CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125320Orig1s005

Trade Name: PROLIA

Generic or Proper Name: denosumab

Sponsor: Amgen Inc.

Approval Date: 09/16/2011

Indication:

Prolia is a RANK ligand (RANKL) inhibitor indicated for:

Treatment of postmenopausal women with osteoporosis at high risk for fracture

Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer

Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer (1.3)

CENTER FOR DRUG EVALUATION AND RESEARCH

BLA 125320Orig1s005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

STN BL 125320/5
STN BL 125320/6

SUPPLEMENT BLA APPROVAL
September 16, 2011

Amgen, Incorporated
Attention: John Bergan
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-1799

Dear Mr. Bergan:

Please refer to your Supplemental Biologics License Applications (sBLAs), dated December 19, 2008, submitted under section 351 of the Public Health Service Act for Prolia® (denosumab).

We acknowledge receipt of your amendments dated through September 15, 2011 and your risk evaluation and mitigation strategy (REMS) assessment dated September 9, 2011.

The March 18, 2011, submissions constituted complete responses to our October 19, 2009, action letter for each of the supplements listed below:

BLA STN 125320/5
This Prior Approval efficacy supplement to your biologics license application provides for a new indication to include treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

BLA STN 125320/6
This Prior Approval efficacy supplement to your biologics license application provides for a new indication to include treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures.

These supplements also provide for a proposed modification to the approved REMS.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide) 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. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STNs 125320/5 and 125320/6**."

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

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for these applications because necessary studies are impossible or highly impracticable because the disease/condition does not exist in children.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Prolia® (denosumab) was originally approved on June 1, 2010, and a REMS modification was approved July 22, 2011. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of a revised REMS document to describe the amended communication plan, updated communication materials reflecting the newly approved indications, and an updated Medication Guide to be consistent with the prescribing information.

Your proposed modified REMS, submitted on July 1, 2011, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on June 1, 2010.

There are no changes to the REMS assessment plan described in our June 1, 2010 letter.

We remind you that assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 125320 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125320
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125320
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the

proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

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

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

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) 796-1273.

Sincerely,

/ Patricia Keegan /
Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

Medication Guide
Dear Healthcare Provider Letter
Website Screenshot

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125332/0
125333/0

COMPLETE RESPONSE
October 19, 2009

Amgen, Incorporated
Attention: Edward S. Burd, Ph.D.
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Burd:

Please refer to your biologics license application, dated and received December 19, 2009, submitted under section 351 of the Public Health Service Act for Prolia (denosumab).

We acknowledge receipt of your amendments dated: February 25, 2009; February 27, 2009; March 3, 2009; March 5, 2009; March 9, 2009; March 11, 2009; March 12, 2009; March 13, 2009; March 18, 2009; April 6, 2009; April 15, 2009; April 17, 2009; April 23, 2009; April 29, 2009; April 30, 2009; May 1, 2009; May 4, 2009; May 15, 2009; May 19, 2009; May 27, 2009; June 5, 2009; June 9, 2009; June 12, 2009; June 25, 2009; July 10, 2009; July 13, 2009; July 20, 2009; August 7, 2009; August 18, 2009; August 26, 2009; August 31, 2009; September 3, 2009; September 10, 2009; September 11, 2009; September 18, 2009; and, September 28, 2009.

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL:

1. You have not provided substantial evidence from adequate and well controlled clinical trials establishing the safety of Prolia (denosumab) in patients with breast cancer receiving aromatase inhibitor therapy or patients with prostate cancer receiving androgen deprivation therapy. Specifically, the data from clinical trials submitted in these license applications are inadequate to determine if Prolia has detrimental effects on breast cancer or prostate cancer outcomes since the trials were not adequately designed to compare disease-free survival and overall survival between treatment arms.

   Provide results from adequate and well-controlled clinical trials demonstrating that Prolia has no detrimental effects on either time-to-disease progression or overall survival.

Provide a justification for each of the studies selected based on adequacy of design and conduct, including but not limited to:

a. adequacy of the sample size to detect a clinically meaningful detrimental effect;

b. assurance that monitoring assessments are performed with appropriate frequency and are adequate in scope to assess disease progression;

c. confirmation that the trial is masked to treatment or determination of disease progression is conducted in a manner that minimizes bias based on knowledge of treatment;

d. the analysis is mature with minimal amounts of missing data; and,

e. treatment arms are well-controlled with respect to prognostic factors (including concomitant anti-neoplastic therapy).

The clinical study report(s) should contain analyses of overall survival and progression-free survival, primary data and programs used to generate all analyses presented, as well as case report forms for all patients who progressed while receiving denosumab and all patients who died during the conduct of the trials.

LABELING:

2. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated 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

POSTMARKETING REQUIREMENTS:

3. Please reference the October 16, 2009 complete response letter issued to you from the Office of Drug Evaluation III, Division of Reproductive and Urologic Products requesting you to conduct postmarketing trials for your other Prolia BLA applications, STNs 125320/0 and 125331/0.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS:

4. Please reference the October 2, 2009 Information Request letter from the Office of Drug Evaluation III, Division of Reproductive and Urologic Products requesting you to submit a Risk Evaluation and Mitigation Strategy (REMS).

OTHER

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a

request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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

Sincerely,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

LABELING

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

Prolia® (denosumab)
Injection, for subcutaneous use

Initial US Approval: 2010

----------RECENT MAJOR CHANGES----------
- Indications and Usage (1.2, 1.3) 09/2011
- Warnings and Precautions (5.1) 07/2011

----------INDICATIONS AND USAGE----------
Prolia is a RANK ligand (RANKL) inhibitor indicated for:
- Treatment of postmenopausal women with osteoporosis at high risk for fracture (1.1)
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer (1.2)
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer (1.3)

----------DOSAGE AND ADMINISTRATION----------
- Prolia should be administered by a healthcare professional (2.1)
- Administer 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen (2.1)
- Instruct patients to take calcium 1000 mg daily and at least 400 IU vitamin D daily (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Single-use prefilled syringe containing 60 mg in a 1 mL solution (3)
- Single-use vial containing 60 mg in a 1 mL solution (3)

----------CONTRAINDICATIONS----------
- Hypocalcemia (4.1, 5.2)

----------WARNINGS AND PRECAUTIONS----------
- Same Active Ingredient: Patients receiving Prolia should not receive XGEVA® (5.1)
- Hypocalcemia: Must be corrected before initiating Prolia. May worsen, especially in patients with renal impairment. Adequately supplement patients with calcium and vitamin D (5.2)
- Serious infections including skin infections: May occur, including those leading to hospitalization. Advise patients to seek prompt medical attention if they develop signs or symptoms of infection, including cellulitis (5.3)
- Dermatologic reactions: Dermatitis, rashes, and eczema have been reported. Consider discontinuing Prolia if severe symptoms develop (5.4)
- Osteonecrosis of the jaw: Has been reported with Prolia. Monitor for symptoms (5.5)
- Suppression of bone turnover: Significant suppression has been demonstrated. Monitor for consequences of bone oversuppression (5.6)

----------ADVERSE REACTIONS----------
- Postmenopausal osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has been reported in clinical trials (6.1)
- Bone loss due to hormone ablation for cancer: Most common adverse reactions (≥ 10% and more common than placebo) were: arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials (6.1)

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

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy Surveillance Program available (8.1)
- Nursing mothers: May impair mammary gland development and lactation. Discontinue drug or nursing (8.3)
- Pediatric patients: Safety and efficacy not established (8.4)
- Renal impairment: No dose adjustment is necessary in patients with renal impairment. Patients with creatinine clearance < 30 mL/min or receiving dialysis are at risk for hypocalcemia. Supplement with calcium and vitamin D, and consider monitoring serum calcium (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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- 1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture
- 1.2 Treatment of Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer
- 1.3 Treatment of Bone Loss in Women Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

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- 2.1 Recommended Dosage
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

Prolia is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures *[see Clinical Studies (14.1)]*.

1.2 Treatment of Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

Prolia is indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures *[see Clinical Studies (14.2)]*.

1.3 Treatment of Bone Loss in Women Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

Prolia is indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Prolia should be administered by a healthcare professional.

The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily *[see Warnings and Precautions (5.2)]*.

If a dose of Prolia is missed, administer the injection as soon as the patient is available. Thereafter, schedule injections every 6 months from the date of the last injection.

2.2 Preparation and Administration

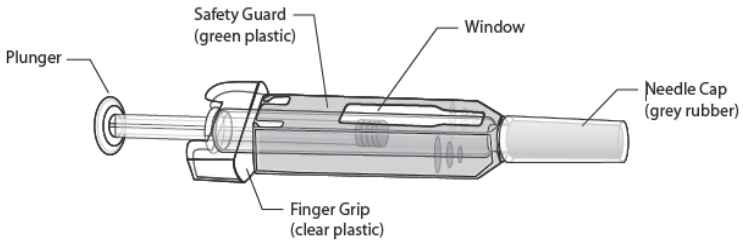
Visually inspect Prolia for particulate matter and discoloration prior to administration whenever solution and container permit. Prolia is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored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

Latex Allergy: People sensitive to latex should not handle the grey needle cap on the single-use prefilled syringe, which contains dry natural rubber (a derivative of latex).

Prior to administration, Prolia 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 Prolia in any other way *[see How Supplied/Storage and Handling (16)]*.

Instructions for Prefilled Syringe with Needle Safety Guard
IMPORTANT: In order to minimize accidental needlesticks, the Prolia single-use prefilled syringe will have a green safety guard; manually activate the safety guard after the injection is given.

DO NOT slide the green safety guard forward over the needle before administering the injection; it will lock in place and prevent injection.

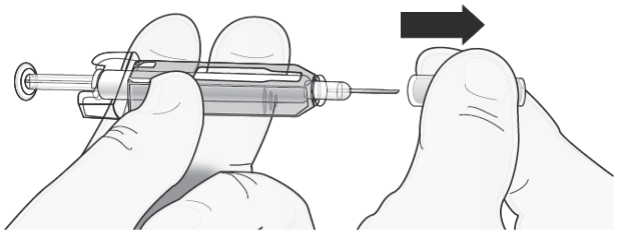


Activate the green safety guard (slide over the needle) after the injection.

The grey needle cap on the single-use prefilled syringe contains dry natural rubber (a derivative of latex); people sensitive to latex should not handle the cap.

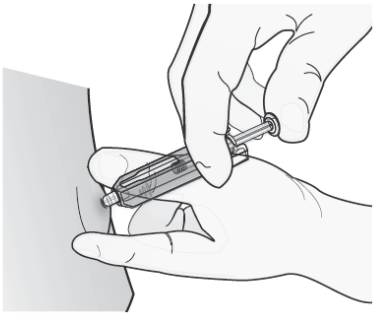
Step 1: Remove Grey Needle Cap

Remove needle cap.



Step 2: Administer Injection

Insert needle and inject all the liquid.



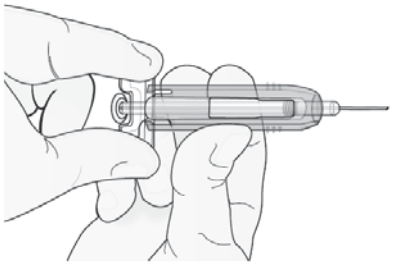
DO NOT put grey needle cap back on needle.

Step 3: Immediately Slide Green Safety Guard Over Needle

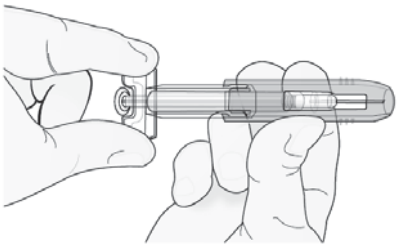
With the *needle pointing away from you…*

Hold the prefilled syringe by the clear plastic finger grip with one hand. Then, with the other hand, grasp the green safety guard by its base and gently slide it towards the needle until the green safety guard locks securely in place and/or you hear a "click." **DO NOT** grip the green safety guard too firmly – it will move easily if you hold and slide it gently.

Hold clear finger grip.



Gently slide green safety guard over needle and lock securely in place. Do not grip green safety guard too firmly when sliding over needle.



Immediately dispose of the syringe and needle cap in the nearest sharps container. **DO NOT** put the needle cap back on the used syringe.

Instructions for Single-use Vial
For administration of Prolia from the single-use vial, use a 27-gauge needle to withdraw and inject the 1 mL dose. Do not re-enter the vial. Discard vial and any liquid remaining in the vial.

3 DOSAGE FORMS AND STRENGTHS

- 1 mL of a 60 mg/mL solution in a single-use prefilled syringe
- 1 mL of a 60 mg/mL solution in a single-use vial

4 CONTRAINDICATIONS

4.1 Hypocalcemia

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with Same Active Ingredient

Prolia contains the same active ingredient (denosumab) found in Xgeva. Patients receiving Prolia should not receive Xgeva.

5.2 Hypocalcemia and Mineral Metabolism

Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g. history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis), clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended.

Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment [creatinine clearance < 30 mL/min], or receiving dialysis. Instruct all patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation.

Adequately supplement all patients with calcium and vitamin D *[see Dosage and Administration (2.1), Contraindications (4.1), Adverse Reactions (6.1), and Patient Counseling Information (17.2)]*.

5.3 Serious Infections

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group *[see Adverse Reactions (6.1)]*. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia. Endocarditis was also reported more frequently in Prolia-treated subjects. The incidence of opportunistic infections was balanced between placebo and Prolia groups, and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. Consider the benefit-risk profile in such patients before treating with Prolia. In patients who develop serious infections while on Prolia, prescribers should assess the need for continued Prolia therapy.

5.4 Dermatologic Adverse Reactions

In a large clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the Prolia group compared to the placebo group. Most of these events were not specific to the injection site *[see Adverse Reactions (6.1)]*. Consider discontinuing Prolia if severe symptoms develop.

5.5 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. ONJ has been reported in patients receiving

denosumab *[see Adverse Reactions (6.1)]*. A routine oral exam should be performed by the prescriber prior to initiation of Prolia treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia in patients with risk factors for ONJ such as invasive dental procedures (e.g. tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g. chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). Good oral hygiene practices should be maintained during treatment with Prolia.

For patients requiring invasive dental procedures, clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit-risk assessment.

Patients who are suspected of having or who develop ONJ while on Prolia should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia therapy should be considered based on individual benefit-risk assessment.

5.6 Suppression of Bone Turnover

In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry *[see Clinical Pharmacology (12.2) and Clinical Studies (14.1)]*. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

6 ADVERSE REACTIONS

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

- Hypocalcemia *[see Warnings and Precautions (5.2)]*
- Serious Infections *[see Warnings and Precautions (5.3)]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.5)]*

The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis.

The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain and have also been reported in clinical trials.

The most common adverse reactions leading to discontinuation of Prolia are back pain and constipation.

The Prolia Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please see www.proliasafety.com or call 1-800-772-6436 for more information about this program.

6.1 Clinical Trials Experience

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

Treatment of Postmenopausal Women with Osteoporosis

The safety of Prolia in the treatment of postmenopausal osteoporosis was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 7808 postmenopausal women aged 60 to 91 years. A total of 3876 women were exposed to placebo and 3886 women were exposed to Prolia administered subcutaneously once every 6 months as a single 60 mg dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 2.3% (n = 90) in the placebo group and 1.8% (n = 70) in the Prolia group. The incidence of nonfatal serious adverse events was 24.2% in the placebo group and 25.0% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 2.1% and 2.4% for the placebo and Prolia groups, respectively.

Adverse reactions reported in ≥ 2% of postmenopausal women with osteoporosis and more frequently in the Prolia-treated women than in the placebo-treated women are shown in the table below.

Table 1. Adverse Reactions Occurring in ≥ 2% of Patients with Osteoporosis and More Frequently than in Placebo-treated Patients

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 3886) n (%)	Placebo (N = 3876) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	129 (3.3)	107 (2.8)
CARDIAC DISORDERS		
Angina pectoris	101 (2.6)	87 (2.2)
Atrial fibrillation	79 (2.0)	77 (2.0)
EAR AND LABYRINTH DISORDERS		
Vertigo	195 (5.0)	187 (4.8)
GASTROINTESTINAL DISORDERS		
Abdominal pain upper	129 (3.3)	111 (2.9)
Flatulence	84 (2.2)	53 (1.4)
Gastroesophageal reflux disease	80 (2.1)	66 (1.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema peripheral	189 (4.9)	155 (4.0)
Asthenia	90 (2.3)	73 (1.9)

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 3886) n (%)	Placebo (N = 3876) n (%)
INFECTIONS AND INFESTATIONS		
Cystitis	228 (5.9)	225 (5.8)
Upper respiratory tract infection	190 (4.9)	167 (4.3)
Pneumonia	152 (3.9)	150 (3.9)
Pharyngitis	91 (2.3)	78 (2.0)
Herpes zoster	79 (2.0)	72 (1.9)
METABOLISM AND NUTRITION DISORDERS		
Hypercholesterolemia	280 (7.2)	236 (6.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	1347 (34.7)	1340 (34.6)
Pain in extremity	453 (11.7)	430 (11.1)
Musculoskeletal pain	297 (7.6)	291 (7.5)
Bone pain	142 (3.7)	117 (3.0)
Myalgia	114 (2.9)	94 (2.4)
Spinal osteoarthritis	82 (2.1)	64 (1.7)
NERVOUS SYSTEM DISORDERS		
Sciatica	178 (4.6)	149 (3.8)
PSYCHIATRIC DISORDERS		
Insomnia	126 (3.2)	122 (3.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	96 (2.5)	79 (2.0)
Pruritus	87 (2.2)	82 (2.1)

Hypocalcemia
Decreases in serum calcium levels to less than 8.5 mg/dL were reported in 0.4% women in the placebo group and 1.7% women in the Prolia group at the month 1 visit. The nadir in serum calcium level occurs at approximately day 10 after Prolia dosing in subjects with normal renal function.

In clinical studies, subjects with impaired renal function were more likely to have greater reductions in serum calcium levels compared to subjects with normal renal function. In a study of 55 patients with varying degrees of renal function, serum calcium levels < 7.5 mg/dL or symptomatic hypocalcemia were observed in 5 subjects. These included no subjects in the normal renal function group, 10% of subjects in the CrCL 50 to 80 mL/min group, 29% of subjects in the CrCL < 30 mL/min group, and 29% of subjects in the hemodialysis group. These subjects did not receive calcium and vitamin D supplementation. In a study of 4550 postmenopausal women with osteoporosis, the mean change from baseline in serum

calcium level 10 days after Prolia dosing was -5.5% in subjects with creatinine clearance < 30 mL/min vs. -3.1% in subjects with CrCL ≥ 30 mL/min.

Serious Infections
Receptor activator of nuclear factor kappa-B ligand (RANKL) is expressed on activated T and B lymphocytes and in lymph nodes. Therefore, a RANKL inhibitor such as Prolia may increase the risk of infection.

In the clinical study of 7808 postmenopausal women with osteoporosis, the incidence of infections resulting in death was 0.2% in both placebo and Prolia treatment groups. However, the incidence of nonfatal serious infections was 3.3% in the placebo group and 4.0% in the Prolia group. Hospitalizations due to serious infections in the abdomen (0.7% placebo vs. 0.9% Prolia), urinary tract (0.5% placebo vs. 0.7% Prolia), and ear (0.0% placebo vs. 0.1% Prolia) were reported. Endocarditis was reported in no placebo patients and 3 patients receiving Prolia.

Skin infections, including erysipelas and cellulitis, leading to hospitalization were reported more frequently in patients treated with Prolia (< 0.1% placebo vs. 0.4% Prolia).

There was no imbalance in the reporting of opportunistic infections.

Dermatologic Reactions
A significantly higher number of patients treated with Prolia developed epidermal and dermal adverse events (such as dermatitis, eczema, and rashes), with these events reported in 8.2% of the placebo and 10.8% of the Prolia groups ($p < 0.0001$). Most of these events were not specific to the injection site *[see Warnings and Precautions (5.4)]*.

Osteonecrosis of the Jaw
ONJ has been reported in the osteoporosis clinical trial program in patients treated with Prolia *[see Warnings and Precautions (5.5)]*.

Pancreatitis
Pancreatitis was reported in 4 patients (0.1%) in the placebo and 8 patients (0.2%) in the Prolia groups. Of these reports, 1 patient in the placebo group and all 8 patients in the Prolia group had serious events, including one death in the Prolia group. Several patients had a prior history of pancreatitis. The time from product administration to event occurrence was variable.

New Malignancies
The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia groups. New malignancies related to the breast (0.7% placebo vs. 0.9% Prolia), reproductive system (0.2% placebo vs. 0.5% Prolia), and gastrointestinal system (0.6% placebo vs. 0.9% Prolia) were reported. A causal relationship to drug exposure has not been established.

<u>Treatment of Bone Loss in Patients Receiving Androgen Deprivation Therapy for Prostate Cancer or Adjuvant Aromatase Inhibitor Therapy for Breast Cancer</u>

The safety of Prolia in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 1468 men aged 48 to 97 years. A total of 725 men were exposed to placebo and 731 men were exposed to Prolia administered once every 6 months as a single 60 mg subcutaneous dose. All men were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of serious adverse events was 30.6% in the placebo group and 34.6% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 6.1% and 7.0% for the placebo and Prolia groups, respectively.

The safety of Prolia in the treatment of bone loss in women with nonmetastatic breast cancer receiving aromatase inhibitor (AI) therapy was assessed in a 2-year, randomized, double-blind, placebo-controlled, multinational study of 252 postmenopausal women aged 35 to 84 years. A total of 120 women were exposed to placebo and 129 women were exposed to Prolia administered once every 6 months as a single 60 mg subcutaneous dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of serious adverse events was 9.2% in the placebo group and 14.7% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 4.2% and 0.8% for the placebo and Prolia groups, respectively.

Adverse reactions reported in ≥ 10% of Prolia-treated patients receiving ADT for prostate cancer or adjuvant AI therapy for breast cancer, and more frequently than in the placebo-treated patients were: arthralgia (13.0% placebo vs. 14.3% Prolia) and back pain (10.5% placebo vs. 11.5% Prolia). Pain in extremity (7.7% placebo vs. 9.9% Prolia) and musculoskeletal pain (3.8% placebo vs. 6.0% Prolia) have also been reported in clinical trials. Additionally in Prolia-treated men with nonmetastatic prostate cancer receiving ADT, a greater incidence of cataracts was observed (1.2% placebo vs. 4.7% Prolia). Hypocalcemia (serum calcium < 8.4 mg/dL) was reported only in Prolia-treated patients (2.4% vs. 0%) at the month 1 visit.

6.2 Immunogenicity

Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescent bridging immunoassay, less than 1% (55 out of 8113) of patients treated with Prolia for up to 5 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None of the patients tested positive for neutralizing antibodies, as was assessed using a chemiluminescent cell-based in vitro biological assay. No evidence of altered pharmacokinetic profile, toxicity profile, or clinical response was 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 drug-drug interaction studies have been conducted with Prolia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Prolia in pregnant women. In genetically engineered mice in which RANK ligand (RANKL) was turned off by gene removal (a "knockout mouse"), absence of RANKL (the target of denosumab) caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice also showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum *[see Use in Specific Populations (8.3)]*.

Prolia should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who become pregnant during Prolia 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.

In an embryofetal developmental study, cynomolgus monkeys received subcutaneous denosumab weekly during organogenesis at doses up to 13-fold higher than the recommended human dose of 60 mg administered once every 6 months based on body weight (mg/kg). No evidence of maternal toxicity or fetal harm was observed. However, this study only assessed fetal toxicity during a period equivalent to the first trimester and fetal lymph nodes were not examined. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. Potential adverse developmental effects resulting from exposures during the second and third trimesters have not been assessed in animals *[see Nonclinical Toxicology (13.2)]*.

8.3 Nursing Mothers

It is not known whether Prolia is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Prolia, 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 Prolia during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway that have shown altered maturation of the maternal mammary gland, leading to impaired lactation postpartum *[see Nonclinical Toxicology (13.2)]*.

8.4 Pediatric Use

Prolia is not recommended in pediatric patients. The safety and effectiveness of Prolia in pediatric patients have not been established.

Treatment with Prolia 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 Prolia 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 dosed with denosumab at 10 and 50 times (10 and 50 mg/kg dose) higher than the recommended human dose of 60 mg administered once every 6 months, based on body weight (mg/kg), had abnormal growth plates *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of the total number of patients in clinical studies of Prolia, 9943 patients (76%) were ≥ 65 years old, while 3576 (27%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary in patients with renal impairment.

