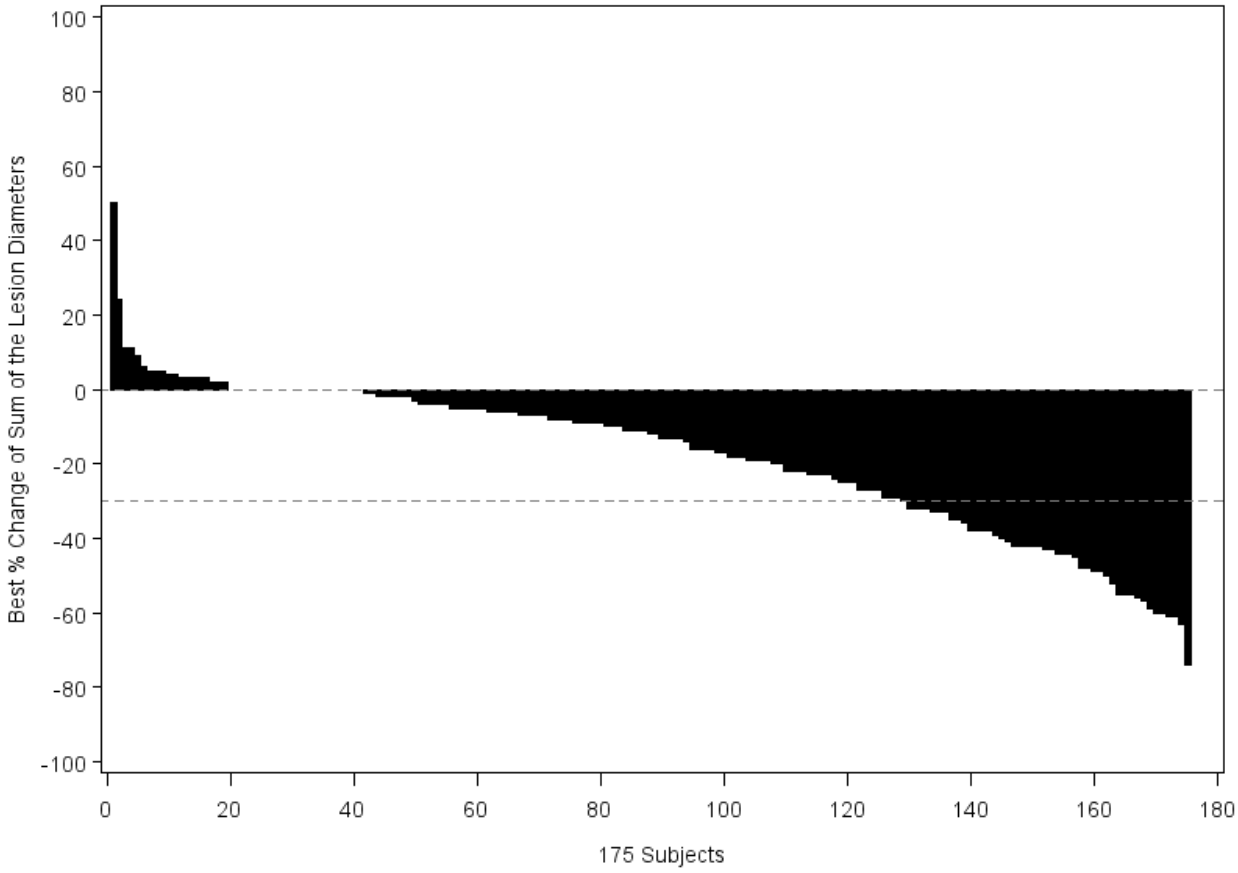
Figure 2. Best Percent Change in Sum of Longest Diameters in RECIST-Evaluable Population



The following figure presents the waterfall plot of best percent change of sum of lesion diameters for target lesions in density/size Evaluable (Inverse Choi) population.

Reference ID: 3309912

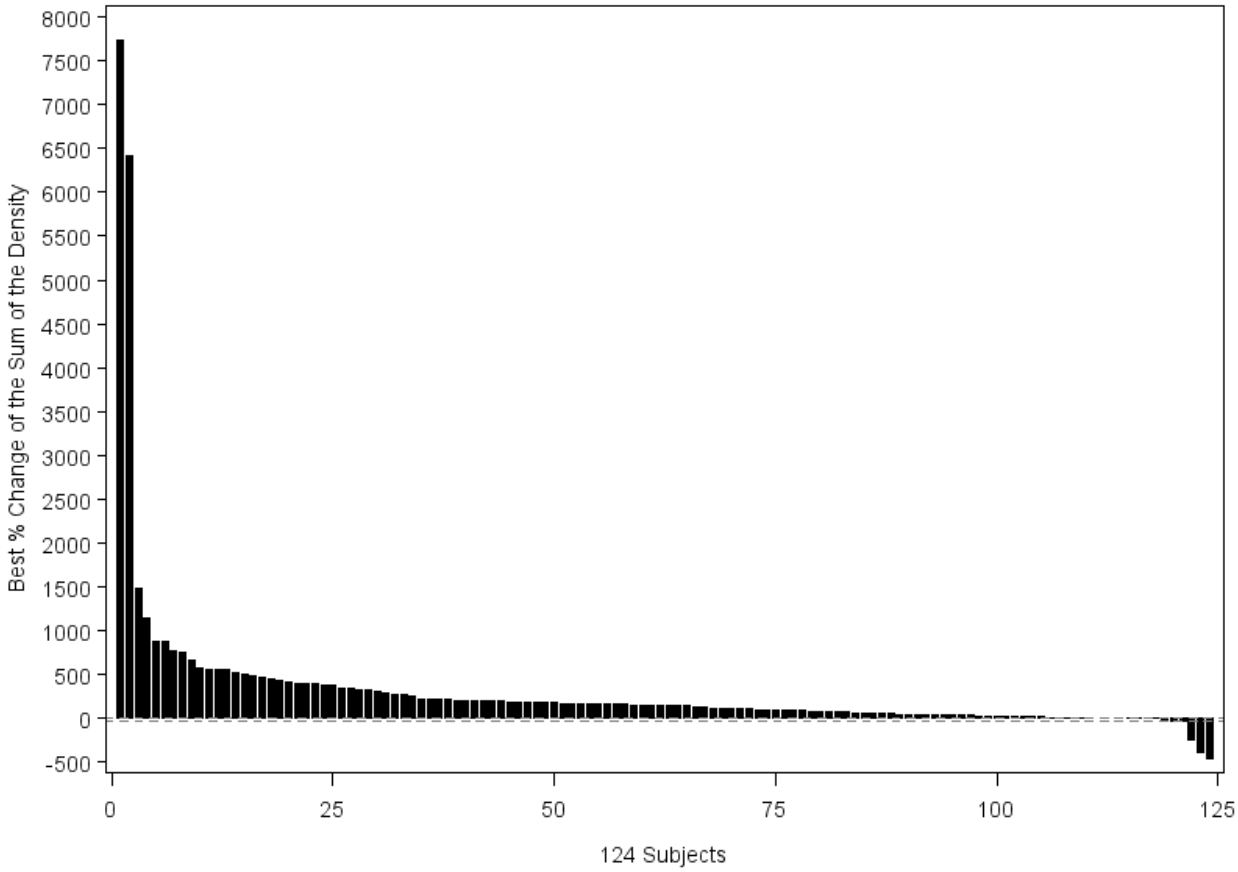
Figure 3. Best Percent Change in Sum of Lesion Diameters in Density/Size Evaluation Population



Reference ID: 3309912

The following figure presents waterfall plot of best percent change of the sum of the density for target lesions in density/size evaluation population.

Figure 4. Best Percent Change of the Sum of the Density for Target Lesions in Density/Size Evaluation Population



Reviewer's Comments

The results based on the RECIST-evaluable population are considered to be the primary analysis for this application. The results by the other three criteria are supportive of the results of the primary analysis.

3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The following table summarizes the subgroup analyses of objective tumor response by gender, race, age and region for the RECIST evaluable population.

Table 9. Subgroup Analysis of Objective Tumor Response

	Number of Responders	Number of Subjects	Percent	95% Exact CI
Gender				
Male	25	84	29.8	(20.3, 40.7)
Female	22	103	21.4	(13.9, 30.5)
Age				
Age < 65	46	182	25.3	(19.1, 32.2)
Age ≥ 65	1	5	20	(0.01, 71.6)
Race				
Caucasian	32	147	21.8	(15.4, 29.3)
Non-Caucasian	15	40	37.5	(22.7, 54.2)
Region				
North America	22	73	30.1	(20.0, 42.0)
Europe	23	93	24.7	(16.4, 34.8)
Australia	2	21	9.5	(1.2, 30.4)

Reviewer's Comments

The results from these subgroup analyses are consistent with the primary analysis results. The subjects in Australia showed a lower response rate than the other two regions. This may due to the small number of subjects in the analysis for this region.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

This application is supported by a retrospective integrated analysis of objective tumor response by independent evaluation which included 190 evaluable subjects who participated in or are currently participating in the two Studies 0215 and 2004. Among these subjects, 187 were evaluable and included in the analysis based on RECIST 1.1 criteria.

The applicant considers the 190 subjects that were evaluable by any of the three criteria: RECIST, EORTC or density/size, as the primary analysis dataset. This reviewer considers the 187 subjects that were evaluable by RECIST 1.1 as the primary analysis data set.

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5.2 Collective Evidence

The data and analyses from current submission showed that the objective tumor response by RECIST 1.1 was 25.1% (47 of 187 subjects) with 95% Confidence Interval (CI): (19.1%, 32.0%). The median time to first objective tumor response is 3.2 months with 95% CI (2.8 months, 4.4 months). All responses were partial responses. Three of 47 responders reported progressive disease following objective tumor response. The median duration of objective tumor response was not estimable.

The results from the other three evaluation criteria: EORTC, density/size, or any best response, are supportive of the results by RECIST criteria.

5.3 Conclusions and Recommendations

Based on the data and analyses, the results showed objective tumor response with denosumab treatment in 25.1% of subjects. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

5.4 Labeling Recommendations

Only the results based on the RECIST 1.1 criteria should be included in the label.

Reference ID: 3309912

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/s/

WEISHI YUAN
05/16/2013

KUN HE
05/16/2013

RAJESHWARI SRIDHARA
05/16/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125320 /94 **Applicant: Amgen** **Stamp Date: Dec. 11, 2012**

Drug Name: Xgeva(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.				
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

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/s/

WEISHI YUAN
02/06/2013

KUN HE
02/06/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW	
BLA	125320 Suppl. 94 (eCTD 255)
Type/Category	Efficacy Supplement
Brand Name	Xgeva™
Generic name	Denosumab
Proposed Indication	(b) (4)
Dosage Form	Injection
Route of Administration	Subcutaneous
Dosing Regimen and Strength	70 mg/ml, 120 mg once weekly (days 1, 8, and 15) for the first three weeks of a four week treatment cycle, and then once monthly starting day 29
Applicant	Amgen, Inc.
OCP Division	Division of Clinical Pharmacology 5
OND Division	Division of Oncology Products 2
Submission Date	December 12, 2012
PDUFA	June 13, 2013
Primary Reviewer	Stacy S. Shord, PharmD
Secondary Reviewer	Hong Zhao, PhD

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1 EXECUTIVE SUMMARY

Denosumab is a human IgG_2 monoclonal antibody that inhibits receptor activation of the nuclear receptor factor κB (RANK) by binding to RANK ligand (RANKL). Denosumab as Xgeva™ was approved on November 18, 2010 for the prevention of skeletal related events (SRE) for patients with bone metastases from solid tumors. The approved dose is 120 mg subcutaneously once every 4 weeks and the approved Xgeva formulation is 70 mg/mL.

In this supplemental application, the applicant proposes an additional indication for Xgeva for the (b) (4)
Three hundred and five (305) patients with GCTB that was either unresectable or for which surgery would be associated with severe morbidity, were enrolled into one of two open-label, single arm trials. Objective tumor responses were achieved in 25% (95% CI 19, 32) of patients but the median time to response could not be estimated using RECIST 1.1 across studies. In general, the safety profile appears similar in patients with GCTB compared to patients with bone metastases, as described in the approved labeling.

Patients received denosumab at a dose of 120 mg once weekly (days 1, 8, and 15) for the first three weeks of a four week treatment cycle, and then once monthly starting day 29. Optimal sparse pharmacokinetic (PK) sampling that was included in one trial demonstrated that steady-state concentrations were achieved by three months and were similar to those reported in the labeling of 20 ± 14 mcg/mL following administration of 120 mg once every 4 weeks. The clinical pharmacology review team recommends stating that steady-state was achieved by 3 months with the proposed regimen in the modified labeling.

1.1 RECOMMENDATIONS

The overall Clinical Pharmacology and Biopharmaceutics data submitted to support the approval of this supplemental BLA are acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the labeling modifications.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

None.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

This submission includes two clinical trials to support an additional indication for denosumab as Xgeva. All patients were administered denosumab subcutaneously at a dose of 120 mg once weekly (days 1, 8, and 15) for the first three weeks of a four week treatment cycle, and then once monthly starting day 29. The smaller study conducted in 37 patients included sparse PK sampling with samples collected before the dose on days 1, 8, 15, 29, 57, 85, 169, and 337. The mean serum concentrations increased by 66%, 92%, 45%, 23%, 5% and 13% on days 15, 29, 57, 85, 169 and 337 compared to day 8. The highest denosumab trough concentration was reached on day 29 at 36 ± 21 mcg/mL; the serum concentrations subsequently declined by 24%, 36%,

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45%, and 41% on days 57, 85, 169, and 337. The steady-state concentrations similar to the concentrations listed in the approved labeling of 20 ± 14 mcg/mL were achieved by day 85 (at 3 months). Comparatively, steady-state concentrations were achieved by 6 months following administration of the approved dose of 120 mg once every 4 weeks. The approved labeling will be modified to reflect that steady-state concentrations were achieved by 3 months using the proposed dosing regimen.

No binding anti-denosumab antibodies were detected in patients enrolled into either clinical trial.

Exploratory biomarker analyses were conducted. (b) (4) .

Signatures:

Stacy S Shord, Pharm.D.	Hong Zhao, Ph.D.
Reviewer	Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DBOP: RPM – M Pierce; MTL – S Demko; MO –M Donoghue
DCP-5: DDD – B Booth; DD – NA Rahman

OCP Briefing: No briefing occurred for this submission.

2 QUESTION BASED REVIEW

On November 18, 2010, denosumab as Xgeva was approved for prevention of SRE in patients with bone metastases from solid tumors (Suppl. 7). Denosumab is also available as Prolia® for other indications. No PMRs or PMCs were proposed by clinical pharmacology for this indication.

A pediatric written request was agreed upon on November 30, 2012. (b) (4)

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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 as they related to clinical pharmacology and biopharmaceutics review?

As stated in the approved labeling for Xgeva:

Xgeva (denosumab) is a human IgG_2 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 supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in a 70 mg/mL vial presentation.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The proposed mechanism of action as described in the proposed labeling is: (b) (4)

The proposed indication is for the (b) (4).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose is 120 mg once weekly (days 1, 8, and 15) for the first three weeks of a four week treatment cycle, and then once monthly starting day 29. The proposed dose regimen is different than the approved dose regimen, as the approved dose is 120 mg once every 4 weeks for the prevention of SRE in patients with bone metastases.

Only one dose was explored for this indication. The applicant states that this dose was selected to achieve at least 95% occupancy of RANKL at steady-state over the dosing interval, as demonstrated in the supplement supporting an indication for the prevention of SRE (Suppl. 7). Furthermore, the applicant justified the dose selection for the approved indication as compared to other doses based on changes in urinary biomarkers. These biomarkers were measured as part of Study 20040215 submitted in support of this supplemental application.

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?

This supplement includes a clinical study report for two clinical trials to support the indication for the treatment of patients with GCTB. These reports have not been previously submitted as part of the original or supplemental applications under this BLA. The remaining nonclinical, clinical and other reports appear to have been previously submitted and reviewed under this application.

Table 1. Description of Study 20040215 and 20062004

Reference ID: 3310941

Study	Study 20040215 (phase 2)	Study 20062004 (phase 2)
Study Design	Ongoing, Open Label	Ongoing, Open Label
Objectives	Efficacy (response rate) Safety Antibody Response Pharmacokinetics Pharmacodynamics	Safety Efficacy (time to disease progression or proportion of patients not requiring surgery)
Treatment	120 mg once weekly (days 1, 8, and 15) for the first three weeks of a four week treatment cycle, and then once monthly starting day 29 until complete resection, disease progression, or withdrawal	120 mg once weekly (days 1, 8, and 15) for the first three weeks of a four week treatment cycle, and then once monthly starting day 29 for 6 doses after pathological confirmation of partial or complete response, after complete tumor resection or disease progression
Population	37 patients ≥ 18 years with unresectable or recurrent GCTB	282 adults or skeletally mature adolescents with • surgically unsalvageable disease (cohort 1, n=170) and • surgically salvageable disease whose planned surgery was associated with severe morbidity (cohort 2, n=101) and • who rolled over from Study 20040215 (cohort 3, n=11)

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?

Response Endpoints

The primary endpoint was objective tumor response for Study 20040215 and safety for Study 20062004. However, as part of the pre-sBLA meeting minutes (September 11, 2012, reference ID: 3186600), FDA recommended using objective tumor response as measured by modified RECIST as the primary efficacy analysis with duration of response by RECIST as a key secondary endpoint. The applicant completed an integrated analysis of objective tumor response that included patients enrolled into both clinical trials. **Table 2** lists the applicant's analysis of best response based on RECIST 1.1, along with other measures of objective tumor response. These findings have been confirmed by the clinical and statistical review teams.

Table 2. Objective Tumor Response Across Studies 20040215 and 20062004 (Applicant's analysis)

	n	N1	Percent	95% CI[a]
Proportion of subjects with an objective tumor response (CR, PR)				
Based on best response	136	190	71.6	(64.6, 77.9)
RECIST 1.1	47	187	25.1	(19.1, 32.0)
EORTC	25	26	96.2	(80.4, 99.9)
Density/size	134	176	76.1	(69.1, 82.2)

n = number of subjects with a response
N1 = number of subjects with at least one evaluable time point assessment
Source: Table 11; summary of clinical efficacy.

Biomarkers

Urine and fasting serum samples were collected from patients enrolled in Study 20040215 at multiple time points to measure bone turnover markers, such as uNTx, sCTx, TRAP-5b, BSAP, and osteocalcin. Urinary uNTx (corrected for urine creatinine) and serum CTx were approximately 80% below baseline from week 5 onward based on the applicant's analysis. Other bone turnover markers (BSAP, osteocalcin, and TRAP-5b) also decreased from baseline and remained below baseline throughout the study. (b) (4) [redacted].

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?

The PK samples were only collected in patients enrolled in Study 20040215. The applicant did not include the bioanalytical report in this submission. The brief description of the assay described in the Pharmacokinetic Appendix (appx 12) of the study report appears to differ from the analytical method listed for this study in the Summary of the Clinical Pharmacology Studies and the Pharmacokinetic Addendum to the clinical study report. An information request was sent on March 13, 2013 to request the bioanalytical report and cross validation if the assay used in this study is different than the assay used to measure serum denosumab concentrations as part of supplemental application that supported the indication for the prevention of SRE (Suppl. 7). The applicant stated that the assay used in this study was the same assay submitted and reviewed as part of Suppl. 7. Refer to Section 2.2.5 and 2.6 of this review for additional information.

2.2.4 Exposure-response

The applicant did not provide E-R analyses in this submission. PK samples were only collected in the smaller clinical trial, which does not permit meaningful E-R analyses.

2.2.5 What are the pharmacokinetic characteristics of the drug and its major metabolite?

Thirty-seven patients enrolled in the Study 20040215 provided pre-dose samples on days 1, 8, 15, 29, 57, 85,169 and 337 to measure serum denosumab trough concentrations. **Table 3 and Figure 1** provide a summary of the denosumab serum trough concentrations following each time point as calculated by the applicant. The mean serum concentrations increased by 66%, 92%, 45%, 23%, 5% and 13% on days 15, 29, 57, 85, 169 and 337 compared to day 1 based on our analysis. The highest denosumab trough concentration of 36 ± 21 mcg/mL was reached on day 29; the serum concentrations subsequently declined by 24%, 36%, 45%, and 41% on days 57, 85, 169, and 337. It appears that steady-state was achieved by day 85 (at 3 months).

Table 3. Summary of the Serum Denosumab Trough Concentrations for Patients Enrolled in

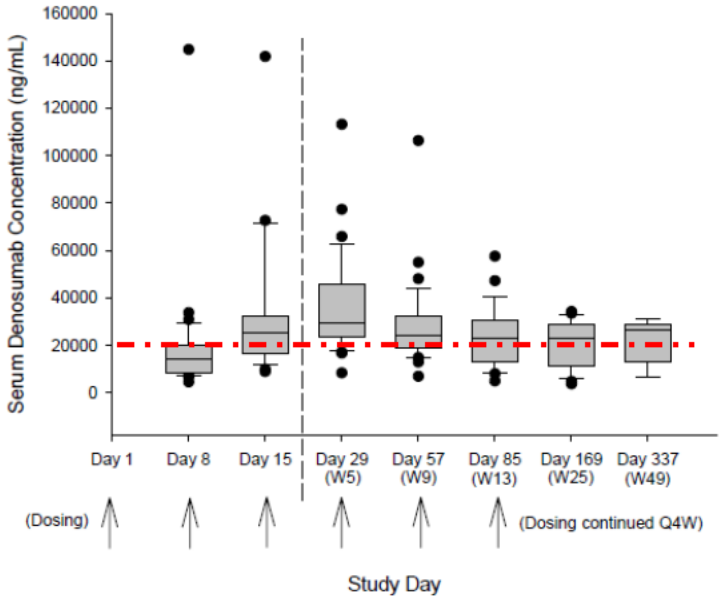
Reference ID: 3310941

Study 20040215 [Applicant Analysis]								
Summary Statistic	Day 1	Day 8	Day 15	Day 29 (Week 5)	Day 57 (Week 9)	Day 85 (Week 13)	Day 169 (Week 25)	Day 337 (Week 49)
N	32	32	28	33	32	25	23	9
Mean	BQL	19000	31600	36400	27500	23300	19900	21400
SD	BQL	24100	27300	20600	17300	12400	9700	8900
Min	BQL	4430	8840	8260	6860	4840	3620	6520
Median	BQL	14400	25400	29600	23900	22800	22600	26300
Max	2.29	145000	142000	113000	106000	57500	34200	30900

Summary statistics are presented to 3 significant figures, except for SD which is presented to the same precision as its respective mean.
BQL = Below the lower limit of quantification (LLOQ = 0.8 ng/mL)

Serum concentrations reported as ng/mL.
Source: table 10, study report 20040215

Figure 1. Serum Denosumab Trough Concentrations



[a]Solid line indicates median values, boxes indicate 25th to 75th percentiles, whiskers indicate 10th and 90th percentiles and circles represent outliers.

Source: Appendix Figure 12.4.1, study report 20040215
The dashed red line represents the mean steady-state concentrations listed in the approved labeling for a dosing regimen of 120 mg once every 4 weeks.

The approved labeling describes the PK of denosumab administered at a dose of 120 mg once every 4 weeks as follows:

> 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.

The supplemental application to support the indication for the prevention of SRE (Suppl. 7) included PK data for patients enrolled into Study 20040113, 20050103, 20050136, and 20050244 following a dose of 120 mg administered once every 4 weeks. The mean serum trough concentration listed in the labeling was calculated following the administration of 120 mg once

monthly in 35 women with metastatic breast cancer. (Study 20040113, Clinical Study Report Table 10-1). As the same bioanalytical assay was used to measure the serum concentrations in this study as was used in Study 20040215, a cross study comparison of the serum concentrations at steady-state is permissible. Steady-state concentrations appear to have been achieved earlier with the proposed dosing regimen, as compared to the approved dosing regimen (approved, 6 months vs. proposed, 3 months). The highest mean trough concentration that was measured on day 29 is higher than the mean steady-state concentration reported in the labeling, as demonstrated in **Figure 1**, but the mean trough concentrations decrease with monthly dosing with the proposed regimen to trough concentrations that are comparable to the mean steady-state concentrations stated in the initial labeling. It is recommended to modify the proposed labeling to state that steady-state concentrations are achieved within three months following administration of denosumab at the proposed dose.

Table 4 compares the populations used to estimate the mean steady-state concentrations listed in the approved labeling and in Study 20040215. Based on population PK analyses submitted as part of Suppl. 7, clearance and volume of distribution were proportional to body weight; steady-state exposure following repeat administration of 120 mg once 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. As the weight appears similar a cross studies, it is unlikely that weight is contributing to differences in serum trough concentrations between the two studies. Of note, age, gender and race do not affect the PK of denosumab, as explored in the population PK analyses.

Table 4. Comparison of the Populations in which Serum Denosumab Trough Concentrations were Calculated

Study No.	Study 20040113 (n = 42) Supplement 7	Study 20040215 (n = 37) Supplement 94
Dose	120 mg once every 4 weeks	120 mg once weekly (days 1, 8, and 15) for the first three weeks of a four week treatment cycle, and then once monthly starting day 29
Age, years mean ± SD min, max	 57 ± 11 33, 82	 37 ± 12 19, 63
Gender (M/ W)[1] (n)	0 / 42	17 / 20
Race (W/ H/ A/ B/ O)[2] (n)	30 / 10 / 1 / 0 / 1	27 / 5 / 3 / 2 / 0
Baseline Weight, kg mean ± SD min, max	 70.7 ± 17.1 48, 123	 78.3 ± 30.3 38, 174

SD = standard deviation
[1]W = women, M = men
[2] W = White, H = Hispanic, A = Asian, B = Black, O = Other
Source = Clinical Study Report 20040113, 20040215; ASLBASE.XPT

2.3 INTRINSIC FACTORS

The applicant did not provide new population PK analyses or dedicated studies to assess intrinsic factors in this submission; these data have been previously reviewed as part of the original or supplemental applications.

2.3.3 Immunogenicity

Serum samples to assess for the presence of denosumab antibodies were collected from patients enrolled into Study 20040215 before the dose on week 25, week 49 and then approximately every 6 months and into Study 20062004 before day 1, at the end of study, and at follow-up visits every 6 months for up to 12 to 24 months dependent on the cohort. Samples from all subjects tested at the time of these reports were negative for anti-denosumab binding antibodies.

The approved labeling describes immunogenicity as follows:

> 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.

As no anti-product antibodies were detected in the two clinical studies submitted to support the proposed indication, no additional analytical assays or labeling revision appears necessary.

2.4 EXTRINSIC FACTORS

The applicant did not provide new population PK analyses or dedicated studies to assess extrinsic factors in this submission; these data have been previously reviewed as part of the original or supplemental applications.

2.5 GENERAL BIOPHARMACEUTICS

Please refer to the clinical pharmacology review of the original and supplemental applications.

For Study 20062004, the dose of 120 mg was administered using a single use vial containing denosumab at a concentration of 70 mg/mL. This vial is the approved dosage form and strength for denosumab as Xgeva.

For Study 20050215, the dose of 120 mg was administered using two single use vials containing denosumab at a concentration of 60 mg/mL. This vial is the approved dosage form and strength for denosumab as Prolia.

As part of the supplemental application to support the indication for the prevention of SRE (Suppl. 7.), the applicant demonstrated that the PK of two-60 mg/mL injections or one-120 mg/1.7 mL injection were comparable in 116 healthy volunteers randomized 1:1 to receive a single dose of 120 mg of denosumab. Therefore, the administration of the dose using two different formulations will not confound the interpretation of the PK or clinical data.

2.6 ANALYTICAL SECTION

Denosumab Serum Concentrations

The bioanalytical report referred to in the Pharmacokinetic Appendix (appx 12) of the study report for Study 20040215 cannot be found. In the appendix, the applicant states that the assay for determining denosumab concentrations in human serum was based upon a method developed at Amgen Inc. CA, [redacted] (b) (4) However, the Summary of the Clinical Pharmacology Studies and the Pharmacokinetic Addendum to the study report indicates that assay study no. 102110 was used to measure denosumab serum concentrations in this study. The method validation report for this assay was submitted on May 19, 2009; this assay was validated at [redacted] (b) (4) and reviewed as part of Suppl. 7. An information request was sent on March 13, 2013 to the applicant to provide the analytical report and cross validation of the assays if different assays were used. The applicant stated that the serum denosumab assay methodology was developed at Amgen Inc., CA and validated at [redacted] (b) (4) (Amgen Validation Study No. 102110), utilizing the [redacted] (b) (4) and that this methodology (Amgen Validation Study No. 102110) was used for Study 20040215 [redacted] (b) (4)) and to support the supplemental biologics license application for the prevention of bone metastases (Study 20050147 [redacted] (b) (4)]) and the advanced cancer application (Studies 20050136 [[redacted] (b) (4)], 20050244 [redacted] (b) (4): [redacted] (b) (4), and 20050103 [redacted] (b) (4)

Immunogenicity – Binding Antibodies

The bioanalytical assay used to measure antibodies in these studies is the same assay used to measure antibodies in Suppl. 7 (MET 002025). The method report was submitted on August 16, 2010 as part of Suppl. 7. (eCTD 71).

3 DETAILED LABELING RECOMMENDATIONS

Clinical pharmacology recommended changes to the Sections 7 and 12 of the approved labeling. A strikethrough indicates text to be removed and underlined indicates text to be added to the approved labeling. These labeling recommendations reflect the labeling recommendations sent to the applicant for consideration.

[redacted] (b) (4)

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

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/s/

STACY S SHORD
05/19/2013

HONG ZHAO
05/19/2013
I concur.

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	125320/94.0	**Brand Name**	Xgeva
OCP Division (I, II, III, IV, V)	DCPV	**Generic Name**	Denosumab
Medical Division	DOP2	**Drug Class**	Monoclonal Antibody
OCP Reviewer	Stacy S. Shord	**Indication(s)**	(b) (4)
OCP Team Leader	Hong Zhao	**Dosage Form**	Intravenous
Pharmacometrics Reviewer		**Dosing Regimen**	120 mg on days 1, 8 and 15 of cycle one, then on day 1 of each subsequent 28-day treatment cycle
Date of Submission	December 11, 2012	**Route of Administration**	Subcutaneous
Estimated Due Date of OCP Review	May 20, 2013	**Sponsor**	Amgen
Medical Division Due Date	May 23, 2013	**Priority Classification**	Priority
PDUFA Due Date	June 13, 2013		

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:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1	1	Study 20040215 (sparse PK)
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 -				
ethnicity:				
gender:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

pediatrics:	X	1	1	Study 20040215 (skeletally mature adolescents)
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	X	1	1	Study 20040215 (NTx, CTx)
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
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	NA			
Bio-waiver request based on BCS	NA			
BCS class	NA			
Dissolution study to evaluate alcohol induced dose-dumping	NA			
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References				
Total Number of Studies		**1**	**1**	The suppl also contains study reports for clin pharm studies that appear to have been previously reviewed under this BLA and a final study report for a phase 2 to support the indication; no PK or PD were included in this latter trial.

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			

Reference ID: 3256062

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
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.

Not applicable.

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

None.

Stacy. Shord, Pharm.D.	02/05/2013
Reviewing Clinical Pharmacologist	Date
Hong Zhao, Ph.D.	02/05/2013
Team Leader/Supervisor	Date

Reference ID: 3256062

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/s/

STACY S SHORD
02/05/2013

HONG ZHAO
02/05/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

<u>OTHER REVIEW(S)</u>

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: June 13, 2013

Applicant Name: Amgen, Incorporated
U.S. License #: 1080
STN(s): 125320/94
Product(s): Xgeva® (denosumab)

Short summary of application: Efficacy Supplement for patients with giant cell tumor in adults and skeletally mature adolescents.

FACILITY INFORMATION

Manufacturing Location:	Colorado
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; Drug substance in-process testing; Drug substance storage

[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."

Reference ID: 3321328

This site was inspected by DEN-DO on March 18 – 29, 2013 and classified VAI. This was a routine GMP surveillance inspection covering denosumab drug substance manufacturing operations. The CBI profile was updated and is acceptable.

Manufacturing Location:	Colorado
Firm Name:	Amgen Inc. (ACO)
Address:	4000 Nelson Road Longmont, CO 80503
FEI:	3002892484

Short summary of manufacturing activities performed: Master cell bank and working cell bank storage; Raw material storage, testing and release; Drug substance in-process, lot release and stability testing; Drug substance storage; Drug product lot release and stability testing.

This site was inspected by DEN-DO on March 18 – 29, 2013 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug substance manufacturing operations. The CBI profile was updated and is acceptable.

Manufacturing Location:	California
Firm Name:	Amgen Inc. (ATO)
Address:	One Amgen Center Drive Thousand Oaks, CA 91320
FEI:	2026154

Short summary of manufacturing activities performed: Master cell bank and working cell bank storage; Working cell bank production; Raw material testing, storage and release; Drug substance storage; Drug product storage and distribution.

This site was inspected by LOS-DO on November 15 – December 12, 2012 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug substance testing and storage operations. The CTB profile was updated and is acceptable.

Manufacturing Location:	Puerto Rico
Firm Name:	Amgen Manufacturing Limited (AML)
Address:	State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777
FEI:	1000110364

Short summary of manufacturing activities performed: Working cell bank storage; Raw material testing, storage, and release; Drug substance manufacturing; Drug substance in-process, lot release and stability testing; Drug substance storage; Drug Product Manufacturing (Formulation; Fill and finish); Drug product in-process and release testing; Drug product stability testing; Packaging/Labeling; Drug product storage

This site was inspected by CDER-OMPQ on June 18 – 22, 2012 and classified NAI. This was a PAI covering denosumab drug substance and drug product manufacturing

operations. The TRP profile was updated following this inspection and is acceptable. This site is considered acceptable from a drug manufacturing perspective.

However, CDRH has indicated that this site should be subjected to a device inspection due to lack of device inspectional history. A FACTS assignment request has been created (FACTS assignment number 1512171).

Manufacturing Location:	Germany
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 lot release testing; Drug substance storage

This site was inspected by IOG on March 5 – 13, 2012 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug substance manufacturing operations. The CBI, SVS and TRP profiles were updated and are acceptable.

Manufacturing Location:	Ireland
Firm Name:	Amgen Technology Ireland
Address:	Pottery Road, Dun Laoghaire, Co. Dublin, Ireland
FEI:	3002808497

Short summary of manufacturing activities performed: Drug product formulation; Drug product fill and finish, Drug product in-process, lot release and stability testing; Drug product storage

This site was inspected by IOG on March 11 – 22, 2013 and classified VAI. This was a PLI covering Xgeva drug product manufacturing and testing operations. The SVS profile was updated and is acceptable.

(b) (4)

[redacted]

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(b) (4)

[redacted]

OVERALL RECOMMENDATION

There are no pending or ongoing compliance actions that prevent approval of this supplement.

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/s/

RANJANI PRABHAKARA
06/07/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

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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: June 13, 2013

Applicant Name: Amgen, Incorporated
U.S. License #: 1080
STN(s):125320/94
Product(s) XGEVA (denosumab)
Short summary of application: Efficacy Supplement for patients with giant cell tumor in adults and skeletally mature adolescents.

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."

Reference ID: 3314789

Drug substance in-process testing
Drug substance storage

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

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

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

Manufacturing Location:
Firm Name: Boehringer Ingelheim Pharma GmbH & Co. Kg
Address: Birkendorfer Strasse 65
88397 Biberach an der Riss
Germany

FEI: 3007748866

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

Manufacturing Location:
Firm Name: Amgen Technology (Ireland)
Address: Pottery Road
Dublin, Ireland

FEI: NAI

Short summary of manufacturing activities performed:
Drug Product in-process, lot release and stability testing

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/s/

MELANIE B PIERCE
05/28/2013

MEMORANDUM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

****Pre-decisional Agency Information****

Memorandum

Date: **May 22, 2013**

To: Melanie Pierce, Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
OPDP

Subject: **OPDP comments on draft product labeling for Xgeva (denosumab) injection**
BLA 125320

In response to your consult request dated January 4, 2013, OPDP has reviewed the proposed product labeling (PI) for Xgeva injection. Specifically, OPDP has reviewed the Highlights and Sections 1, 2, 5, 6, 7, 8.4, 8.7, 12, 13, 14.2, and 17.

If you have any questions about OPDP's comments on the PI, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov.

Section	Statement from draft	Comment
• **8 USE IN SPECIAL POPULATIONS-** **8.7 Females and Males of Reproductive Potential**	Males- The extent to which denosumab is present in seminal fluid is unknown. There is potential for fetal exposure to denosumab when a male-treated with Xgeva has unprotected sexual intercourse with a pregnant partner. (b) (4) (b) (4) Advise males of this potential risk.	Does the review division agree that (b) (4) it the extent to which denosumab is present in seminal fluid is unknown?
• **14 CLINICAL** (b) (4) **14.2 Giant Cell Tumor of the**	(b) (4) independent review (b) (4) (b) (4) patients enrolled (b) (4) Trials 4 and (b) (4)	Does the review division feel that results from this (b) (4) review provide substantial evidence?

Bone		

APPEARS THIS WAY ON ORIGINAL

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/s/

MARYBETH TOSCANO
05/22/2013

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

Pediatric and Maternal Health Staff Review

Date: May 8, 2013

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari, Ph.D., DABT, Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Hari Cheryl Sachs, MD, Team leader Pediatrics
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Oncology Products 2 (DOP2)

Drug: Xgeva™ (denosumab) BLA 125320/94

Applicant: Amgen

Route of Adminstration: Subcutaneous Injection

Subject: Pregnancy, Nursing Mothers, Pediatric Use Labeling

Materials Reviewed:

- Proposed labeling for Xgeva (denosumab) subcutaneous injection, submitted December 12, 2012
- Summary of Clinical Safety, submitted December 12, 2012

Reference ID: 3305771

Consult Question:

- Pediatrics: Please review subsection 8.4 Pediatric Use to determine if the proposed language is appropriate.
- Maternal Health: Please ensure section 8 Use in Specific Populations is appropriately updated

INTRODUCTION

On December 12, 2012, AMGEN submitted an Efficacy Supplement for Xgeva (denosumab) for the [redacted] (b) (4)
Xgeva was initially approved on November 18, 2010 for the prevention of skeletal-related events in patients with bone metastases from solid tumors. Orphan Designation was granted for this indication on December 20, 2010. Xgeva received initial U.S. approval on November 18, 2010, for the prevention of skeletal-related events in patients with bone metastases from solid tumors (indication resides in Division of Oncology Products 1 - DOP1).

Denosumab is also approved under the tradename Prolia for: 1) treatment of postmenopausal women with osteoporosis at high risk of fracture; 2) treatment to increase bone mass in men with osteoporosis at high risk of fracture; 3) treatment to increase bone mass in men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer; and, 4) treatment to increase bone mass in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

On February 5, 2013, the Division of Oncology Products 2 (DOP2) consulted the Pediatric and Maternal Health Staff (PMHS) to review and update pregnancy, nursing mothers and pediatric use information in Xgeva labeling as needed.

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 is 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. Pregnant cynomolgus monkeys treated with denosumab at pharmacologic active doses had an increased risk of stillbirths and

[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

Reference ID: 3305771

overall infant mortality. Additional adverse developmental findings included abnormal bone growth resulting in reduced bone strength, reduced hematopoiesis, tooth malalignment, absence of peripheral lymph nodes and decreased neonatal growth. Many of the adverse developmental findings, with the exception of absence of peripheral lymph nodes, were reversible within 180 days (± 2 days) after birth. However, maternal dosing was only done during the period of organogenesis, so the effects of denosumab on later fetal development were not assessed.

Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.[4] Therefore, exposure of the fetus to Xgeva, and the potential effects of exposure are likely to be greater during the second and third trimesters of pregnancy.

Pregnancy Exposure

Amgen has a Pregnancy Surveillance Program[5] that incorporates all Amgen medications marketed worldwide as well as those investigated in clinical studies. This program is voluntary and collects maternal and infant data at specified timepoints during pregnancy and infancy.