In clinical studies, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcemia. Consider the benefit-risk profile when administering Prolia to patients with severe renal impairment or receiving dialysis. Clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis *[see Warnings and Precautions (5.2), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of Prolia.

10 OVERDOSAGE

There is no experience with overdosage with Prolia.

11 DESCRIPTION

Prolia (denosumab) is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

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

Each 1 mL single-use prefilled syringe of Prolia contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol, 17 mM acetate, 0.01% polysorbate 20, Water for Injection (USP), and sodium hydroxide to a pH of 5.2.

Each 1 mL single-use vial of Prolia contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol, 17 mM acetate, Water for Injection (USP), and sodium hydroxide to a pH of 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prolia binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Prolia prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

12.2 Pharmacodynamics

In clinical studies, treatment with 60 mg of Prolia resulted in reduction in the bone resorption marker serum type 1 C-telopeptide (CTX) by approximately 85% by 3 days, with maximal reductions occurring by 1 month. CTX levels were below the limit of assay quantitation (0.049 ng/mL) in 39% to 68% of subjects 1 to 3 months after dosing of Prolia. At the end of each dosing interval, CTX reductions were partially attenuated from a maximal reduction of ≥ 87% to ≥ 45% (range: 45% to 80%), as serum denosumab levels diminished, reflecting the reversibility of the effects of Prolia on bone remodeling. These effects were sustained with continued treatment. Upon reinitiation, the degree of inhibition of CTX by Prolia was similar to that observed in patients initiating Prolia treatment.

Consistent with the physiological coupling of bone formation and resorption in skeletal remodeling, subsequent reductions in bone formation markers (i.e. osteocalcin and procollagen type 1 N-terminal peptide [PlNP]) were observed starting 1 month after the first dose of Prolia. After discontinuation of Prolia therapy, markers of bone resorption increased to levels 40% to 60% above pretreatment values but returned to baseline levels within 12 months.

12.3 Pharmacokinetics

In a study conducted in healthy male and female volunteers (n = 73, age range: 18 to 64 years) following a single subcutaneously administered Prolia dose of 60 mg after fasting (at least for 12 hours), the mean maximum denosumab concentration (C_{max}) was 6.75 mcg/mL (standard deviation [SD] = 1.89 mcg/mL). The median time to maximum denosumab concentration (T_{max}) was 10 days (range: 3 to 21 days). After C_{max}, serum denosumab concentrations declined over a period of 4 to 5 months with a mean half-life of 25.4 days (SD = 8.5 days; n = 46). The mean area-under-the-concentration-time curve up to 16 weeks ($AUC_{0\text{-}16\ weeks}$) of denosumab was 316 mcg·day/mL (SD = 101 mcg·day/mL).

No accumulation or change in denosumab pharmacokinetics with time was observed upon multiple dosing of 60 mg subcutaneously administered once every 6 months.

Prolia pharmacokinetics were not affected by the formation of binding antibodies.

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. This analysis showed no notable differences in pharmacokinetics with age (in postmenopausal women), race, or body weight (36 to 140 kg).

<u>Drug Interactions</u>
No drug-drug interaction studies have been conducted with Prolia.

Specific Populations
Gender: Mean serum denosumab concentration-time profiles observed in a study conducted in healthy men ≥ 50 years were similar to those observed in a study conducted in postmenopausal women using the same dose regimen.

Age: The pharmacokinetics of denosumab were not affected by age across all populations studied whose ages ranged from 28 to 87 years.

Race: The pharmacokinetics of denosumab were not affected by race.

Renal Impairment: In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab; thus, dose adjustment for renal impairment is not necessary.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Mutagenicity
The genotoxic potential of denosumab has not been evaluated.

Impairment of Fertility
Denosumab had no effect on female fertility or male reproductive organs in monkeys at doses that were 13- to 50-fold higher than the recommended human dose of 60 mg administered once every 6 months, based on body weight (mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Prolia is an inhibitor of osteoclastic bone resorption via inhibition of RANKL.

In ovariectomized monkeys, once-monthly treatment with denosumab suppressed bone turnover and increased bone mineral density (BMD) and strength of cancellous and cortical bone at doses 50-fold higher than the recommended human dose of 60 mg administered once every 6 months, based on body weight (mg/kg). Bone tissue was normal with no evidence of mineralization defects, accumulation of osteoid, or woven bone.

Adolescent primates treated with denosumab at doses > 10 times (10 and 50 mg/kg dose) higher than the recommended human dose of 60 mg administered once every 6 months, based on mg/kg, had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab *[see Use in Specific Populations (8.4)]*.

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, namely OPG-Fc, provided additional information on the pharmacodynamic properties of denosumab. RANK/RANKL knockout mice 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). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats given the RANKL inhibitor OPG-Fc also 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 *[see Use in Specific Populations (8.1, 8.4)]*.

14 CLINICAL STUDIES

14.1 Postmenopausal Women with Osteoporosis

The efficacy and safety of Prolia in the treatment of postmenopausal osteoporosis was demonstrated in a 3-year, randomized, double-blind, placebo-controlled trial. Enrolled women had a baseline BMD T-score between -2.5 and -4.0 at either the lumbar spine or total hip. Women with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that affect bone were excluded from this study. The 7808 enrolled women were aged 60 to 91 years with a mean age of 72 years. Overall, the mean baseline lumbar spine BMD T-score was -2.8, and 23% of women had a vertebral fracture at baseline. Women were randomized to receive SC injections of either placebo (N = 3906) or Prolia 60 mg (N = 3902) once every 6 months. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

The primary efficacy variable was the incidence of new morphometric (radiologically-diagnosed) vertebral fractures at 3 years. Vertebral fractures were diagnosed based on lateral spine radiographs (T4-L4) using a semiquantitative scoring method. Secondary efficacy variables included the incidence of hip fracture and nonvertebral fracture, assessed at 3 years.

Effect on Vertebral Fractures

Prolia significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years ($p < 0.0001$), as shown in Table 2. The incidence of new vertebral fractures at year 3 was 7.2% in the placebo-treated women compared to 2.3% for the Prolia-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at year 3.

Table 2. The Effect of Prolia on the Incidence of New Vertebral Fractures in Postmenopausal Women

	Proportion of Women With Fracture (%)[+]		**Absolute Risk Reduction (%)* (95% CI)**	**Relative Risk Reduction (%)* (95% CI)**
	Placebo N = 3691 (%)	**Prolia N = 3702 (%)**		
0-1 Year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)
0-2 Years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)
0-3 Years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)

[*] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group variable.

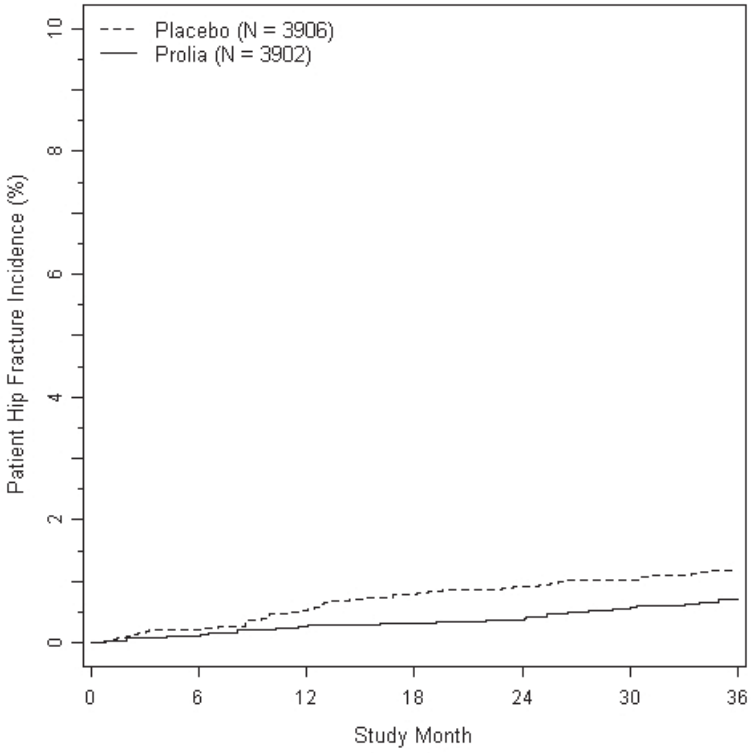
[+] Event rates based on crude rates in each interval.

Prolia was effective in reducing the risk for new morphometric vertebral fractures regardless of age, baseline rate of bone turnover, baseline BMD, baseline history of fracture, or prior use of a drug for osteoporosis.

Effect on Hip Fractures

The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for Prolia-treated women at year 3. The age-adjusted absolute risk reduction of hip fractures was 0.3% with a relative risk reduction of 40% at 3 years (p = 0.04) (Figure 1).

Figure 1. Cumulative Incidence of Hip Fractures Over 3 Years



N = number of subjects randomized

Effect on Nonvertebral Fractures

Treatment with Prolia resulted in a significant reduction in the incidence of nonvertebral fractures (Table 3).

Table 3. The Effect of Prolia on the Incidence of Nonvertebral Fractures at Year 3

	Proportion of Women With Fracture (%)[+]		**Absolute Risk Reduction (%) (95% CI)**	**Relative Risk Reduction (%) (95% CI)**
	Placebo N = 3906 (%)	**Prolia N = 3902 (%)**		
Nonvertebral fracture[1]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)[*]

[*] p-value = 0.01.

[+] Event rates based on Kaplan-Meier estimates at 3 years.

[1] Excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, and finger and toe phalanges.

Effect on Bone Mineral Density (BMD)

Treatment with Prolia significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at

the femoral neck. Consistent effects on BMD were observed at the lumbar spine, regardless of baseline age, race, weight/body mass index (BMI), baseline BMD, and level of bone turnover.

After Prolia discontinuation, BMD returned to approximately baseline levels within 12 months.

Bone Histology and Histomorphometry
A total of 115 transiliac crest bone biopsy specimens were obtained from 92 postmenopausal women with osteoporosis at either month 24 and/or month 36 (53 specimens in Prolia group, 62 specimens in placebo group). Of the biopsies obtained, 115 (100%) were adequate for qualitative histology and 7 (6%) were adequate for full quantitative histomorphometry assessment.

Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with Prolia.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In subjects treated with Prolia, 35% had no tetracycline label present at the month 24 biopsy and 38% had no tetracycline label present at the month 36 biopsy, while 100% of placebo-treated patients had double label present at both time points. When compared to placebo, treatment with Prolia resulted in virtually absent activation frequency and markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

14.2 Treatment of Bone Loss in Men with Prostate Cancer

The efficacy and safety of Prolia in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) were demonstrated in a 3-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Men less than 70 years of age had either a BMD T-score at the lumbar spine, total hip, or femoral neck between -1.0 and -4.0, or a history of an osteoporotic fracture. The mean baseline lumbar spine BMD T-score was -0.4, and 22% of men had a vertebral fracture at baseline. The 1468 men enrolled ranged in age from 48 to 97 years (median 76 years). Men were randomized to receive SC injections of either placebo (n = 734) or Prolia 60 mg (n = 734) once every 6 months for a total of 6 doses. Randomization was stratified by age (< 70 years vs. ≥ 70 years) and duration of ADT at trial entry (≤ 6 months vs. > 6 months). Seventy-nine percent of patients received ADT for more than 6 months at study entry. All men received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 24. An additional key secondary efficacy variable was the incidence of new vertebral fracture through month 36 diagnosed based on x-ray evaluation by two independent radiologists. Lumbar spine BMD was higher at 2 years in Prolia-treated patients as compared to placebo-treated patients [-1.0% placebo, +5.6% Prolia; treatment difference 6.7% (95% CI: 6.2, 7.1); $p < 0.0001$].

With approximately 62% of patients followed for 3 years, treatment differences in BMD at 3 years were 7.9% (-1.2% placebo, +6.8% Prolia) at the lumbar spine, 5.7% (-2.6% placebo, +3.2% Prolia) at the total hip, and 4.9% (-1.8% placebo, +3.0% Prolia) at the femoral neck. Consistent effects on BMD were observed at the lumbar spine in relevant subgroups defined by baseline age, BMD, and baseline history of vertebral fracture.

Effect on Vertebral Fractures
Prolia significantly reduced the incidence of new vertebral fractures at 3 years (p = 0.0125), as shown in Table 4.

Table 4. The Effect of Prolia on the Incidence of New Vertebral Fractures in Men with Nonmetastatic Prostate Cancer

	Proportion of Men With Fracture (%)[+]		Absolute Risk Reduction (%)* (95% CI)	Relative Risk Reduction (%)* (95% CI)
	Placebo N = 673 (%)	Prolia N = 679 (%)		
0-1 Year	1.9	0.3	1.6 (0.5, 2.8)	85 (33, 97)
0-2 Years	3.3	1.0	2.2 (0.7, 3.8)	69 (27, 86)
0-3 Years	3.9	1.5	2.4 (0.7, 4.1)	62 (22, 81)

[*] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group and ADT duration variables.
[+] Event rates based on crude rates in each interval.

14.3 Treatment of Bone Loss in Women with Breast Cancer

The efficacy and safety of Prolia in the treatment of bone loss in women receiving adjuvant aromatase inhibitor (AI) therapy for breast cancer was assessed in a 2-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck, and had not experienced fracture after age 25. The mean baseline lumbar spine BMD T-score was -1.1, and 2.0% of women had a vertebral fracture at baseline. The 252 women enrolled ranged in age from 35 to 84 years (median 59 years). Women were randomized to receive subcutaneous injections of either placebo (n = 125) or Prolia 60 mg (n = 127) once every 6 months for a total of 4 doses. Randomization was stratified by duration of adjuvant AI therapy at trial entry (≤ 6 months vs. > 6 months). Sixty-two percent of patients received adjuvant AI therapy for more than 6 months at study entry. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 12. Lumbar spine BMD was higher at 12 months in Prolia-treated patients as compared to placebo-treated patients [-0.7% placebo, +4.8% Prolia; treatment difference 5.5% (95% CI: 4.8, 6.3); p < 0.0001].

With approximately 81% of patients followed for 2 years, treatment differences in BMD at 2 years were 7.6% (-1.4% placebo, +6.2% Prolia) at the lumbar spine, 4.7 % (-1.0% placebo, +3.8% Prolia) at the total hip, and 3.6% (-0.8% placebo, +2.8% Prolia) at the femoral neck.

16 HOW SUPPLIED/STORAGE AND HANDLING

Prolia is supplied in a single-use prefilled syringe with a safety guard or in a single-use vial. The grey needle cap on the single-use prefilled syringe contains dry natural rubber (a derivative of latex).

60 mg/1 mL in a single-use prefilled syringe	1 per carton	NDC 55513-710-01
60 mg/1 mL in a single-use vial	1 per carton	NDC 55513-720-01

Store Prolia in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Prior to administration, Prolia may be allowed to reach room temperature (up to 25°C/77°F) in the original container. Once removed from the refrigerator, Prolia must not be exposed to temperatures above 25°C/77°F and must be used within 14 days. If not used within the 14 days, Prolia should be discarded. Do not use Prolia after the expiry date printed on the label.

Protect Prolia from direct light and heat.

Avoid vigorous shaking of Prolia.

17 PATIENT COUNSELING INFORMATION

See Medication Guide.

17.1 Drug Products with Same Active Ingredient

Advise patients that denosumab is also marketed as Xgeva, and if taking Prolia, they should not receive Xgeva.

17.2 Hypocalcemia

Adequately supplement patients with calcium and vitamin D and instruct them on the importance of maintaining serum calcium levels while receiving Prolia *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*. Advise patients to seek prompt medical attention if they develop signs or symptoms of hypocalcemia.

17.3 Serious Infections

Advise patients to seek prompt medical attention if they develop signs or symptoms of infections, including cellulitis *[see Warnings and Precautions (5.3)]*.

17.4 Dermatologic Reactions

Advise patients to seek prompt medical attention if they develop signs or symptoms of dermatological reactions (dermatitis, rashes, and eczema) *[see Warnings and Precautions (5.4)]*.

17.5 Osteonecrosis of the Jaw

Advise patients to maintain good oral hygiene during treatment with Prolia and to inform their dentist prior to dental procedures that they are receiving Prolia. Patients should inform their physician or dentist if they experience persistent pain and/or slow healing of the mouth or jaw after dental surgery *[see Warnings and Precautions (5.5)]*.

17.6 Schedule of Administration

If a dose of Prolia is missed, administer the injection as soon as convenient. Thereafter, schedule injections every 6 months from the date of the last injection.

AMGEN®

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

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

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1xxxxxx – v3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

REMS

BL 125320 PROLIA® (denosumab)

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805-447-1000

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1. Goals

- To inform healthcare providers (HCP) about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw, associated with Prolia® (denosumab).
- To inform patients about the serious risks associated with the use of Prolia.

2. REMS Elements

2.1 Medication Guide

Amgen will ensure the Prolia Medication Guide is distributed in accordance with 21CFR 208.24.

The Medication Guide is part of the REMS and is appended.

2.2 Communication Plan

Amgen will implement a communication plan (CP) to inform Healthcare Providers (HCP) about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw, associated with Prolia.

The CP consists of a Dear Healthcare Provider (DHCP) Letter, which will be sent within 60 days of the most recent REMS approval to oncologists and urologists who are likely to prescribe or have prescribed hormone ablation as a method of treatment for patients with prostate or breast cancer by mass mailing or electronic mailing. Amgen will obtain HCP email addresses from the American Medical Association (AMA). If a targeted HCP's email address is not available, or if an email is undeliverable, the provider will receive the letter through the mail. A copy of the US Prescribing Information and Medication Guide will accompany the DHCP Letter.

The DHCP Letter will be sent to the American Society of Clinical Oncology within 60 days of the most recent REMS approval requesting they provide this letter to their members.

Amgen will resend the DHCP Letter to the following professional societies annually from the date of the initial REMS approval (6/2010) for 3 years: National Osteoporosis Foundation, American Society of Bone Mineral Research, American College of Rheumatology, American Association of Clinical Endocrinologists, the American College of Physicians, the American Academy of Family Physicians, the Endocrine Society, and the American Society of Clinical Oncology.

Any known new prescribers of Prolia who were not previously sent the DHCP Letter will be sent a DHCP Letter for up to 2 years from the date of the initial REMS approval. New prescribers of Prolia will be identified using the Healthcare Professional Data Management database, obtained from Intercontinental Marketing Services (IMS).

The DHCP Letter, US Prescribing Information, and Medication Guide will also be distributed to HCPs via sales representatives and medical science liaisons at the time of initial contact, when inquired about the risks outlined in the REMS, or upon request; through the Amgen toll-free medical information line (1-800-772-6436); and through a REMS-dedicated link [www.proliahcp.com] from the website.

The DHCP Letter and web page are part of the REMS and are appended.

3. Timetable for Submission

Amgen will submit REMS Assessments to FDA at 18 months, 3 years and 7 years from the date of the initial approval (June 1, 2010) of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Amgen will submit each assessment so that it will be received by the FDA on or before the due date.

MEDICATION GUIDE

Prolia® (PRÓ-lee-a)

(denosumab)
Injection, for subcutaneous use

Read the Medication Guide that comes with Prolia before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about Prolia.

What is the most important information I should know about Prolia?

If you receive Prolia, you should not receive XGEVA®. Prolia contains the same medicine as Xgeva (denosumab).

Prolia can cause serious side effects including:

1. **Low calcium levels in your blood (hypocalcemia).**
   Prolia may lower the calcium levels in your blood. If you have low blood calcium before you start receiving Prolia, it may get worse during treatment. Your low blood calcium must be treated before you receive Prolia. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:
   - Spasms, twitches, or cramps in your muscles
   - Numbness or tingling in your fingers, toes, or around your mouth

   Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Prolia. Take calcium and vitamin D as your doctor tells you to.

2. **Serious infections.**
   Serious infections in your skin, lower stomach area (abdomen), bladder, or ear may happen if you take Prolia. Inflammation of the inner lining of the heart (endocarditis) due to an infection also may happen more often in people who take Prolia. You may need to go to the hospital for treatment if you develop an infection.

   Prolia is a medicine that may affect your immune system. People who have weakened immune system or take medicines that affect the immune system may have an increased risk for developing serious infections.

   Call your doctor right away if you have any of the following symptoms of infection:
   - Fever or chills
   - Skin that looks red or swollen and is hot or tender to touch
   - Severe abdominal pain
   - Frequent or urgent need to urinate or burning feeling when you urinate

3. **Skin problems.**
   Skin problems such as inflammation of your skin (dermatitis), rash, and eczema may happen if you take Prolia. Call your doctor if you have any of the following symptoms of skin problems that do not go away or get worse:
   - Redness
   - Itching
   - Small bumps or patches (rash)
   - Your skin is dry or feels like leather
   - Blisters that ooze or become crusty
   - Skin peeling

4. **Severe jaw bone problems (osteonecrosis).**
   Severe jaw bone problems may happen when you take Prolia. Your doctor should examine your mouth before you start Prolia. Your doctor may tell you to see your dentist before you start Prolia. It is important for you to practice good mouth care during treatment with Prolia.

Call your doctor right away if you have any of these side effects.

What is Prolia?

Prolia is a prescription medicine used to:

- Treat osteoporosis (thinning and weakening of bone) in women after menopause ("change of life") who:
  - have an increased risk for fractures (broken bones).
  - cannot use another osteoporosis medicine or other osteoporosis medicines did not work well.
- Treat bone loss in men who have an increased risk for fractures receiving certain treatments for prostate cancer that has not spread to other parts of the body.
- Treat bone loss in women who have an increased risk for fractures receiving certain treatments for breast cancer that has not spread to other parts of the body.

Prolia is not recommended for use in children.

Who should not receive Prolia?

Do not take Prolia if you have been told by your doctor that your blood calcium level is too low.

What should I tell my doctor before receiving Prolia?

Before taking Prolia, tell your doctor if you:

- Are taking a medicine called Xgeva (denosumab). Xgeva contains the same medicine as Prolia.
- Have low blood calcium.
- Cannot take daily calcium and vitamin D.
- Had parathyroid or thyroid surgery (glands located in your neck).
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome).
- Have kidney problems or are on kidney dialysis.
- Plan to have dental surgery or teeth removed.
- Are pregnant or plan to become pregnant. Prolia may harm your unborn baby. Tell your doctor right away if you become pregnant while taking Prolia.
  Pregnancy Surveillance Program: Prolia is not intended for use in pregnant women. If you become pregnant while taking Prolia, talk to your doctor about enrolling with Amgen's Pregnancy Surveillance Program or call 1-800-772-6436 (1-800-77-AMGEN). The purpose of this program is to collect information about women who have become pregnant while taking Prolia.
- Are breast-feeding or plan to breast-feed. It is not known if Prolia passes into your breast milk. You and your doctor should decide if you will take Prolia or breast-feed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and nonprescription drugs, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of medicines with you to show to your doctor or pharmacist when you get a new medicine.

How will I receive Prolia?

- Prolia is an injection that will be given to you by a healthcare professional. Prolia is injected under your skin (subcutaneous).
- You will receive Prolia 1 time every 6 months.
- You should take calcium and vitamin D as your doctor tells you to while you receive Prolia.
- If you miss a dose of Prolia, you should receive your injection as soon as you can.
- Take good care of your teeth and gums while you receive Prolia. Brush and floss your teeth regularly.
- Tell your dentist that you are receiving Prolia before you have dental work.

What are the possible side effects of Prolia?

Prolia may cause serious side effects.

- See **"What is the most important information I should know about Prolia?"**
- **Long-term effects on bone:** It is not known if the use of Prolia over a long period of time may cause slow healing of broken bones or unusual fractures.

The most common side effects of Prolia in women who are being treated for osteoporosis after menopause are:

- back pain
- pain in your arms and legs
- high cholesterol
- muscle pain
- bladder infection

The most common side effects of Prolia in patients receiving certain treatments for prostate or breast cancer are:

- joint pain
- back pain
- pain in your arms and legs
- muscle pain

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

These are not all the possible side effects of Prolia. For more information, ask your doctor or pharmacist.

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

How should I store Prolia if I need to pick it up from a pharmacy?

- Keep Prolia in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton.
- Do not freeze Prolia.
- When you remove Prolia from the refrigerator, Prolia must be kept at room temperature [up to 77°F (25°C)] in the original carton and must be used within 14 days.
- Do not keep Prolia at temperatures above 77°F (25°C). Warm temperatures will affect how Prolia works.
- Do not shake Prolia.
- Keep Prolia in the original carton to protect from light.

Keep Prolia and all medicines out of reach of children.

General information about Prolia.