Xgeva

Thirteen pregnancies with Xgeva use were reported from the inception of the clinical development program through May 26, 2012:

- 1 pregnancy was reported postmarketing by a healthcare professional
- 12 pregnancies were reported during the GCTB clinical trials.
  - 8/12 pregnancies were reported in female study subjects and 4/12 were paternal exposure cases
    - 4 healthy live births (2 were paternal exposures)
    - 4 elective terminations
    - 1 spontaneous abortion
    - 4 unknown outcomes (2 were paternal exposures)

Reviewer Comments:

1. *GCTB usually occurs in skeletally mature individual between the ages of 20 to 50 years and is more common in females than males.*
2. *The informed consent for denosumab clinical trials provides fetal risk information and provided information on the use of highly effective contraception methods. It is unknown if study subjects received contraceptive counseling in addition to the informed consent.*
3. *Current approved Xgeva labeling does not include a contraception use statement for females of reproductive potential.*
4. *The amount of denosumab present in semen is unknown; however, the risk of fetal harm via exposure to a pregnant partner is likely to be low. Amgen has a postmarketing requirement (PMR) for a clinical trial to investigate the levels of denosumab in the semen of men treated with Prolia. The final study report is due December 2014.*

---

[4] Kane S, Acquah L. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Amer J Gastroent; 2009, Jan;104(1):228-32

[5] www.amgenpregnancy.com

Reference ID: 3305771

Prolia

Five pregnancies were reported with Prolia from inception of the clinical development program through May 26, 2012.

- 5 maternal exposures; 1 both maternal and paternal exposure
  - 2 healthy live births
  - 1 spontaneous abortion
  - 2 unknown outcomes (lost to follow-up)

PREA

This Efficacy Supplement does not trigger the Pediatric Research Equity Act (PREA) because of the Orphan Designation granted for the indication of GCTB. In response to Amgen's July 2, 2012, Proposed Pediatric Study Request (PPSR), FDA issued a pediatric Written Request (WR) on November 30, 2012, (b) (4) . The applicant agreed to the WR on December 10, 2012. Reports of the WR studies must be submitted to the Agency on or before January 31, 2021, for pediatric exclusivity determination.

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, only the presence or absence of drug in human milk is noted and presented in the labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

PMHS assisted the Division of Oncology Products 1 (DOP1) with prior revisions to Xgeva pregnancy, nursing mothers, and pediatric use labeling (see PMHS Labeling Review dated March 29, 2012). Those PMHS recommendations are reflected in the currently approved Xgeva labeling.

Twelve pregnancies occurred in the clinical trials with Xgeva for Giant Cell Tumor of Bone (GCTB). Prior to these reports only one other pregnancy was reported with the use of Xgeva. GCTB occurs mainly in populations that include females of reproductive potential. The Informed Consent for denosumab clinical trials provides fetal risk information and provides information on the use of highly effective contraception methods; however, it is unknown if patients are offered or given contraceptive counseling. Four of the pregnancies occurred with

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paternal exposure to Xgeva. The amount of Xgeva present in semen is unknown; however, the risk of fetal harm via semen exposure to a pregnant partner is likely to be low. Amgen has a postmarketing requirement (PMR) for a clinical trial to investigate the levels of denosumab in the semen of men treated with Prolia. The final study report is due in December 2014. Prolia labeling labeling contains semen fetal risk information, while the current approved Xgeva labeling lacks this risk information. Information on contraception use for females of reproductive potential as well as semen fetal risk information for males should be placed in the optional labeling subsection *Females and Males of Reproductive Potential* because the current approved Xgeva labeling does not include this important information for females and males of reproductive potential.

Amgen has a Pregnancy Surveillance Program to gather data about pregnancies in women who have had exposure to any marketed or investigational Amgen product prior to conception or during pregnancy. Information is also gathered when the male sexual partner was exposed to an Amgen product prior to conception, or during the pregnancy. The intent of the program is to collect sufficient pregnancy exposure data in order to communicate clinically relevant human data to healthcare providers who treat and counsel patients who are pregnant or are considering pregnancy.[6] PMHS provided a review of the Amgen Pregnancy Surveillance Elements on February 8, 2010, as a consult request for Neulasta (pegfilgrastin) 125031/120/1, for the former Division of Biologic Oncology Products (DBOP). Pregnancy Surveillance Program information appears in both Xgeva and Prolia pregnancy labeling.

Pediatric Use Labeling

The Pediatric Use subsection of labeling should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted. 21 CFR 201.57(c)(9)(iv) describes the appropriate pediatric use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

The Xgeva pediatric use subsection has been revised to include the new indication for the treatment of unrespectable GCTB in skeletally mature adolescents.

CONCLUSIONS

PMHS has proposed revisions to Highlights of prescribing Information, Warnings and Precautions, and recommends the optional subsection Females and males of Reproductive information to provide important fetal risk information and contraception advice for females and males of reproductive potential. No revisions are required for Pregnancy, Nursing Mother, or Pediatric Use subsections of Xgeva labeling. Xgeva pregnancy already contains contact information for Amgen's Pregnancy Surveillance Program.

PMHS recommends that Xgeva and Prolia labeling be aligned to contain consistent risk information for females and males of reproductive potential as pregnancies have occurred with the use of both drugs.

[6] http://amgenpregnancy.com/

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

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

/s/

JEANINE A BEST
05/08/2013

LYNNE P YAO
05/10/2013

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: June 13, 2013

Applicant Name: Amgen, Incorporated
U.S. License #: 1080
STN(s):125320/7; formerly 125320/94
Product(s) XGEVA (denosumab)
Short summary of application: Efficacy Supplement for patients with giant cell tumor in adults and skeletally mature adolescents.

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
Drug substance in-process testing

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[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."

Reference ID: 3264221

Drug substance storage

Inspected by DEN-DO December 14, 2011 – January 6, 2012 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug substance manufacturing operations. The CBI profile was updated and is 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 by DEN-DO December 12, 2011 – January 6, 2012 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug substance manufacturing operations. The CBI profile was updated and is acceptable.

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 November 15 – December 12, 2012 and classified VAI. This was a routine GMP surveillance inspection covering biotech responsibilities at this site. This site is acceptable for the purposes of the supplement.

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 by SJN-DO April 14 – April 29, 2011 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug substance and drug product manufacturing operations. The TRP and BTP profiles were updated and are 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

(b) (4)

Manufacturing Location:
Firm Name: Amgen Technology
(Ireland)
Address: Pottery Road
Dublin, Ireland

FEI: NAI

Short summary of manufacturing activities performed:
Drug Product in-process, lot release and stability testing

This site, under the management of Amgen does not have any FDA inspectional history. An inspection is scheduled to be conducted in March. It will cover drug product manufacturing and testing operations.

(b) (4)

(b) (4)

[redacted]

OVERALL RECOMMENDATION

There are no pending or ongoing compliance actions that prevent approval of this supplement. Please resubmit this TB-EER 15-30 days prior to the planned action date.

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

/s/

TIMOTHY J POHLHAUS
02/20/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 125320/94

Application Type: Efficacy Supplement

Name of Drug: Xgeva (denosumab)

Applicant: Amgen, Incorporated

Submission Date: December 11, 2012

Receipt Date: December 12, 2012

1.0 Regulatory History and Applicant's Main Proposals

Xgeva (denosumab) is presently indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors and for the [redacted] (b) (4) (b) (4)

Denosumab initially received approval for the treatment of postmenopausal osteoporosis in women with high risk of fracture under the trade name Prolia®. On November 18, 2010, FDA approved a sBLA for denosumab, under the trade name XgevaTM, for the prevention of skeletal-related events in patients with bone metastases from solid tumors. On December 20, 2010, Amgen received orphan drug designation for denosumab for the treatment of patients with GCTB. On April 5, 2011 a type B, pre-s-BLA meeting was held with Amgen to discuss the clinical development of denosumab to support a supplemental BLA for the treatment of patients with GCTB. A type C meeting was held on August 4, 2011 to discuss Amgen's draft proposal regarding radiographic image assessments for the proposed GCTB indication for Xgeva (denosumab).

On December 11, 2012, Amgen, Incorporated submitted supplemental biological application 125320/94 for the [redacted] (b) (4).

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

The following labeling issue was identified and communicated to Amgen in the filing letter:

> In the Full Package Insert: Postmarketing Experience subsection of ADVERSE REACTIONS the following statement is missing: *"Because these reactions are reported*

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voluntarily from a population of uncertain size, it is not always possible to reliably estimae their frequency or establish a causal relationship to drug exposure.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

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Selected Requirements of Prescribing Information (SRPI)

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

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Selected Requirements of Prescribing Information (SRPI)

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

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YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **“See 17 for PATIENT COUNSELING INFORMATION”**

If a product **has** FDA-approved patient labeling:

- **“See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.”**
- **“See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.”**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY** or **Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

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YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS

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Selected Requirements of Prescribing Information (SRPI)

7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

N/A 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

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N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

NO 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *Missing "Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.*

Patient Counseling Information

N/A 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

Reference ID: 3257523

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/s/

MELANIE B PIERCE
02/07/2013

MONICA L HUGHES on behalf of KAREN D JONES
02/07/2013

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 Supplement # 125320/94	Efficacy Supplement Type SE-
Proprietary Name: Xgeva Established/Proper Name: denosumab Dosage Form: Injection Strengths: 120 mg/1.7 mL		
Applicant: Amgen, Incorporated Agent for Applicant (if applicable): NA		
Date of Application: December 11, 2012 Date of Receipt: December 12, 2012 Date clock started after UN: NA		
PDUFA Goal Date: June 13, 2013	Action Goal Date (if different): NA	
Filing Date: February 10, 2013	Date of Filing Meeting: February 5, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NA		
Proposed indication(s)/Proposed change(s): [redacted] (b) (4)		

Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 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 (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

Reference ID: 3257494

☐ 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):	

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 New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.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/OMPQ 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			

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User Fee Status	Payment for this application:
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.	☒ 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?			X	
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)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

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Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				

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***				
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	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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(*BLAs/BLA efficacy supplements*) including: ☒ 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 #			**X**	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**X**	
• If yes, were all of them submitted on time?				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
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, a 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)?			X	
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)?	X			

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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.*				
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? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both 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)(1) 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…"*	X			
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.***			X	This is an sBLA

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: 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:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			**X**	

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Pediatrics	YES	NO	NA	Comment
PREA 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		Orphan drug status for adults and skeletally-mature adolescents
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
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***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
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/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

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	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
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 applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	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?	X			

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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If no, request in 74-day letter.				
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):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 11, 2012 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			X	

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ATTACHMENT

MEMO OF FILING MEETING

DATE: February 5, 2013

BLA/NDA/Supp #: 125320/94

PROPRIETARY NAME: Xgeva

ESTABLISHED/PROPER NAME: denosumab

DOSAGE FORM/STRENGTH: Injection for subcutaneous use

APPLICANT: Amgen, Incorporated

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): [redacted] (b) (4) [redacted] (b) (4).

BACKGROUND: Xgeva (denosumab) is presently indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors and for the [redacted] (b) (4) [redacted] (b) (4).

Denosumab initially received approval for the treatment of postmenopausal osteoporosis in women with high risk of fracture under the trade name Prolia®. On November 18, 2010, FDA approved a sBLA for denosumab, under the trade name XgevaTM, for the prevention of skeletal-related events in patients with bone metastases from solid tumors. On December 20, 2010, Amgen received orphan drug designation for denosumab for the treatment of patients with GCTB. On April 5, 2011 a type B, pre-s-BLA meeting was held with Amgen to discuss the clinical development of denosumab to support a supplemental BLA for the treatment of patients with GCTB. A type C meeting was held on August 4, 2011 to discuss Amgen's draft proposal regarding radiographic image assessments for the proposed GCTB indication for Xgeva (denosumab).

On December 11, 2012, Amgen, Incorporated submitted supplemental biological application 125320/94 for the [redacted] (b) (4) [redacted] (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Melanie Pierce	Y
	CPMS/TL:	Karen D. Jones/ Monica Hughes	N
Cross-Discipline Team Leader (CDTL)	Suzanne Demko		Y

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Clinical	Reviewer:	Martha Donoghue	Y
	TL:	Suzanne Demko	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:	Stacy Shord	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Vivian Yuan	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shawna Weis	Y
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	NA	
	TL:		
Product Quality (CMC)	Reviewer:	Lixin Xu	Y
	TL:	Chana Fuchs	N
Quality Microbiology *(for sterile products)*	Reviewer:	NA	
	TL:		
CMC Labeling Review	Reviewer:	Kimberly Rains	N
	TL:	Marylyn Welschenbach	N
Facility Review/Inspection	Reviewer:	NA	

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	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	NA	
	TL:		
OSE/DRISK (REMS)	Reviewer:	Suzanne Robottom	N
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	NA	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	NA	
	TL:		
Other reviewers-OPDP	Carole Broadnax		
Other attendees	Jeffrey Summers		Y

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

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• Clinical study site(s) inspections(s) needed? **If no,** explain: No protocol deviations, no safety signals, Amgen was recently inspected by OSI, lack of sites responsible for driving the results of the study, and there was an IRC for the primary endpoint.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• 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)	☐ YES

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needed?	☐ 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**:	☒ 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
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☒ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO

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Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted. **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**: NA	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Patricia Keegan, MD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): NA **Comments**: No 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

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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 OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☒	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 [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Reference ID: 3257494

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
02/07/2013

MONICA L HUGHES on behalf of KAREN D JONES
02/07/2013

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: June 13, 2013

Applicant Name: Amgen, Incorporated
U.S. License #: 1080
STN(s):125320/7; formerly 125320/94
Product(s) XGEVA (denosumab)
Short summary of application: Efficacy Supplement for patients with giant cell tumor in adults and skeletally mature adolescents.

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

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[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."

Reference ID: 3255025

Drug substance in-process testing
Drug substance storage

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

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

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

Manufacturing Location:
Firm Name: Boehringer Ingelheim Pharma GmbH & Co. Kg
Address: Birkendorfer Strasse 65
88397 Biberach an der Riss
Germany

FEI: 3007748866

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

Manufacturing Location:
Firm Name: Amgen Technology (Ireland)
Address: Pottery Road
Dublin, Ireland

FEI: NAI

Short summary of manufacturing activities performed:
Drug Product in-process, lot release and stability testing

(b) (4)

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

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

/s/

MELANIE B PIERCE
02/04/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

RISK ASSESSMENT and RISK MITIGATION 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
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	May 21, 2013
Reviewer(s):	Suzanne Robottom, Pharm.D. Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D. DRISK
Division Associate Director:	Mary B Willy, Ph.D., DRISK
Subject:	Review evaluates if a risk evaluation and mitigation strategy (REMS) is needed
Drug Name(s):	Xgeva (denosumab)
Therapeutic Class:	RANK ligand inhibitor
Dosage and Route:	120 mg subcutaneous injection on day 1, 8, and 15 then every 4 weeks
Application Type/Number:	BLA 125320/94
Applicant/sponsor:	Amgen
OSE RCM #:	2013-103

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for Xgeva (denosumab) BLA 125320, supplement 94. The applicant submitted a "pharmacovigilance plan."

1.1 BACKGROUND

Xgeva (denosumab), a human IgG2 monoclonal antibody that inhibits receptor activation of the nuclear receptor factor κB (RANK) by binding to RANK ligand (RANKL), is under review for (b) (4) [redacted]. The proposed dosing is 120 mg subcutaneously every 4 weeks with additional, "loading" 120 mg injections on days 1, 8, and 15.

Xgeva is approved for prevention of skeletal-related events in patients with bone metastases from solid tumor at a dose of 120 mg administered subcutaneously every 4 weeks. A REMS was not necessary for that indication to ensure the benefits of the Xgeva outweighed the risk.

(b) (4) [redacted]

Prolia

Denosumab is also available under the trade name Prolia and approved for the following indications at a dose of 60 mg administered subcutaneously by a healthcare provider every 6 months:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men with osteoporosis at high risk for facture, defined as history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Prolia was initially approved with a REMS consisting of a Medication Guide and communication plan to inform healthcare providers and patients about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw.

2 MATERIALS REVIEWED

(b) (4) [redacted]

Reference ID: 3312274

- Donoghue M. Denosumab Clinical Review signed May 20, 2013.
- Amgen's Information Request Response received May 13, 2013.
- FDA draft Xgeva revised label to include GCTB indication dated May 8, 2013.
- Midcycle meeting slides – Clinical Presentation by M. Donoghue. March 13, 2013.
- Amgen's Pharmacovigilance Plan – Denosumab XGEVA Indications. Version dated October 3, 2012 and submitted on December 11, 2012.
- Prolia (denosumab) [package insert]. Thousand Oaks, CA: Amgen; 2012.
- Xgeva (denosumab) [package insert]. Thousand Oaks, CA: Amgen; 2013.
- Best J. Maternal Health Team Memorandum for Denosumab Pregnancy Registry Protocol dated September 8, 2009. Signed October 14, 2009.
- Amgen's Denosumab Pregnancy Exposure Registry Protocol (Number 20090589) dated September 8, 2009.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

There are two, multi-center, open-label, single arm studies providing the basis for the GCTB application. Study 20040215 included 37 patients and Study 20062004 included 282 patients. Slightly more females were enrolled with the median age of 30 years (range 19, 63 yo) and 33 years (13, 83 yo), respectively. The median duration of exposure was 21 months (2, 49 months) for study 20040215 and 10 months (3, 28) and 14 months (2, 29) for Study 20062004 depending on the cohort. Depending on the criteria, the treatment response was 25% (by RECIST[2] 1.1; vs 8% imaging control group) or 76% (density/size; vs 35% imaging control group).

DOP2 acknowledges the rare nature of GCTB, the lack of treatment alternatives, and limitations with the current data. (b) (4) "adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity" (b) (4) (b) (4) and approving the use under accelerated approval pending the final study report of Study 20062004.

Please refer to the clinical review by Dr. Martha Donoghue, M.D. for the full review of efficacy.

3.2 SAFETY CONCERNS

3.2.1 Sponsor's Safety Concerns

The Sponsor identifies the following risks in their "pharmacovigilance plan"

- Hypocalcemia

[2] Response Evaluation Criteria in Solid Tumors (RECIST)

Reference ID: 3312274

- Osteonecrosis of the jaw (ONJ)

Reviewer Comment: No serious adverse events of hypocalcemia were reported in the GCTB trials.

Both of the above events are known risks and listed in the Warnings section of the approved Xgeva labeling. The approved Xgeva labeling cites 3.1% incidence of severe hypocalcemia. In the Prolia label, hypocalcemia is listed as both a Contraindication and a Warning.

Additional information regarding ONJ is provided in Section 3.2.2 of this review.

The risks listed below are risks the sponsor identifies as "under surveillance but have no specific signal in the GCTB population":

- Hypersensitivity reactions

  Reviewer Comment: Hypersensitivity is listed as a Contraindication in the approved Xgeva and Prolia labeling. Based on the draft clinical review, the incidence of adverse events potentially related to hypersensitivity was 10% in the GCTB clinical program. No cases of anaphylaxis were reported.

  The Division of Pharmacovigilance is reviewing case reports reported through FAERS. The review of this possible signal is ongoing and any additional risk management considerations will be addressed in a separate review, if necessary.

- Immunogenicity

  Reviewer Comment: The draft clinical review states that anti-denosumab antibodies were not detected in any patient enrolled in Studies 20040215 or 20062004, through the third interim analysis.

  Immunogenicity is listed in the Adverse Reactions section of Xgeva and Prolia labeling.

- Cataracts in men with prostate cancer undergoing androgen deprivation therapy

  Reviewer Comment: Not applicable to current population.

- Infections

  Reviewer Comment: The draft clinical review states that the per-patient incidence of adverse events in the MedDRA infections and infestations was 35.9% overall with the majority characterized as mild to moderate in severity.

  Infection is not listed in the Xgeva labeling but has a Warning in the Prolia labeling. Risk of infection is a well-established risk in cancer patients receiving treatment.

Reference ID: 3312274

- Cardiovascular events

  Reviewer Comment: The draft clinical review states that in the GCTB development program, all cardiac adverse events were of Grade 2 or lesser severity, and none were considered serious. The 120-day safety update included a report of two patients who experienced cardiac adverse events that were considered serious; denosumab was not discontinued following these adverse events.

  Cardiovascular risk is not specifically addressed in the approved Xgeva labeling.

- Malignancy

  Reviewer Comment: Additional information regarding malignancy is provided in Section 3.2.2 of this review.

3.2.2 FDA Safety Concerns

Please refer to the clinical review by Dr. Martha Donoghue, M.D. for the full review of the safety. The following is a summary of the key findings from the clinical presentation at the midcycle meeting on March 13, 2013, draft clinical review, and review team discussions.