Do not give Prolia to other people even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Prolia. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Prolia that is written for health professionals.

For more information, go to www.Prolia.com or call Amgen at 1-800-772-6436.

What are the ingredients in Prolia?
Active ingredient: denosumab
Inactive ingredients: sorbitol, acetate, polysorbate 20 (prefilled syringe only), Water for Injection (USP), and sodium hydroxide

AMGEN®

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

1xxxxxx – v3
Revised: 09/2011

IMPORTANT DRUG WARNING
Regarding Prolia® (denosumab)

Subject: **- Risk of serious infections, dermatologic adverse events and suppression of bone turnover, including osteonecrosis of the jaw, with use of Prolia**
- New indications for Prolia

<Insert date>

Dear Healthcare Provider:

Amgen would like to inform you of important safety information for Prolia® (denosumab) and updates to the Prescribing Information.

Prolia was originally approved by the US Food and Drug Administration (FDA) in 2010 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. At that time, FDA approved Prolia with a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of serious infection and dermatological adverse events observed in the pivotal postmenopausal osteoporosis study, as well as the unknown risk of suppression of bone turnover, including osteonecrosis of the jaw, with long-term treatment with Prolia.

In 2011, Prolia was approved for two new indications as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer and as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In patients with prostate cancer, Prolia reduced the incidence of vertebral fractures.

Important Information about the Risks of Prolia

The REMS associated with Prolia is intended to ensure the benefits of the drug outweigh the risks of:

- **serious infections,**
- **dermatologic adverse events, and**
- **suppression of bone turnover, including osteonecrosis of the jaw.**

Serious infections

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia. Endocarditis was also reported more frequently in the Prolia-treated subjects.

Dermatologic adverse events

In a clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the Prolia group compared to the placebo group.

Suppression of bone turnover (including osteonecrosis of the jaw (ONJ) and fracture healing complications)

Prolia results in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as ONJ, atypical fractures and delayed fracture healing. ONJ has been reported in the osteoporosis clinical trial in patients receiving denosumab.

Prolia Post-marketing Active Safety Surveillance Program

To monitor the long-term safety of Prolia, Amgen is soliciting adverse event reporting of 9 pre-specified adverse events of special interest (AESI) including serious infections, dermatologic adverse events and suppression of bone turnover. Data collection includes an AESI soliciting questionnaire and AESI-specific questionnaire. Prolia prescribers are invited to voluntarily participate in this study and are encouraged to register and may do so online at www.proliasafety.com or by calling Amgen at 1-800-77-AMGEN (1-800-772-6436).

Medication Guide

Prolia has a **Medication Guide** that accompanies the Full Prescribing Information. You should review the information in the Medication Guide with your patients. Provide each patient with a Medication Guide every time you administer Prolia to your patients as the information contained within may change over time.

Reporting Patient Adverse Events

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.

Please read the accompanying FDA-approved full prescribing information for Prolia. We urge you to contact our Medical Information department at 1-800-772-6436 or visit www.proliahcp.com if you have any questions about the information contained in this letter or the safe and effective use of PROLIA.

Sean E. Harper, MD
Senior Vice President, Global Development
and Chief Medical Officer
Amgen Inc.

Prolia ® (denosumab) Risk Evaluation and Mitigation Strategy

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

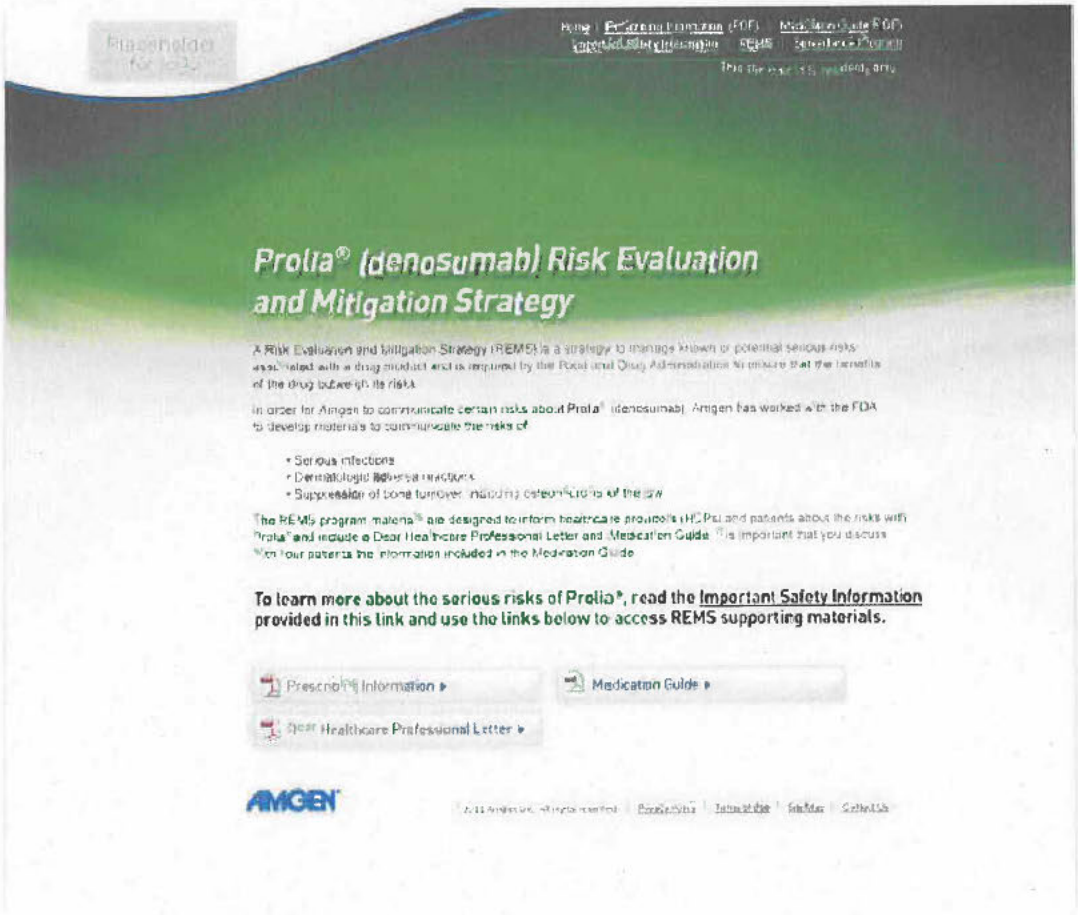
In order for Amgen to communicate certain risks about Prolia® (denosumab), Amgen has worked with the FDA to develop materials to communicate the risks of:

- Serious infections
- Dermatologic adverse reactions
- Suppression of bone turnover, including osteonecrosis of the jaw

The REMS program materials are designed to inform healthcare providers (HCPs) and patients about the risks with Prolia and include a Dear Healthcare Professional Letter and Medication Guide. It is important that you discuss with your patients the information included in the Medication Guide.

To learn more about the serious risks of Prolia, read the Important Safety Information provided in this link and use the links below to access REMS supporting materials:

Prescribing Information ▸
Medication Guide ▸
Dear Healthcare Professional Letter ▸


Prolia® (denosumab) Risk Evaluation and Mitigation Strategy
A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks
In order for Amgen to communicate certain risks about Prolia® (denosumab), Amgen has worked with the FDA
• Serious infections
• Suppression of bone turnover, resulting in atypical fractures of the
The REMS program materials are designed to inform healthcare providers (HCPs) and patients about the risks with
Prolia® and include a Dear Healthcare Professional Letter and Medication Guide. It is important that you discuss
To learn more about the serious risks of Prolia®, read the Important Safety Information
provided in this link and use the links below to access REMS supporting materials.
Prescribing Information
Medication Guide
Dear Healthcare Professional Letter
AMGEN

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	September 15, 2011
From	Patricia Keegan, M.D. Director, Division of Biologic Oncology Products
Subject	Division Director Summary Review
BLA #	BL STN 125320/5
Applicant Name	Amgen, Inc.
Date of Submission	December 19, 2008
Complete Response letter	October 19, 2009
Resubmission	March 18, 2011
PDUFA Goal Date	September 17, 2011
Proprietary Name / Established (USAN) Name	Prolia®/ denosumab
Dosage Forms / Strength	Solution for subcutaneous injection / 60 mg denosumab/ 1 mL in vials or prefilled syringes
Proposed Indication	Prolia is indicated for the treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer
Recommended Action:	Approval

Reference ID: 3168397

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Melanie Pierce
Medical Officer Reviews	Suzanne Demko, P.A. Shan Pradhan, M.D.
Cross-Discipline Team Leader Reviews	Steven Lemery, M.D.
Deputy Director for Safety Review	Jeffrey Summers, M.D.
Statistical Review	Jenny (Jing) Zhang, Ph.D.
Statistical TL Review	Mark Rothmann, Ph.D.
Statistical Review	Leslie Kenna, Ph.D.
Statistical Review	Mandi Yu, Ph.D.
Statistical Review	John Stephen Yap, Ph.D.
CMC OBP Review	Sarah Kennett, PhD. Michele Dougherty, PhD.
CMC OBP Team Leader Review	Chana Fuchs, Ph.D.
Microbiology Product Quality Reviews	Donald C. Obenhuber, Ph.D. Kalvati Suvarna, Ph.D.
Nonclinical Pharmacology/Toxicology Review	Michael Orr, Ph.D., D.A.B.T.
Nonclinical Toxicology Supervisory Review	Anne Pilaro, Ph.D.
Clinical Pharmacology Review	Sarah J. Schrieber, Pharm. D.
OSE/DMEPA Review	Judy Park, PharmD.
Pediatric & Maternal Health Team Review	Jeanine Best, MSN, RN, PNP
OC/DSI Review	John Lee, M.D.
OSE/DRISK Reviews	Amarilys Vega, M.D. MPH Kate Heinrich Oswell, MA Cynthia LaCivita, Pharm.D.

OND=Office of New Drugs
OBP=Office of Biotechnology Products
OC=Office of Compliance
OSE= Office of Surveillance and Epidemiology
DDMAC=Division of Drug Marketing, Advertising and Communication
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Communication

Reference ID: 3168397

Division Director Summary Review

1. Introduction

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

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

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

This efficacy supplement was submitted to expand labeling to include a new proposed claim for Prolia for the treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer is supported primarily by evidence of increased bone mineral density in a single, multicenter, placebo-controlled randomized trial (Protocol 20040135), supported by consistent effects on bone mineral density and reduction in fractures with the same dose and schedule of denosumab in post-menopausal women at high risk for fracture (Protocol 20030216) and consistent effects on bone mineral density in men with prostate cancer receiving androgen deprivation therapy (Protocol 20040138).

In Protocol 20040135 was a randomized (1:1), placebo-controlled, multicenter, multinational, trial conducted in 225 women receiving adjuvant aromatase inhibitor (AI) therapy for the adjuvant treatment of breast cancer. Patients were required to be at high risk for fracture (defined as baseline BMD T-scores of -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck). Among the participants, mean baseline lumbar spine BMD T-score was -1.1 and 2.0% of women had a vertebral fracture at baseline. Patients received Prolia 60 mg subcutaneously every 6 months for a total of 4 doses and were followed for an additional 1 year for safety evaluation.

Reference ID: 3168397

Protocol 20040135 met its primary endpoint with a statistically significant increase in lumbar spine BMD from baseline to month 12 [-0.7% placebo, +4.8% Prolia; treatment difference 5.5% (95% CI: 4.8, 6.3); $p < 0.0001$]. At the end of treatment, there was persistent evidence of increase in BMD, with a difference in the change in BMD from baseline to 2 years of 7.6% (-1.4% placebo, +6.2% Prolia) at the lumbar spine, 4.7 % (-1.0% placebo, +3.8% Prolia) at the total hip, and 3.6% (-0.8% placebo, +2.8% Prolia) at the femoral neck.

Supportive data were obtained from Protocol 20030216, which provided evidence of consistency of the treatment effect and established the relationship between an increase in BMD with a reduction in the incidence of fracture. Protocol 20030215 enrolled 7808 women at high risk for fracture (mean baseline lumbar spine BMD T-score was -2.8 and history of vertebral fracture in 23%) who were randomized (1:1) to receive Prolia 60 mg subcutaneously once every 6 months or placebo. In this trial, Prolia significantly increased bond mineral density (BMD) at all anatomic sites measured at 3 years. The trial also met the primary endpoint , demonstrating that Prolia treatment significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years ($p < 0.0001$) and that the effects on BMD correlated with effects on fracture. The incidence of new vertebral fractures at year 3 was 7.2% in the placebo-treated women compared to 2.3% for the Prolia-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at year 3. The incidence of hip fracture was also reduced (1.2% for placebo-treated women compared to 0.7% for Prolia-treated women) at year 3. The age-adjusted absolute risk reduction of hip fractures was 0.3% with a relative risk reduction of 40% at 3 years ($p = 0.04$).

This application is also supported by consistent treatment effects in Protocol 20040138, conducted in 1468 men at high risk for fracture undergoing androgen deprivation therapy (ADT) in a trial that employed the same dose and schedule of Prolia as in Protocols 20040135 and 20030216. This randomized (1:1), placebo-controlled, multicenter trial demonstrated an increase in bone mass (as measured by changed in lumbar spine BMD from baseline to month 24) and a reduction in the incidence of new vertebral fracture from study entry through month 36.

The safety of denosumab for the proposed indication is supported by the trials (20040135, 20030216, and 20040138) supporting efficacy. However, since Protocol 20040135 was not designed to assess designed to collect data on and exclude adverse effects on tumor outcomes, most notably on time-to-disease progression and overall survival. In addition, in Protocol 20030216, there was a modest imbalance in the incidence of new cancers, with no dominant primary tumor, among denosumab-treated post-menopausal women as compared with the control group in Protocol 20030216. Therefore, in the October 2009 Complete Response letter, FDA requested the results of additional studies capable of assessing for adverse effects on tumor outcomes.

In their resubmission Amgen Inc. provided the results of three additional trials (Protocols 20050103, 20050136, and 20050244) administering denosumab at a two-fold higher dose and more frequent schedule (denosumab 120 mg by subcutaneous injection every four weeks until toxicity or study termination), demonstrating no adverse effects on tumor growth or survival. In the March 18, 2011 resubmission, extended follow-up data from Trials 20040135 and 20040138 were provided in a safety update to this efficacy supplement. Trials 20050103, 20050136, and

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20050244 enrolled 1904 patients with hormone-refractory, metastatic prostate cancer, 2409 patients with metastatic breast cancer, and 1779 patients with osseous metastases due to multiple myeloma or metastatic cancers other than breast and prostate cancer, respectively. These randomized, double-blind, double-dummy, active-controlled trials were designed to demonstrate that denosumab is not inferior to zoledronic acid (Zometa®, an active control) for the composite efficacy endpoint of time-to-first skeletal-related event (SRE). All three studies met their primary endpoint, demonstrating that denosumab is non-inferior to zoledronic acid in the time-to-first skeletal-related event. In addition, two of the trials (20050103 and 20050136) demonstrated that denosumab significantly delayed the time to first SRE as compared to zoledronic acid.

The designs of Trials 20050103, 20050136, and 20050244 were not optimal for assessment of progression-free survival since eligibility criteria did not limit entry for all relevant prognostic characteristics nor did the randomization plan stratify for all relevant variables for a given tumor type. With these caveats, there was no evidence of an adverse effect on tumor growth rate or impairment of PFS among denosumab-treated patients compared to the control arm. Similarly, analyses of overall survival did not suggest adverse impact on survival with one exception. In an exploratory subset analysis conducted in 180 patients with multiple myeloma enrolled in Protocol 20050244, the results suggested poorer survival for patients receiving denosumab with a hazard ratio of 2.26 (95% CI: 1.13, 4.50). This finding is described as a limitation of use stating that Xgeva labeling; Prolia is not labeled for use in patients with metastatic disease or primary bone marrow malignancies, such as multiple myeloma.

All members of the review team recommended approval of this efficacy supplement and there are no unresolved issues which preclude approval.

2. Background

Osteoporosis is characterized by low bone mass, disruption of the microarchitecture of the bone, and skeletal fragility; these changes lead to an increased risk of skeletal fractures. Fractures of the hip and spine are associated with increased mortality rate and can result in limited mobility and chronic pain, thus the goal of treatment of osteoporosis is the prevention of such fractures.

Treatment measures should always include general lifestyle measures aimed at reducing bone loss; these include adequate dietary calcium supplemental intake, supplemental vitamin D, regular moderate exercise, and smoking cessation. Additional preventive measures in the form of pharmacologic treatment with anti-bone resorptive agents should be initiated in post-menopausal women with osteoporosis and those at high risk for osteoporosis due to drug or hormonal therapy, age, low body weight, or a history of recent fractures, particularly recent hip fractures. Identification of patients at risk for osteoporotic fractures also involves screening for bone mass through measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA).

In the United States, initiation of pharmacologic treatment of osteoporosis is largely guided by the risk of fractures, as described in the 2008 WHO task force Fracture Risk Assessment Tool

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(FRAX) or the National Osteoporosis Foundation (NOF). Use of the 2008 NOF guidelines as selection criteria for patients who will benefit from pharmacologic treatment has not been evaluated in clinical trials. The women enrolled in Protocol 20040135 were likely to be at increased risk of skeletal fractures as compared to healthy adults based on osteopenia as determined by BMD t-score and concurrent use of hormone ablation, although the risk was not sufficiently high that administration of placebo was unethical.

Drugs which have received FDA approval for treatment of osteoporosis have been shown to improve or stabilize the loss of BMD. In addition, randomized trials have shown that adendronate, risedronate, and zoledronic acid reduces the risk of vertebral, non-vertebral, and hip fractures. Raloxifene and ibandronate have been shown to reduce the incidence of vertebral fracture but not hip fractures. The correlation between treatment-induced improvement in BMD and the reduction in the incidence of fractures was evaluated in a meta-analysis of twelve clinical trials (Cummings SR, et al; Am J Med. 112(4) 281-289, 2002). The authors concluded that an improvement in vertebral BMD correlated with a reduction in fracture risk however the reduction in risk observed was larger than would have been predicted based on BMD score alone. Since denosumab has a novel mechanism of action, the validity of denosumab-induced improvements in BMD as a predictor of reduction in skeletal fractures required verification rather than extrapolation from data obtained with bisphosphonates. Evidence that the relationship between denosumab-induced improvement in BMD and reduction in the incidence of skeletal fractures was obtained in Protocol 20030216 and supported by data obtained in protocol 20040138.

Regulatory History of the BLA

The original Investigational New Drug Application (IND 9837) for denosumab was received at FDA on May 22, 2001. An end-of-Phase 2 (EOP2) meeting was held on April 21, 2004 to discuss the clinical development program intended to support an indication for treatment of patients with cancer who had bone loss due to hormone ablation therapy, based on one trial to be conducted in women with non-metastatic breast cancer and one study in men with non-metastatic prostate cancer. The following key agreements were reached:

- Approval for denosumab for the treatment of bone loss associated with hormone ablation therapy would be contingent upon adequate anti-fracture efficacy being demonstrated in the three year postmenopausal osteoporosis treatment trial. This trial would then validate that denosumab-induced increases in BMD are associated with anti-fracture efficacy
- The results of Protocol 20010223 supported the preliminary activity and safety of denosumab 60 mg administered subcutaneously every 6 months.
- The proposed trials in breast cancer and prostate cancer were adequate in design to support registration for treatment of osteoporosis, provided that adequate anti-fracture efficacy was demonstrated in the trial of treatment of osteoporosis, validating that improvement in BMD in denosumab-treated patients is a surrogate for reduction skeletal fractures.

FDA stated that Protocol 20040138, the randomized, placebo-controlled trial in osteoporotic men with localized prostate cancer, (b) (4) (b) (4).

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Pre-BLA meetings were held to discuss the submission of CMC information (July 8, 2008) and non-clinical/clinical information (October 21, 2008). Key issues discussed during the CMC pre-BLA meeting included the type of information needed to characterize quality attributes and information needed to support proposed specifications, the submission format for various strengths and presentations, and that the comparability of different drug substance manufacturing sites could only be addressed upon review of the primary data. FDA recommended that the application include a single strength (60 mg/mL) based on the potential for medication errors between the proposed 60 and 70 mg/mL strengths. Amgen agreed.

Key issues discussed during the preBLA meeting of October 21, 2008 included the following: the extent of information on supportive clinical studies to be included in the BLA, the contents of the 120-day safety update, data and analyses to be submitted characterizing bone density, impact on QT interval, hypersensitivity reactions, infections, and hypocalcemia, and the plan for submission of manufacturing runs to assist FDA in setting dates for facilities inspections. FDA did not raise major objections to the four proposed indications supported by the four randomized trials, acknowledged that presentation to an advisory committee was planned, and stated that although the final decision would be made during the review, the application would likely receive a standard review.

Amgen was notified that the submission was administratively split into four applications, with separate indications, in a letter dated Jan 30, 2009. In that letter, BLA STN 125330 identified as the "parent" BLA for any information common to more than one application, with a letter cross-referencing this information to be submitted to the other three applications. The proposed indications are BL STN 125330, supporting the proposed indication of denosumab for the treatment of women with post-menopausal osteoporosis (PMO), which relied primarily on the results of Protocol 20030216 and a separate potential supplement supporting the proposed indication of prevention of osteoporosis, which relied primarily on the results of Protocol 20040132, 125320/5, supporting the proposed indication of the treatment and prevention of osteoporosis is women with breast cancer receiving hormone ablation therapy, which relied primarily on the results of Protocol 20040135, and BL STN 125230/6, supporting the proposed indication of the treatment and prevention of osteoporosis in men with prostate cancer receiving hormone ablation therapy, which relies primarily on the results of Protocol 20040138. The Division of Reproductive and Urology Products (DRUP) is the lead division reviewing BL STN 12520, while the Division of Biologic Oncology Products is the lead division reviewing BL STN 125320/5 and 125320/6.

The Biologics License Applications for denosumab were designated as standard review priority since no evidence was provided in these applications to demonstrate that denosumab treatment provides an advance over available therapies.

A complete response letter was issued October 19, 2009. The issues precluding approval were

- institution of a REMS to communicate risks
- agreement on post-marketing studies to further assess risks
- evidence of an absence of adverse effects on tumor outcomes.

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The need for additional measures to assess and monitor product safety are consistent with the recommendations of the Reproductive Health Drugs Advisory Committee, supplemented by medical oncologists serving as Special Government Employees, and were recommended by all members of the clinical review team.

These first two issues were addressed in Amgen's Complete Response resubmission to BL STN 125320/0 and identified in the approval letter issued June 1, 2010.

The third bullet was addressed in the resubmission to this efficacy supplement on March 18, 2011.

3. CMC/Device

Denosumab is a human IgG2 human monoclonal antibody that is directed against the the RANK (receptor activator for nuclear factor-kB) ligand, also referred to as RANKL. Denosumab binds to both the circulating and membrane-bound forms of RANK ligand, preventing the binding of the RANK ligand to RANK, thus inhibiting activation of this receptor. Denosumab binds specifically to RANKL and does not recognize TNFα, TNFβ, TNF-related apoptosis-inducing ligand (TRAIL), or CD40L. There is no evidence at this time that binding of denosumab to membrane-bound RANKL induces RANKL signaling.

The pharmacodynamic effects of denosumab are mediated through its prevention of the binding of the RANK ligand to its receptor, RANK; inhibition of binding of RANKL results in failure to initiate the intracellular signaling cascades necessary to promote osteoclast formation, fusion, differentiation, activation, and survival and to inhibit terminal differentiation and activation of osteoclasts. Interruption of RANK signaling leads to an immediate decrease in bone resorption and bone turnover, which is reversible upon discontinuation of denosumab.

Denosumab is produced by a genetically-engineered CHO cell line through standard fermentation technology and standard column chromatography purification procedures. The manufacturing process is well-controlled and results in a pure and potent product. The product presentations are in single-use vials or pre-filled syringes containing 1 mL liquid at a concentration of 60 mg denosumab/mL. The acetate formulation buffer for the two presentations differs somewhat in excipients.

The facilities and manufacturing processes for the drug product and drug substance were determined to have acceptable sterility assurance and microbiology product quality.

I concur with the conclusions of the CMC review staff that there are no outstanding CMC issues that would preclude approval. All post-marketing commitments recommended by the CMC reviewer were addressed in the original approval for STN BL 125320/0.

4. Nonclinical Pharmacology/Toxicology

The pharmacology of denosumab was evaluated in healthy cynomolgus monkeys, oophorectomized female cynomolgus monkeys, and in a transgenic mouse model with knock-in human RANKL and human RANK. In the oophorectomized monkeys, the administration of

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denosumab alone or in combination with aledronate resulted in significant reductions of serum markers of bone resorption and prevented the loss of BMD as compared to animals receiving vehicle control. Fracture healing was evaluated in RANKL/RANK transgenic mice; in this model, treatment with denosumab alone or in combination with aledronate resulted in delayed fracture healing but did not adversely impact bone morphology or tensile strength as compared to control animals.

Toxicology studies were performed in cynomulgus monkeys as the only relevant species. Denosumab binds to RANKL in non-human primates but not in rodents. Toxicology studies included 1- month and 12-month studies (an interim sacrifice was performed at 6 months). Additional pharmacology studies of long-duration included a 12-month and a 16-month pharmacology study at multiples of 16- to 50-times the proposed human dose (dependent on the approach to establishing exposure, as discussed in Dr. Pilaro's review). The toxicology findings were consistent with the expected pharmacology of denosumab, with inhibition of bone resorption and abnormal growth plates in juvenile animals; these effects were present despite the development of anti-product binding antibodies in a majority and neutralizing antibodies in a minority of animals after prolonged exposure.

Reproductive toxicology studies demonstrated exaggerated pharmacologic effects (reduction in bone resorption); there were no off-target effects, including no evidence of abnormal mammary gland development. In a RANKL knock-out model, there was an absence of mammary gland development which may not be relevant for mature adults but would have impact on fetal exposure in pregnant women. This information was included in product labeling, and is being monitored under the pregnancy registry.

Carcinogenicity studies were not performed. In extended dosing in primate, there was no evidence of carcinogenic effects. Larger studies in primates, the only relevant model, are not recommended and the potential for carcinogenicity will be assessed in the results of ongoing clinical studies and in post-marketing surveillance,

I concur with the nonclinical pharm/tox reviewers that there are no outstanding nonclinical pharmacology or toxicology issues that would preclude approval. There are no recommendations for post-marketing commitments for nonclinical toxicology.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology of denosumab was investigated in 13 clinical studies, which included drug substance and drug product from an early manufacturing process and the to-be-marketed process. The pharmacodynamic profile at the recommended dose suggested rapid onset of action with 70% inhibition in bone resorption within 6 hours of the initial dose and 85% inhibition within 3 days, as determined by reduction in serum Type 1 C-telopeptide levels. Changes in lumbar spine BMD were detectable as early as one month after dosing. Based on changes in lumbar spine BMD, treatment effects were observed with doses as low as 14 mg, however there was an apparent plateau in efficacy with comparable effects at 60, 100, and 210 mg doses.

The pharmacokinetics of denosumab supported the proposed every 6 month dosing regimen, with a mean half-life of 25.4 days and no evidence of accumulation after 4 years of dosing.

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Clearance was dependent on targeted (RANKL binding) and non-targeted elimination mechanisms; targeted clearance mechanisms were more apparent at lower serum levels of denosumab. No significant differences in dosing were observed by age, gender, or race; no dosing adjustments are recommended in patients in renal insufficiency based on an intrinsic factor PK study in 55 patients with renal insufficiency. Due to the known metabolism of protein products, adjustments due to hepatic insufficiency are not anticipated and studies investigating such effects were not conducted. The pharmacokinetics of denosumab are dependent on weight, however the proposed fixed dose was efficacious across a range body weight therefore dosing adjustments based on body weight were not recommended.

The clinical pharmacology reviewer recommended that a post-marketing study be conducted to assess the impact of denosumab on CYP substrate metabolism. This is based on evidence with other antibodies directed against cytokines (RANKL is in the TNF family) in which alteration in cytokine levels impact cytokine effects on CYP substrate metabolism. This was conveyed with the original approval of Prolia (BL STN 125320/0).

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

6. Clinical Microbiology

There were no clinical microbiology data provided in this supplement and such data were not required for review of the supplement.

7. Clinical/Statistical-Efficacy

The data supporting claims of efficacy of denosumab for the treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer are derived primarily from Protocol 20040135 but are supported by the results of Protocols 20030216 (treatment of PMO) and 20040138 (treatment/prevention in men with prostate cancer receiving androgen deprivation therapy or ADT).

Protocol 20040135
Protocol 20040135 was a multinational, multicenter, double-blind, placebo-controlled trial that enrolled 252 patients with non-metastatic breast cancer who were receiving adjuvant aromatase inhibitor (AI) therapy following definitive local therapy. Key eligibility criteria included no evidence of metastatic disease, no concurrent chemotherapy, no skeletal fractures after age 25 years, and lumbar spine, total hip, and/or femoral neck BMD T-score between -1.0 and -2.5 with no BMD T-score of less than -2.5 (osteopenia). Patients were randomized 1:1 to denosumab 600 mg (n=127) or placebo (n=125) administered as a subcutaneous injection once every 6 months for a total of 4 doses. All patients received daily calcium ($\geq$ 1 g) and vitamin D ($\geq$ 400 IU) supplementation throughout the trial. Randomization was stratified by the duration of prior aromatase inhibitor therapy ($\leq$ 6 months vs. > 6 months) at study entry. After completion of denosumab/placebo, all patients were to be followed for an additional 24 months to assess durability of treatment effect and obtain additional safety data.

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The primary efficacy endpoint was the percentage change in bone mineral density (BMD) in the lumbar spine from baseline to month 12. Key secondary efficacy endpoints were percentage change in BMD in the lumbar spine from baseline to month 6 and percentage change in BMD in the total hip and in the femoral neck from baseline to month 6 and baseline to month 12. There was no systematic assessment of tumor staging/evaluation as part of the clinical protocol and such data was not captured on case report forms.

Efficacy analyses were conducted in the intent-to-treat population with additional analyses performed in the "per-protocol" population by Amgen. Safety analyses were conducted in the "as-treated" population. There were 127 patients randomized to densumab and 125 patients to placebo. Approximately three-quarters of the patients in both treatment arms received all four planned doses of investigational drug. The treatment arms were generally well-balanced, although there were some imbalances in histologic diagnosis, tumor stage, and extent of prior treatment that are likely to occur given the small sample size and relatively broad inclusion criteria. Although the intended study population was patients with low bone mass, approximately 30% of the patients had BMD T-scores within the "normal" bone mass range and 1% were osteoporotic.

There was a statistically significant difference in the percentage change in lumbar spine BMD at 12 months between the two study arms of 5.5% (95% CI: 4.8%, 6.3%) based on a least square mean estimate. The difference in the estimated mean change was based on an estimated mean increase in BMD of 4.8% in the denosumab arm and an estimated mean decrease in BMD of 0.7% in the placebo arm from baseline to month 12. The treatment effect on the primary endpoint was consistent across relevant subgroups based on age, duration of prior aromatase inhibitor therapy, weight, body mass index (BMI), prior chemotherapy, prior selective estrogen receptor modulator use, and time since menopause. The percentage of patients with missing lumbar spine BMD scores at 12 months was 9% in the denosumab arm and 15% in the placebo arm. The applicant confirmed that the treatment effect was robust through a series of sensitivity analyses, including a repeated measures model, ANCOVA model using mean of the other group imputation methods, and the per protocol analysis set, an ANCOVA model using subjects analyzed in the appropriate stratum based on baseline characteristics rather than the incorrect stratum used at randomization, and in univariate and multivariate covariate analyses.

There were also significant treatment effects, favoring denosumab, for key pre-specified secondary efficacy endpoints. There were highly significant differences in the change in total hip BMD and in femoral neck BMD from baseline to month 12, with improvement in BMD at month 12 compared to baseline for denosumab-treated patients. Although the number of events were small with 2 deaths (1%) in each arm at 24 months, there were no differences in the 2-year, all cause mortality rates between the two arms.

Protocol 20030216

As previously agreed-upon, the results of Protocol 20030216 were utilized to validate that changes in BMD resulting from denosumab treatment will predict a change in the rate of skeletal fractures. This finding was required since the pharmacodynamic effects of denosumab which affect BMD are different from the effects of bisphosphonates, therefore FDA required that the

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validity of the surrogate be confirmed for denosumab, rather than extrapolated from the experience with bisphosphonates. Protocol 20030216 was a multicenter, randomized (1:1), double-blind placebo-controlled trial designed to show that denosumab treatment, administered at 60 mg every 6 months for three years reduced the incidence of new vertebral fractures in postmenopausal women with osteoporosis. Randomization was stratified by age at study entry: 60 to 64 years, 65 to 69 years, 70 to 74 years, and ≥ 75 years. BMD T-scores were required to be ≤ - 2.5 and ≥ - 4.0 at baseline. Concomitant treatment with calcium (≥ 1 g/day) and vitamin D (≥ 400 IU/day) supplementation was required for the duration of the study.

Efficacy analyses were conducted in 7808 patients who were randomized (1:1) to receive denosumab (n=3902) or placebo (n= 3906). There was a statistically significant reduction in the risk of new vertebral, non-vertebral, and hip fractures among denosumab-treated patients compared to controls, based on pre-specified sequential testing procedures. The risk reduction for new vertebral fractures at month 36 was 68% (95% CI: 0.26, 0.41; $p < 0.0001$). The risk reductions in non-vertebral fractures and in hip fractures were 20% (95% CI: 0.67, 0.95; $p = 0.01$) and 40% (95% CI: 0.37, 0.97; $p = 0.036$), respectively. The treatment effects were consistent across relevant subgroups, including patients with two or more prevalent vertebral fractures or with prevalent vertebral fractures that were moderate or severe; patients with femoral neck T-scores of ≤ - 2.5; and patients age ≥ 75 years.

Protocol 20040138
The efficacy of denosumab in the treatment of osteoporosis in patients undergoing hormone ablation therapy is also supported by the results of Protocol 20040138. Protocol 20040138 is a multicenter, double-blind, randomized (1:1), placebo-controlled trial that registered and randomized 1468 men with non-metastatic prostate cancer, who had received definitive local therapy and at study entry were receiving androgen deprivation therapy (ADT) either medically through gonadotropin-releasing hormone (GnRH) agonists or surgically (orchiectomy).

Patients were randomized 1:1 to either denosumab (734) or placebo (734) once every 6 months for a total of 6 doses over a 36-month treatment period. All patients received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation throughout the trial. Randomization was stratified by age (< 70 years vs. ≥ 70 years) and by duration of prior ADT (≤ 6 months vs. > 6 months) at the time of entry. The primary efficacy endpoint was the percent change in lumbar spine BMD from baseline to month 24. Key secondary endpoints were percentage change in femoral neck BMD and total hip BMD from baseline to month 24, percentage change in lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36, subject incidence of any fracture, and subject incidence of new vertebral fracture over the 36-month treatment period. Tumor re-staging consisted of a repeat bone scan at 36 months and measurement of PSA levels every 6 months during denosumab treatment.

There was a statistically significant difference in lumbar spine BMD between denosumab and placebo treated groups at 2 years [difference of 6.7% (95% CI: 6.2%, 7.1%)] based on an increase in BMD of 5.6% in the denosumab arm and a decrease of -1% in the placebo arm between baseline and 24 months, based on a least square mean estimate. Consistent treatment effects on lumbar spine BMD favoring the denosumab arm were observed in subgroups defined

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by age, race, geographical region, weight/BMI, BMD, and duration of androgen deprivation therapy.

Statistically significant treatment differences favoring the denosumab arm were also observed in change from baseline to month 24 in femoral neck BMD [difference 3.9% (95% CI: 3.5%, 4.4%; $p < 0.01$)] and total hip BMD [difference 4.8% (95% CI: 4.4%, 5.1%; $p < 0.01$).

Additional analyses, using a hierarchical procedure for alpha adjustment, demonstrated a statistically significant reduction in the incidence of new vertebral fractures at 36 months [1.5% vs. 3.5% (odds ratio: 0.37, 95% CI: 0.18, 0.78: p=0.013)] but no significant difference in all fractures (5.2% vs. 7.2%; p=0.1) at 36 months. All cause mortality was the same, 5.9%, in both treatment arms at 36 months.

I concur with the major conclusions reached by the clinical and statistical reviewers regarding efficacy. The clinical and statistical review team members concluded that the major outcome measure for efficacy, a statistically significant difference in the percentage change in lumbar spine BMD from study entry to 12 months, for Protocol 20040135 was met. This finding was supported by the finding of improvement in BMD and the decreased incidence of new fractures in men receiving hormone ablation therapy in Protocol 20040138. The demonstration of an effect on BMD as a measure of clinical efficacy is acceptable since the validity of this surrogate in denosumab-treated patients for reduction in skeletal fractures was confirmed by the results of Protocol 20030216. The findings from Protocol 20030216, reviewed by the Division of Reproductive and Urologic Products (DRUP) under BL STN 125330, established the efficacy of denosumab for the treatment of post-menopausal osteoporosis women as well as validating the surrogate endpoint of effects on BMD with reduction in skeletal fractures.

8. Safety

The evaluation of clinical safety considered data obtained in approximately 14,000 patients in 30 clinical trials with up to 5 years of exposure to denosumab. These trials included patients with normal, low and osteoporotic bone density. The strategy for primary safety analysis included:

- Separate analyses for safety were conducted for each of the major efficacy trials (Protocols 216, 132, 135, and 138).

- Analyses for general, overall safety was conducted in an integrated dataset containing results of the four major efficacy trials (Protocols 216, 132, 135, and 138).

- Analyses for specific safety issues, based on signals in the initial safety program for denosumab, potential signals based on pharmcodynamics of denosumab, and signals observed with bisphosphonate products in osteoporotic patients. These analyses, except where noted differently below, conducted a review of the safety information from nine randomized, clinical studies (seven trials in women with PMO [(20010223, 20030216, 20040132, 20050141, 20050172, 20050179, 20050234) and two trials in patients with cancer receiving hormone-ablation (20040135, 20040138)]. The safety analyses were conducted in the "as-treated" population defined by the treatment administered (rather than treatment assigned) in patients receiving one or more doses of investigational drug. These trials were

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selected based on relevance of the population (PMO or HA) and dose (60 mg SC every 6 months) to the proposed indications under review.

The most common adverse reactions due to denosumab (per-patient incidence ≥ 5% and higher incidence in denosumab-treated group compared to placebo-treated) were back pain, arthralgia, extremity pain, osteoarthritis, constipation, musculoskeletal pain, hypercholesterolemia, dizziness, peripheral edema, and upper respiratory tract infection. Focused safety analyses also confirmed that hypocalcemia, bradycardia, ischemic heart disease and rash occurred at a low but increased incidence in denosumab-treated patients as compared to the control group. The incidence of osteonecrosis of the jaw, a known toxicity of bisphosphonates, did not occur at a higher incidence in denosumab-treated patients in clinical studies. The increased incidence of cataract formation was observed only in denosumab-treated men with prostate cancer undergoing androgen-deprivation therapy.

The most common serious adverse reactions occurring in denosumab-treated patients is infections. The potential for an adverse impact on the rate of tumor growth has not been adequately investigated in controlled clinical trials.

The approach and results of focused safety reviews to evaluate for incidence and relative risks of the following adverse events considered possibly-related to denosumab are summarized in greater detail below. The identification of potential risks requiring focused evaluation were based on data obtained in the clinical development program (cardiac toxicity, hypocalcemia, immune responses directed against denosumab), the known pharmacodynamic effects of denosumab (infection, delayed fracture healing, tumor promotion, hypocalcemia) and serious adverse effects of observed with bisphosphonates (osteonecrosis of the jaw, cardiac toxicity).

Osteonecrosis of the jaw (ONJ), delayed fracture healing, and secondary malignancies
A focused safety review was conducted by Dr. Anita Abraham, Dr PH in the Division of Biometrics VI to evaluate for increased risks of osteonecrosis of the jaw (ONJ), delayed fracture healing, and secondary malignancies. Dr. Abraham's review considered safety data from nine randomized, placebo-controlled trials as discussed above. Comparisons of between-arm differences in adverse events and determination of relative risks of these events were conducted in the individual studies and in a pooled analysis of the seven trials conducted in PMO patients. The incidence of ONJ was 4% in the integrated analysis across trials in women with PMO. The statistical reviewer concluded that there was no increased risk of ONJ compared with placebo-controls, using either the more narrow definition as applied by the ONJ adjudication group or a broader definition. As noted by Dr. Pradhan, no patient experienced an event of ONJ during the extended follow-up phases of Trials 135 and 138.

The evaluation of delay in fracture healing was limited to the four major efficacy studies as these were the only studies designed to collect this information. Only in Protocol 20030216 was there a sufficient number of cases of delayed fracture healing (more than one per treatment group) to conduct an evaluation of the relative risk. Among patients enrolled in Protocol 20030216, the relative risk of any complication in patients with fractures was 0.99 (95% CI: 0.55, 1.77). Dr. Abraham concluded that there was no evidence of an increased risk of delayed fracture healing, while noting that additional follow-up may be needed to identify all events.

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Tumor Promotion Potential

Based on the potential for perturbation of TNF regulation (through inhibition of membrane-bound RANKL signaling on T cells), an evaluation of the relative risk of secondary malignancies was conducted. Analyses included safety data from the nine randomized studies identified above. Search terms included all adverse events in the Neoplasms SOC of MedDRA with the exception of those terms that included the term "benign". With the exception of Protocol 20040138, there was no evidence of an increased risk in malignancies in denosumab-treated patients as compared to controls. There was a significant difference (relative risk 1.32, p=0.46) in the risk of malignancies reported as adverse events in Protocol 20040138; on further evaluation, this was driven by a higher rate of reports of metastatic disease as an adverse event. Metastases were reported as an adverse event in 48 of the 731 (6.57%) denosumab-treated patients compared to 31 of the 725 (4.28%) placebo-treated patients. In the integrated analysis of studies conducted in women with PMO, there were 206 (4.06%) reports of second malignancies in 5073 denosumab-treated patients and 175 (4.14%) reports of second malignancies in 4231 placebo-treated patients. The most common primary cancer sites were skin, breast, GI, respiratory/mediastinal, and reproductive/urologic. Dr. Abraham concluded that the increase rate in reported metastases, particularly bone metastases, was of concern in men with prostate cancer, but that in general, there did not appear to be a risk of second malignancies.

Based on this concern, Amgen provided the results of Protocols 20050103, 20050136, and 20050244. Trials 20050103, 20050136, and 20050244 enrolled 1904 patients with hormone-refractory, metastatic prostate cancer, 2409 patients with metastatic breast cancer, and 1779 patients with osseous metastases due to multiple myeloma or metastatic cancers other than breast and prostate cancer, respectively. These randomized, double-blind, double-dummy, active-controlled trials were designed to demonstrate that denosumab is not inferior to zoledronic acid (Zometa®, an active control) for the composite efficacy endpoint of time-to-first skeletal-related event (SRE). All three studies met their primary endpoint, demonstrating that denosumab is non-inferior to zoledronic acid in the time-to-first skeletal-related event. In addition, two of the trials (20050103 and 20050136) demonstrated that denosumab significantly delayed the time to first SRE as compared to zoledronic acid.

Eligibility criteria for this trials was not restricted based on relevant prognostic characteristics and the randomization plan stratify for all relevant variables for a given tumor type. However all studies required systemic, routine assessment of tumor status and disease progression, were of sufficient size that many prognostic factors would be expected to have been equally allocated across study arms. The results of exploratory analyses to assess for effects on progression-free and overall survival show that these outcomes are not statistically different from those in the control (zoledronic acid) arms for each individual trial (displayed in the following table excerpted from Dr. Lemery's review). In a pooled analysis, the upper bound of the confidence interval for OS excludes a hazard ratio of 1.07 and the upper bound of the confidence interval for PFS excludes a hazard ratio of 1.08.

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Table 4: PFS and OS Results from Advanced Cancer Studies (FDA Analyses)

Endpoint	Number of events (%)		Median (in mos.)		HR
	D	ZA	D	ZA	(95% CI)
Trial 103 Prostate Cancer (n = 950 denosumab; n = 951 zoledronic acid)					
OS	474 (49.9)	461 (48.5)	19.4	19.8	1.05 (0.91, 1.20)
PFS	767 (80.7)	735 (77.3)	8.1	8.0	1.03 (0.92, 1.14)
Trial 136 Breast Cancer (n = 1,026 denosumab; n = 1,020 zoledronic acid)					
OS	301 (29.3)	305 (29.9)	29.4	NR	0.96 (0.82, 1.13)
PFS	683 (66.6)	698 (68.4)	11.8	11.7	1.01 (0.91, 1.13)
Trial 244 Other Tumors (n = 886 denosumab; n = 890 zoledronic acid)					
OS	479	474	12	12.6	0.95 (0.84, 1.08)
PFS	687	679	5.4	5.5	1.01 (0.91, 1.12)

(b) (4)

[redacted]

It is my opinion that there does not appear to be an increased risk of second malignancies, although additional surveillance is prudent, given the availability of other therapeutic options for this indication. Of note, there is no difference between arms in the number of lymphoproliferative malignancies, which would be expected if the risk of malignancy was mediated by inhibition of TNF. The potential for an increase in the risk or rate of tumor progression could not be addressed by the studies supporting efficacy claims (20040135 and 20040138) but have been addressed in the resubmission, responding to the 2009 Complete Response letter, which referenced the results of three additional trials (Protocols 20050103, 20050136, and 20050244). In these trials, denosumab was administered at a two-fold higher dose and more frequent schedule (denosumab 120 mg by subcutaneous injection every four weeks until toxicity or study termination). Even with this much greater exposure, there was no evidence of a clinically important adverse effect on tumor growth or survival.

Cardiac toxicity

At the time of the pre-BLA meeting (Oct 21, 2008), FDA raised concerns regarding evidence of an apparent dose-dependent prolongation of the QT interval observed in studies conducted in patients with rheumatoid arthritis. Based on this concern, the Division of Biometrics VI was consulted to evaluate the integrated safety database for evidence of cardiotoxicity. Dr. Leslie Kenna, the safety evaluator consultant conducted a review of the safety information from nine randomized, clinical studies as discussed above. Analyses were performed individual within each trials and in a pooled analysis; per-patient incidence and relative risk analyses were performed using the applicant's classification system for cardiotoxicity and broad and narrow scope SMQ analyses. Based on Dr. Kenna's review, bradyarrhthymia (relative risks ranging from 1.7-2.0 for denosumab compared to placebo) and ischemic heart disease (relative risks ranging from 1.4-1.8) were the only consistent signals in the denosumab-treated group. The incidence of these events was low, and in the case of bradyarrhythmias was driven primarily by the results of conduction

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defects in study 216. The number of moderate (106 vs. 75) and severe (68 vs. 34) ischemic heart disease events were increased among denosumab-treated patients (n=3886) compared with the placebo-treated (n=3876) patients in protocol 216. Similarly, the number of events resulting in differences in bradyarrhythmic events was driven the differences in conduction defect events. Across pooled analysis involving either Protocols 216 and 138 (pooled efficacy trials n=4617 denosumab/ n=4601 placebo) or across placebo-controlled trials, the number of conduction defects were higher in the denosumab-treated patients for number of patients with AV block (8 vs. 4 patients; pooled efficacy trials and 5 vs. 3 patients; pooled placebo-controlled dataset) and right bundle branch block (11 vs. 7 patients; efficacy trial dataset; 10 vs. 7, placebo-controlled dataset).

Hypocalcemia

A focused safety review of the integrated safety database was conducted by Dr. Mandi Yu, Div of Biometrics VII, to assess the incidence and relative risks of hypocalcemia secondary to denosumab administration. Hypocalcemia was recognized as a treatment-related adverse reaction early in the clinical development program, therefore all four of the registration trials required that patients receive oral calcium and vitamin D supplementation and that serum calcium be regularly monitored throughout the clinical study.

Dr. Yu conducted analyses separately across the 9 studies discussed above and also pooled the data from the two major efficacy studies in post-menopausal women (Protocols 20030216 and 20040132). There was no significant difference in the incidence of clinically symptomatic events (including events requiring hospitalization) between the denosumab-treated and control arms among women with PMO (incidence rates of approximately 2.7% in both groups); the incidence of serious events of hypocalcemia was the same in both denosumab- and placebo-treated patients (5 events in four patients, two patients in each treatment group). There was a higher incidence of hypocalcemia reported as adverse events among denosumab-treated patients with cancer receiving hormone ablation as compared to placebo-treated patients [6.2% vs. 3.3% (Protocol 20050135); 3.0% vs. 2.2% (Protocol 20050138)]. These events were generally symptomatic and graded as mild to moderate in severity.