- ONJ: In the GCTB clinical trials, four subjects (n=304; 1.3%) were reported with ONJ.

  Reviewer Comment: In the clinical trials in patients with bone metastasis from solid tumors, the Xgeva label states "ONJ was confirmed in 1.8% of patients in the Xgeva group and 1.3% in the zoledronic acid group. 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)."

- Malignant Transformation/Secondary Malignancy: Nine patients (3%) developed malignant transformation of GCTB or secondary malignancy
  - 1 patient had a misdiagnosis
  - 1 patient had prior radiation therapy
  - 2 patients had osteosarcoma at baseline
  - 5 patients developed malignant transformation of GCTB (1.6%) or a new sarcoma within one year of denosumab treatment (duration of therapy 38 – 257 days) that could otherwise not be explained.

(b) (5)

[redacted]

Reference ID: 3312274

The Adverse Reactions section of the Prolia label states "the overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia groups" in patients with osteoporosis. In the clinical trial to increase bone mass in men, 4 Prolia treated patients (3.3%; 3 prostate cancer, 1 basal cell carcinoma) and no patients in the placebo group had new malignancies.

- Pregnancy: Amgen did not identify pregnancy exposure as a risk of concern. However, most notably, Amgen reports 18 pregnancies - 17 in clinical trials and 1 post-marketing report. Fifteen of the 18 pregnancies were reported in the two GCTB studies.
  - 4 healthy, full-term births without complication (2 cases = paternal exposure)
  - 4 elective terminations for "family planning purposes"
  - 1 elective termination without further information available
  - 2 spontaneous abortions
  - 4 pregnancies with birth outcomes unknown (information pending; 1 case is the post-marketing report))
  - 3 pregnancies lost to follow-up (2 cases = paternal exposure)

Current labeling for Xgeva includes Pregnancy Category D and addresses the use of Xgeva during pregnancy as follows (in pertinent part):

Warnings section:

> *Xgeva can cause fetal harm when administered to a pregnant woman. Based on findings in animals, Xgeva is expected to result in adverse reproductive effects. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent peripheral lymph nodes, abnormal bone growth and decreased neonatal growth.*
>
> *There are no adequate and well-controlled studies with Xgeva in pregnant women. Women should be advised not to become pregnant when taking Xgeva.*

Use in Specific Populations

> *The effects of Xgeva are likely to be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.*
>
> *In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy at a pharmacologically active dose, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia and tooth mal-alignment; and decreased neonatal growth. At birth out to one month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels).*

Reference ID: 3312274

Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated.

In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation.

The text pertaining to pregnancy in Prolia labeling is similar but lists Pregnancy as a Contraindication and Pregnancy Category X. Amgen administers a Pregnancy Surveillance Program for denosumab with contact information for reporting a pregnancy listed in labeling for both Prolia and Xgeva.

4 DISCUSSION

Currently, standard treatment for GCTB is surgery or radiation. If resectable, surgery can be curative. In some cases, extensive surgery may be required that is likely to cause severe morbidity and reduce quality of life. Recurrence risk ranges from 10 to 75%. There are no approved drugs for the treatment of GCTB.

Largely, the risks identified with denosumab treatment in the GCTB population are consistent with what is known and addressed through the current Xgeva label. However, it is important to note the difference in populations with GCTB and patients with bone metastases from solid tumor and its impact on the risks associated with denosumab. Patients with GCTB tend to be younger and in overall relatively good health compared to patients with bone metastases from solid tumors. Therefore, there is potential for a much longer duration of treatment for GCTB patients compared to patients with advanced cancer. DOP2 is requiring a post-marketing study (PMR) that will provide data collected from all patients enrolled in Study 20062004 and followed for a minimum of five years. Longer term data on the risk of ONJ, malignancy transformation, and pregnancy exposure in patients with GCTB treated with denosumab is necessary to better characterize these risks and will be useful in determining if risk mitigation beyond labeling are necessary.

- ONJ: Based on the available data, ONJ does not appear more concerning for GCTB patients than patients with bone metastases from solid tumor. However, some data indicate that the risk may increase with longer duration of treatment.

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ONJ will be evaluated in the planned PMRs. Should new safety information become available, additional risk mitigation strategies should be evaluated.

- Malignant Transformation: Given the duration of the clinical trials and relatively small number of patients, it is not clear what impact denosumab has on transformation or the development of a new sarcoma. This type of adverse event is a well-established risk for drugs that affect cell growth and development. In absence of a more definitive/concerning signal or specific recommendations, risk factors, or actionable activities for prescribers or patients, addressing the risk through labeling seems most appropriate.

  In addition, DOP2 is requiring a retrospective cohort study PMR to investigate the lifetime and yearly per-patient incidence and the risk factors associated with malignant transformation of GCTB and development of new sarcoma.

- Pregnancy: A number of cancer treatments are known teratogens or have concerning animal signals. Currently there are ten products with teratogenic potential that have approved REMS to address this risk. With the exception of thalidomide, lenalidomide, and pomalidomide, the risk of teratogenicity associated with oncology drugs has been managed through professional labeling only. The Division of Oncology Products 2 (DOP2) believes a REMS is not necessary to address the risk of teratogenicity because of the premise that the standard of medical care in oncology provides adequate safeguards for risk communication and patient monitoring, de facto restricted distribution programs exist in oncology for cancer drugs; and concerns regarding the burden to the healthcare system that would be imposed by a restrictive REMS. [3]

  In evaluating the appropriate level of risk management for denosumab for GCTB, we considered that pregnancy exposure is more of a concern given the typical age of the GCTB patient population (compared to the solid tumor and osteoporosis indications) and the number of pregnancies that occurred during the clinical trials. However, no specific malformations have been identified in humans based on the information provided through Amgen's Pregnancy Surveillance Program. Further, according to the approved labeling, the risk increases as the pregnancy progresses due to the increased transport of monoclonal antibodies across the placenta. This provides a wider window of opportunity (i.e., compared to thalidomide) to identify the pregnancy and determine if the benefits of continuing denosumab treatment outweigh its risks to the mother and fetus before the second or third trimester.

  DOP2, in conjunction with the Maternal Health Team, revised the Xgeva labeling to include a recommendation to counsel females of reproductive potential on pregnancy planning and prevention and to use "highly effective" contraception

[3] Vega A. Vismodegib (Erivedge) REMS Options review. Signed January 9, 2012 by Vega A and Karwoski C.

Reference ID: 3312274

during treatment and for at least five months following the last dose of denosumab. The Pregnancy subsection of the Warnings section was revised from "Pregnancy" to "Embryo-Fetal Toxicity."

In summary, DRISK does not recommend a REMS to address any of the risks associated denosumab for the treatment of GCTB at this time; the identified risks can be adequately addressed through labeling. This recommendation is based on the available safety data, severity of the disease, limited treatment alternatives and their associated risks/toxicities, and the potential benefit of denosumab for GCTB. This view is shared by DOP2.

5 CONCLUSION

In conclusion, DRISK and DOP2 agree that a REMS is not required for denosumab for treating GCTB at this time. If new safety information becomes available or use includes a new patient population, the risk-benefit of this drug should be re-evaluated.

Reference ID: 3312274

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

/s/

SUZANNE C BERKMAN ROBOTTOM
05/21/2013

MARY E WILLY
05/21/2013
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s094

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Summary of SGE Teleconference Discussion

Amgen's Supplemental Biologics Application sBLA 125320/94 for Xgeva (denosumab)

Date: May 24, 2013

Attendees

Melanie Pierce, FDA

Suzanne Demko, FDA

Martha Donoghue, FDA

Patricia Keegan, FDA

Dr. Angela Myers, SGE Patient Representative

Background

On March 18, 2013, the Division of Advisory Committee and Consultant Management at the Center for Drug Evaluation and Research notified DOP2 that Dr. Myers was cleared as a Special Government Employee to consult on sBLA 125320/94. Dr. Angela Myers is [redacted] (b) (6) (b) (6) pediatrician who agreed to give advice to DOP2 regarding the sBLA for Xgeva in the treatment of patients with Giant Cell Tumor of Bone (GCTB).

DOP2 sent a briefing document for Dr. Myers to review in preparation for this teleconference (Appendix 1). In the cover letter to the briefing document, DOP2 posed the following questions to Dr. Myers:

1. Based upon your review of the summary of data provided, do you think the risk/benefit assessment favors treatment of adult patients with GCTB with Xgeva?

2. Based upon your review of the summary of data provided, do you think the risk/benefit assessment favors treatment of skeletally mature adolescent patients with GCTB with Xgeva?

3. Do you have concerns regarding the use of Xgeva in the proposed patient population? If there are concerns, please recommend how you think these concerns might best be addressed.

Summary of SGE Teleconference Discussion

Amgen's Supplemental Biologics Application sBLA 125320/94 for Xgeva (denosumab)

Summary of Discussion

DOP2 thanked Dr. Myers for agreeing to consult on the denosumab sBLA and answered questions posed by Dr. Myers regarding the nature of the adverse events of osteonecrosis of the jaw and incidence of malignant transformation of GCTB observed in the trials supporting the sBLA.

After Dr. Myers stated that she had no additional questions, DOP2 asked Dr. Myers to provide advice regarding the questions included in the cover letter to the briefing document.

Dr. Myers stated that she thought that the overall risk/benefit assessment favored treatment of adult and skeletally mature adolescent patients with GCTB with Xgeva. She stated that while it was difficult to make a firm conclusion regarding the safety of Xgeva in skeletally mature adolescent patients due to the small number of adolescent patients treated in the GCTB studies, there is no reason to think that the toxicity profile in skeletally mature adolescents would differ from that of adults. Dr. Myers also stated that she did not have concerns regarding the use of Xgeva in adult and skeletally mature adolescent patients with GCTB that is unresectable for whom curative surgery is likely to cause severe morbidity.

DOP2 then concluded the teleconference after thanking Dr. Myers for her time and thoughtful consideration of the application.

Appendix 1

Dear Dr. Myers,

Thank you for agreeing to provide advice regarding the supplemental Biologics License Application (sBLA) for Xgeva (denosumab), submitted by Amgen. Please note that information concerning this application is confidential.

In this sBLA, Amgen seeks approval for Xgeva [redacted] (b) (4)

Enclosed is a summary of data derived from two single arm studies of denosumab conducted in patients with GCTB that Amgen submitted to support this sBLA.

We will contact you shortly to schedule a brief teleconference to discuss this application and seek advice regarding the following questions:

1. Based upon your review of the summary of data provided, do you think the risk/benefit assessment favors treatment of adult patients with GCTB with Xgeva?

2. Based upon your review of the summary of data provided, do you think the risk/benefit assessment favors treatment of skeletally mature adolescent patients with GCTB with Xgeva?

3. Do you have concerns regarding the use of Xgeva in the proposed patient population? If there are concerns, please recommend how you think these concerns might best be addressed.

Thank you again for your time and insights.

Sincerely,

Briefing Document for SGE Teleconference to Discuss Amgen's Supplemental Biologics Application sBLA 125320/94 for Xgeva (denosumab)

Introduction

- On December 11, 2012, Amgen submitted NDA sBLA 125320/94 seeking approval of Xgeva (denosumab) [redacted] (b) (4) .
- Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human receptor activator of nuclear factor kappa B ligand (RANKL), thereby preventing RANKL from activating its receptor, receptor activator of nuclear factor kappa B (RANK).
  - RANKL is considered essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption.
  - Xgeva received initial approval by FDA in 2010 for the prevention of skeletal-related events in patients with bone metastases from solid tumors. The approved dose for this indication is 120 mg administered as a subcutaneous injection every 4 weeks.
  - Denosumab is also marketed under the trade name Prolia. Prolia is approved for multiple indications, including: the treatment of postmenopausal women with osteoporosis at high risk for fracture; to increase bone mass in women at high risk for fracture who are receiving adjuvant aromatase inhibitor therapy for breast cancer; and to increase bone mass in men who are at high risk of fracture who have osteoporosis or who are receiving androgen deprivation therapy for nonmetastatic prostate cancer. The approved dose for Prolia is 60 mg administered as a subcutaneous injection every six months.
  - The Warnings and Precautions section of current Xgeva labeling describes the risks of severe hypocalcemia, osteonecrosis of the jaw, and fetal harm with denosumab therapy.
  - Another supplement for Xgeva is a currently under review by another division within the Office of Hematology and Oncology Products to include the risk of hypersensitivity (including anaphylactic reactions) and atypical femoral fractures in approved product labeling and to include information regarding the increased incidence of osteonecrosis of the jaw with longer duration of exposure to denosumab.
- Giant Cell tumor of Bone (GCTB) is a rare osteolytic bone tumor that can cause rapid and extensive local destruction of bone, which can in turn cause pain, pathologic fractures, joint destruction, physical deformity, and loss of function.
  - GCTB consists of mononuclear mesenchymal cells that express RANKL and RANK-expressing giant cells and giant cell precursors.
  - GCTB is diagnosed in approximately 800 patients per year in the U.S.
  - Peak incidence is in the third decade of life, but rarely occurs in pediatric (mostly skeletally mature) patients.

Reference ID: 3324392

- There are no approved therapies for treatment of GCTB.
- If GCTB is resectable, surgery can be curative. However, curative surgery can involve aggressive surgical procedures (such as joint resection, limb amputation, or hemi-pelvectomy) that can result in substantial morbidity. Once resected, GCTB can recur in an estimated 10 to 20% of patients following an en bloc excision and between 40% and 75% of patients who undergo curettage.

Design of Studies Supporting the Xgeva sBLA

- Data from two single arm studies provide the basis for this sBLA (Table 1)

Table 1: Basis for Xgeva GCTB sBLA

Study Number	Population	Pre-specified efficacy endpoints	Status
20040215	Adults with recurrent or unresectable GCTB (N = 37)	Response rate based upon histopathologic or radiographic measurement	Complete; follow-up ongoing
20062004	Adults or skeletally mature adolescents with: • unresectable GCTB *(Cohort 1, n = 170)* • GCTB for which planned surgical resection would cause substantial morbidity *(Cohort 2, n = 101)* • recurrent or unresectable GCTB and previously enrolled in 20050215 *(Cohort 3, n = 11)*	Time to disease progression (Cohort 1) Proportion of patients not requiring surgery by Month 6 (Cohort 2)	Ongoing; final Study Report for third interim analysis submitted.

- In both studies, patients received denosumab at a dose of 120 mg subcutaneously on Day 1, 8, and 15 of the first month of therapy, then every four weeks starting on Day 29. Patients received denosumab until disease progression, unacceptable toxicity, or until discontinuation at the request of the patient or treating physician.
- The protocols recommended but did not require that patients receive Vitamin D and calcium supplementation for the prevention of hypocalcemia (a known adverse reaction to Xgeva).

Reference ID: 3324392

Adolescent patients were required to weigh at least 45 kg and have documented radiological evidence of skeletal maturity to be eligible for enrollment.

Efficacy Results in GCTB studies

- A total of 305 unique patients with GCTB enrolled across both trials and 304 patients received denosumab (11 patients who enrolled into Study 20062004 Cohort 3 from Study 20040215 and 3 patients who discontinued Study 20040215 and later entered into Study 20062004 Cohort 1 are counted only once).

- Fifty-eight percent of the enrolled patients were women and 80.3% were White. The median age was 33 years (range: 13 to 83); a total of 10 patients were skeletally mature adolescents 13 to 17 years of age.

- Study 20040125 enrolled 37 adult patients with histologically confirmed unresectable or recurrent giant cell tumor of bone. The major pre-specified endpoint of the trial was the proportion of patients who exhibited at least 90% elimination of giant cells relative to baseline (or complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells), or a lack of progression of the target lesion by radiographic measurements in cases where histopathology was not available.

- Study 20062004 enrolled 282 adult or skeletally mature adolescents with giant cell tumor of bone. Of these patients, 10 were aged 13-17 years. Patients were assigned to one of three cohorts: Cohort 1 included patients with surgically unsalvageable disease (e.g. sacral, spinal, or multiple lesions, including pulmonary metastases); Cohort 2 included patients with surgically salvageable disease whose planned surgery was associated with severe morbidity (e.g. joint resection, limb amputation, or hemipelvectomy); Cohort 3 included patients who previously participated in Study 20040215 and wished to continue denosumab. The pre-specified outcome measures of the study were time to disease progression (based on investigator assessment) for Cohort 1 and the proportion of patients without any surgery at month 6 for Cohort 2.

- Disease characteristics of the patients enrolled in both GCTB studies are summarized in Table 2

Table 2: GCTB Characteristics of Enrolled Patients

	Study 20040215 N = 37	**Study 20062004 N =282**
Primary resectable	0 (0)	63 (22)
Primary unresectable	13 (35)	50 (18)
Recurrent resectable	6 (16)	38 (14)
Recurrent unresectable	18 (49)	131 (47)

Reference ID: 3324392

	Study 20040215 N = 37	**Study 20062004 N =282**
Target Lesion Longest Diameter (mm) Median (range)	47 (6, 170)	59 (3, 308)
Target Lesion Location n (%)		
Pelvis	10 (37)	85 (30)
Lower Extremity	8 (22)	72 (26)
Lung	9 (26)	47 (17)
Upper Extremity	5 (14)	29 (10)
Spine	4 (9)	27 (10)
Other	1 (3)	22 (8)

- After receiving feedback from FDA, Amgen performed a retrospective independent review of radiographic imaging data obtained from patients enrolled in Study 20040215 and Study 20062004. In a meeting held prior to submission of this sBLA, FDA informed Amgen that evidence of durable objective response, as determined by independent blinded radiographic assessment using Modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, could provide the primary basis to support approval of Xgeva for the treatment of patients with unresectable GCTB. FDA also advised Amgen that additional analyses would be considered supportive.

Radiographic Assessment of GCTB Response

- Of the 305 patients enrolled in Study 20040215 and Study 20062004, 190 had imaging available for retrospective analysis of objective tumor response:
- The following criteria were used in the Independent Radiology Review Committee (IRC) assessment of radiographic response:
  - Modified RECIST 1.1 to evaluate tumor burden based on computed tomography (CT)/magnetic resonance imaging (MRI).
  - Modified European Organisation for Research and Treatment of Cancer (EORTC) criteria to evaluate metabolic response using fluorodeoxyglucose positron emission tomography (FDG-PET).
  - Modified Inverse Choi criteria to evaluate tumor size and density using Hounsfield units based on CT/MRI (Density/Size).
    - A response using Density/Size criteria required one or both of the following conditions to be met:
      - either a ≥ 10% decrease in the sum of the measurements of the longest diameter for each target lesion measuring at least 10 mm, or

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- An increase in CT density [%Δ Hounsfield Units $(HU)_{mean}$] of at least 15% compared to baseline.
- For bone lesions with a soft tissue component, the longest diameter included both the bone and soft tissue components. For bone lesions without a soft tissue component, the longest diameter included the bone component of the lesion.

- Table 3 provides a summary of objective tumor response, as determined by the IRC using modified RECIST 1.1, EORTC, or Density/Size criteria. An objective response (all partial responses) was observed in 47 of 187 (25.1%) patients who were evaluable by RECIST. The median time to response was 3.1 months (95% CI 2.89, 3.65). The median duration of response was not estimable because few patients experienced disease progression within a median follow-up of 13.4 months. Efficacy results in skeletally mature adolescents appeared to be similar to those observed in adults.

Table 3: Objective Response in Patients with Giant Cell Tumor of Bone Treated with Denosumab

	Number of patients evaluable for the endpoint	Number of patients with the endpoint	Proportion (%) (95% CI) [a]	KM estimate of median (95% CI) (Months)
Proportion of patients with an objective tumor response (CR, PR)				
Based on best response[b]	190	136	71.6 (64.6, 77.9)	-
RECIST 1.1	187	47	25.1 (19.1, 32.0)	-
EORTC	26	25	96.2 (80.4, 99.9)	-
Density/Size[b]	176	134	76.1 (69.1, 82.2)	-
Duration of objective tumor response (time to PD from the first objective tumor response)				
Based on best response[b]	136	1	0.7	NE (NE, NE) [c]
RECIST 1.1	47	3	6.4	NE (19.94, NE)
EORTC	25	0	0.0	NE (NE, NE)
Density/Size	134	1	0.7	NE (NE, NE)
Time to first objective tumor response				
Based on best response[b]	190	136	71.6	3.1 (2.89, 3.65)
RECIST 1.1	187	47	25.1	NE (20.93, NE)
EORTC	26	25	96.2	2.7 (1.64, 2.79)
Density/Size	176	134	76.1	3.0 (2.79, 3.48)

[a] Exact Confidence Interval

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[b] Using any of the three sets of criteria for evaluation of objective tumor response (Modified RECIST, EORTC, or Density Size criteria)
[c] NE = Not Estimable

- Progressive disease following response occurred in 3 of 47 (6%) RECIST responders.
- Table 4 provides a summary of the minimum response duration among RECIST responders observed at the time of data cut-off.