In contrast to the clinically-detected adverse event reports of hypocalcemia, there was an approximately 3.5-fold (95% CI: 2.2, 5.9) increase in the incidence of hypocalcemia as determined by laboratory measurements of serum calcium among women with PMO and an approximately 5.4-fold increase in hypocalcemia based on laboratory measurements in Protocol 20050138; no increase risk of laboratory-detected hypocalcemia was identified in Protocol 20050135 patients. Hypocalcemia was detected within the first month of treatment in 58% of denosumab-treated patients.

The incidence of severe hypocalcemia appeared to be increased in a single dose, open label trial designed to assess the pharmacokinetics, safety and tolerability of denosumab in patients with both normal and abnormal renal function. Patients in this study did not receiving calcium or vitamin D supplementation. The study demonstrated that the pharmacokinetics of denosumab was not influenced by renal dysfunction of any severity. However, in patients with severe (creatinine clearance < 30 mL/min) or end-stage renal disease, an increased incidence and severity of hypocalcemia was observed.

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Hypersensitivity and Dermatologic toxicity
There is always a potential for immune responses to protein products. Surveillance for anti-denosumab binding and neutralizing antibodies were conducted as part of the clinical development program. The incidence of anti-denosumab binding antibodies was low [0.5% (43 positive samples among 8113 denosumab-treated patients)], consistent with the findings for other fully human antibody products. Assessment for neutralizing antibodies was conducted only in those patients with a positive screen test for binding antibodies. No patient tested positive for neutralizing antibodies. Among the 6 patients in the four major efficacy studies who had evidence of anti-denosumab binding antibodies, there was no evidence of alteration in pharmacokinetics or in efficacy, as measured by an increased in lumbar spine BMD and in hip BMD T-score from baseline in all six patients.

In addition to laboratory screening for humoral immune responses, a focused safety review of the integrated safety database was conducted by Dr. John Yap, Ph.D., Div of Biometrics VII, to assess the incidence and relative risks of hypersensitivity reactions in patients receiving denosumab. In addition to the 9 trials listed above, Dr. Yap included data from Protocols 20040245, 20050233, and 20050237 in the integrated analysis for hypersensitivity. The analysis for hypersensitivity included a narrow list of preferred terms proposed by the sponsor with additional terms identified by the reviewer to be directly related to hypersensitivity. In these analyses, a significant increase in multiple dermatologic terms was noted in Protocol 20030216 alone as well as in the overall safety database (in which patients enrolled under Protocol 20030216 accounted for 80% of the integrated database). The terms that were identified as occurring more frequently in denosumab-treated patients included dermatitis (3.1% vs. 1.7%), eczema (1.3% vs. 0.7%; relative risk 1.96), and rash (2.6% vs. 1.9%; relative risk 1.34). As noted, the incidence rates were low ($\geq$ 3%) with an approximately 1.5-2-fold increase in relative risk for denosumab-treated patients. The incidence of dermatologic adverse events did not appear to be increased in patients with cancer undergoing hormone ablation therapy.

I disagree with Dr. Yap's conclusions regarding hypersensitivity. While Dr. Yap concluded that denosumab is not immunogenic, the evidence of development of anti-denosumab antibodies in a sensitive, validated assay indicate that denosumab is immunogenic albeit at a low incidence rate. The dermatologic toxicities appear not to be mediated by anti-drug antibody responses but by another mechanism that may reflect an unintended targeted effect rather than a manifestation of "hypersensitivity". Categorizing dermatologic toxicity as hypersensitivity in product labeling would be inappropriate as it suggests a mechanism for which there is little evidence. I recommend that the specific toxicities be identified and that product labeling remain silent on speculated mechanism of the toxicity, which may suggest an inappropriate and ineffective management course of affected patients.

Risk Evaluation and Mitigation Strategies (REMS)
The applicant submitted a proposal for a risk management plan based solely on adequate physician product labeling. As noted by DRISK and the clinical review divisions, these risks may not be adequately communication through physician labeling alone and for other agents with a similar level of risk, therefore a REMS containing a Medication Guide and communication plan has been required. The DRISK consultant noted that although the Advisory

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Committee members advised that a patient registry be established, this is unlikely to mitigate risks (since patients are not required to undergo special screening to receive the drug). The DRISK consultant noted that post-marketing surveillance studies would be a more effective means of collecting data to better characterize risks. The applicant will be asked to provide surveillance program to assess risks in the Complete Response letter.

The Agency informed Amgen of the need for post-marketing required trials to further evaluate these risks. Amgen was notified of FDA's determination of the need for a REMS on October 2, 2009. The REMS was approved at the time of the original approval for Prolia in June 2010 and contains a Medication Guide and communication plan regarding the risks of serious infections, dermatologic toxicity, and over-suppression of bone turn-over that occur with denosumab administration.

Marketing approval of Prolia was granted in June 2010 and marketing approval of Xgeva (denosumab) was granted in November 2010. Since these approvals, no new safety signals or risks have been identified in the post-marketing experience not already identified prior to June 2010. The REMS was modified in conjunction with this supplement to include information on the new indication under this supplement and BL STN 125320/6, as well as to include the risks of osteonecrosis of the jaw as a specific potential outcome of suppression of bone turnover, in the REMS template, the REMS supporting materials, the Communication Plan, and the Medication Guide. The Communication Plan was amended to include distribution of a second Dear Health Care Provider Letter (DHCPL) to medical specialists (oncologists and urologists) who treat patients with breast and prostate cancer as well as to the medical community who treat women with post-menopausal osteoporosis.

The following clinical post-marketing studies were identified in the original approval letter for Prolia.

- 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 denosumab (Protocol 20090522)

- A long-term surveillance study in postmenopausal women administered denosumab to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turn-over (Protocol 20090601).

- A long-term pregnancy exposure registry study in denosumab users who become pregnant on the drug (Protocol 20090589)

9. Advisory Committee Meeting

The findings in these four applications were presented to the Reproductive Health Drugs Advisory Committee on August 13, 2009. The committee was supplemented with three medical oncologists serving as Special Government Employees to serve as expert advisors on issues

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relating to the risk of adverse effects on tumor growth. The committee was asked a series of questions regarding the risk-benefit ratio of denosumab across the various indications. All members advised that there is a population of post-menopausal women in whom treatment benefit is likely to outweigh risks, however the majority advised that benefits of prevention of osteoporosis in any population with low bone mass in any of the proposed clinical settings (post-menopausal women, women receiving hormone ablation for adjuvant treatment of breast cancer, and men receiving hormone ablation for non-metastatic prostate cancer) were not likely to outweigh risks. The majority of the members also advised that the risk-benefit ratio in women receiving hormone ablation for adjuvant treatment of breast cancer was not favorable, given the inadequate information on the potential risks of adverse effects on tumor growth. While the majority of members advised that the benefits of denosumab treatment of osteoporosis *were* likely to outweigh the risks in men receiving hormone ablation for non-metastatic prostate cancer, all three oncologists disagreed with this recommendation. Finally, the members of the advisory committee recommended that a REMS be established for mitigation of risks through adequate communication of risks to patients and healthcare providers.

10. Pediatrics

A request for a full waiver was reviewed by the PeRC on June 30, 2009. The waiver was granted for all proposed indications based on a determination that the necessary studies would be impossible or highly impractical because the disease/condition does not exist in children.

11. Other Relevant Regulatory Issues

The Division of Scientific Integrity conducted clinical audits of two study sites for Study 20040135, a sponsor site, and the Contract Research Organization (CRO) site. The clinical study sites were selected based on the high number of patients enrolled and the high number of reported protocol violations, relative to other study sites. All audited data from clinical sites were verified to be accurate and inspections at the two clinical sites did not reveal deficiencies that would preclude approval. However it was noted that primary study data (DXA scans and electronic medical records) were not maintained at the study sites; DXA scans for determination of bone-mineral density, the primary efficacy outcome measure, were sent to the CRO, (b) (4) and electronic records were maintained in a database at Amgen. Inspections were conducted of both (b) (4) and Amgen; although violations were noted, there are no outstanding issues which would preclude approval.

With regard to financial conflicts of interest, there were no issues identified that are outstanding and would not permit approval. The clinical reviewer determined that the majority of investigators had no arrangements or financial interests that required disclosure or for those who reported disclosable financial interest, the Statement of Actions to Minimize Bias was completed and the actions taken were reviewed and are acceptable.

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12. Labeling

- Proprietary name review: I concur with the conclusions of the DMEPA reviewer and the clinical reviewer that the proposed proprietary name of Prolia is acceptable. Proprietary name issues were addressed with the original approval of Prolia (BL STN 125320/0).

- Physician labeling: As noted in Dr. Lemery's review, the advice of all review team members in OND and OSE and consultant reviewers in DDMAC were considered in the development of final labeling. The following sections physician labeling have been modified based on the data in this efficacy supplement:
  - Indications and Usage
    The applicant's proposed indication was modified and the final agreed upon indication "treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer" was modified to state the clinical benefit demonstrated (increase bone mass) and to restrict the indication to the patient population study through the additional of "high risk for fracture" and specification of the hormonal treatment (adjuvant aromatase inhibitor therapy) rather than all potential hormonal therapies.
  - Warnings and Precautions
    Modified to include recently added new section 5.1 "Drug Products with Same Active Ingredient" approved under BL STN 125320/20 on July 22, 2011. Related changes made to section 17 (new 17.1) and to Medication Guide. Of note, the language added in 5.1, 17.1, and the MG, i.e., "Patients receiving Prolia should not receive Xgeva" may be confusing to prescribers and patients as it is expected that some patients with breast or prostate cancer will discontinue Prolia and initiate Xgeva at the time of development of osseous metastases; alternative wording that should be considered by DRUP in future labeling changes.
  - Adverse Reactions
    - Description of adverse reactions are provided separately for women with post-menopausal osteoporosis and patients with breast or prostate cancer, based on differences in approach of the review teams for each indication in assessing the relatedness of certain events to denosumab (e.g., cystitis). At the request of the oncology review team, DRUP agreed to remove the term "breast cancer" as a common adverse reaction of Prolia, based on the data in this efficacy supplement which failed to confirm an increased risk of malignancies in patients receiving Prolia.
    - Description of adverse reactions identified in Protocols 20040135 and 20040138.
  - Use in Specific Populations
    Section 8.1 revised to remove the statement [redacted (b) (4)] based on expanded labeling claims approved with this application.
  - Clinical Studies
    - Tables retitled to specify patient population studied.
    - Descriptions of the results of 20040135 and 20040138 revised to include details of the clinical study design, descriptive statistics of the population studied, and for consistency with data presentation of efficacy results for the original approval of Prolia and other products approved to increase bone mass in patients at high risk for fracture.

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- Results based on exploratory analyses or for which there is no correlation with fracture risk were removed.

- Carton/Container labeling: Review of carton and container labeling incorporated comments from the DMEPA, DMA, and the clinical review divisions; these were addressed under the initial approval (BL STN 125320/0).

- Medication Guide: A medication guide was requested as part of a REMS on October 2, 2009 and the proposed REMS, including the Medication Guide was submitted on October 8, 2009. The REMS was modified under BL STN 125320/20 and has been further based on the data provided in this application to include the following
  - Description of additional indicated populations
  - Separate description of the common adverse events, reflecting data from section 6 of the physician labeling

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment:
  The clinical development program for denosumab demonstrated that in patients with low bone mass or osteoporosis as defined by a BMD score, due to age (PMO) or medical therapy (HA trials), denosumab treatment significantly increases BMD score at one year (Protocol 20040135), a surrogate endpoint for risk of skeletal fracture. The validity of this surrogate in denosumab-treated patients was established in Protocol 20030216 and supported by the findings of Study 20040138.

  Based on the potential but unexpected impact of other supportive care agents (erythropoesis-stimulating agents) on shortening time to progression and death demonstrated in multiple controlled clinical trials, FDA now considers that for novel products, even those without a clearly established mechanism for tumor growth promotion, data should be provided that rule out the potential for adverse impact on tumor growth. Neither of the trials conducting in patients with cancer receiving hormone ablation therapy was adequate in design to rule out such effects. Therefore, FDA reviewed the results of three additional trials conducted in patients with metastatic cancer or advanced stage disease (Protocols 20050103, 20050136, and 20050244). Although not specifically designed to address non-inferiority, these additional randomized, placebo-controlled trials included systematic, comprehensive monitoring of primary and potential metastatic disease sites in a manner which would allow one to evaluate for clinically significant impairments in progression-free survival and overall survival. Neither the individual trials nor the pooled analyses identified adverse effects on PFS or OS that were clinically important. Based on the confidence intervals around the pooled data, a clinically important adverse effect on OS or PFS appears to be excluded.

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- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  At the time of the original approval of Prolia for the treatment of postmenopausal osteoporosis, a REMS consisting of a Medication Guide and a communication plan to mitigate risks of serious infection, dermatologic toxicity, and over-suppression of bone turn-over through communication of these risks to patients and healthcare providers, was also approved. This REMS was modified on July 22, 2011 following approval of denosumab, under the proprietary name Xgeva (BL STN 125320/7), to denote that Prolia and Xgeva contain the same active ingredient. The current application further amends the REMS through (1) revisions to the Medication Guide to reflect the expanded indications for Prolia and include additional safety data, along with editorial revisions recommended by DRISK for consistency with current MG labeling policy, and (2) through modification of the communication plan with a second Dear HealthCare Provider Letter to be issued to healthcare professionals prescribing for both the original and expanded indications. .

- Recommendation for other Postmarketing Requirements and Commitments
  No additional post-marketing requirements or commitments are needed to support approval or further define risks for the proposed new claim.

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Signature Page

/Patricia Keegan/s/ September 15, 2011

Patricia Keegan, M.D., Director Date
Division of Oncology Drug Products 2
Office of Hematology and Oncology Products
CDER/FDA

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Summary Review for Regulatory Action

Date	October 16, 2009
From	Patricia Keegan, M.D. Director, Division of Biologic Oncology Products
Subject	Division Director Summary Review
BLA #	BL STN 125332/0
Applicant Name	Amgen, Inc.
Date of Submission	December 19, 2008
PDUFA Goal Date	October 19, 2009
Proprietary Name / Established (USAN) Name	Prolia®/ Denosumab
Dosage Forms / Strength	Solution for subcutaneous injection / 60 mg denosumab/ 1 mL in vials or prefilled syringes
Proposed Indication	Prolia is indicated for the treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer
Recommended Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Melanie Pierce
Medical Officer Review	Suzanne Demko
Cross-Discipline Team Leader Review	Jeff Summers, M.D.
Statistical Review	Jenny (Jing) Zhang, Ph.D.
Statistical TL Review	Mark Rothmann, Ph.D.
Statistical Review	Leslie Kenna, Ph.D.
Statistical Review	Mandi Yu, Ph.D.
Statistical Review	John Stephen Yap, Ph.D.
CMC OBP Review	Sarah Kennett, PhD. Michele Dougherty, PhD.
CMC OBP Team Leader Review	Chana Fuchs, Ph.D.
Microbiology Product Quality Reviews	Donald C. Obenhuber, Ph.D. Kalvati Suvarna, Ph.D.
Nonclinical Pharmacology/Toxicology Review	Michael Orr, Ph.D., D.A.B.T.
Nonclinical Toxicology Supervisory Review	Anne Pilaro, Ph.D.
Clinical Pharmacology Review	Sarah J. Schrieber, Pharm. D.
OSE/DMEPA Review	Judy Park, PharmD.
Pediatric & Maternal Health Team Review	Jeanine Best, MSN, RN, PNP
OC/DSI Review	John Lee, M.D.

OND=Office of New Drugs
OBP=Office of Biotechnology Products
OC=Office of Compliance
OSE= Office of Surveillance and Epidemiology
DDMAC=Division of Drug Marketing, Advertising and Communication
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Communication

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Division Director Summary Review

1. Introduction

The issues precluding a recommendation for approval by clinical reviewers across both Divisions reviewing the four related Biologics License Applications (BLAs) for denosumab are institution of a REMS to communicate risks and agreement on post-marketing studies to further assess risks for all requested indications and additional evidence to demonstrate safety, as it relates to the potential for adverse effects on tumor growth, for the two indications in men and women receiving hormone ablation therapy. The need for additional measures to assess and monitor product safety are consistent with the recommendations of the Reproductive Health Drugs Advisory Committee, supplemented by medical oncologists serving as Special Government Employees, and were recommended by all members of the clinical review team.

The original Investigational New Drug Application (IND 9837) for denosumab was received at FDA on May 22, 2001. An end-of-Phase 2 (EOP2) meeting was held on April 21, 2004 to discuss the clinical development program intended to support an indication for treatment of patients with cancer who had bone loss due to hormone ablation therapy, based on one trial to be conducted in women with non-metastatic breast cancer and one study in men with non-metastatic prostate cancer. The following key agreements were reached:

- Approval for denosumab for the treatment of bone loss associated with hormone ablation therapy would be contingent upon adequate anti-fracture efficacy being demonstrated in the three year postmenopausal osteoporosis treatment trial. This trial would then validate that denosumab-induced increases in BMD are associated with anti-fracture efficacy
- The results of Protocol 20010223 supported the preliminary activity and safety of denosumab 60 mg administered subcutaneously every 6 months.
- The proposed trials in breast cancer and prostate cancer were adequate in design to support registration for treatment of osteoporosis, provided that adequate anti-fracture efficacy was demonstrated in the trial of treatment of osteoporosis, validating that improvement in BMD in denosumab-treated patients is a surrogate for reduction skeletal fractures.

FDA stated that Protocol 20040138, the randomized, placebo-controlled trial in osteoporotic men with localized prostate cancer, (b) (4).

Pre-BLA meetings were held to discuss the submission of CMC information (July 8, 2008) and non-clinical/clinical information (October 21, 2008). Key issues discussed during the CMC pre-BLA meeting included the type of information needed to

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characterize quality attributes and information needed to support proposed specifications, the submission format for various strengths and presentations, and that the comparability of different drug substance manufacturing sites could only be addressed upon review of the primary data. FDA recommended that the application include a single strength (60 mg/mL) based on the potential for medication errors between the proposed 60 and 70 mg/mL strengths. Amgen agreed.

Key issues discussed during the preBLA meeting of October 21, 2008 included the following: the extent of information on supportive clinical studies to be included in the BLA, the contents of the 120-day safety update, data and analyses to be submitted characterizing bone density, impact on QT interval, hypersensitivity reactions, infections, and hypocalcemia, and the plan for submission of manufacturing runs to assist FDA in setting dates for facilities inspections. FDA did not raise major objections to the four proposed indications supported by the four randomized trials, acknowledged that presentation to an advisory committee was planned, and stated that although the final decision would be made during the review, the application would likely receive a standard review.

Amgen was notified that the submission was administratively split into four applications, with separate indications, in a letter dated Jan 30, 2009. In that letter, BLA STN 125330 identified as the "parent" BLA for any information common to more than one application, with a letter cross-referencing this information to be submitted to the other three applications. The four applications and their accompanying proposed indications are BL STN 125330, supporting the proposed indication of denosumab for the treatment of women with post-menopausal osteoporosis (PMO), which relies primarily on the results of Protocol 20030216; BL STN 125331, supporting the proposed indication of prevention of osteoporosis, which relies primarily on the results of Protocol 20040132, BL STN 125332, supporting the proposed indication of the treatment and prevention of osteoporosis is women with breast cancer receiving hormone ablation therapy, which relies primarily on the results of Protocol 20040135, and BL STN 125333, supporting the proposed indication of the treatment and prevention of osteoporosis in men with prostate cancer receiving hormone ablation therapy, which relies primarily on the results of Protocol 20040138. The Division of Reproductive and Urology Products (DRUP) is the lead division reviewing BL STN 125330 and 125331, while the Division of Biologic Oncology Products is the lead division reviewing BL STN 125332 and 125333.

The Biologics License Applications for denosumab were designated as standard review priority since no evidence was provided in these applications to demonstrate that denosumab treatment provides an advance over available therapies.

2. Background

Osteoporosis is characterized by low bone mass, disruption of the microarchitecture of the bone, and skeletal fragility; these changes lead to an increased risk of skeletal fractures. Fractures of the hip and spine are associated with increased mortality rate and

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can result in limited mobility and chronic pain, thus the goal of treatment of osteoporosis is the prevention of such fractures.

Treatment measures should always include general lifestyle measures aimed at reducing bone loss; these include adequate dietary calcium supplemental intake, supplemental vitamin D, regular moderate exercise, and smoking cessation. Additional preventive measures in the form of pharmacologic treatment with anti-bone resorptive agents should be initiated in post-menopausal women with osteoporosis and those at high risk for osteoporosis due to drug or hormonal therapy, age, low body weight, or a history of recent fractures, particularly recent hip fractures. Identification of patients at risk for osteoporotic fractures also involves screening for bone mass through measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA).

In the United States, initiation of pharmacologic treatment of osteoporosis is largely guided by the risk of fractures, as described in the 2008 WHO task force Fracture Risk Assessment Tool (FRAX) or the National Osteoporosis Foundation (NOF). Use of the 2008 NOF guidelines as selection criteria for patients who will benefit from pharmacologic treatment has not been evaluated in clinical trials. The women enrolled in Protocol 20040135 were likely to be at increased risk of skeletal fractures as compared to healthy adults based on osteopenia as determined by BMD t-score and concurrent use of hormone ablation, although the risk was not sufficiently high that administration of placebo was unethical.

Drugs which have received FDA approval for treatment of osteoporosis have been shown to improve or stabilize the loss of BMD. In addition, randomized trials have shown that adendronate, risedronate, and zoledronic acid reduces the risk of vertebral, non-vertebral, and hip fractures. Raloxifene and ibandronate have been shown to reduce the incidence of vertebral fracture but not hip fractures. The correlation between treatment-induced improvement in BMD and the reduction in the incidence of fractures was evaluated in a meta-analysis of twelve clinical trials (Cummings SR, et al; Am J Med. 112(4) 281-289, 2002). The authors concluded that an improvement in vertebral BMD correlated with a reduction in fracture risk however the reduction in risk observed was larger than would have been predicted based on BMD score alone. Since denosumab has a novel mechanism of action, the validity of denosumab-induced improvements in BMD as a predictor of reduction in skeletal fractures required verification rather than extrapolation from data obtained with bisphosphonates. Evidence that the relationship between denosumab-induced improvement in BMD and reduction in the incidence of skeletal fractures was obtained in Protocol 20030216 and supported by data obtained in protocol 20040138.

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3. CMC/Device

Denosumab is a human IgG2 human monoclonal antibody that is directed against the the RANK (receptor activator for nuclear factor-kB) ligand, also referred to as RANKL. Denosumab binds to both the circulating and membrane-bound forms of RANK ligand, preventing the binding of the RANK ligand to RANK, thus inhibiting activation of this receptor. Denosumab binds specifically to RANKL and does not recognize TNFα, TNFβ, TNF-related apoptosis-inducing ligand (TRAIL), or CD40L. There is no evidence at this time that binding of denosumab to membrane-bound RANKL induces RANKL signaling.

The pharmacodynamic effects of denosumab are mediated through its prevention of the binding of the RANK ligand to its receptor, RANK; inhibition of binding of RANKL results in failure to initiate the intracellular signaling cascades necessary to promote osteoclast formation, fusion, differentiation, activation, and survival and to inhibit terminal differentiation and activation of osteoclasts. Interruption of RANK signaling leads to an immediate decrease in bone resorption and bone turnover, which is reversible upon discontinuation of denosumab.

Denosumab is produced by a genetically-engineered CHO cell line through standard fermentation technology and standard column chromatography purification procedures. The manufacturing process is well-controlled and results in a pure and potent product. The product presentations are in single-use vials or pre-filled syringes containing 1 mL liquid at a concentration of 60 mg denosumab/mL. The acetate formulation buffer for the two presentations differs somewhat in excipients.

The facilities and manufacturing processes for the drug product and drug substance were determined to have acceptable sterility assurance and microbiology product quality.

I concur with the conclusions of the CMC review staff that there are no outstanding CMC issues that would preclude approval. There are four recommended post-marketing commitments by CMC staff that will be conveyed when/if the drug is approved.

4. Nonclinical Pharmacology/Toxicology

The pharmacology of denosumab was evaluated in healthy cynomolgus monkeys, oophorectomized female cynomolgus monkeys, and in a transgenic mouse model with knock-in human RANKL and human RANK. In the oophorectomized monkeys, the administration of denosumab alone or in combination with aledronate resulted in significant reductions of serum markers of bone resorption and prevented the loss of BMD as compared to animals receiving vehicle control. Fracture healing was evaluated in RANKL/RANK transgenic mice; in this model, treatment with denosumab alone or in combination with aledronate resulted in delayed fracture healing but did not adversely impact bone morphology or tensile strength as compared to control animals.