Table 4: Duration of Objective Tumor Response by Modified RECIST 1.1

Minimum Response Duration	N	No. Responders	% Response
4 weeks	150	32	21
8 weeks	144	32	22
12 weeks	141	32	23
24 weeks	109	26	24

Additional Supportive Efficacy Results – Study 20040125

- In Study 20040125, at least 90% elimination of giant cells relative to baseline (or complete elimination of giant cells in cases where giant cells represented < 5% of tumor cells) or a lack of progression of the target lesion by radiographic measurements (in cases where histopathology was not available) was observed in 30 of the 35 (85.7%) evaluable patients.

Additional Supportive Efficacy Results – Study 20062004

- In Cohort 2 (patients enrolled who had resectable GCTB but whose planned surgery was associated with severe morbidity), 64 of the 71 (90.1%; 95% CI: 80.7%, 95.9%) evaluable patients treated with denosumab had not undergone surgery by month 6. Overall, of 100 patients for whom surgery was planned, 74 patients (74%) had no surgery performed, and 16 patients (16%) underwent a less morbid surgical procedure from that planned at baseline (Table 5).

Reference ID: 3324392

Table 5: Distribution of Planned Versus Actual Surgery in Patients with Giant Cell Tumor of Bone (Cohort 2)

Surgical Procedure	Baseline Planned (n) [a]	Actual Total (n) [a]
Total number of surgeries	100	26
Major surgeries	44	3
Hemipelvectomy	4	0
Amputation	17	0
Joint/prosthesis replacement	9	1
Joint resection	14	2
Marginal excision, en bloc excision, or en bloc resection	42	6
Curettage	13	16
Other	1	1
No surgery	0	74

[a] n = number of patients

Table 6, copied from Amgen's submission, provides a summary of symptom improvement by patient report:

Table 6: Summary of Change in Patient Symptoms for Study 20062004

	N1 (%)	Pain Reduction n (%)	Improved Mobility n (%)	Improved Function n (%)	Other n (%)
Cohort 1 (N = 169)	67 (39.6)	48 (28.4)	38 (22.5)	32 (18.9)	6 (3.6)
Cohort 2 (N = 100)	61 (61.0)	50 (50.0)	33 (33.0)	23 (23.0)	10 (10.0)
Cohort 3 (N = 11)	3 (27.3)	3 (27.3)	2 (18.2)	2 (18.2)	1 (9.1)
Cohorts 1 and 2 (N = 269)	128 (47.6)	98 (36.4)	71 (26.4)	55 (20.4)	16 (5.9)

N = number of enrolled subjects who were eligible for the study and received at least one dose of denosumab
N1 = Number of subjects who reported clinical benefit
For an individual subject, within each category, if multiple responses are present in the same time frame, the best response is presented.
Percentages based on N

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Output: t14-04-003-006-clinical.rtf (Date Generated: 14NOV2011:10:26:58) Source Data: adam.adfcb

- At enrollment, 25% of patients had strong opioid use (i.e., an analgesic score ≥ 3). During the study, the proportion of patients who shifted from strong opioid use to no/low analgesic use at any study visit ranged from 4.2% to 38.5%. The proportion of patients who shifted from no/low analgesic use to strong opioid use at any study visit was ≤ 4.7%.

Reference ID: 3324392

Analysis of Safety Data from GCTB Studies

- Of the 304 patients who received Xgeva, 145 patients were treated with Xgeva for ≥ 1 year, 44 patients for ≥ 2 years, and 15 patients for ≥ 3 years. The median number of doses received was 14 (range: 1 – 60) and the median number of months on study was 11.2 (range: 0.0 – 54.1).

- Due to the single arm nature of the studies, determination of whether there is a causal relationship between denosumab and adverse events is challenging. However, the overall toxicity profile of denosumab in patients with giant cell tumor of bone appears similar to that reported in placebo-controlled trials of patients with bone metastases from solid tumors. The adverse reaction profile in skeletally mature adolescents and adults with GCTB also appeared to be similar.

- The most common adverse reactions in patients (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. Table 7 provides the per-patient incidence of adverse events that occurred in at least 5 percent of patients who received denosumab in either study.

Table 7: Per-Patient Incidence of Adverse Events Across GCTB Studies

Preferred Term	All Grades N = 304		≥ Grade 3 Severity N = 304	
	n	%	n	%
Arthralgia	64	21.1	2	0.7
Headache	56	18.4	2	0.7
Nausea	54	17.8	1	0.3
Back pain	53	17.4	4	1.3
Fatigue	51	16.8	0	0.0
Pain in extremity	49	16.1	4	1.3
Vomiting	28	9.2	0	0.0
Musculoskeletal pain	26	8.6	3	1.0
Nasopharyngitis	24	7.9	0	0.0
Peripheral edema	24	7.9	0	0.0
Upper respiratory tract infection	23	7.6	0	0.0
Constipation	22	7.2	0	0.0
Diarrhea	21	6.9	0	0.0
Cough	20	6.6	0	0.0
Weight increased	19	6.3	2	0.7
Hypophosphatemia	17	5.6	9	3.0
Muscle spasms	17	5.6	0	0.0
Toothache	17	5.6	0	0.0

Reference ID: 3324392

Preferred Term	All Grades N = 304		≥ Grade 3 Severity N = 304	
	n	%	n	%
Abdominal pain	16	5.3	0	0.0
Bone pain	16	5.3	1	0.3
Insomnia	16	5.3	0	0.0
Myalgia	16	5.3	0	0.0
Non-cardiac chest pain	16	5.3	0	0.0
Paresthesia	16	5.3	0	0.0

- The most common serious adverse reactions (per-patient incidence of 1%) were osteonecrosis and osteomyelitis. The most common adverse reactions (per-patient incidence of 1%) resulting in discontinuation of Xgeva were osteonecrosis, tooth abscess or infection, and development of sarcoma or malignant transformation of GCTB.
- One patient died within thirty days of receiving study therapy; this patient died of respiratory insufficiency due to cardiac and pulmonary tumor compression from lung metastases that were present at enrollment and progressed during therapy.
- In Trials 4 and 5, osteonecrosis of the jaw (ONJ) was confirmed in 4 of 304 (1.3%) of patients who received Xgeva. The median duration of Xgeva therapy at the time of ONJ diagnosis was 17 months (range: 13 to 21).
- Malignant transformation of GCTB or development of a new sarcoma occurred in 5 of 304 (1.6%) patients treated with Xgeva. The median duration of exposure for these patients was 95 days (range: 29 to 257).

Reference ID: 3324392

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/s/

MARTHA B DONOGHUE
06/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 7, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; LabelingTeleconference Xgeva (denosumab)

FDA Attendees:	**Amgen, Inc.**
Patricia Keegan	Bruce Bach,
Martha Donoghue	Monica Batra
Suzanne Demko	Ada Braun
Melanie Pierce	Eureka Dias, Manager
Whitney Helms	Rhian Thomas
Shawna Weis	David Chang,
Vivian Yuan	Thomas M DeMelfi Jr
Lixin Xu	William Dougall
	Chunlei Ke

Date and time of teleconference: June 7, 2013; 3:30PM

This was an FDA initiated teleconference to discuss Amgen's proposed labeling revisions sent via email on June 7, 2013.

Amgen proposed changes to the following sections of the package insert:

WARNINGS AND PRECAUTIONS (5.3)
USE IN SPECIFIC POPULATIONS (8.7)
CLINICAL PHARMACOLOGY (12.1)
CLINICAL PHARMACOLOGY (12.3)
CLINICAL [redacted] (b) (4) (14.2)
PATIENT COUNSELING INFORMATION (17)

During the teleconference, both Amgen and FDA provided their rational for either accepting or rejecting each proposed change. The final agreed-upon language is contained in the attached label.

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

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/s/

MELANIE B PIERCE
06/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 29, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

FDA Attendees:
Jeff Summers
Martha Donoghue
Suzanne Demko
Melanie Pierce

Amgen Attendees
Bruce Bach,
Monica Batra
Oswaldo Bracco
Daniel Branstetter
Ada Braun,
Jeanine Bussiere,
David Chang,
Mary Ellen Cosenza,
Thomas M DeMelfi Jr,
William Dougall,
Chunlei Ke,
Alexander Liede,

Date and time of teleconference: May 29, 2013; 11:30AM

FDA stated that the purpose of the teleconference was to discuss proposed PMR/PMC language for the giant cell tumor of the bone (GCTB) supplemental application and to address potential inconsistencies in the written request (WR) and the proposed post-marketing requirements (PMR).

PMR1:
FDA expressed understanding of Amgen's concerns regarding the inconsistencies between the written Request (WR) and PMR1 and agreed that the proposed language for this PMR did not make it clear that FDA would not require additional radiographic assessment of objective response by an independent radiology review committee. (b) (4)

FDA stated that Amgen must conduct additional radiographic analyses that include an analysis of objective response (OR) by local investigator review of radiographic assessments obtained in Study 004, and provide timelines for completion of the final study report. Amgen agreed to submit the proposed dates within one week of the teleconference.

FDA informed Amgen that the accelerated approval pathway is being considered for the GCTB indication. When Amgen submits the final study report and FDA determines that PMR1 is fulfilled, the application will convert from accelerated to regular approval. FDA clarified that although accelerated approval is typically granted for products approved using a surrogate endpoint, accelerated approval can also be granted to products that have been studied for the treatment of a serious illness when FDA determines there is a need to verify and further characterize the clinical benefit in a particular patient population. FDA stated that because many patients with GCTB may receive Xgeva chronically, an analysis of long-term safety and efficacy data might be necessary to verify and describe the clinical benefit conferred to patients with GCTB by Xgeva. Amgen stated

that the risk/benefit analysis is unlikely to change with long-term follow-up. FDA acknowledged Amgen's position and will follow up with Amgen once a final decision is made.

PMR 2:
Amgen stated that safety follow-up for up to 5 years is reasonable and agreed to send proposals for completion of the final study report via email.

Regarding PMR3:
Amgen stated that they provided information for the safety assessment of the potential risk of malignant transformation of GCTB or development of a new sarcoma (MT/NS) in Amgen's May 28, 2013 response to FDA's proposed label revisions. FDA reviewed Amgen's response as well as data from the 120-day safety report and determined there was insufficient information to assess the potential risks of MT/NS with use of Xgeva in patients with GCTB. FDA requested that Amgen submit additional safety information, including a systematic analysis of available data to describe the yearly and lifetime incidence of MT/NS in GCTB, and potential risk factors for MT/NS in order for FDA to more accurately assess whether use of Xgeva increases the risk of MT/NS in patients with GCTB.

Amgen stated that public literature references regarding the incidences of MT/NS were generated from North American databases; however, the data did not provide a more complete understanding of the incidence of MT/NS in patients receiving Xgeva**.** FDA stated that it was acceptable for Amgen to search public databases outside of North America to estimate the average incidence and risk factors for MT/NS.

FDA asked Amgen to provide provisional dates for the PMRs and PMCs final study reports and build in extra time to for completion of the studies to prevent future delays.

Nonclinical PMC:
FDA stated that there are no plans to include a nonclinical PMC. FDA agreed to follow up regarding this issue within the next few days.

Labeling:
FDA asked why Amgen removed the contraceptive language from the package insert (PI) and explained that labeling of Category D drugs approved to treat patient populations of reproductive age now contain this standard language. FDA emphasized that patients taking Xgeva should not become pregnant while taking the drug. Amgen stated that they wanted to align the language in the Xgeva label with the Prolia label and expressed belief that the current label contains appropriate warnings and instructions.

Amgen proposed to delete the term "highly effective contraception", because it is vague and may be interpreted differently by other regulatory agencies. Amgen asked FDA to provide examples of labels that contain the term "highly effective contraception". FDA agreed to follow up with the maternal health team and provide additional examples of labels that contain the term "highly effective contraception".

The call ended.

Reference ID: 3323949

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/s/

MELANIE B PIERCE
06/12/2013

Summary of SGE Teleconference Discussion

Amgen's Supplemental Biologics Application sBLA 125320/94 for Xgeva (denosumab)

Date: May 28, 2013

Attendees

Melanie Pierce, FDA

Suzanne Demko, FDA

Martha Donoghue, FDA

Dr. Nita Seibel, Special Government Employee and Head of Pediatric Solid Tumor Therapeutics, Clinical Investigations Branch of the Cancer Therapy Evaluation Program, National Cancer Institute

Background

On March 18, 2013, the Division of Advisory Committee and Consultant Management at the Center for Drug Evaluation and Research notified DOP2 that Dr. Seibel was cleared as Special Government Employee to consult on sBLA 125320/94. Dr. Nita Seibel is pediatric oncologist with expertise in pediatric sarcomas who agreed to give advice to DOP2 regarding the sBLA for Xgeva in the treatment of patients with Giant Cell Tumor of Bone (GCTB).

DOP2 sent a briefing document for Dr. Seibel to review in preparation for this teleconference (Appendix 1). In the cover letter to the briefing document, DOP2 posed the following questions to Dr. Seibel:

1. Based upon your review of the summary of data provided, do you think the risk/benefit assessment favors treatment of adult patients with GCTB with Xgeva?

2. Based upon your review of the summary of data provided, do you think the risk/benefit assessment favors treatment of skeletally mature adolescent patients with GCTB with Xgeva?

3. Do you have concerns regarding the use of Xgeva in the proposed patient population? If there are concerns, please recommend how you think these concerns might best be addressed.

Summary of SGE Teleconference Discussion

Amgen's Supplemental Biologics Application sBLA 125320/94 for Xgeva (denosumab)

Summary of Discussion

DOP2 thanked Dr. Seibel for agreeing to consult on the denosumab sBLA and answered questions posed by Dr. Seibel regarding the assessment of patient reported outcomes in the sBLA, the methodology used to assess radiographic response of GCTB to denosumab treatment, and the adverse reactions (including osteonecrosis of the jaw, skeletal fractures, and malignant transformation of GCTB) observed in the GCTB studies.

After Dr. Seibel stated that she had no additional questions, DOP2 asked Dr. Seibel to provide advice regarding the questions included in the cover letter to the briefing document.

Dr. Seibel stated that she thought that the overall risk/benefit assessment favored treatment of adult and skeletally mature adolescent patients with GCTB with Xgeva. Dr. Seibel concurred with DOP2's assessment that review of long-term safety data from the use of denosumab in patients with GCTB is warranted when it becomes available. Dr. Seibel also stated that she did not have concerns regarding the use of Xgeva in adult and skeletally mature adolescent patients with GCTB that is unresectable or for whom curative surgery is likely to cause severe morbidity.

DOP2 then concluded the teleconference after thanking Dr. Seibel for her time and thoughtful consideration of the application.

Appendix 1

Dear Dr. Seibel,

Thank you for agreeing to provide advice regarding the supplemental Biologics License Application (sBLA) for Xgeva (denosumab), submitted by Amgen. Please note that information concerning this application is confidential.

In this sBLA, Amgen seeks approval for Xgeva for the [redacted] (b) (4)

Enclosed is a summary of data derived from two single arm studies of denosumab conducted in patients with GCTB that Amgen submitted to support this sBLA.

We will contact you shortly to schedule a brief teleconference to discuss this application and seek advice regarding the following questions:

1. Based upon your review of the summary of data provided, do you think the risk/benefit assessment favors treatment of adult patients with GCTB with Xgeva?

2. Based upon your review of the summary of data provided, do you think the risk/benefit assessment favors treatment of skeletally mature adolescent patients with GCTB with Xgeva?

3. Do you have concerns regarding the use of Xgeva in the proposed patient population? If there are concerns, please recommend how you think these concerns might best be addressed.

Thank you again for your time and insights.

Sincerely,

Briefing Document for SGE Teleconference to Discuss Amgen's Supplemental Biologics Application sBLA 125320/94 for Xgeva (denosumab)

Introduction

- On December 11, 2012, Amgen submitted NDA sBLA 125320/94 seeking approval of Xgeva (denosumab) for [redacted] (b) (4)
- Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human receptor activator of nuclear factor kappa B ligand (RANKL), thereby preventing RANKL from activating its receptor, receptor activator of nuclear factor kappa B (RANK).
  - RANKL is considered essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption.
  - Xgeva received initial approval by FDA in 2010 for the prevention of skeletal-related events in patients with bone metastases from solid tumors. The approved dose for this indication is 120 mg administered as a subcutaneous injection every 4 weeks.
  - Denosumab is also marketed under the trade name Prolia. Prolia is approved for multiple indications, including: the treatment of postmenopausal women with osteoporosis at high risk for fracture; to increase bone mass in women at high risk for fracture who are receiving adjuvant aromatase inhibitor therapy for breast cancer; and to increase bone mass in men who are at high risk of fracture who have osteoporosis or who are receiving androgen deprivation therapy for nonmetastatic prostate cancer. The approved dose for Prolia is 60 mg administered as a subcutaneous injection every six months.
  - The Warnings and Precautions section of current Xgeva labeling describes the risks of severe hypocalcemia, osteonecrosis of the jaw, and fetal harm with denosumab therapy.
  - Another supplement for Xgeva is a currently under review by another division within the Office of Hematology and Oncology Products to include the risk of hypersensitivity (including anaphylactic reactions) and atypical femoral fractures in approved product labeling and to include information regarding the increased incidence of osteonecrosis of the jaw with longer duration of exposure to denosumab.
- Giant Cell tumor of Bone (GCTB) is a rare osteolytic bone tumor that can cause rapid and extensive local destruction of bone, which can in turn cause pain, pathologic fractures, joint destruction, physical deformity, and loss of function.
  - GCTB consists of mononuclear mesenchymal cells that express RANKL and RANK-expressing giant cells and giant cell precursors.
  - GCTB is diagnosed in approximately 800 patients per year in the U.S.
  - Peak incidence is in the third decade of life, but rarely occurs in pediatric (mostly skeletally mature) patients.

Reference ID: 3324412

- There are no approved therapies for treatment of GCTB.
- If GCTB is resectable, surgery can be curative. However, curative surgery can involve aggressive surgical procedures (such as joint resection, limb amputation, or hemi-pelvectomy) that can result in substantial morbidity. Once resected, GCTB can recur in an estimated 10 to 20% of patients following an en bloc excision and between 40% and 75% of patients who undergo curettage.

Design of Studies Supporting the Xgeva sBLA

- Data from two single arm studies provide the basis for this sBLA (Table 1)

Table 1: Basis for Xgeva GCTB sBLA

Study Number	Population	Pre-specified efficacy endpoints	Status
20040215	Adults with recurrent or unresectable GCTB (N = 37)	Response rate based upon histopathologic or radiographic measurement	Complete; follow-up ongoing
20062004	Adults or skeletally mature adolescents with: • unresectable GCTB *(Cohort 1, n = 170)* • GCTB for which planned surgical resection would cause substantial morbidity *(Cohort 2, n = 101)* • recurrent or unresectable GCTB and previously enrolled in 20050215 *(Cohort 3, n = 11)*	Time to disease progression (Cohort 1) Proportion of patients not requiring surgery by Month 6 (Cohort 2)	Ongoing; final Study Report for third interim analysis submitted.

- In both studies, patients received denosumab at a dose of 120 mg subcutaneously on Day 1, 8, and 15 of the first month of therapy, then every four weeks starting on Day 29. Patients received denosumab until disease progression, unacceptable toxicity, or until discontinuation at the request of the patient or treating physician.
- The protocols recommended but did not require that patients receive Vitamin D and calcium supplementation for the prevention of hypocalcemia (a known adverse reaction to Xgeva).

Reference ID: 3324412

Adolescent patients were required to weigh at least 45 kg and have documented radiological evidence of skeletal maturity to be eligible for enrollment.