Toxicology studies were performed in cynomulgus monkeys as the only relevant species. Denosumab binds to RANKL in non-human primates but not in rodents. Toxicology studies included 1- month and 12-month studies (an interim sacrifice was performed at 6

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months). Additional pharmacology studies of long-duration included a 12-month and a 16-month pharmacology study at multiples of 16- to 50-times the proposed human dose (dependent on the approach to establishing exposure, as discussed in Dr. Pilaro's review). The toxicology findings were consistent with the expected pharmacology of denosumab, with inhibition of bone resorption and abnormal growth plates in juvenile animals; these effects were present despite the development of anti-product binding antibodies in a majority and neutralizing antibodies in a minority of animals after prolonged exposure.

Reproductive toxicology studies demonstrated exaggerated pharmacologic effects (reduction in bone resorption); there were no off-target effects, including no evidence of abnormal mammary gland development. In a RANKL knock-out model, there was an absence of mammary gland development which may not be relevant for mature adults but would have impact on fetal exposure in pregnant women This information will be included in product labeling, when/if the denosumab is approved and monitored under the pregnancy registry.

Carcinogenicity studies were not performed. In extended dosing in primate, there was no evidence of carcinogenic effects. Larger studies in primates, the only relevant model, are not recommended and the potential for carcinogenicity will be assessed in the results of ongoing clinical studies and in post-marketing surveillance, when/if this product is approved.

I concur with the nonclinical pharm/tox reviewers that there are no outstanding nonclinical pharmacology or toxicology issues that would preclude approval. There are no recommendations for post-marketing commitments for nonclinical toxicology.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology of denosumab was investigated in 13 clinical studies, which included drug substance and drug product from an early manufacturing process and the to-be-marketed process. The pharmacodynamic profile at the recommended dose suggested rapid onset of action with 70% inhibition in bone resorption within 6 hours of the initial dose and 85% inhibition within 3 days, as determined by reduction in serum Type 1 C-telopeptide levels. Changes in lumbar spine BMD were detectable as early as one month after dosing. Based on changes in lumbar spine BMD, treatment effects were observed with doses as low as 14 mg, however there was an apparent plateau in efficacy with comparable effects at 60, 100, and 210 mg doses.

The pharmacokinetics of denosumab supported the proposed every 6 month dosing regimen, with a mean half-life of 25.4 days and no evidence of accumulation after 4 years of dosing. Clearance was dependent on targeted (RANKL binding) and non-targeted elimination mechanisms; targeted clearance mechanisms were more apparent at lower serum levels of denosumab. No significant differences in dosing were observed by age, gender, or race; no dosing adjustments are recommended in patients in renal insufficiency based on an intrinsic factor PK study in 55 patients with renal insufficiency. Due to the known metabolism of protein products, adjustments due to hepatic insufficiency are not anticipated and studies investigating such effects were not conducted. The

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pharmacokinetics of denosumab are dependent on weight, however the proposed fixed dose was efficacious across a range body weight therefore dosing adjustments based on body weight were not recommended.

The clinical pharmacology reviewer recommended that a post-marketing study be conducted to assess the impact of denosumab on CYP substrate metabolism. This is based on evidence with other antibodies directed against cytokines (RANKL is in the TNF family) in which alteration in cytokine levels impact cytokine effects on CYP substrate metabolism. This request will not be conveyed at this time, but will be requested when and if approval is recommended.

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

6. Clinical Microbiology

There were no clinical microbiology data provided in this supplement and such data were not required for review of the supplement.

7. Clinical/Statistical-Efficacy

The data supporting claims of efficacy of denosumab for the treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer are derived primarily from Protocol 20040135 but are supported by the results of Protocols 20030216 (treatment of PMO) and 20040138 (treatment/prevention in men with prostate cancer receiving androgen deprivation therapy or ADT).

Protocol 20040135
Protocol 20040135 was a multinational, multicenter, double-blind, placebo-controlled trial that enrolled 252 patients with non-metastatic breast cancer who were receiving adjuvant aromatase inhibitor (AI) therapy following definitive local therapy. Key eligibility criteria included no evidence of metastatic disease, no concurrent chemotherapy, no skeletal fractures after age 25 years, and lumbar spine, total hip, and/or femoral neck BMD T-score between -1.0 and -2.5 with no BMD T-score of less than -2.5 (osteopenia). Patients were randomized 1:1 to denosumab 600 mg (n=127) or placebo (n=125) administered as a subcutaneous injection once every 6 months for a total of 4 doses. All patients received daily calcium ($\geq$ 1 g) and vitamin D ($\geq$ 400 IU) supplementation throughout the trial. Randomization was stratified by the duration of prior aromatase inhibitor therapy ($\leq$ 6 months vs. > 6 months) at study entry. After completion of denosumab/placebo, all patients were to be followed for an additional 24 months to assess durability of treatment effect and obtain additional safety data.

The primary efficacy endpoint was the percentage change in bone mineral density (BMD) in the lumbar spine from baseline to month 12. Key secondary efficacy endpoints were percentage change in BMD in the lumbar spine from baseline to month 6 and percentage

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change in BMD in the total hip and in the femoral neck from baseline to month 6 and baseline to month 12. There was no systematic assessment of tumor staging/evaluation as part of the clinical protocol and such data was not captured on case report forms.

Efficacy analyses were conducted in the intent-to-treat population with additional analyses performed in the "per-protocol" population by Amgen. Safety analyses were conducted in the "as-treated" population. There were 127 patients randomized to densumab and 125 patients to placebo. Approximately three-quarters of the patients in both treatment arms received all four planned doses of investigational drug. The treatment arms were generally well-balanced, although there were some imbalances in histologic diagnosis, tumor stage, and extent of prior treatment.that are likely to occur given the small sample size and relatively broad inclusion criteria. Although the intended study population was patients with low bone mass, approximately 30% of the patients had BMD T-scores within the "normal" bone mass range and 1% were osteoporotic.

There was a statistically significant difference in the percentage change in lumbar spine BMD at 12 months between the two study arms of 5.5% (95% CI: 4.8%, 6.3%) based on a least square mean estimate. The difference in the estimated mean change was based on an estimated mean increase in BMD of 4.8% in the denosumab arm and an estimated mean decrease in BMD of 0.7% in the placebo arm from baseline to month 12. The treatment effect on the primary endpoint was consistent across relevant subgroups based on age, duration of prior aromatase inhibitor therapy, weight, body mass index (BMI), prior chemotherapy, prior selective estrogen receptor modulator use, and time since menopause. The percentage of patients with missing lumbar spine BMD scores at 12 months was 9% in the denosumab arm and 15% in the placebo arm. The applicant confirmed that the treatment effect was robust through a series of sensitivity analyses, including a repeated measures model, ANCOVA model using mean of the other group imputation methods, and the per protocol analysis set, an ANCOVA model using subjects analyzed in the appropriate stratum based on baseline characteristics rather than the incorrect stratum used at randomization, and in univariate and multivariate covariate analyses.

There were also significant treatment effects, favoring denosumab, for key pre-specified secondary efficacy endpoints. There were highly significant differences in the change in total hip BMD and in femoral neck BMD from baseline to month 12, with improvement in BMD at month 12 compared to baseline for denosumab-treated patients. Although the number of events were small with 2 deaths (1%) in each arm at 24 months, there were no differences in the 2-year, all cause mortality rates between the two arms.

Protocol 20030216

As previously agreed-upon, the results of Protocol 20030216 were utilized to validate that changes in BMD resulting from denosumab treatment will predict a change in the rate of skeletal fractures. This finding was required since the pharmacodynamic effects of denosumab which affect BMD are different from the effects of bisphosphonates, therefore FDA required that the validity of the surrogate be confirmed for denosumab, rather than extrapolated from the experience with bisphosphonates. Protocol 20030216

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was a multicenter, randomized (1:1), double-blind placebo-controlled trial designed to show that denosumab treatment, administered at 60 mg every 6 months for three years reduced the incidence of new vertebral fractures in postmenopausal women with osteoporosis. Randomization was stratified by age at study entry: 60 to 64 years, 65 to 69 years, 70 to 74 years, and ≥ 75 years. BMD T-scores were required to be ≤ - 2.5 and ≥ - 4.0 at baseline. Concomitant treatment with calcium (≥ 1 g/day) and vitamin D (≥ 400 IU/day) supplementation was required for the duration of the study.

Efficacy analyses were conducted in 7808 patients who were randomized (1:1) to receive denosumab (n=3902) or placebo (n= 3906). There was a statistically significant reduction in the risk of new vertebral, non-vertebral, and hip fractures among denosumab-treated patients compared to controls, based on pre-specified sequential testing procedures. The risk reduction for new vertebral fractures at month 36 was 68% (95% CI: 0.26, 0.41; $p < 0.0001$). The risk reductions in non-vertebral fractures and in hip fractures were 20% (95% CI: 0.67, 0.95; $p = 0.01$) and 40% (95% CI: 0.37, 0.97; $p = 0.036$), respectively. The treatment effects were consistent across relevant subgroups, including patients with two or more prevalent vertebral fractures or with prevalent vertebral fractures that were moderate or severe; patients with femoral neck T-scores of ≤ - 2.5; and patients age ≥ 75 years.

Protocol 20040138

The efficacy of denosumab in the treatment of osteoporosis in patients undergoing hormone ablation therapy is also supported by the results of Protocol 20040138. Protocol 20040138 is a multicenter, double-blind, randomized (1:1), placebo-controlled trial that registered and randomized 1468 men with non-metastatic prostate cancer, who had received definitive local therapy and at study entry were receiving androgen deprivation therapy (ADT) either medically through gonadotropin-releasing hormone (GnRH) agonists or surgically (orchiectomy).

Patients were randomized 1:1 to either denosumab (734) or placebo (734) once every 6 months for a total of 6 doses over a 36-month treatment period. All patients received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation throughout the trial. Randomization was stratified by age (< 70 years vs. ≥ 70 years) and by duration of prior ADT (≤ 6 months vs. > 6 months) at the time of entry. The primary efficacy endpoint was the percent change in lumbar spine BMD from baseline to month 24. Key secondary endpoints were percentage change in femoral neck BMD and total hip BMD from baseline to month 24, percentage change in lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36, subject incidence of any fracture, and subject incidence of new vertebral fracture over the 36-month treatment period. Tumor re-staging consisted of a repeat bone scan at 36 months and measurement of PSA levels every 6 months during denosumab treatment.

There was a statistically significant difference in lumbar spine BMD between denosumab and placebo treated groups at 2 years [difference of 6.7% (95% CI: 6.2%, 7.1%)] based on an increase in BMS of 5.6% in the denosumab arm and a decrease of -1% in the placebo arm between baseline and 24 months, based on a least square mean estimate.

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Consistent treatment effects on lumbar spine BMD favoring the denosumab arm were observed in subgroups defined by age, race, geographical region, weight/BMI, BMD, and duration of androgen deprivation therapy.

Statistically significant treatment differences favoring the denosumab arm were also observed in change from baseline to month 24 in femoral neck BMD [difference 3.9% (95% CI: 3.5%, 4.4%; $p < 0.01$)] and total hip BMD [difference 4.8% (95% CI: 4.4%, 5.1%; $p < 0.01$).

Additional analyses, using a hieirarchical procedure for alpha adjustment, demonstrated a statistically significant reduction in the incidence of new vertebral fractures at 36 months [1.5% vs. 3.5% (odds ratio: 0.37, 95% CI: 0.18, 0.78: p=0.013)] but no significant difference in all fractures (5.2% vs. 7.2%; p=0.1) at 36 months. All cause mortality was the same, 5.9%, in both treatment arms at 36 months.

I concur with the major conclusions reached by the clinical and statistical reviewers regarding efficacy. The clinical and statistical review team members concluded that the major outcome measure for efficacy, a statistically significant difference in the percentage change in lumbar spine BMD from study entry to 12 months, for Protocol 20040135 was met. This finding was supported by the finding of improvement in BMD in men receiving hormone ablation therapy in Protocol 20040138. The demonstration of an effect on BMD as a measure of clinical efficacy is acceptable since the validity of this surrogate in denosumab-treated patients for reduction in skeletal fractures was confirmed by the results of protocol **216**. The findings from Protocol **216**, reviewed by the Division of Reproductive and Urologic Products (DRUP) under BL STN 125330, established the efficacy of denosumab for the treatment of post-menopausal osteoporosis women as well as validating the surrogate endpoint of effects on BMD with reduction in skeletal fractures.

8. Safety

The evaluation of clinical safety considered data obtained in approximately 14,000 patients in 30 clinical trials with up to 5 years of exposure to denosumab. These trials included patients with normal, low and osteoporotic bone density. The strategy for safety analysis included:

- Separate analyses for safety were conducted for each of the major efficacy trials (Protocols 216, 132, 135, and 138) under the four separate applications (BL STN 125330, 225331, 125332, and 125333).

- Analyses for general, overall safety was conducted in an integrated dataset containing results of the four major efficacy trials (Protocols 216, 132, 135, and 138).

- Analyses for specific safety issues, based on signals in the initial safety program for denosumab, potential signals based on pharmcodynamics of denosumab, and signals observed with bisphosphonate products in osteoporotic patients. These analyses, except where noted differently below, conducted a review of the safety information from nine randomized, clinical studies (seven trials in women with PMO [(20010223,

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20030216, 20040132, 20050141, 20050172, 20050179, 20050234) and two trials in patients with cancer receiving hormone-ablation (20040135, 20040138)]. The safety analyses were conducted in the "as-treated" population defined by the treatment administered (rather than treatment assigned) in patients receiving one or more doses of investigational drug. These trials were selected based on relevance of the population (PMO or HA) and dose (60 mg SC every 6 months) to the proposed indications under review.

The most common adverse reactions due to denosumab (per-patient incidence ≥ 5% and higher incidence in denosumab-treated group compared to placebo-treated) were back pain, arthralgia, extremity pain, osteoarthritis, constipation, musculoskeletal pain, hypercholesterolemia, dizziness, peripheral edema, and upper respiratory tract infection. Focused safety analyses also confirmed that hypocalcemia, bradycardia, ischemic heart disease and rash occurred at a low but increased incidence in denosumab-treated patients as compared to the control group. The incidence of osteonecrosis of the jaw, a known toxicity of bisphosphonates, did not occur at a higher incidence in denosumab-treated patients in clinical studies. The increased incidence of cataract formation was observed only in denosumab-treated men with prostate cancer undergoing androgen-deprivation therapy.

The most common serious adverse reactions occurring in denosumab-treated patients is infections. The potential for an adverse impact on the rate of tumor growth has not been adequately investigated in controlled clinical trials.

The approach and results of focused safety reviews to evaluate for incidence and relative risks of the following adverse events considered possibly-related to denosumab are summarized in greater detail below. The identification of potential risks requiring focused evaluation were based on data obtained in the clinical development program (cardiac toxicity, hypocalcemia, immune responses directed against denosumab), the known pharmacodynamic effects of denosumab (infection, delayed fracture healing, tumor promotion, hypocalcemia) and serious adverse effects of observed with bisphosponates (osteonecrosis of the jaw, cardiac toxicity).

Osteonecrosis of the jaw (ONJ), delayed fracture healing, and secondary malignancies
A focused safety review was conducted by Dr. Anita Abraham, DrPH in the Division of Biometrics VI to evaluate for increased risks of osteonecrosis of the jaw (ONJ), delayed fracture healing, and secondary malignancies. Dr. Abraham's review considered safety data from nine randomized, placebo-controlled trials as discussed above. Comparisons of between-arm differences in adverse events and determination of relative risks of these events were conducted in the individual studies and in a pooled analysis of the seven trials conducted in PMO patients. The incidence of ONJ was 4% in the integrated analysis across trials in women with PMO. The statistical reviewer concluded that there was no increased risk of ONJ compared with placebo-controls, using either the more narrow definition as applied by the ONJ adjudication group or a broader definition.

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The evaluation of delay in fracture healing was limited to the four major efficacy studies as these were the only studies designed to collect this information. Only in Protocol 20030216 was there a sufficient number of cases of delayed fracture healing (more than one per treatment group) to conduct an evaluation of the relative risk. Among patients enrolled in Protocol 20030216, the relative risk of any complication in patients with fractures was 0.99 (95% CI: 0.55, 1.77). Dr. Abraham concluded that there was no evidence of an increased risk of delayed fracture healing, while noting that additional follow-up may be needed to identify all events.

Based on the potential for perturbation of TNF regulation (through inhibition of membrane-bound RANKL signaling on T cells), an evaluation of the relative risk of secondary malignancies was conducted. Analyses included safety data from the nine randomized studies identified above. Search terms included all adverse events in the Neoplasms SOC of MedDRA with the exception of those terms that included the term "benign". With the exception of Protocol 20040138, there was no evidence of an increased risk in malignancies in denosumab-treated patients as compared to controls. There was a significant difference (relative risk 1.32, p=0.46) in the risk of malignancies reported as adverse events in Protocol 20040138; on further evaluation, this was driven by a higher rate of reports of metastatic disease as an adverse event. Metastases were reported as an adverse event in 48 of the 731 (6.57%) denosumab-treated patients compared to 31 of the 725 (4.28%) placebo-treated patients. In the integrated analysis of studies conducted in women with PMO, there were 206 (4.06%) reports of second malignancies in 5073 denosumab-treated patients and 175 (4.14%) reports of second malignancies in 4231 placebo-treated patients. The most common primary cancer sites were skin, breast, GI, respiratory/mediastinal, and reproductive/urologic. Dr. Abraham concluded that the increase rate in reported metastases, particularly bone metastases, was of concern in men with prostate cancer, but that in general, there did not appear to be a risk of second malignancies.

It is my opinion that there does not appear to be an increased risk of second malignancies, although additional surveillance would be prudent, given the availability of other therapeutic options for this indication. Of note, there is no difference between arms in the number of lymphoproliferative malignancies, which would be expected if the risk of malignancy was mediated by inhibition of TNF. The potential for an increase in the risk or rate of tumor progression is much less clear. Adverse event reporting is an unreliable and imprecise way to assess for a negative impact of denosumab on tumor control. These data must come from studies employing regular and standard evaluations of potential sites of metastatic disease. Since such routine tumor restaging procedures were not employed in either Protocol 20040135 or 20040138, additional studies are needed to address this question.

Cardiac toxicity

At the time of the pre-BLA meeting (Oct 21, 2008), FDA raised concerns regarding evidence of an apparent dose-dependent prolongation of the QT interval observed in studies conducted in patients with rheumatoid arthritis. Based on this concern, the Division of Biometrics VI was consulted to evaluate the integrated safety database for

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evidence of cardiotoxicity. Dr. Leslie Kenna, the safety evaluator consultant conducted a review of the safety information from nine randomized, clinical studies as discussed above. Analyses were performed individual within each trials and in a pooled analysis; per-patient incidence and relative risk analyses were performed using the applicant's classification system for cardiotoxicity and broad and narrow scope SMQ analyses. Based on Dr. Kenna's review, bradyarrhthymia (relative risks ranging from 1.7-2.0 for denosumab compared to placebo) and ischemic heart disease (relative risks ranging from 1.4-1.8) were the only consistent signals in the denosumab-treated group. The incidence of these events were low, and in the case of bradyarrhythmias were driven primarily by the results of conduction defects in study 216. The number of moderate (106 vs. 75) and severe (68 vs. 34) ischemic heart disease events were increased among denosumab-treated patients (n=3886) compared with the placebo-treated (n=3876) patients in protocol 216. Similarly, the number of events resulting in differences in bradyarrhythmic events was driven the differences in conduction defect events. Across pooled analysis involving either Protocols 216 and 138 (pooled efficacy trials n=4617 denosumab/ n=4601 placebo) or across placebo-controlled trials, the number of conduction defects were higher in the denosumab-treated patients for number of patients with AV block (8 vs. 4 patients; pooled efficacy trials and 5 vs. 3 patients; pooled placebo-controlled dataset) and right bundle branch block (11 vs. 7 patients; efficacy trial dataset; 10 vs. 7, placebo-controlled dataset).

Hypocalcemia

A focused safety review of the integrated safety database was conducted by Dr. Mandi Yu, Div of Biometrics VII, to assess the incidence and relative risks of hypocalcemia secondary to denosumab administration. Hypocalcemia was recognized as a treatment-related adverse reaction early in the clinical development program, therefore all four of the registration trials required that patients receive oral calcium and vitamin D supplementation and that serum calcium be regularly monitored throughout the clinical study.

Dr. Yu conducted analyses separately across the 9 studies discussed above and also pooled the data from the two major efficacy studies in post-menopausal women (Protocols 20030216 and 20040132). There was no significant difference in the incidence of clinically symptomatic events (including events requiring hospitalization) between the denosumab-treated and control arms among women with PMO (incidence rates of approximately 2.7% in both groups); the incidence of serious events of hypocalcemia was the same in both denosumab- and placebo-treated patients (5 events in four patients, two patients in each treatment group). There was a higher incidence of hypocalcemia reported as adverse events among denosumab-treated patients with cancer receiving hormone ablation as compared to placebo-treated patients [6.2% vs. 3.3% (Protocol 20050135); 3.0% vs. 2.2% (Protocol 20050138)]. These events were generally symptomatic and graded as mild to moderate in severity.

In contrast to the clinically-detected adverse event reports of hypocalcemia, there was an approximately 3.5-fold (95% CI: 2.2, 5.9) increase in the incidence of hypocalcemia as determined by laboratory measurements of serum calcium among women with PMO and

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an approximately 5.4-fold increase in hypocalcemia based on laboratory measurements in Protocol 20050138; no increase risk of laboratory-detected hypocalcemia was identified in Protocol 20050135 patients. Hypocalcemia was detected within the first month of treatment in 58% of denosumab-treated patients.

The incidence of severe hypocalcemia appeared to be increased in a single dose, open label trial designed to assess the pharmacokinetics, safety and tolerability of denosumab in patients with both normal and abnormal renal function. Patients in this study did not receiving calcium or vitamin D supplementation. The study demonstrated that the pharmacokinetics of denosumab are not influenced by renal dysfunction of any severity. However, in patients with severe (creatinine clearance < 30 mL/min) or end-stage renal disease, an increased incidence and severity of hypocalcemia was observed.

Hypersensitivity and Dermatologic toxicity
There is always a potential for immune responses to protein products. Surveillance for anti-denosumab binding and neutralizing antibodies were conducted as part of the clinical development program. The incidence of anti-denosumab binding antibodies was low [0.5% (43 positive samples among 8113 denosumab-treated patients)], consistent with the findings for other fully human antibody products. Assessment for neutralizing antibodies were conducted only in those patients with a positive screen test for binding antibodies. No patient tested positive for neutralizing antibodies. Among the 6 patients in the four major efficacy studies who had evidence of anti-denosumab binding antibodies, there was no evidence of alteration in pharmacokinetics or in efficacy, as measured by an increased in lumbar spine BMD and in hip BMD T-score from baseline in all six patients.

In addition to laboratory screening for humoral immune responses, a focused safety review of the integrated safety database was conducted by Dr. John Yap, Ph.D., Div of Biometrics VII, to assess the incidence and relative risks of hypersensitivity reactions in patients receiving denosumab. In addition to the 9 trials listed above, Dr. Yap included data from Protocols 20040245, 20050233, and 20050237 in the integrated analysis for hypersensitivity. The analysis for hypersensitivity included a narrow list of preferred terms proposed by the sponsor with additional terms identified by the reviewer to be directly related to hypersensitivity. In these analysis, a significant increase in multiple dermatologic terms was noted in Protocol 20030216 alone as well as in the overall safety database (in which patients enrolled under Protocol 20030216 accounted for 80% of the integrated database). The terms that were identified as occurring more frequently in denosumab-treated patients included dermatitis (3.1% vs. 1.7%), eczema (1.3% vs. 0.7%; relative risk 1.96), and rash (2.6% vs. 1.9%; relative risk 1.34). As noted, the incidence rates were low ($\geq$ 3%) with an approximately 1.5-2-fold increase in relative risk for denosumab-treated patients. The incidence of dermatologic adverse events did not appear to be increased in patients with cancer undergoing hormone ablation therapy.

I disagree with Dr. Yap's conclusions regarding hypersensitivity. While Dr. Yap concluded that denosumab is not immunogenic, the evidence of development of anti-denosumab antibodies in a sensitive, validated assay indicate that denosumab is immunogenic albeit at a low incidence rate. The dermatologic toxicities appear not to be

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mediated by anti-drug antibody responses but by another mechanism that may reflect an unintended targeted effect rather than a manifestation of "hypersensitivity". Categorizing dermatologic toxicity as hypersensitivity in product labeling would be inappropriate as it suggests a mechanism for which there is little evidence. I recommend that the specific toxicities be identified and that product labeling remain silent on speculated mechanism of the toxicity, which may suggest an inappropriate and ineffective management course of affected patients.