Efficacy Results in GCTB studies

- A total of 305 unique patients with GCTB enrolled across both trials and 304 patients received denosumab (11 patients who enrolled into Study 20062004 Cohort 3 from Study 20040215 and 3 patients who discontinued Study 20040215 and later entered into Study 20062004 Cohort 1 are counted only once).

- Fifty-eight percent of the enrolled patients were women and 80.3% were White. The median age was 33 years (range: 13 to 83); a total of 10 patients were skeletally mature adolescents 13 to 17 years of age.

- Study 20040125 enrolled 37 adult patients with histologically confirmed unresectable or recurrent giant cell tumor of bone. The major pre-specified endpoint of the trial was the proportion of patients who exhibited at least 90% elimination of giant cells relative to baseline (or complete elimination of giant cells in cases where giant cells represent < 5% of tumor cells), or a lack of progression of the target lesion by radiographic measurements in cases where histopathology was not available.

- Study 20062004 enrolled 282 adult or skeletally mature adolescents with giant cell tumor of bone. Of these patients, 10 were aged 13-17 years. Patients were assigned to one of three cohorts: Cohort 1 included patients with surgically unsalvageable disease (e.g. sacral, spinal, or multiple lesions, including pulmonary metastases); Cohort 2 included patients with surgically salvageable disease whose planned surgery was associated with severe morbidity (e.g. joint resection, limb amputation, or hemipelvectomy); Cohort 3 included patients who previously participated in Study 20040215 and wished to continue denosumab. The pre-specified outcome measures of the study were time to disease progression (based on investigator assessment) for Cohort 1 and the proportion of patients without any surgery at month 6 for Cohort 2.

- Disease characteristics of the patients enrolled in both GCTB studies are summarized in Table 2

Table 2: GCTB Characteristics of Enrolled Patients

	Study 20040215 N = 37	**Study 20062004 N =282**
Primary resectable	0 (0)	63 (22)
Primary unresectable	13 (35)	50 (18)
Recurrent resectable	6 (16)	38 (14)
Recurrent unresectable	18 (49)	131 (47)

Reference ID: 3324412

	Study 20040215 N = 37	**Study 20062004 N =282**
Target Lesion Longest Diameter (mm) Median (range)	47 (6, 170)	59 (3, 308)
Target Lesion Location n (%)		
Pelvis	10 (37)	85 (30)
Lower Extremity	8 (22)	72 (26)
Lung	9 (26)	47 (17)
Upper Extremity	5 (14)	29 (10)
Spine	4 (9)	27 (10)
Other	1 (3)	22 (8)

- After receiving feedback from FDA, Amgen performed a retrospective independent review of radiographic imaging data obtained from patients enrolled in Study 20040215 and Study 20062004. In a meeting held prior to submission of this sBLA, FDA informed Amgen that evidence of durable objective response, as determined by independent blinded radiographic assessment using Modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, could provide the primary basis to support approval of Xgeva for the treatment of patients with unresectable GCTB. FDA also advised Amgen that additional analyses would be considered supportive.

Radiographic Assessment of GCTB Response

- Of the 305 patients enrolled in Study 20040215 and Study 20062004, 190 had imaging available for retrospective analysis of objective tumor response:
- The following criteria were used in the Independent Radiology Review Committee (IRC) assessment of radiographic response:
  - Modified RECIST 1.1 to evaluate tumor burden based on computed tomography (CT)/magnetic resonance imaging (MRI).
  - Modified European Organisation for Research and Treatment of Cancer (EORTC) criteria to evaluate metabolic response using fluorodeoxyglucose positron emission tomography (FDG-PET).
  - Modified Inverse Choi criteria to evaluate tumor size and density using Hounsfield units based on CT/MRI (Density/Size).
    - A response using Density/Size criteria required one or both of the following conditions to be met:
      - either a ≥ 10% decrease in the sum of the measurements of the longest diameter for each target lesion measuring at least 10 mm, or

Reference ID: 3324412

- An increase in CT density [%Δ Hounsfield Units $(HU)_{mean}$] of at least 15% compared to baseline.
- For bone lesions with a soft tissue component, the longest diameter included both the bone and soft tissue components. For bone lesions without a soft tissue component, the longest diameter included the bone component of the lesion.

- Table 3 provides a summary of objective tumor response, as determined by the IRC using modified RECIST 1.1, EORTC, or Density/Size criteria. An objective response (all partial responses) was observed in 47 of 187 (25.1%) patients who were evaluable by RECIST. The median time to response was 3.1 months (95% CI 2.89, 3.65). The median duration of response was not estimable because few patients experienced disease progression within a median follow-up of 13.4 months. Efficacy results in skeletally mature adolescents appeared to be similar to those observed in adults.

Table 3: Objective Response in Patients with Giant Cell Tumor of Bone Treated with Denosumab

	Number of patients evaluable for the endpoint	Number of patients with the endpoint	Proportion (%) (95% CI) [a]	KM estimate of median (95% CI) (Months)
Proportion of patients with an objective tumor response (CR, PR)				
Based on best response[b]	190	136	71.6 (64.6, 77.9)	-
RECIST 1.1	187	47	25.1 (19.1, 32.0)	-
EORTC	26	25	96.2 (80.4, 99.9)	-
Density/Size[b]	176	134	76.1 (69.1, 82.2)	-
Duration of objective tumor response (time to PD from the first objective tumor response)				
Based on best response[b]	136	1	0.7	NE (NE, NE) [c]
RECIST 1.1	47	3	6.4	NE (19.94, NE)
EORTC	25	0	0.0	NE (NE, NE)
Density/Size	134	1	0.7	NE (NE, NE)
Time to first objective tumor response				
Based on best response[b]	190	136	71.6	3.1 (2.89, 3.65)
RECIST 1.1	187	47	25.1	NE (20.93, NE)
EORTC	26	25	96.2	2.7 (1.64, 2.79)
Density/Size	176	134	76.1	3.0 (2.79, 3.48)

[a] Exact Confidence Interval

Reference ID: 3324412

[b] Using any of the three sets of criteria for evaluation of objective tumor response (Modified RECIST, EORTC, or Density Size criteria)
[c] NE = Not Estimable

- Progressive disease following response occurred in 3 of 47 (6%) RECIST responders.
- Table 4 provides a summary of the minimum response duration among RECIST responders observed at the time of data cut-off.

Table 4: Duration of Objective Tumor Response by Modified RECIST 1.1

Minimum Response Duration	N	No. Responders	% Response
4 weeks	150	32	21
8 weeks	144	32	22
12 weeks	141	32	23
24 weeks	109	26	24

Additional Supportive Efficacy Results – Study 20040125

- In Study 20040125, at least 90% elimination of giant cells relative to baseline (or complete elimination of giant cells in cases where giant cells represented < 5% of tumor cells) or a lack of progression of the target lesion by radiographic measurements (in cases where histopathology was not available) was observed in 30 of the 35 (85.7%) evaluable patients.

Additional Supportive Efficacy Results – Study 20062004

- In Cohort 2 (patients enrolled who had resectable GCTB but whose planned surgery was associated with severe morbidity), 64 of the 71 (90.1%; 95% CI: 80.7%, 95.9%) evaluable patients treated with denosumab had not undergone surgery by month 6. Overall, of 100 patients for whom surgery was planned, 74 patients (74%) had no surgery performed, and 16 patients (16%) underwent a less morbid surgical procedure from that planned at baseline (Table 5).

Reference ID: 3324412

Table 5: Distribution of Planned Versus Actual Surgery in Patients with Giant Cell Tumor of Bone (Cohort 2)

Surgical Procedure	Baseline Planned (n) [a]	Actual Total (n) [a]
Total number of surgeries	100	26
Major surgeries	44	3
Hemipelvectomy	4	0
Amputation	17	0
Joint/prosthesis replacement	9	1
Joint resection	14	2
Marginal excision, en bloc excision, or en bloc resection	42	6
Curettage	13	16
Other	1	1
No surgery	0	74

[a] n = number of patients

Table 6, copied from Amgen's submission, provides a summary of symptom improvement by patient report:

Table 6: Summary of Change in Patient Symptoms for Study 20062004

	N1 (%)	Pain Reduction n (%)	Improved Mobility n (%)	Improved Function n (%)	Other n (%)
Cohort 1 (N = 169)	67 (39.6)	48 (28.4)	38 (22.5)	32 (18.9)	6 (3.6)
Cohort 2 (N = 100)	61 (61.0)	50 (50.0)	33 (33.0)	23 (23.0)	10 (10.0)
Cohort 3 (N = 11)	3 (27.3)	3 (27.3)	2 (18.2)	2 (18.2)	1 (9.1)
Cohorts 1 and 2 (N = 269)	128 (47.6)	98 (36.4)	71 (26.4)	55 (20.4)	16 (5.9)

N = number of enrolled subjects who were eligible for the study and received at least one dose of denosumab
N1 = Number of subjects who reported clinical benefit
For an individual subject, within each category, if multiple responses are present in the same time frame, the best response is presented.
Percentages based on N

Program: /stat/amg162/therapeutic/20062004/analysis/interim_3/tables/program/t-clinical.sas
Output: t14-04-003-006-clinical.rtf (Date Generated: 14NOV2011:10:26:58) Source Data: adam.adfcb

- At enrollment, 25% of patients had strong opioid use (i.e., an analgesic score ≥ 3). During the study, the proportion of patients who shifted from strong opioid use to no/low analgesic use at any study visit ranged from 4.2% to 38.5%. The proportion of patients who shifted from no/low analgesic use to strong opioid use at any study visit was ≤ 4.7%.

Reference ID: 3324412

Analysis of Safety Data from GCTB Studies

- Of the 304 patients who received Xgeva, 145 patients were treated with Xgeva for ≥ 1 year, 44 patients for ≥ 2 years, and 15 patients for ≥ 3 years. The median number of doses received was 14 (range: 1 – 60) and the median number of months on study was 11.2 (range: 0.0 – 54.1).

- Due to the single arm nature of the studies, determination of whether there is a causal relationship between denosumab and adverse events is challenging. However, the overall toxicity profile of denosumab in patients with giant cell tumor of bone appears similar to that reported in placebo-controlled trials of patients with bone metastases from solid tumors. The adverse reaction profile in skeletally mature adolescents and adults with GCTB also appeared to be similar.

- The most common adverse reactions in patients (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. Table 7 provides the per-patient incidence of adverse events that occurred in at least 5 percent of patients who received denosumab in either study.

Table 7: Per-Patient Incidence of Adverse Events Across GCTB Studies

Preferred Term	All Grades N = 304		≥ Grade 3 Severity N = 304	
	n	%	n	%
Arthralgia	64	21.1	2	0.7
Headache	56	18.4	2	0.7
Nausea	54	17.8	1	0.3
Back pain	53	17.4	4	1.3
Fatigue	51	16.8	0	0.0
Pain in extremity	49	16.1	4	1.3
Vomiting	28	9.2	0	0.0
Musculoskeletal pain	26	8.6	3	1.0
Nasopharyngitis	24	7.9	0	0.0
Peripheral edema	24	7.9	0	0.0
Upper respiratory tract infection	23	7.6	0	0.0
Constipation	22	7.2	0	0.0
Diarrhea	21	6.9	0	0.0
Cough	20	6.6	0	0.0
Weight increased	19	6.3	2	0.7
Hypophosphatemia	17	5.6	9	3.0
Muscle spasms	17	5.6	0	0.0
Toothache	17	5.6	0	0.0

Reference ID: 3324412

Preferred Term	All Grades N = 304		≥ Grade 3 Severity N = 304	
	n	%	n	%
Abdominal pain	16	5.3	0	0.0
Bone pain	16	5.3	1	0.3
Insomnia	16	5.3	0	0.0
Myalgia	16	5.3	0	0.0
Non-cardiac chest pain	16	5.3	0	0.0
Paresthesia	16	5.3	0	0.0

- The most common serious adverse reactions (per-patient incidence of 1%) were osteonecrosis and osteomyelitis. The most common adverse reactions (per-patient incidence of 1%) resulting in discontinuation of Xgeva were osteonecrosis, tooth abscess or infection, and development of sarcoma or malignant transformation of GCTB.
- One patient died within thirty days of receiving study therapy; this patient died of respiratory insufficiency due to cardiac and pulmonary tumor compression from lung metastases that were present at enrollment and progressed during therapy.
- In Trials 4 and 5, osteonecrosis of the jaw (ONJ) was confirmed in 4 of 304 (1.3%) of patients who received Xgeva. The median duration of Xgeva therapy at the time of ONJ diagnosis was 17 months (range: 13 to 21).
- Malignant transformation of GCTB or development of a new sarcoma occurred in 5 of 304 (1.6%) patients treated with Xgeva. The median duration of exposure for these patients was 95 days (range: 29 to 257).

Reference ID: 3324412

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

/s/

MARTHA B DONOGHUE
06/13/2013

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.

NDA/BLA #	BLA 125320/94
Product Name:	Denosumab (Xgeva)
PMR/PMC Description:	Submit a final report of follow-up safety data of Xgeva (denosumab) in patients with giant cell tumor of bone enrolled in the ongoing open label study through November 2012 for a minimum of five years or until death or lost to follow-up, whichever comes first. Comprehensively collect information regarding survival status, disease progression, serious adverse events, and adverse events of special interest, including osteonecrosis of the jaw, pregnancy-related complications, atypical fractures, malignant transformation of giant cell tumor of bone, and secondary malignancies. Perform descriptive analyses of these safety data, including a subset analysis comparing the long-term safety of denosumab in adolescent and adult patients.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	12/2018
	Final Report Submission:	12/2019

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

   Giant cell tumor of bone is a rare tumor affecting approximately 800 patients per year in the United States. This tumor is typically slow growing and can have a benign course, but also is capable of metastasizing and transforming to a malignant sarcoma. Additionally, giant cell tumor of bone can cause debilitating pain and joint dysfunction. Surgical resection is the treatment of choice, but in some cases the extent of resection required to remove the tumor can result in severe morbidity (e.g., limb amputation or joint resection). There are no approved therapies for giant cell tumor of the bone that is unresectable or in cases where curative surgery is likely to result in severe morbidity.

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."

Reference ID: 3324012

This is a FDAA PMR to provide more comprehensive safety information regarding the risks associated with long term use of Xgeva in adolescent and adult patients with giant cell tumor of bone (GCTB). Limited information was available at the time of approval, and long term safety data is needed in this patient population because Xgeva is likely to be used indefinitely in a proportion of patients for treatment of GCTB. Malignant transformation and secondary malignancy are newly identified potential risks of Xgeva. The anticipated long duration of therapy (up to several years) and the underlying pathophysiology of GCTB may place patients at greater risk of development of these adverse events compared to patients with metastatic solid tumors receiving Xgeva for prevention of skeletal related events. Furthermore, the risk of adverse outcomes with denosumab exposure during pregnancy is not currently well characterized and is relevant to this population. GCTB most commonly occurs in patients 20-30 years of age (as opposed to patients with metastatic solid tumors who are generally older and less likely to be of reproductive potential). Finally, further characterization of the known serious risks of osteonecrosis of the jaw and atypical fractures with long term use of denosumab in this population is needed.

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? (Osteonecrosis of the jaw and atypical fractures)
     ☒ Assess signals of serious risk related to the use of the drug? (malignant transformation and secondary malignancy)
     ☐ 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.

Reference ID: 3324012

This PMR is to obtain the long term follow-up safety data from patients treated with denosumab who enrolled in the ongoing open label trial.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ 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

Continuation of Question 4

☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
The studies supporting approval are open label trials in which a total of 304 patients were treated with denosumab. The bulk of the data came from the third interim analysis of the trial outlined in this PMR. Longer term data from treatment of patients enrolled in this trial are needed to further assess the risks of long-term use of denosumab in patients with GCTB.

☐ 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?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

Reference ID: 3324012

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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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)

Reference ID: 3324012

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.

NDA/BLA #	BLA 125320/94
Product Name:	Denosumab (Xgeva)
PMR/PMC Description:	Submit the final report including primary datasets, derived datasets, and analysis programs used to generate the safety and efficacy results for the ongoing multicenter trial of denosumab in patients with giant cell tumor of bone. Include an analysis of radiographic response as determined by the local investigator in evaluable patients who received at least one dose of denosumab and underwent at least one post-baseline Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) tumor assessment during the trial. The primary analysis should be conducted after patients enrolled through November 2012 have had the opportunity to complete 12 months of treatment.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	12/2018
	Final Report Submission:	12/2019

6. 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

   Giant cell tumor of the bone is a rare tumor affecting approximately 800 patients per year in the United States. This tumor is typically slow growing and can have a benign course, but also is capable of metastasizing and transforming to a malignant sarcoma. Additionally giant cell tumor of bone can cause debilitating pain and joint dysfunction. Surgical resection is the treatment of choice, but in some cases the extent of resection required to remove the tumor can result in severe morbidity (e.g., limb amputation or joint resection). There are no approved therapies for giant cell tumor of the bone that is unresectable or in cases where curative surgery is likely to result in severe morbidity.

7. 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."

Reference ID: 3324012

The purpose of this PMC is to obtain the final analyses and data from an ongoing open label trial in adult and skeletally mature adolescent patients with giant cell tumor of the bone. Longer term follow-up data from patients enrolled prior to the cut-off date for the third interim analysis of this trial and additional data from treatment of the 200 + additional patients enrolled after the cut-off date for the third interim analysis will provide important information regarding the safety and use of denosumab in this patient population.

8. 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?

9. 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.

This PMC is to obtain the final analyses and data from an ongoing trial in adult and skeletally mature adolescent patients with giant cell tumor of the bone.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial

Reference ID: 3324012

☐ 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

Continuation of Question 4

☐ 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

This PMC is for provision of data from the primary analysis of an ongoing trial. The trials supporting approval are open label trials in which a total of 304 patients were treated with denosumab. The bulk of the data came from the third interim analysis of the trial outlined in this PMC. Longer term data from patients enrolled prior to the cut-off date for the third interim analysis and new data from treatment of the 200 + additional patients enrolled after the cut-off date for the third interim analysis will provide important information regarding the safety and use of denosumab in this patient population.

10. 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?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 3324012

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)

Reference ID: 3324012

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.

NDA/BLA #	BLA 125320/94
Product Name:	Denosumab (Xgeva)
PMR/PMC Description:	Provide a detailed and thoughtful analysis of the risk factors associated with malignant transformation of GCTB and development of new sarcoma and the lifetime and annual incidences of these events in denosumab naïve patients. For this analysis, use data from a minimum of two representative databases in addition to information from published literature. Include subset analyses based on specific risk factors identified from the comprehensive investigation.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	6/2015
	Study/Trial Completion:	12/2017
	Final Report Submission:	12/2018

11. 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

Giant cell tumor of bone is a rare tumor affecting approximately 800 patients per year in the United States. This tumor is typically slow growing and can have a benign course, but also is capable of metastasizing and transforming to a malignant sarcoma. Additionally, giant cell tumor of bone can cause debilitating pain and joint dysfunction. Surgical resection is the treatment of choice, but in some cases the extent of resection required to remove the tumor can result in severe morbidity (e.g., limb amputation or joint resection). There are no approved therapies for giant cell tumor of the bone that is unresectable or in cases where curative surgery is likely to result in severe morbidity.

12. 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 incidence and risk factors associated with malignant transformation of GCTB and secondary malignancy in patients with GCTB are not well characterized. This PMC will provide a basis for comparison of the incidence of malignant transformation and secondary malignancy in patients exposed to Xgeva in the ongoing open label trial with the incidence in patients who have not received denosumab, thus enabling a more informed assessment of this potential risk.

Reference ID: 3324012

13. 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? (malignant transformation and secondary malignancy)
☐ 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?

14. 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.

This PMC will use data from published studies and available databases to identify the incidence and risk factors associated with malignant transformation or development of new sarcoma in patients with GCTB.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ 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

Reference ID: 3324012

☐ Dosing trials

Continuation of Question 4

☐ 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

This PMC consists of a pooled analysis of available historical data to identify the baseline incidence and risks associated with malignant transformation or development of a new sarcoma in patients with GCTB who have not been exposed to denosumab.

15. 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?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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)

Reference ID: 3324012

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

/s/

MARTHA B DONOGHUE
06/12/2013

SUZANNE G DEMKO
06/12/2013

JEFFERY L SUMMERS
06/13/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125320	NDA Supplement # BLA Supplement # 94	If NDA, Efficacy Supplement Type:
Proprietary Name: Xgeva Established/Proper Name: denosumab Dosage Form: Injection		Applicant: Amgen, Incorporated Agent for Applicant (if applicable): NA
RPM: Melanie Pierce		Division: DOP2

NDAs and NDA Efficacy Supplements:

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.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] 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 _____	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None

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

❖ 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 _____	☐ Received
❖ Application Characteristics [3]	

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
☐ MedGuide w/o REMS
☒ 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 6.12.13
❖ 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*

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Reference ID: 3324314

❖ 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

Reference ID: 3324314

- [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).*

Reference ID: 3324314

(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[4]	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(s) and date(s) June 13, 2013
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.	6.12.13
• Original applicant-proposed labeling	12.11.12
• Example of class labeling, if applicable	NA

[4] Fill in blanks with dates of reviews, letters, etc.

Reference ID: 3324314

❖ 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	NA
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	NA
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 2.07.13 ☐ DMEPA ☐ DMPP/PLT (DRISK) ☒ ODPD (DDMAC) 5.22.13 ☐ SEALD ☐ CSS ☒ Other reviews MHT 5.10.13
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	2.07.13 ☐ Not a (b)(2) ☐ 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 ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan drug designation December 20, 2010 • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Reference ID: 3324314

❖ 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, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)* ❖	6.12.13-labeling 6.11.13-IR 6.10.13-labeling 6.07.13-tcon 6.07.13-labeling 6.04.13-labeling 5.29.13-tcon 5.28.13-PMR/PMC 5.28.13-SGE tcon 5.24.13-SGE tcon 5.17.13-labeling 5.14.13-IR 5.14.13-IR 5.10.13-IR 5.06.13-IR 5.03.13-IR 3.13.13-IR 3.04.13-IR 3.01.13-IR 2.27.13-IR 2.08.13-filing ltr 1.25.13-IR 1.18.13-IR 1.09.13-IR 12.20.13- Ack Ltr
❖ Internal memoranda, telecons, etc.	6.07.13-labeling mtg minutes 5.31.13-labeling mtg minutes 5.22.13-wrap up mtg minutes 5.08.13-labeling mtg minutes 5.07.13-labeling mtg minutes 4.30.13-labeling mtg minutes 4.16.13-team mtg minutes 3.13.13-Mid-cycle minutes 2.05.13-filing mtg minutes 1.04.13
❖ 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 April 5, 2011; September 11, 2012
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	NA
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	

Reference ID: 3324314

Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 6.13.13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☒ None 6.13.13
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Concurrence in clinical review
• Clinical review(s) *(indicate date for each review)*	5.20.13; 2.05.13
• 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 24 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 5.21.13
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
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 concurrence in stats review signed 5.16.13
Statistical Review(s) *(indicate date for each review)*	☐ None 5.16.13; 2.06.13
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 in the clin/pharm review signed 5.19.13
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 5.19.13; 2.05.13
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

Reference ID: 3324314

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 concurrence in nonclinical review signed 5.22.13
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 5.22.13; 2.07.13
❖ 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
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI 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 in quality review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 5.20.13; 1.25.13
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ 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 2 of the quality review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ 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[7])*	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: 6.04.13; 2.20.13; ☒ Acceptable ☐ Withhold recommendation

[7] 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.

Reference ID: 3324314

❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

Reference ID: 3324314

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.

Reference ID: 3324314

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/s/

MELANIE B PIERCE
06/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 10, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

FDA sent the attached label containing FDA's proposed changes to the package insert, to Amgen, Incorporated on June 10, 2013.

Changes to the package insert were made to the following sections:

- ADVERSE REACTIONS, section 6.1
- USE IN SPECIFIC POPULATIONS, section 8.7
- CLINICAL TRIALS, section 14.2

In addition, the following comment was conveyed regarding section 12.3:

> Clin pharm does not agree with the proposed numerical change to Section 12.3. According to table 10 found in study report 20040215, the mean serum trough concentration was [redacted] (b) (4) as previously written in the draft labeling. Unfortunately, the annotated pdf labeling file does not provide a source for the revised data.
>
> Please provide the data source to support the proposed change to the labeling in regards to the mean trough concentrations observed at 3 months.

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/s/

MELANIE B PIERCE
06/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 12, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

FDA sent the attached label containing FDA's proposed minor, editorial changes to the package insert, to Amgen, Incorporated on June 12, 2013.

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Reference ID: 3323885

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/s/

MELANIE B PIERCE
06/12/2013

Pierce, Melanie

From: Pierce, Melanie
Sent: Tuesday, June 11, 2013 10:59 AM
To: DeMelfi Jr., Tom (tdemelfi@amgen.com)
Subject: PMR's/PMCs

Hi Tom,
Just a quick email to let you know that the PMR's and PMC language will be similar if not the same in the action letter as what is outlined below.
Melanie

1. Submit a final report of follow-up safety data of Xgeva (denosumab) in patients with giant cell tumor of bone enrolled in the ongoing single arm study through November 2012 for a minimum of five years or until death or lost to follow-up, whichever comes first. Comprehensively collect information regarding survival status, disease progression, serious adverse events, and adverse events of special interest including osteonecrosis of the jaw, pregnancy-related complications, atypical fractures, malignant transformation of giant cell tumor of bone, and secondary malignancies. Perform descriptive analyses of these safety data, including a subset analysis comparing the long-term safety of denosumab in adolescent and adult patients.

   The timetable you submitted on June 5, 2013, states that you will conduct this study according to the following schedule:

   Final Report Submission: December 2019

2. Submit the final report including primary datasets, derived datasets, and analysis programs used to generate the safety and efficacy results for the ongoing single arm multicenter trial of denosumab in patients with giant cell tumor of bone. Include an analysis of radiographic response as determined by the local investigator in evaluable patients who received at least one dose of denosumab and underwent at least one post-baseline Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) tumor assessment during the trial. The primary analysis should be conducted after patients enrolled through November 2012 have had the opportunity to complete 12 months of treatment.

   The timetable you submitted on June 5, 2013, states that you will conduct this study according to the following schedule:

   Final Report Submission: December 2019

3. Provide a detailed and thoughtful analysis of the risk factors associated with malignant transformation of GCTB and development of new sarcoma and the lifetime and annual incidences of these events in denosumab naïve patients. For this analysis, use data from a minimum of two representative databases in addition to information from published literature. Include subset analyses based on specific risk factors identified from the comprehensive investigation.

Reference ID: 3323698

The timetable you submitted on June 5, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2018

Melanie B. Pierce
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Melanie.Pierce@fda.hhs.gov
Phone: 301-796-1273

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Reference ID: 3323698

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/s/

MELANIE B PIERCE
06/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 7, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

FDA sent the attached label containing FDA's proposed changes to the package insert, to Amgen, Incorporated on June 7, 2013.

Changes to the package insert were made during a labeling meeting conducted June 7, 2013 to the following sections:

- WARNINGS AND PRECAUTIONS, section 5.3
- ADVERSE REACTIONS, sections6.1 and 6.3
- DRUG INTERACTIONS, section 7
- USE IN SPECIFIC POPULATIONS, section 8.7
- CLINICAL PHARMACOLOGY, sections 12.1 and 12.3
- CLINICAL TRIALS, section 14.2
- Minor editorial changes throughout the label

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/s/

MELANIE B PIERCE
06/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 10, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

The following email was sent to Amgen on May 10, 2013

> What is the meaning of the variable rsctrl and how was it derived from the RS data set to the analysis data set?

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/s/

MELANIE B PIERCE
06/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 7, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Minutes: Xgeva (denosumab): BL STN 125320/94

FDA's proposed labeling revisions as discussed during the June 7, 2013, labeling meeting.

Attendees: Suzanne Demko, Martha Donoghue, Whitney Helms, Patricia Keegan, Melanie Pierce, Lixin Xu, and Vivian Yuan.

Changes to the package insert were made during a labeling meeting conducted on June 7, 2013, to the following sections:

- WARNINGS AND PRECAUTIONS, section 5.3
- ADVERSE REACTIONS, sections6.1 and 6.3
- DRUG INTERACTIONS, section 7
- USE IN SPECIFIC POPULATIONS, section 8.7
- CLINICAL PHARMACOLOGY, sections 12.1 and 12.3
- CLINICAL TRIALS, section 14.2
- Minor editorial changes throughout the label

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/s/

MELANIE B PIERCE
06/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 4, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

FDA sent the attached label containing FDA's proposed changes to the package insert, to Amgen, Incorporated on June 4, 2013.

Changes to the package insert were made during a labeling meeting conducted on May 31, 2013. Additional changes were made on May 30, 2013, June 3, 2013, and June 4, 2013 to the following sections:

- WARNINGS AND PRECAUTIONS, section 5.3
- ADVERSE REACTIONS, sections 6, 6.1 and 6.3
- DRUG INTERACTIONS, section 7
- USE IN SPECIFIC POPULATIONS, sections 8.4 and 8.7
- CLINICAL PHARMACOLOGY, sections 12.1, 12.2, and 12.3
- CLINICAL TRIALS, section 14.2
- PATIENT CONSELING INFORMATION, section 17

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

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/s/

MELANIE B PIERCE
06/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Memorandum

Date: June 4, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

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/s/

MELANIE B PIERCE
06/04/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125320 Supplement Number: 94 NDA Supplement Type (e.g. SE5): _____

Division Name: DOP2 PDUFA Goal Date: June 13, 2013 Stamp Date: _____

Proprietary Name: Xgeva

Established/Generic Name: denosumab

Dosage Form: Injection

Applicant/Sponsor: Amgen, Incorporated

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Prevention of skeletal-related events in patients with bone metastases from solid tumors.
(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: treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity

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.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda hhs.gov) OR AT 301-796-0700.

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∆
☐	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.*)

∆ 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:

{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.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: 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∆
☐	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:

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∆ 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 Section 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 some or all 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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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/s/

MELANIE B PIERCE
06/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 30, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

FDA's proposed labeling revisions as discussed during the April 30, 2013 labeling meeting:

Attendees: Jeanine Best, Suzanne Demko, Martha Donoghue, Chana Fuchs, Whitney Helms, Patricia Keegan, Amy McKee, Melanie Pierce, Marybeth, Toscano, Tracy Salaam, Shawna Weis, Lixin Xu, and Vivian Yuan.

Sections covered include:

Indications and Usage (1); Dosage and Administration (2.1), Warnings and Precautions (5.3) Adverse Reactions (6); Use in Specific Populations (8.7) and Clinical Pharmacology (12.1).

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/s/

MELANIE B PIERCE
05/31/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 7, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

FDA's proposed labeling revisions as discussed during the May 7, 2013 labeling meeting:

Attendees: Karen Boyd, Suzanne Demko, Martha Donoghue, Patricia Keegan, Stacy Shord, Marybeth Toscano, and Vivian Yuan.

Sections covered include:

Clinical Pharmacology (12.2, 12.3) and Clinical (b) (4) (14.2)

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MELANIE B PIERCE
05/31/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 8, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

FDA's proposed labeling revisions as discussed during the May 8, 2013 labeling meeting:

Attendees: Suzanne Demko, Martha Donoghue, Patricia Keegan, Melanie Pierce, Lixin Xu, and Vivian Yuan.

Sections covered include:

Clinical (b) (4) (14.2); Indications and Usage (1.2), and Use in Specific Populations (8.4)

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MELANIE B PIERCE
05/31/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 31, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

FDA's proposed labeling revisions as discussed during the May 31, 2013 labeling meeting:

Attendees: Suzanne Demko, Martha Donoghue, Whitney Helms, Patricia Keegan, Melanie Pierce, Stacy Shord, Marybeth Toscano, Shawna Weis, Lixin Xu.

Sections covered include:

Use in Specific Populations (8.4, 8.7), Adverse Reactions (6.1, 6.3), Drug Interactions (7), and Clinical (b) (4) (14.1).

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MELANIE B PIERCE
05/31/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 28, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: sBLA 125320/94; **Proposed** PMC/PMR language

Mr. DeMelfi,

Please see FDA's post-marketing requirement proposals for Xgeva (denosumab) application 125320/94:

POST-MARKETING REQUIREMENTS:

CLINICAL:

Clinical Benefit:

1. Submit the final report including primary datasets, derived datasets, and analysis programs used to generate the safety and efficacy results for the ongoing single arm multicenter trial of denosumab in patients with giant cell tumor of bone. Include an analysis of radiographic response [redacted] (b) (4) The primary analysis should be conducted [redacted] (b) (4) completed 12 months of treatment.

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion Date:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY
Other:	MM/DD/YYYY

Long Term Safety Data:

2. [redacted] (b) (4) a final report [redacted] (b) (4) follow-up safety data of Xgeva in patients with giant cell tumor of bone. Comprehensively collect information regarding survival status, disease progression, serious adverse events, and adverse events of special interest [redacted] (b) (4) osteonecrosis of the jaw, pregnancy-related complications, skeletal fractures, malignant transformation of giant cell tumor of bone, and secondary malignancies. Perform descriptive analyses of these safety data, including a subset analysis comparing the long-term safety of denosumab in adolescent and adult patients.

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion Date:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY
Other:	MM/DD/YYYY

Reference ID: 3315237

Malignant Transformation:

3. Provide a detailed and thoughtful analysis (b) (4) (b) (4) of malignant transformation of GCTB and the development of new sarcoma in denosumab naïve patients. Include subset analyses based on specific risk factors identified from the comprehensive investigation.

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion Date:	MM/DD/YYYY
Final Report Submission:	MM/DD/YYYY
Other:	MM/DD/YYYY

If you have any questions, please call me at 301-796-1273.

Reference ID: 3315237

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/s/

MELANIE B PIERCE
05/28/2013

Wrap-up Meeting Minutes
May 22, 2013

BLA: 125320/94

Product: Xgeva (denosumab)
Submission Date: December 11, 2012
Received Date: December 12, 2012
Sponsor: Amgen, Inc.

Proposed Indication: Treatment of Giant cell tumor of the bone (GCTB) in adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

MEETING ATTENDEES:
Katherine Coyle, Suzanne Demko, Martha Donoghue, Frances Fahnbulleh, Kun He, Whitney Helms, Ruby Leong, Melanie Pierce, Suzanne Robottom, Tracy Salaam, Shawna Weis, Lixin Xu, and Vivian Yuan

DISCUSSION TOPICS:

- All review disciplines recommended approval for Xgeva (denosumab) application 125320/94.
- FDA recommends accelerated approval of Xgeva in adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- There are three potential PMRs:
  - Submit a final study report for trial 20062004 to confirm clinical benefit in the proposed patient population.
  - Provide an analyses of the long term safety of Xgeva in patients on trial 20062004.
  - Investigate the risk factors associated with malignant transformation of GCTB and development of new sarcoma in patients who have not received treatment with denosumab.
- Labeling negotiations are ongoing.
- A teleconference with Amgen will be scheduled to discuss potential PMCs/PMRs.

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/s/

MELANIE B PIERCE
05/24/2013

Mid-Cycle Meeting Minutes
March 13, 2013

BLA: 125320/94

Product: Xgeva (denosumab)
Submission Date: December 11, 2012
Received Date: December 12, 2012
Sponsor: Amgen, Inc.

Proposed Indication: [redacted] (b) (4) .

PRESENTATION SCHEDULE:

Melanie Pierce	5 minutes
Martha Donoghue	30 Minutes

MEETING ATTENDEES:

Suzanne Demko, Martha Donoghue, Kun He, Whitney Helms, Patricia Keegan, Melanie Pierce, Suzanne Robottom, Stacy Shord, Jeff Summers, Peter Waldron, Shawna Weis, Lixin Xu, Vivian Yuan, and Hong Zhao

SUMMARY OF FINDINGS:

- A Durable objective response by modified RECIST observed in approximately one quarter of patients with GCTB who were evaluated in the retrospective analysis.
- Response by density/size criteria appears to be more sensitive but less reliable measure of objective response.
  - higher percentage of patients in control group had "responses."
- The efficacy of denosumab in adult and skeletally mature adolescent patients with unresectable or difficult to resect GCTB is supported by the retrospective analysis of durable objective response
- The toxicity profile observed in GCTB studies is consistent with current labeling
- The number of pregnancies observed in GCTB studies is concerning.
- Additional monitoring of long term safety is needed (secondary malignancies, ONJ, etc.).

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/s/

MELANIE B PIERCE
05/24/2013

Team Meeting Minutes
April 16, 2013

BLA: 125320/94

Product: Xgeva (denosumab)
Submission Date: December 11, 2012
Received Date: December 12, 2012
Sponsor: Amgen, Inc.

Proposed Indication: [redacted] (b) (4) .

MEETING ATTENDEES:
Suzanne Demko, Martha Donoghue, Frances Fahnbulleh, Melanie Pierce, Suzanne Robottom, Stacy Shord, Jeffrey Summers Shawna Weis, Lixin Xu, and Vivian Yuan

DISCUSSION TOPICS/UPDATES:

- Clinical:
  - Three special government employees (SGEs) were identified; two are cleared. A brief teleconference with the SGE's will be scheduled late April or early May, 2013.
  - FDA may consider strengthening the wording in the pregnancy registry to address the increased rate of pregnancy observed during the clinical trial.
  - FDA may seek additional safety data for pregnant patients or require a post marketing requirement (PMR).
  - FDA expressed concern about secondary malignancies or malignant transformations in patients treated with denosumab.
- Statistics:
  - Under review; no updates.
- Nonclinical:
  - Under review; no updates.
- Clinical Pharmacology:
  - See CMC information below
  - A cross-analysis was performed
  - The clinical pharmacology sections of the package insert were revised.
- Chemistry, Manufacturing and Controls:
  - Will request an update of the immunogenicity data in the clinical study reports.

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/s/

MELANIE B PIERCE
05/21/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 17, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Xgeva (denosumab): BL STN 125320/94

FDA sent the attached label containing FDA's proposed changes to the package insert, to Amgen, Incorporated on May 17, 2013.

Changes to the package insert were made during labeling meetings conducted on the following days:

- April 30, 2013
- May 7, 2013
- May 8, 2013

Additional changes were made:

- May 15, 2013

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

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MELANIE B PIERCE
05/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 14, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following request for additional information:

> Please explain why the following RECIST-evaluable patients do not have an entry in the BPTARDIA (Best RECIST% Chg of Sum Lesion Diameters) data field in the ATPRSUM1 analysis dataset. The ASLBASE dataset indicates that all of these patients except Patient (b) (6) had a target lesion at baseline.
>
> (b) (6)
>
> Please respond by the morning of May 17, 2013.
>
> Please call me at 301-796-1273 if you have any additional questions.

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/s/

MELANIE B PIERCE
05/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 14, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following request for additional information:

> The Division of Oncology Products 2 (DOP2) is currently discussing potential postmarketing commitments related to the Xgeva sBLA for the giant cell tumor of bone (GCTB) indication. One potential safety issue identified during the review of the sBLA is the potential for increased risk of malignant transformation of GCTB or development of a new sarcoma with Xgeva. The Division acknowledges the difficulty in assessing this potential risk using clinical data derived from single arm trials, particularly when there is a limited historical database to characterize the baseline risk of malignant transformation or development of a new sarcoma in the proposed patient population. Therefore, the Division is considering whether data from nonclinical study(ies) may be helpful to characterize the potential risk of malignant transformation of GCTB with exposure to denosumab at the proposed dosage. The Division does not think that traditional carcinogenicity studies would be helpful to address this concern. Please provide a proposal for one or more nonclinical studies to assess the potential risk of malignant transformation of GCTB (or the formation of a new sarcoma) with Xgeva therapy. Please include justification for the predictivity of the recommended model(s) for risk of malignant transformation and/or formation of a new sarcoma in the proposed patient population.

Please call me at 301-796-1273 if you have any additional questions.

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MELANIE B PIERCE
05/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 6, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following request for additional information:

> Regarding patient [redacted] (b) (6): Page 107 of the clinical study report for Study 20062004 indicates that patient [redacted] (b) (6) had prior radiotherapy, but page 321 of the case report form for this patient indicates that this patient did not have a history of prior radiotherapy to treat GCTB. Please explain this discrepancy.

Please call me at 301-796-1273 if you have any additional questions.