Risk Evaluation and Mitigation Strategies (REMS)
The applicant submitted a proposal for a risk management plan based solely on adequate physician product labeling. As noted by DRISK and the clinical review divisions, these risks may not be adequately communication through physician labeling alone and for other agents with a similar level of risk, therefore a REMS containing a Medication Guide and communication plan has been required. The DRISK consultant noted that although the Advisory Committee members advised that a patient registry be established, this is unlikely to mitigate risks (since patients are not required to undergo special screening to receive the drug). The DRISK consultant noted that post-marketing surveillance studies would be a more effective means of collecting data to better characterize risks. The applicant will be asked to provide surveillance program to assess risks in the Complete Response letter.

The Agency informed Amgen of the need for post-marketing required trials to further evaluate these risks. Amgen was notified of FDA's determination of the need for a REMS on October 2, 2009. The requested REMS will contain a Medication Guide and communication plan regarding the risks of serious infections, dermatologic toxicity, and over-suppression of bone turn-over that occur with denosumab administration.

Amgen was also informed of the need to conduct the following clinical post-marketing studies

- 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 denosumab (Protocol 20090522)

- A long-term surveillance study in postmenopausal women administered denosumab to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turn-over (Protocol 20090601).

- A long-term pregnancy exposure registry study in denosumab users who become pregnant on the drug (Protocol 20090589)

9. Advisory Committee Meeting

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The findings in these four applications were presented to the Reproductive Health Drugs Advisory Committee on August 13, 2009. The committee was supplemented with three medical oncologists serving as Special Government Employees to serve as expert advisors on issues relating to the risk of adverse effects on tumor growth. The committee was asked a series of questions regarding the risk-benefit ratio of denosumab across the various indications. All members advised that there is a population of post-menopausal women in whom treatment benefit is likely to outweigh risks, however the majority advised that benefits of prevention of osteoporosis in any population with low bone mass in any of the proposed clinical settings (post-menopausal women, women receiving hormone ablation for adjuvant treatment of breast cancer, and men receiving hormone ablation for non-metastatic prostate cancer) were not likely to outweigh risks. The majority of the members also advised that the risk-benefit ratio in women receiving hormone ablation for adjuvant treatment of breast cancer was not favorable, given the inadequate information on the potential risks of adverse effects on tumor growth. While the majority of members advised that the benefits of denosumab treatment of osteoporosis *were* likely to outweigh the risks in men receiving hormone ablation for non-metastatic prostate cancer, all three oncologists disagreed with this recommendation. Finally, the members of the advisory committee recommended that a REMS be established for mitigation of risks through adequate communication of risks to patients and healthcare providers.

10. Pediatrics

A request for a full waiver was reviewed by the PeRC on June 30, 2009. The waiver was granted for all proposed indications based on a determination that the necessary studies would be impossible or highly impractical because the disease/condition does not exist in children.

11. Other Relevant Regulatory Issues

The Division of Scientific Integrity conducted clinical audits of two study sites for Study 20040135, a sponsor site, and the Contract Research Organization (CRO) site. The clinical study sites were selected based on the high number of patients enrolled and the high number of reported protocol violations, relative to other study sites. All audited data from clinical sites were verified to be accurate and inspections at the two clinical sites did not reveal deficiencies that would preclude approval. However it was noted that primary study data (DXA scans and electronic medical records) were not maintained at the study sites; DXA scans for determination of bone-mineral density, the primary efficacy outcome measure, were sent to the CRO, (b) (4), and electronic records were maintained in a database at Amgen. Inspections were conducted of both (b) (4) and Amgen; although violations were noted, there are no outstanding issues which would preclude approval.

With regard to financial conflicts of interest, there were no issues identified that are outstanding and would not permit approval. The clinical reviewer determined that the

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majority of investigators had no arrangements or financial interests that required disclosure or for those who reported disclosable financial interest, the Statement of Actions to Minimize Bias was completed and the actions taken were reviewed and are acceptable.

12. Labeling

- Proprietary name review: I concur with the conclusions of the DMEPA reviewer and the clinical reviewer that the proposed proprietary name of Prolia is acceptable.

- Physician labeling: Physician labeling negotiations have not been finalized.

- Carton/Container labeling: Review of carton and container labeling incorporated comments from the DMEPA, DMA, and the clinical review divisions.

- Medication Guide: A medication guide was requested as part of a REMS on October 2, 2009 and the proposed REMS, including the Medication Guide was submitted on October 8, 2009. Agreement on the REMS will be contingent upon receipt of the information requested in the complete response letters for these applications.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete response letter requesting the submission of data from one or more adequately designed clinical trials that evaluate and rule out a significant adverse effect on progression-free survival in patients with cancer.

  In addition, a final risk:benefit determination will be made based on agreement on a REMS containing a communication plan and Medication Guide to mitigate the risks of serious infections, dermatologic toxicity, and over-suppression of bone turn-over that occur with denosumab administration. In addition, Amgen must submit an acceptable plan for targeted and non-targeted, post-marketing surveillance to further assess the risks of serious infections, dermatologic toxicity, and over-suppression of bone turn-over and to obtain data through a pregnancy registry regarding the risks of exposure to denosumab during pregnancy.

  The following additional information is required in order for FDA to complete its risk:benefit determination. In the complete response letters, FDA has requested the following information:

  - In support of an approval for denosumab for the treatment of post-menopausal osteoporosis, Amgen must submit the results of the methodology and background adverse event rate assessment study, Protocol 20090521 (Phase A): "Denosumab Global Safety Methodology and Background (AE) Rate

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Assessment Among Women With Postmenopausal Osteoporosis (PMO) Using Multiple Observational Databases"). These data are required for FDA to reach agreement on an acceptable study design for Protocol 20090522 (Phase B). Agreement on the design of Phase B should be completed prior to approval.

- In support of an approval for denosumab for the prevention of post-menopausal osteoporosis, Amgen must conduct a clinical and clinical pharmacology development program that defines a dose and schedule that is efficacious and has acceptable, long-term safety profile. The proposed development program should be submitted to FDA for review and determination of its acceptability.

- In addition, Amgen must provide the results of Protocol 20090521 (Phase A) and reach agreement with the Division of Reproductive and Urologic Products on the design of Protocol 20090522.

- Risk Benefit Assessment:
  The clinical development program for denosumab demonstrated that in patients with low bone mass or osteoporosis as defined by a BMD score, due to age (PMO) or medical therapy (HA trials), denosumab treatment significantly increases BMD score at one year (Protocol 10040135), a surrogate endpoint for risk of skeletal fracture. The validity of this surrogate in denosumab-treated patients was established in Study 216 and supported by the findings of Study 138. However, the benefit of reducing the risk of skeletal fractures cannot be weighed against the unknown level of risk of an adverse effect on tumor progression.

  Based on the potential but unexpected impact of other supportive care agents (erythropoesis-stimulating agents) on shortening time to progression and death demonstrated in multiple controlled clinical trials, FDA now considers that for novel products, even those without a clearly established mechanism for tumor growth promotion, data should be provided that rule out the potential for adverse impact on tumor growth. Neither of the trials conducting in patients with cancer receiving hormone ablation therapy was adequate in design to rule out such effects. Specifically, these trials did not include systematic, comprehensive monitoring of primary and potential metastatic disease sites in a manner which would allow one to conclude that a clinically significant impairment in progression-free survival did not exist.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  The applicant has been requested to submit a REMS consisting of a Medication Guide and a communication plan to mitigate risks of serious infection, dermatologic toxicity, and over-suppression of bone turn-over through communication of these risks to patients and healthcare providers.

- Recommendation for other Postmarketing Requirements and Commitments

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The applicant has been requested to conduct post-marketing surveillance to further characterize the risks of serious infection, dermatologic toxicity, and over-suppression of bone turnover.

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Signature Page

/Patricia Keegan/s/ October 19,2009

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

OFFICER/EMPLOYEE LIST

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Application: 125320/5/6

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August, 19, 2011
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
BLA #	sBLA #125320/5 and 6
Applicant	Amgen, Inc.
Receipt Date	March 18, 2011 (receipt of resubmission)
PDUFA Goal Date	September 17, 2011
Proprietary Name / Established Name	Prolia (denosumab)
Dosage forms / Strength	60 mg denosumab (60 mg/mL) in single-use pre-filled syringes or single-use vials
Proposed Indication(s)	Prolia is indicated for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. In patients with prostate cancer, Prolia reduces the incidence of vertebral fractures.
Recommended:	*Approval*

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1. Introduction

This abbreviated CDTL review primarily addresses issues related to Amgen's complete response safety update to efficacy supplements 125320/5 and 125320/6. Refer to Section 2 of this review for the history regarding the submission of these supplements.

Denosumab is a monoclonal human IgG2 antibody that binds to human RANKL and is manufactured using genetically engineered Chinese hamster ovary cells. The RANK/RANKL (receptor activator for nuclear factor κ B ligand) pathway is involved in the formation, function, and survival of osteoclasts (responsible for bone resorption).

To support this sBLA, the applicant primarily relied on the results of two randomized trials:

- Trial 20040135 (135): A Randomized, Phase III, Double-blind, Placebo-controlled Trial to Evaluate AMG162 in the Treatment of Bone Loss in Patients Undergoing Aromatase Inhibitor Therapy for Nonmetastatic Breast Cancer
- Trial 20040138 (138): A Randomized, Double-blind, Placebo-controlled Trial to Evaluate AMG 162 in the Treatment of Bone Loss in Patients Undergoing Androgen-deprivation Therapy for Nonmetastatic Prostate Cancer

Amgen supported these applications by submitting the results of Trial 20030216, demonstrating a reduction in the risk of fractures in women with osteoporosis at high risk for fractures. The Agency reviewed data from this trial as part of the original approval of denosumab as Prolia (refer to Section 7 below).

The primary regulatory consideration of the complete response to this application was whether denosumab causes deleterious effects on tumor outcomes. To address this issue, Amgen submitted the results of three studies evaluating denosumab in cancer patients with bony metastases (See Section 2 below).

2. Background

FDA received two Biologics License Applications (STN 125332/00 and 125333/00) for denosumab (proposed trade name Prolia) on December 19, 2008 for the treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate or breast cancer. FDA designated October 19, 2009 as the PDUFA goal date. Following the review of these applications, DBOP issued a Complete Response letter on October 19, 2009. The response letter contained the following reason for not approving the original application.

> You have not provided substantial evidence from adequate and well controlled clinical trials establishing the safety of Prolia (denosumab) in patients with breast cancer receiving aromatase inhibitor therapy or patients with prostate cancer receiving androgen deprivation therapy. Specifically, the data from clinical trials submitted in these license applications are inadequate to determine if Prolia has detrimental effects on breast cancer or prostate cancer outcomes since the trials were not adequately

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designed to compare disease-free survival and overall survival between treatment arms. Provide results from adequate and well-controlled clinical trials demonstrating that Prolia has no detrimental effects on either time-to-disease progression or overall survival.

Provide a justification for each of the studies selected based on adequacy of design and conduct, including but not limited to:

a. adequacy of the sample size to detect a clinically meaningful detrimental effect;
b. assurance that monitoring assessments are performed with appropriate frequency and are adequate in scope to assess disease progression;
c. confirmation that the trial is masked to treatment or determination of disease progression is conducted in a manner that minimizes bias based on knowledge of treatment;
d. the analysis is mature with minimal amounts of missing data; and,
e. treatment arms are well-controlled with respect to prognostic factors (including concomitant anti-neoplastic therapy).

The clinical study report(s) should contain analyses of overall survival and progression free survival, primary data and programs used to generate all analyses presented, as well as case report forms for all patients who progressed while receiving denosumab and all patients who died during the conduct of the trials.

Subsequently, FDA approved denosumab, as Prolia, on June 1, 2010, for the treatment of postmenopausal women with osteoporosis at high risk for fracture. This review will not describe the pertinent regulatory history of denosumab prior to the October 19, 2009, CR action. Suzanne Demko described this regulatory history in her clinical review of the original applications (STN 125332/00 and 125333/00).

Following the CR action, Amgen submitted a proposal to the Agency on February 18, 2010 to submit the results of three trials reviewed as part of the Xgeva efficacy supplement (STN 125320/7) to address the deficiencies identified in the CR letter. These trials included assessments of disease progression and overall survival, and these trials explored a higher dose intensity of denosumab (120 mg subcutaneously every four weeks). FDA responded in a memorandum dated March 2, 2010 that the Agency would accept the data from these trials that enrolled approximately 5,700 patients (2,862 received denosumab); however, overall acceptance of the data to support approval would be a review issue.

3. CMC

Review staff identified no new quality issues during the review cycle for this resubmission. As summarized in the Division Director's summary review dated October 16, 2009, there were no outstanding CMC issues that precluded approval. CMC-related post-marketing commitments described in Dr. Keegan's review memo were instituted as part of the initial Prolia BLA approval for osteoporosis (refer to approval letter for STN 125320/0 dated June 1, 2010).

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4. Nonclinical Pharmacology/Toxicology

Non-clinical review staff identified no new issues during the review cycle for this resubmission. At the time of the original review of these two applications, non-clinical review staff stated that no outstanding nonclinical pharmacology or toxicology issues existed that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology review staff from the Clinical Pharmacology 5 Division of OCP found the clinical pharmacology and biopharmaceutics data as acceptable to support the approval of these efficacy supplements.

5.1 General clinical pharmacology/biopharmaceutics considerations

5.1.1 Dose selection

Clinical pharmacology review staff submitted an updated review following the CR response by Amgen. Refer to page 9 of the Clinical Pharmacology Biopharmaceutics Review [http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125320s000ClinPharmR.pdf (accessed July 15, 2011)] for a discussion of clinical studies used to support dosing. Amgen investigated the same doses [60 mg subcutaneous (SC) every six months] in the two oncology osteoporosis studies that Amgen investigated in the postmenopausal osteoporosis studies.

5.1.2 Pharmacokinetics

As identified in the OCP review, Amgen did not provide additional pharmacokinetic data in this resubmission of the efficacy supplements. Refer to product labeling and the original BLA reviews for information regarding the pharmacokinetics of denosumab at the dose and schedule proposed in these efficacy supplements.

5.2 Drug-drug interactions

OCP determined, during the review of STN 125320/7 (Xgeva supplement), that concomitant anticancer therapy did not appear to influence the pharmacokinetics or pharmacodynamics of denosumab. Additionally, prior intravenous bisphosphonate therapy did not appear to affect denosumab concentrations (at one and three months post dosing) or uNTx/Cr concentrations (evaluated in Studies 20040114 and 20040113).

5.3 Immunogenicity

As identified in the OCP review, Amgen did not provide additional immunogenicity data in this resubmission of the efficacy supplements. The original submission contained data (as summarized by OCP) that less than 1% of patients (43 out of 8,113) tested positive for binding antibodies; none of these patients developed neutralizing antibodies. These binding antibodies did not influence the PK, PD, tolerability, or efficacy of denosumab according to OCP review staff.

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5.4 Demographic interactions/special populations

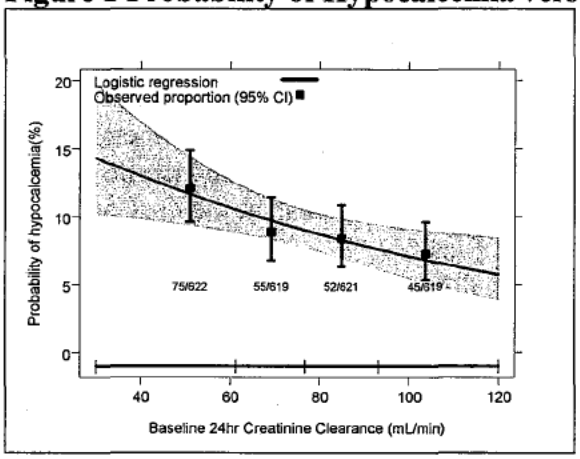
5.4.1 Body weight

As summarized by OCP in the review of the original submission, the final population pharmacokinetic model demonstrated an association between body weight and denosumab pharmacokinetic parameters in postmenopausal women. OCP confirmed this finding during the review of an updated population PK model (STN 125320/7) that explored a higher dose and more frequent dosing schedule of denosumab. Nevertheless, as stated in the OCP review, "denosumab at a fixed dose of 60 mg provides a similar time course of serum concentrations as to a dose of 1 mg/kg over a wide body weight range of 44 kg to 113 kg."

5.4.2 Renal insufficiency

Pharmacokinetic parameters appeared unaffected or minimally effected by varying degrees of renal dysfunction as described in the OCP review of Study 20040245 (a dedicated renal impairment study). However, the analysis below, copied from Dr. Shord's review of STN 125320/7, shows a higher probability of hypocalcemia in patients with reduced creatinine clearance. Product labeling describes this finding of hypocalcemia in patients with reduced creatinine clearance.

Figure 1 Probability of Hypocalcemia versus Baseline Creatinine Clearance



5.4.3 Other demographic populations

OCP reported no differences in pharmacokinetic parameters in patients older than 65 years treated with denosumab. As described during the review of STN 125320/7, clearance values of denosumab were higher in Black and Hispanic patients treated with denosumab compared to Asian and White patients; however, these differences were within the reported PK variability at high denosumab concentrations estimated from phase 2 and 3 studies.

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

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

5.5 Thorough QT study or other QT assessment

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

6. Clinical Microbiology

This section is not applicable to this indication.

7. Clinical/Statistical-Efficacy

Suzanne Demko was the primary reviewer of safety and efficacy for this application and her review was completed on December 19, 2008. Suzanne Demko recommended against approval in her original review because the effects of denosumab on cancer outcomes were not adequately elucidated at the time of the complete response action. Suzanne Demko stated that "any future consideration of this application is predicated on a demonstration that there are no detrimental effects on cancer outcomes from analyses of data from completed and ongoing clinical trials in patients with metastatic cancers."

The statistical reviewers summarized that the data from the studies reviewed in these applications supported the claimed treatment effects.

This review will contain only a brief synopsis of efficacy as efficacy results were described and summarized at the time of the original review of these two applications.

7.1 Summary of clinical program

Four major efficacy trials supported the use of denosumab for the treatment of patients with osteoporosis at high risk for fracture: Trials 20040135, 20030216, 20040138, and 20040132. The Division of Reproductive and Urology Products (DRUP) reviewed the primary efficacy data for Trial 20030216 under STN 125320, supporting the use of denosumab for the treatment of women with post-menopausal osteoporosis and Trial 20040132 supporting the proposed indication of prevention of osteoporosis. Following a review of these applications, an indication was granted for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Denosumab is not indicated for the prevention of osteoporosis.

For the two applications subject to this review (now classified as efficacy supplements), the applicant submitted the results from Trials 20040135 and 20040138. These trials are summarized in Table 1 below.

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Table 1: Overall Design of Efficacy Trials 20040135 and 20040138

Trial	Population	Design	Subjects Randomized	Duration of treatment (mo)	Primary Endpoint
135	Women with non-metastatic breast cancer receiving aromatase inhibitor therapy with a T-score of -1.0 to -2.5 at the LS, hip, or femoral neck	Randomized (1:1) double-blind, placebo controlled	252 (U.S, Canada)	24	Lumbar Spine BMD at 12 months
138	Men with non-metastatic prostate cancer at high risk for fracture receiving ADT		1468 (U.S., Europe, Canada, Mexico)	36	Lumbar Spine BMD at 24 months

Ultimately, a determination of clinical benefit from Trials 135 and 138 relied upon the results of Trial 20030216 reviewed by DRUP. Trial 216 was a large (n=7,808) multinational, multicenter, randomized (1:1) double-blind, placebo controlled trial designed to evaluate whether denosumab administered every 6 months would reduce the risk of new vertebral fractures in postmenopausal women (aged 60 to 91) with osteoporosis (T-score between -2.5 and -4) during the 36-month treatment period. In addition to denosumab or placebo, patients received calcium (≥ 1 gram) and vitamin D (≥ 400 IU). As summarized in Suzanne Demko's review, denosumab resulted in a statistically significant reduction in the risk of new vertebral, nonvertebral, and hip fractures when compared with placebo based on a pre-specified sequential testing procedure. The protocol stipulated testing of the primary endpoint at month 36.

Table 2: Primary Efficacy Results of Trial 136

Site	Relative Risk Reduction (%) at Month 36 (95% CI)	P value	Absolute Risk Reduction (%) at Month 36 (95% CI)
Vertebral fracture	68 (59, 74)	< 0.0001	4.8 (3.9, 5.8)
Non-vertebral fracture	20 (5, 33)	0.0106	1.5 (0.3, 2.7)

Table 2 shows that denosumab reduced the risk of vertebral and non-vertebral fractures. Denosumab also reduced the relative risk of hip fractures by 40% at 3 years with an age-adjusted absolute risk-reduction of 0.3% at 3 years. In addition to the effects of denosumab on fractures, treatment with denosumab increased bone mineral density (BMD) at 3 years at the lumbar spine, hip, and femoral neck.

The effects of denosumab on fractures and BMD in the postmenopausal osteoporosis trial allowed the Agency to consider the results of Trial 136, a smaller clinical trial evaluating the effects of denosumab on BMD (a surrogate) in women with non-metastatic breast cancer

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receiving aromatase inhibitors. The results of Trial 138 demonstrated improvements in BMD and on vertebral fractures.

Amgen subsequently supported these applications by submitting the results from three randomized controlled trials comparing the effects on skeletal related events (SREs) of denosumab against zoledronic acid. Amgen designed all three trials to demonstrate non-inferiority of denosumab as compared to zoledronic acid in time to first on-study SRE. This CDTL reviewer summarized efficacy results from these three trials as part of the review of the application of sBLA 125320/7 (Xgeva SRE applications). Additional safety results pertinent to these applications are summarized in Section 8 below.

Table 3: Studies Submitted by Amgen that Evaluated Tumor Outcomes in Patients with Cancer Metastatic to Bone

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

*SC = subcutaneous; IV = intravenous

7.2 Trial 135

Trial 135 randomized (1:1) 252 women with breast cancer receiving adjuvant aromatase inhibitor therapy (AI) to receive either denosumab (60 mg every 6 months) or placebo. The trial randomized 127 patients to the denosumab arm and 125 patients to the placebo arm and stratified patients by duration of aromatase inhibitor therapy ($\leq$ 6 months versus > 6 months). An additional key eligibility criterion included a requirement for a lumbar spine, total hip, and/or femoral neck BMD T-score of -1.0 to -2.5.

As described in Table 1, the primary efficacy endpoint was the percentage change in BMD in the lumber spine at 12 months. Key secondary endpoints included percentage change in lumbar spine density at 6 months and percentage change in the BMD from baseline to months 6 and 12 in the hip and femoral neck. The protocol stipulated monitoring of BMD by dual x-ray absorptiometry (DXA) of the spine, femoral neck, and total hip at baseline and at months 1, 3, 6, 12, and 24 (or during the early termination visit). The protocol also required X-rays at baseline and month 24. This trial did not include a systematic plan to assess patient outcomes related to cancer. Amgen designed the trial with adequate power to detect a 2% difference in the treatment effect at the lumbar spine between arms.

In general, demographic characteristics of the patient populations were reasonably balanced between treatment arms. Most patients were White (91% receiving denosumab and 95% receiving placebo) and $\geq$ 96% of patients in both arms were enrolled in the United States. Median age was 59 years in the denosumab arm and 60 years in the placebo arm. More

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patients in the denosumab arm had infiltrating ductal carcinoma histology (86% versus 74%) and more patients in the denosumab arm had N0 lymph node status (68% versus 57%). Some imbalances may be attributable to the relatively small sample size of Trial 135.

Exposure to study drug or placebo was reasonably similar between the two arms (refer to Table 8 of Suzanne Demko's review).

The primary efficacy analyses were assessed using the intent-to-treat population. Treatment with denosumab resulted in a statistically significant ($p < 0.0001$) increase in lumbar spine BMD between denosumab and placebo at the 12 month time-point based on a least square mean estimate (denosumab + 4.8% versus placebo – 0.7%). The difference between arms was 5.5% with a 95% CI of 4.8 to 6.3. Despite missing BMD scores at 12 months in 9% of patients in the denosumab arm and 15% in the placebo arm, sensitivity analyses confirmed the robustness of the overall treatment effects. The effects on BMD at 12 months were maintained in the supportive analyses of BMD at 24 months.