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MELANIE B PIERCE
05/06/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 3, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following request for additional information:

> Please clarify if you have specific questionnaires for the 6 month and 12 month time points for the denosumab pregnancy surveillance program. If so, please submit them to us for our review. In addition, please provide any information you have regarding health outcomes during the neonatal period through the first year of life for the infant (or infants) born to mothers who either became pregnant while being treated with denosumab and for infant(s) born to mothers who became pregnant from a partner who was receiving denosumab (paternal exposure).

Please call me at 301-796-1273 if you have any additional questions.

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/s/

MELANIE B PIERCE
05/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 13, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following request for additional information:

Please provide the information requested below, if it is available, regarding patients who were considered responders in the imaging control group used for the retrospective analysis of objective tumor response in the GCTB sBLA:

CLINICAL PHARMACOLOGY:

1. Submit the bioanalytical report for the method used to measure denosumab serum trough concentrations in samples collected from patients enrolled into Study 20040215.

   In the efficacy submission, it is not clear what assay method was used to measure denosumab serum trough concentrations in samples collected from patients enrolled into Study 20040215. The pharmacokinetic (PK) appendix (app 12) of the study report for Study 20040215 references a Bioanalytical Report [redacted] (b) (4) but the report is not included in this supplemental application. It also states that assay for measuring denosumab concentrations in human serum was based upon a method developed at Amgen Inc. CA, [redacted] (b) (4) however, Table 15 of the Summary of Clinical Pharmacology Studies and the Pharmacokinetic Report Addendum lists assay no. 102110 as the method used to measure denosumab serum concentrations in PK samples in Study 20040215.

   Please notify FDA if the same assay was used to support this supplemental application and

the previous supplemental application for the prevention of bone metastases and no analytical bridging is needed. If different assays were used, please provide supporting data to demonstrate that both analytical methods provide comparable concentrations to allow cross study comparison of serum trough concentrations following the subcutaneous administration of a dose of 120 mg.

STATISTICS:

2. Please submit the SAS program that generated Figure 3 and Figure in the Summary of Clinical Efficacy.

Please provide a response by close of business, Friday, March 22, 2013.

Please call me at 301-796-1273 if you have any additional questions.

Reference ID: 3275735

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/s/

MELANIE B PIERCE
03/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 27, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

The following email was sent to Thomas DeMelfi, Jr, authorized representative for Amgen application sBLA 125320/94, on February 27, 2013:

Pierce, Melanie

From: Pierce, Melanie
Sent: Wednesday, February 27, 2013 1:40 PM
To: 'DeMelfi Jr., Tom'
Subject: RE: IND 113617; Teleconference request to discuss WR

Dear Mr. Di Melfi,

The clinical team has reviewed your request for a teleconference to discuss the proposed changes to the Written Request for denosumab and has determined that your proposal can be addressed via written correspondence instead of a teleconference. Please see DOP2's responses (in blue) to your requests for clarification and changes to the language in the Written Request. If these responses adequately address your concerns, please submit a request for changes to the WR as a formal submission to the BLA. Once received, DOP2 will schedule a meeting with the Pediatric Review Committee to obtain concurrence with the proposed changes.

(b) (4)

[redacted]

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MELANIE B PIERCE
03/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 4, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following request for additional information:

Please provide the following clarifying information regarding the imaging data disposition efficacy analysis set:

1. Table tiae1-1.1 of Section 5.3.5.3 (Integrated Summary of Efficacy) indicates that 166 of 169 subjects who received denosumab in Cohort 1 were eligible for the retrospective collection of images for the radiographic determination of objective response. It appears that the following 3 subjects enrolled to Cohort 1 were not considered to be part of this eligible set: [redacted] (b) (6), [redacted] (b) (6), and [redacted] (b) (6). Please explain why these subjects were not considered to be part of the imaging efficacy analysis set and clarify if it is because they had previously participated in Study 20040215.

2. Additionally, it appears that subject [redacted] (b) (6) in Cohort 2 was not eligible for the retrospective analysis of objective tumor response. Please clarify if this subject was omitted due to the prior issue regarding treatment without informed consent or for some other reason.

3. If FDA is incorrect in the identification of subjects enrolled in Study 20062004 who were excluded from the imaging efficacy analysis set, please list the subjects that were excluded and the reasons for not including them in this set.

Please respond by COB, Friday, March 8, 2013.

Please call me at 301-796-1273 if you have any additional questions.

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/s/

MELANIE B PIERCE
03/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 1, 2013

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following request for additional information:

Please provide the information requested below, if it is available, regarding patients who were considered responders in the imaging control group used for the retrospective analysis of objective tumor response in the GCTB sBLA:

1. For patient [redacted] (b) (6) the type of chemotherapy received prior to enrollment in study 20062004 and the dates that this chemotherapy was administered.

2. For patient [redacted] (b) (6)
   a. The type of chemotherapy administered prior to study enrollment, and the dates of receipt of this chemotherapy
   b. The date of the GCTB surgery that occurred prior to denosumab treatment
   c. The date bisphosphonate therapy was started and finished.

3. For patient [redacted] (b) (6) the date bisphosphonate therapy was started and finished.

4. For patient [redacted] (b) (6)
   a. The date bisphosphonate therapy was started and finished.
   b. The date of the GCTB surgery that occurred prior to denosumab treatment.

5. Subject (b) (6) was assessed by the independent radiology review committee as having achieved a PR by RECIST and density/size criteria on day -44. Table 16 in the Clinical Summary of Efficacy implies that the assessments of PR can be explained by surgery and embolization that took place over a year earlier, and there are prior post-intervention images on day -151 (approximately 4 months after the therapeutic interventions, control baseline) and day -112 that presumably would have reflected the results of these interventions. However, the Clinical Summary of Efficacy implies that these interventions provide an explanation for the assessment of PR on day -44. Did Subject (b) (6) undergo additional therapeutic interventions between day -151 and day -44 that could account for the assessment of PR?

Please respond by Thursday, March 7, 2013.

Please call me at 301-796-1273 if you have any additional questions.

Reference ID: 3269634

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/s/

MELANIE B PIERCE
03/01/2013

1st Planning Meeting Minutes
January 4, 2013

BLA: 125320/94

Product: Xgeva (denosumab)
Submission Date: December 11, 2012
Received Date: December 12, 2012
Sponsor: Amgen, Inc.

Proposed Indication: Treatment of Giant cell tumor of the bone (GCTB) in adults and skeletally mature adolescents.

Meeting Attendees:
Patricia Keegan, Melanie Pierce, Martha Donoghue, Vivian Yuan, Kun He, Stacy Shord, Hong Zhao, Shawna Weis, Whitney Helms, Lixin Xu, and Sue Kang.

DISCUSSION TOPICS:

- The review status is designated as priority.
- The application will not be presented before an advisory committee.
- A consult from the Pediatric and Maternal Health team will not be required.
- The Medical Officer will determine the necessity for Special Government Employees (SGE's).
- Clinical site discussions with OSI will be conducted to determine if clinical site inspections are warranted.

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/s/

MELANIE B PIERCE
02/08/2013

Filing Meeting Minutes
February 5, 2013

BLA: 125320/94

Product: Xgeva (denosumab)
Submission Date: December 11, 2012
Received Date: December 12, 2012
Sponsor: Amgen, Inc.

Proposed Indication: [redacted] (b) (4) .

MEETING ATTENDEES:

Patricia Keegan, Melanie Pierce, Suzanne Demko, Martha Donoghue, Hong Zhao, Stacy Shord, Shawna Weis, Whitney Helms, Lixin Xu, Jeffrey Summers, Kun He, Vivian Yuan, and Sue Kang,.

DISCUSSION TOPICS:

- The Medical Officer is in the process of clearing two SGEs and will determine if a patient representative from the Office of Special Health Issues is needed.
- The Medical Officer and OSI determined that clinical inspections are not necessary.
- A Pediatric and Maternal Health consult was requested to review section 8, USE IN SPECIFIC POPULATIONS of the package insert.

AGREEMENT/NON-AGREEMENT REGARDING FILING DECISION BY DISCIPLINE:

- Clinical: No issues to preclude filing
- Statistical: no issues to preclude filing
- Pharmacology/Toxicology: no issues to preclude filing
- Clinical Pharmacology: no issues to preclude filing
- CMC: no issues to preclude filing

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/s/

MELANIE B PIERCE
02/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/94

FILING COMMUNICATION

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA) dated December 11, 2012, received December 12, 2012, submitted under section 351(a) of the Public Health Service Act for Xgeva® (denosumab).

We also refer to your amendments dated December 12, 2012, January 15, 2013, January 24, 2013, and February 4, 2013.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Priority**. Therefore, the user fee goal date is June 13, 2013.

We are reviewing your supplemental 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, midcycle, 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 requirement/commitment requests by May 23, 2013.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of 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.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

> In the Full Package Insert: Postmarketing Experience subsection of ADVERSE REACTIONS, the following statement is missing: *"Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.*

We request that you resubmit labeling (Microsoft Word format) that addresses this issue by March 1, 2013. The resubmitted labeling will be used for further labeling discussions.

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because you were granted orphan-drug designation for giant cell tumor of the bone on December 20, 2010, none of these criteria apply to your application; you are exempt from this requirement.

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

Sincerely,

{See appended electronic signature page}

Patricia Keegan, MD
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
02/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**Pediatric and Maternal Health Staff Request for Consultation**	
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics ☐ Maternal Health ☐ Both ☒			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Melanie Pierce/OHOP/DOP2; 301-796-1273	
DATE February 5, 2013	IND NO.	BLA NO. 125320/94	TYPE OF DOCUMENT Supplemental Biologics License Application	DATE OF DOCUMENT December 12, 2013
NAME OF DRUG Xgeva (denosumab)	NAME OF FIRM Amgen, Incorporated		CLASSIFICATION OF DRUG Monoclonal Antibody-RANK ligand inhibitor	PDUFA Goal Date June 13, 2013
Requested Consult Completion Date:	☐ Urgent* (< 14 days)		☐ Priority (14-29 days)	☒ Routine ≥ 30 days

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
☒ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☐ PeRC Preparation Assistance ☐ Other (please explain):	☒ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): EDR Location: \\Cbsap58\M\eCTD_Submissions\STN125320\0255	Materials to be reviewed: Package Insert

1. Please briefly describe the submission including drug's indication(s):
This supplemental biologics license application proposes to add the [redacted] (b) (4) as a new clinical indication

2. Describe in detail the reason for your consult. Include specific questions:
   - For Pediatrics, please review USE IN SPECIFIC POPULATIONS; subsection 8.4 Pediatric Use to determine if the proposed language added is appropriate.
   - For the Maternal Health Team, please ensure section 8 USE IN SPECIFIC POPULATIONS is appropriately updated

3. Meeting dates:
The labeling meetings for this application are as follows:
   - April 30, 2013
   - May 7, 2013
   - May 8, 2013
   - May 21, 2013

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):

Review team:
Project Manager: Melanie Pierce
Clinical reviewer & Team Leader: Martha Donoghue/Suzanne Demko
Pharmacology/Toxicology reviewer & Team Leader: Shawna Weis/ Whitney Helms
Clinical Pharmacology reviewer & Team Leader: Stacy Shord/Hong Zhao
Other: Statistical reviewer: Vivian Yuan/Kun He

CMC reviewer: Lixin, Xu/Chana Fuchs OPDP reviewer: Carole Broadnax	
PRINTED NAME or SIGNATURE OF REQUESTOR: Melanie Pierce	METHOD OF DELIVERY (Please check) ☒ DARRTS ☐ EMAIL ☐ HAND ☐ OTHER

Version: DARRTS 06/01/2011

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/s/

MELANIE B PIERCE
02/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 25, 2013

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following request for additional information:

1. Please provide the standard operating procedures (SOPs) used to obtain informed consent for image transfer to [redacted] (b) (4) for the retrospective substudy. In addition, please clarify if investigators were given SOPs for attempting to obtain informed consent (e.g., how many times they should attempt to contact patients who are off study) and if documentation is available to confirm that these SOPs were followed for the patients that did not provide informed consent. For each of the 40 subjects that did not provide informed consent, please indicate whether informed consent was not obtained due to patient refusal or because patients were not successfully contacted.

2. Your January 14, 2013 response to our information request indicated that CRAs supervised prompt compliance and proper documentation during regular visits. Please clarify if these CRAs were employees of the investigator sites or external CRAs. Additionally, does this refer to oversight of the conduct of the substudy (the procedures for obtaining images for IRC review)?

3. Please clarify if Amgen monitored and/or audited the procedures for obtaining images for retrospective IRC review or rely on CRAs employed at each site to ensure that due diligence was applied to the collection of images.

4. Regarding your response to FDA Question 2, for each site that was "unable to obtain images," please list the number of patients at each site whose images were not provided because they were unobtainable, along with the specific reasons that investigators could

not obtain them for the retrospective review (or provide information directing us to where this information is located in the sBLA).

5. Please clarify if there a protocol in the sBLA that specifically addresses the conduct of the retrospective radiographic review substudy. We found the (b) (4) radiology charter and statistical analysis plan for clinical summary of efficacy for the GCTB indication but are not sure if there is also a protocol that we couldn't locate.

6. Please clarify if Amgen obtained an updated agreement with investigators to support the retrospective collection of radiographic images at the sites.

Please respond by Friday, February 1, 2013.

Please call me at 301-796-1273 if you have any additional questions.

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
01/25/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 18, 2013

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following request for additional information:

> Please provide the requested information contained in the attached document to facilitate the development of clinical investigator and sponsor/monitor/CRO inspection assignments.

Please respond by Wednesday, January 23, 2013 at 12:00 p.m.

Please call me at 301-796-1273 if you have any additional questions.

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

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

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original BLA for the Phase 2 clinical trial [specifically, *Study No. 20062004: "An Open-Label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone"]* :
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   e. Identify sites that were terminated for any reason. Provide explanation for each termination that occurred, and whether data from those sites were used or not in study analyses.

2. Please include the following information in a tabular format by site in the original BLA for the Phase 2 clinical trial (specifically, *Study No. 20062004*):
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

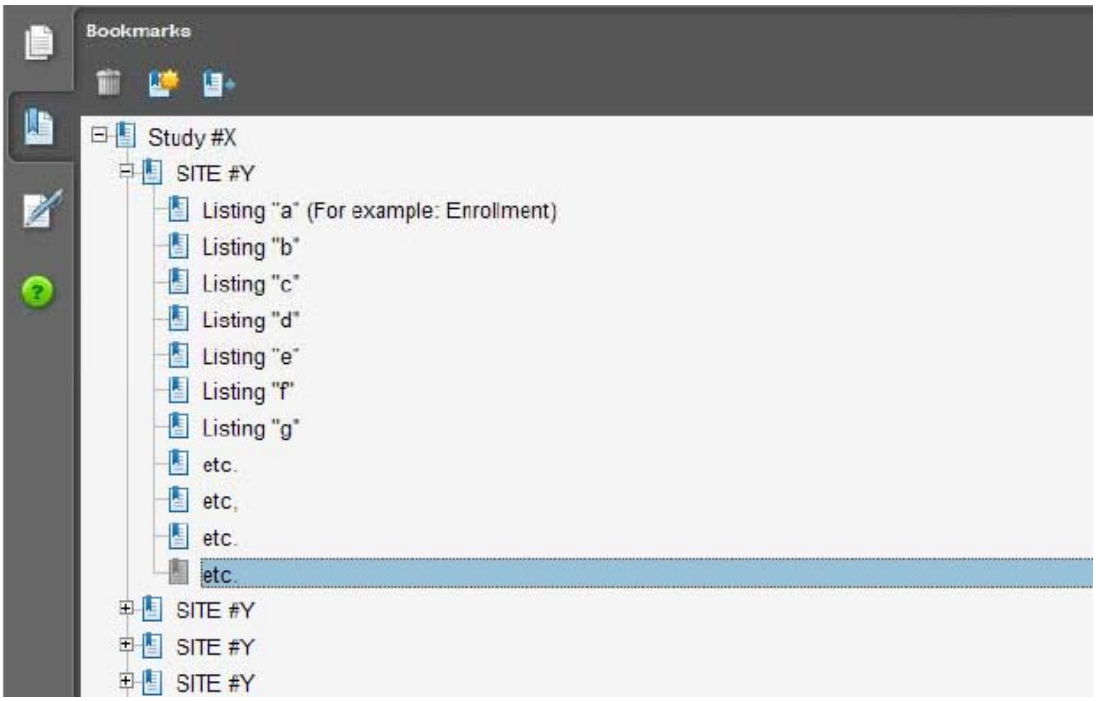
3. Please include the following information in a tabular format in the BLA for the Phase 2 clinical trial (specifically, *Study No. 20062004*):
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trial
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies

   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For the Phase 2 clinical trial (specifically, *Study No. 20062004*) provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For the Phase 2 Study (specifically, *Study No. 20062004*) provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For the Phase 2 clinical trial (specifically, *Study No. 20062004*): *"An Open-Label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone"*]: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization); if appropriate
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the BLA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for the study (specifically, *Study No. 20062004*) using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for the pivotal study [specifically, *Study No. 20062004: "An Open-Label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone"*] submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy (specifically, *Study No. 20062004*), the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	(b) (4)
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to descr be the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2

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

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

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

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

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

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

References:

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

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

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

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/s/

MELANIE B PIERCE
01/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 9, 2013

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/94; Information request Xgeva (denosumab)

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Xgeva® (denosumab).

We are in the process of reviewing your supplemental BLA application (125320/94) and have the following requests for additional information:

In the Integrated Summary of Efficacy, Table tiae1-1.2, the following statistics are provided:

The reason "Unable to obtain informed consent" was provided to explain why 7 of 37 patients in Study 20040215 and 33 of 266 patients in Study 20062004 could not be included in the independent analysis of radiographic response.

Similarly, "Unable to obtain images" was cited to explain why 20 of 266 patients in Study 20062004 could not be included in the independent analysis of radiographic response.

It appears that these issues were more commonly encountered in some sites than others. For example, images could not be obtained in all 8 patients enrolled from Site 202 (Inv: Alex Powell) and informed consent could not be obtained in 7 of 27 patients enrolled in site 306 (Inv: Stefano Ferrari). Please provide a response to the following questions:

1. Were uniform procedures for obtaining informed consent and radiographic images for the retrospective IRC review provided to the sites? If so, is there documentation that these procedures were followed that can be provided to FDA?

2. Please explain whether "Unable to obtain images" means that radiographic studies were performed but images couldn't be obtained due to technical problems or loss of images. If not, please describe the scenarios that are covered by this category.

Please respond by Monday, January 14, 2013. Please call me at 301-796-1273 if you have any

additional questions.

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/s/

MELANIE B PIERCE
01/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADM NISTRATION	REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**	FROM: Melanie Pierce: Project Manager/OHOP/DOP2-301-796-1273

DATE	IND NO.	BLA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 4, 2013		BLA 125320/94	Efficacy supplement	December 12, 2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xgeva (denosumab)	Priority	Monoclonal antibody	May 20, 2013

NAME OF FIRM: Amgen, Incorporated

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Review of the pharmacovigilance plan

\\Cbsap58\M\eCTD_Submissions\STN125320\0255

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

MELANIE B PIERCE
01/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: Melanie Pierce: Project Manager/OHOP/DOP2-301-796-1273

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
January 4, 2013	113617	BLA 125320/94	Efficacy supplement

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Xgeva (denosumab)	Priority	Monoclonal antibody	May 20, 2013

NAME OF FIRM:
Amgen, Inc.

PDUFA Date: June 13, 2013

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:
Review of promotional labeling for this new BLA efficacy supplement.

EDR Location: \\Cbsap58\M\eCTD_Submissions\STN125320\0255

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: TBD
Labeling Meetings:TBD
Wrap-Up Meeting: TBD

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☒ eMAIL ☐ HAND

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/s/

MELANIE B PIERCE
01/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/94

PRIOR APPROVAL SUPPLEMENT - ACKNOWLEDGEMENT

Amgen, Incorporated
Attn: Thomas M. DeMelfi, Jr., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. DeMelfi:

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

BLA SUPPLEMENT NUMBER: 125320/94

PRODUCT NAME: Xgeva (denosumab)

DATE OF SUBMISSION: December 11, 2012

DATE OF RECEIPT: December 12, 2012

US LICENSE NUMBER: 1080

This supplemental application proposes to include a new indication for [redacted] (b) (4) [redacted] (b) (4) .

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 10, 2013, in accordance with 21 CFR 601.2(a).

CONTENT OF LABELING

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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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 content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN D JONES
12/20/2012