This CDTL reviewer agrees with Suzanne Demko that the results of this trial alone were not sufficient to determine that denosumab provides clinical benefit in this population because the trial was designed to measure an effect on a surrogate endpoint. However, the results of Trial 216, summarized above, support a fracture reduction benefit for patients at high risk for fracture. Study 135 was too small and of too short duration to assess for any meaningful differences in fracture rate (Study 135 enrolled 252 patients versus 7,808 patients in the post-menopausal osteoporosis study). Amgen also demonstrated an effect on fracture reduction in the lumbar region as a secondary endpoint in Trial 138 (supporting clinical benefit in appropriately selected patients).

7.3 Trial 138

Trial 138 randomized (1:1) 1,468 men with non-metastatic prostate cancer receiving hormone ablation therapy to receive either denosumab (60 mg every 6 months) or placebo. Acceptable forms of androgen deprivation therapy included gonadotropin-releasing hormone (GnRH) agonist therapy expected to be continued for at least 12 months or surgery (orchiectomy). The trial randomized 734 patients to receive denosumab and 734 patients to receive placebo for up to 36 months. Stratification factors included age (< 70 years versus ≥ 70 years) and duration of prior ADT at the time of study entry (≤ 6 months versus > 6 months). An additional key eligibility criterion included a requirement for a T-score measurement of < -1.0 at the lumbar spine, total hip, or femoral neck or a history of osteoporotic fracture for patients younger than 70 years.

As described in Table 1, the primary efficacy endpoint was the percentage change in BMD in the lumber spine at 24 months. Key secondary endpoints included percentage change in BMD at 24 months; percentage change in lumbar spine, femoral neck, and total hip BMD at 36 months; per-patient incidence of any fracture; and per-patient incidence of vertebral fracture over the 36 month time-period. The protocol stipulated monitoring of BMD by dual x-ray absorptiometry (DXA) of the spine, femoral neck, and total hip at baseline, and at months 1, 3, 6, 12, 34, and 36 (or during the early termination visit). A randomized subset of 1/3 of the patients also underwent screening and post-treatment DXA scans of the total body and distal

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radius. This trial did not include a systematic plan to assess patient outcomes related to cancer. Amgen designed the trial with adequate power to detect a 2% difference in treatment effect on BMD at the lumbar spine between arms.

In general, demographic characteristics of the patient populations were reasonably balanced between treatment arms. The majority of patients were enrolled in either the United States or Canada. Median age in both arms was 76 years. Enrollment by demographic status (denosumab versus placebo) was 84% versus 83% for White patients; 10.5% versus 11% for Hispanic or Latino patients; 4.9% versus 4.4% for Black or African American patients; and 0.7% versus 0.4% for Asian patients. A total of 74.1% of patients enrolled in the denosumab arm versus 71.4% of patients enrolled in the placebo arm were stage II. Gleason score was < 7 for 68% of patients randomized to the denosumab arm versus 73% randomized to the placebo arm.

Exposure to study drug or placebo was reasonably similar between the two arms (refer to Table 18 of Suzanne Demko's review).

The primary efficacy analyses were assessed using the intent-to-treat population. Treatment with denosumab resulted in a statistically significant ($p < 0.0001$) increase in lumbar spine BMD between denosumab and placebo at the 24 month time-point (denosumab + 5.6% versus placebo – 1.0%). The difference between arms was 6.7% with a 95% CI of 6.2 to 7.1. BMD results in the femoral neck and total hip also favored patients in the denosumab arm compared to the placebo arm. Finally, a reduction in vertebral fractures but not total fractures was observed at 36 months among patients who received denosumab [vertebral fractures: 1.5% vs. 3.5% (odds ratio: 0.37, 95% CI: 0.18, 0.78: p=0.013)].

This reviewer concurs with the efficacy conclusions made by the clinical and statistical reviewers. The study met the primary outcome measures for BMD at 12 and 24 months for Trials 135 and 138, respectively. These improvements in BMD were supported by a reduction in vertebral fractures in the prostate cancer trial and a reduction in fractures in the larger osteoporosis trial (216) reviewed by DRUP. Overall, these studies established the effectiveness of denosumab as a drug that can reduce the risk of fractures in patients at high risk for fracture (this was based on a surrogate endpoint in the breast cancer study). The study results did not justify the use of denosumab in patient populations at lower risk of fracture (i.e., for the prevention of osteoporosis in men or women at low risk of fracture). Refer to Suzanne Demko's review and the minutes of the August 13, 2009 Advisory Committee for more detailed discussions of the prevention indications.

8. Safety

8.1 Adequacy of database, major safety findings

This reviewer considered the size of the safety database as adequate. At the time of Suzanne Demko's original review of the efficacy supplements, Amgen submitted safety data from over 14,000 subjects enrolled in denosumab clinical trials. Following the CR action, FDA also reviewed data on 2,841 patients with cancer who received denosumab in Clinical Trials 103, 136, and 244 [refer to Xgeva efficacy supplement reviews (STN 125320/7)]. Safety

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conclusions from the Xgeva application differed from those from the Prolia applications due to the different dosing regimens used for the different indications. Patients enrolled in the Xgeva trials specifically appeared at higher risk for osteonecrosis of the jaw. This review will focus on the safety of denosumab when administered at a dose of 60 mg subcutaneously every 6 months. Nevertheless, the Xgeva trials were useful in the evaluation of tumor outcomes as they enrolled a large number of patients with cancer.

In addition to the safety information described in Suzanne Demko's initial review and the Division Director's summary review, Amgen submitted new safety data in the resubmission of the efficacy supplements. This data consisted of extended safety follow-up of patients enrolled in HALT Trials 20040135 and 20040138 (135 and 138). A total of 186 patients completed the 24-month treatment phase of Trial 135 and participated in extended follow-up (n = 96 for denosumab). In Trial 138, a total of 802 patients (n = 417 for denosumab) completed the 36-month treatment phase and participated in extended follow-up. Dr. Pradhan completed the review of this extended follow-up safety data. In general, unless otherwise specified, no new safety signals were found in the extended follow-up data compared to the review of the original HALT applications.

The following were the primary submission specific safety concerns identified by Suzanne Demko:

- Tumor Promotion and Malignancy: This was the primary concern identified by Suzanne Demko resulting in a CR action by the Agency. A signal of tumor promotion was not observed in Trials 135 and 138; however, these trials did not rigorously assess tumor outcomes. Based on experience with other supportive care drugs, additional data on the effects of denosumab on tumor outcomes were considered necessary prior to the approval of the HALT efficacy supplements. Amgen provided this data in this response. Refer to Section 8.4 below for further discussion.

  Labeling previously agreed to by DRUP and Amgen states that breast cancer was one of the most common adverse reactions leading to treatment discontinuation. Although breast cancer may have been a reason for treatment discontinuation, this CDTL is not convinced that sufficient evidence exists that breast cancer should be considered an adverse reaction. For example, although there was a slight imbalance in discontinuation events in the post-menopausal osteoporosis trials (20 versus 10 patients), the overall incidence of breast cancer was 4% in each arm. Additionally, refer to Section 8.4 below regarding progression events for breast and prostate cancer. *During labeling discussions with DRUP and OSE, breast cancer was removed from the most common adverse reactions leading to treatment discontinuation (as breasts cancer did not meet the criteria for listing as an adverse reaction).*

- Infections: Suzanne Demko reported a slightly increased incidence of serious infections in patients receiving denosumab and more serious infections of the skin, ear, abdominal system and urinary tract. However, deaths due to infections occurred more frequently in patients receiving placebo. Notably infection did not occur more frequently in studies evaluating a higher dose of denosumab (Xgeva trials) when compared to zoledronic acid. The total pooled incidence of infection in the three advanced cancer trials was 0.9% for denosumab and 0.7% for zoledronic acid.

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- Osteonecrosis of the jaw (and changes in bone histomorphometry): No cases of ONJ occurred in the PMO or HALT trials and no additional cases occurred during the extended follow-up of the HALT trials. ONJ occurred in 2.2% of patients enrolled in Xgeva clinical trials. As noted, patients in the Xgeva trials received a higher dose intensity of denosumab.
- Hypocalcemia: Hypocalcaemia appeared transient without serious clinical sequelae in the HALT trials. Patients in the HALT trials received calcium and vitamin D. The risk of hypocalcemia increased in patients with a creatinine clearance of ≤ 30 mL/min. Severe hypocalcemia may be more frequent in patients receiving the higher Xgeva dose (3.1% of patients developed a corrected serum calcium less than 7 mg/dL in the Xgeva trials).
- Dermatologic adverse reactions: Dermatological adverse reactions occurred with higher frequency in the postmenopausal osteoporosis studies. The Prolia label contains a Warning for these reactions. This finding was not confirmed in the Xgeva advanced cancer trials.
- Cataracts: Suzanne Demko reported an increased incidence of cataracts occurring in the prostate cancer trial (138) and noted that this safety finding may necessitate additional study. A total of 4.7% of patients developed cataracts in the denosumab group versus 1.2% of patients in the placebo group. This finding was not replicated in the postmenopausal osteoporosis trials or in Trial 135. In the extended follow-up of Trial 138, a total of 4 patients in the prior denosumab group and 7 patients in the prior placebo group developed cataracts.

  The unexpectedly high incidence of cataracts observed in Trial 138 was not replicated in Xgeva Trial 103 that enrolled patients with prostate cancer. The per-patient incidence rate of cataracts in Trial 103 was 0.4% in the denosumab group versus 0.5% in the zoledronic acid group. Trial 103 was a double-blind trial and the median number of doses of denosumab administered to patients in Trial 103 was 13.5 (with median 13 months on study).

(b) (4)

[redacted]

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

8.2.1 Deaths

Clinical reviewers found the causes of death, including cardiac, to be balanced between treatment arms in the postmenopausal osteoporosis studies and in the HALT studies.

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8.2.2 SAEs

Clinical review staff found no statistically significant or clinically meaningful differences in SAEs between treatment groups in Trials 135 or 138. A higher overall rate of SAEs (generally balanced between arms) occurred in the prostate cancer study. This higher rate may be related to the higher age of the population and longer duration of follow-up compared to the trial conducted in women with breast cancer.

8.2.3 Drop-outs and discontinuations due to adverse events

The numbers of patients who discontinued therapy or withdrew from the trials were balanced between treatment groups in Trials 135 and 138.

8.2.4 Common adverse events

There were no adverse events that occurred at an (per-patient) incidence rate of > 5% and with an increased per-patient incidence rate of 5% or higher in the denosumab groups as compared to the placebo groups. Product labeling lists the following most common adverse reactions in patients receiving denosumab: back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions in patients receiving denosumab in the HALT trials were arthralgia, back pain, pain in the extremity, and musculoskeletal pain.

8.3 Immunogenicity

Refer to Section 5.3 above.

8.4 Special safety concerns

The primary safety concern regarding these two efficacy supplements involved the potential for adverse cancer outcomes in patients who receive supportive care drugs. To address this concern, Amgen submitted analyses of progression free survival (PFS) and overall survival (OS) from three trials that evaluated denosumab at a higher dose (120 mg) and more frequent schedule in patients with advanced cancer and bony metastases.

Dr. Shan Pradhan (clinical), Dr. Michael Axelson (clinical), Dr. Weishi Yuan (statistical), and Dr. Jing Zhang (statistical) reviewed the data from three trials submitted to application STN 125320/7. Table 3 above lists the titles and basic descriptions of the three trials. These three trials established the effectiveness of denosumab in preventing skeletal related events in patients with solid tumors metastatic to bone. PFS and OS were prospectively monitored; however, they were considered exploratory endpoints for purposes of statistical testing. Amgen did not utilize an independent radiology review to determine a patient's date of progression; however, adequate blinding minimized the potential for bias. A review of data by the clinical review team determined that specific adverse events were unlikely to result in unmasking of the blind status for most patients.

In the resubmission, Amgen provided data from a combined 5,520 patients. Amgen evaluated survival status for all patients except those who withdrew full consent or who were lost to follow-up. The applicant stated that the size of this population provided sufficient power to provide approximately 98% power to detect a 15% increased risk of worse survival and an

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84% power to detect a 10% increase in risk. Regarding PFS, Amgen stated that the size of the advanced cancer population from these 3 studies (combined) was sufficient to provide approximately > 99% power to detect a 15% increase in risk, and 90% power to detect a 10% increase in risk.

Table 4 contains the PFS and OS results from the three advanced cancer trials (103, 136, and 244) that Amgen submitted as part of this complete response. The hazard ratios for PFS and OS all are close to 1.0. Amgen performed an integrated analysis of OS from the three trials and computed a HR of 0.99 [0.91, 1.07]. A total of 1,254 (43.8%) death events occurred among patients treated with denosumab versus 1,240 (43.3%) receiving zoledronic acid. Table 5 below shows that the FDA integrated analyses of PFS and OS from Trials 103, 136, and 244 produced results similar to Amgen's results.

Table 4: PFS and OS Results from Advanced Cancer Studies (FDA Analyses)

Endpoint	Number of events (%)		Median (in mos.)		HR
	D	ZA	D	ZA	(95% CI)
Trial 103 Prostate Cancer (n = 950 denosumab; n = 951 zoledronic acid)					
OS	474 (49.9)	461 (48.5)	19.4	19.8	1.05 (0.91, 1.20)
PFS	767 (80.7)	735 (77.3)	8.1	8.0	1.03 (0.92, 1.14)
Trial 136 Breast Cancer (n = 1,026 denosumab; n = 1,020 zoledronic acid)					
OS	301 (29.3)	305 (29.9)	29.4	NR	0.96 (0.82, 1.13)
PFS	683 (66.6)	698 (68.4)	11.8	11.7	1.01 (0.91, 1.13)
Trial 244 Other Tumors (n = 886 denosumab; n = 890 zoledronic acid)					
OS	479	474	12	12.6	0.95 (0.84, 1.08)
PFS	687	679	5.4	5.5	1.01 (0.91, 1.12)

(b) (4)

[redacted]

Comment: In each study, the power to detect small differences in PFS or OS was low. The combined analysis of the three studies provided some increase in power. The 95% CI excluded a HR of 1.07 for OS and 1.08 for PFS. OS effects observed in the HALT trials (b) (4) [redacted] *provided further evidence that there is unlikely to be a clinically important effect on tumor outcomes in patients receiving denosumab. Additionally, Amgen, as a PMC following the approval of STN 125320/7, agreed to provide complete survival information from Trials 103, 136, and 244 by October 1, 2012. FDA requested this additional data to confirm the consistent effects across trials regarding a lack of effect on either PFS or OS in patients with cancer. It should be stressed that these studies do not provide definitive evidence of non-inferiority regarding PFS or OS.* (b) (4) [redacted]

Nevertheless, the totality of the evidence suggests that treatment with denosumab does not result in a large detrimental effect on OS or PFS.

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Table 5: Pooled Analysis of OS and PFS from Trials 103, 136, and 244 (FDA analyses)

Pooled Survival All Three Trials	Pooled OS		Pooled PFS	
	Denosumab	ZA	Denosumab	ZA
	N = 2862	N = 2861	N = 2862	N = 2861
Number of Events (%)	1254 (43.8%)	1240 (43.3%)	2137 (74.7%)	2112 (73.2%)
Median Survival (95% CI)	22.5 (21.3, 23.6)	22.3 (20.9, 23.5)	8.3 (7.9, 8.5)	8.3 (7.9, 8.5)
HR (95% CI)	0.98 (0.90, 1.06)		1.01 (0.95, 1.07)	

*ZA = zoledronic acid

(b) (4)



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

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

9. Advisory Committee Meeting

FDA convened a meeting of the Advisory Committee for Reproductive Health Drugs on August 13, 2009 to discuss the denosumab osteoporosis indications. The committee included representation from oncologists in addition to endocrinologists, infectious disease specialists, dermatologists, statisticians, a consumer representative, a patient representative, and an industry representative. The following, as stated in Susanne Demko's review, summarizes the recommendations made by the committee:

a. Approve denosumab for the treatment of post menopausal osteoporosis (PMO); but limit to high risk patients
b. Do not approve for the prevention of PMO
c. Do not approve for the treatment or prevention of bone loss in patients with breast cancer receiving aromatase inhibitor therapy
d. Approve for the treatment of bone loss in men with prostate cancer receiving androgen deprivation therapy

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e. Do not approve for prevention of bone loss in men with prostate cancer receiving androgen deprivation therapy
f. Include a Risk Evaluation and Mitigation Strategy (REMS) as a condition of approval

Regarding the cancer osteoporosis indications, the minutes from the meeting stated that "the committee indicated that studies should show safety, with no adverse outcome on clinical course of cancer treatment." Recommendations against approval for patients with cancer were made based on the lack of data on the effects of denosumab on tumor outcomes. The three oncologists on the panel disagreed with the recommendation to approve denosumab for the treatment of bone loss in men with prostate cancer receiving androgen deprivation therapy (based on the lack of knowledge of the effects of denosumab on tumor outcomes).

10. Pediatrics

The PeRC reviewed and granted the applicant's request for a full waiver of PREA requirements on June 20, 2009 during the original review cycle. PeRC granted the waiver for the proposed indications because the diseases/conditions (breast cancer, prostate cancer, and osteoporosis) do not exist in the pediatric population.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

Based on the review of CRFs by the clinical reviewer and preliminary inspection findings of study sites by DSI (verbally communicated during an internal review-team meeting), the primary data submitted to this application were found to be reliable for the primary analyses of safety and efficacy.

11.2 Financial disclosures

Section 3.3 of Suzanne Demko's clinical review describes investigators and sub-investigators with financial conflicts of interest who participated in the conduct of the two trials supporting these applications. Suzanne Demko found that the applicant's Statement of Actions to Minimize Bias for the few investigators who disclosed financial interests to be acceptable. Additionally, the design of the studies minimized the chance that these investigators unduly influenced the outcomes of the studies (i.e., large placebo controlled international studies).

11.3 GCP issues

The applicant, in the clinical study report for Trial 216, described numerous GCP violations at Site 803, located in Lithuania. Violations included enrollment of patients without informed consent, under-reporting of SAEs, and eligibility criteria violations. Based on these findings, the applicant excluded data from all subjects at this site (n = 60) from efficacy and safety analyses. Suzanne Demko found that based upon this information, it is unlikely that these violations introduced bias that would affect the overall study results.

11.4 DSI audits

During the original review cycle, DBOP consulted DSI to inspect four sites that enrolled patients into the two trials (refer to Suzanne Demko's review). DSI also inspected a CRO

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acting as the independent radiologic vender and found that the procedures employed by the applicant and the CRO were adequate.

11.5 DRISK consult

Refer to Section 13.3 of this review regarding DRISK consultation regarding the REMS. Refer to Section 12.4 for DRISK consultation regarding the Medication Guide.

12. Labeling

12.1 Labeling issues raised by DDMAC

DBOP received DDMAC's consult on August 18, 2011. DDMAC raised the following labeling issues:

- DDMAC recommended adding the term "nonmetastatic" prior to prostate cancer and breast cancer in the Highlights section, in the indication statement, and in Section 14.3 (breast cancer). *Comment: This reviewer agrees with adding the term "nonmetastatic" prior to prostate cancer to clarify the intended population; however, this reviewer disagrees with the addition prior to the breast cancer indication, as this term is redundant (the proposed indication is for patients receiving adjuvant aromatase inhibitor therapy for breast cancer: by definition, this means non-metastatic breast cancer).*
- DDMAC recommended removal of the following from the indication statements.
  - 1.2: (b) (4)
  - 1.3: (b) (4)

  Comment: Following internal labeling discussions with DRUP, DBOP agreed to the removal of the statements (b) (4) *consistent with other labels in PLR format. Both divisions agreed to allow the statement that Prolia reduced the incidence of vertebral fractures* (b) (4) *(consistent with prior practice).*
- DDMAC inquired whether the ONJ sections should be the same regarding the Prolia and Xgeva labels. *Comment: As discussed with DRUP during labeling meetings, the two labels are not consistent because the risk of ONJ is markedly higher among patients receiving denosumab as Xgeva.*
- DDMAC requested that DBOP consider adding a qualifier (i.e. ≥ 10%) to most common adverse reactions in Section 6 of the label. *Comment: DBOP agreed to make this change.*
- DDMAC made comments regarding the incidence of serious adverse events in Section 6.1 of the label stating that two paragraphs appeared redundant. *Comment: DBOP considered the two prior paragraphs as adequate clarification that the two paragraphs (in question) that begin with "the incidence of serious* (b) (4) *refer to different patient populations.*
- DDMAC requested that DBOP consider adding "most common" to adverse reactions reported in ≥ 10% of patients (last paragraph of Section 6.1). *In labeling meetings, DBOP review staff considered "most common" redundant in this section of the label, so this section of the label was not revised.*

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- DDMAC asked DBOP to consider removing the words "the target of denosumab" following "RANKL" in Sections 8.1 and 8.4. *DDOP did not revise these sections because these sections contained previously agreed upon language (between Amgen and DRUP).*
- DDMAC asked DBOP to consider adding 95% CI's next to the p-value under the following Section: Effect on Vertebral Fractures. *Comment: Because the table proposed by Amgen includes the CIs, DDOP did not change this paragraph of the label to add the CIs.*

12.2 Physician labeling

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

1. Indications and Usage

Revised the indication statement to identify each of the two new indications (breast and prostate cancer) and to stipulate exactly who should receive denosumab (i.e., only patients with breast cancer receiving aromatase inhibitors as adjuvant therapy). DBOP review staff and DRUP agreed to remove the word "prevention" from the indication statement as the risk/benefit profile was not considered favorable for an osteoporosis prevention indication for patients at less than high risk for fracture.

4. Adverse Reactions

- DBOP recommended replacement of the phrase "(b) (4) with "receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer" to ensure consistency with the revised indication statement.
- DBOP removed (b) (4) as an adverse reaction because the per-patient incidence rate was similar between denosumab and placebo groups.
- DBOP recommend removal of the proposed statement regarding (b) (4) (b) (4)

14. Clinical Studies Section

- DBOP added additional information describing the study designs (including stratification factors) and included demographic information (as recommended by the PLR guidance).
- DBOP added absolute difference values to the BMD information for lumbar spine, total hip, and femoral neck.
- DBOP removed BMD information (from Trial 138) regarding measurements of the (b) (4) (b) (4). Either substantial evidence did not exist for these sites (i.e., information came from a sub-study) or the relevance of these surrogate endpoints is not known in regards to the clinical endpoint of an improvement in fractures.

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- [redacted] information of BMD from Trial 138 due to lack of an alpha allocation plan regarding these measurements.
- DBOP recommended removing [redacted] as this figure was redundant and included information regarding [redacted] BMD (from Trial 138) not supported by substantial evidence.
- DBOP recommended removing [redacted] as it included redundant information [redacted] for vertebral fractures at three different time points (from Trial 138). However, inclusion of the p-value at three years for vertebral fractures was permitted.
- DBOP recommended removing [redacted] as this table was redundant and included information on BMD from body sites [redacted]) without clear relationship between these surrogate endpoints and fractures.
- DBOP recommended removal of a statement about [redacted] from the "Treatment of Bone Loss in Women with Breast Cancer" Section as these subgroups were either not relevant to the overall treatment effect or considered exploratory.

Amgen responded to the FDA label recommendations on August 8, 2011. Amgen accepted most of the recommendations and proposed some administrative updates to the label. FDA subsequently communicated the following additional labeling changes following final labeling meetings held with representatives from DBOP, DRUP, and OSE on August 31 and September 1, 2011.

- DBOP revised the label consistent with Section 12.1 of this review.
- DBOP revised the indication statements in the Highlights Section for consistency with Section 1.2 and 1.3 of the label.
- DBOP revised the titles to Tables 2 and 4 to highlight the populations described in the tables.

12.3 Carton and immediate container labels

No changes to the carton and immediate container were proposed in these efficacy supplements.

12.4 Patient labeling/Medication Guide

Amgen submitted a revised Medication Guide that incorporated the new indications addressed in these efficacy supplements.

The clinical team recommended the following changes to the Medication Guide:

- Removal of the word "prevent" from the section describing the uses of Prolia, as Prolia will not be indicated for the prevention of bone loss.
- Inclusion of only one section regarding "the most common side effects of Prolia" rather than separate sections for the treatment of bone loss due to osteoporosis and for the treatment of bone loss in cancer patients.

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- Removal of the adverse reaction [redacted] (b) (4) Clinical review staff recommended removal of this term from product labeling (similar incidence in denosumab and placebo groups).
- Additionally, the Medication Guide was revised to ensure consistency with labeling changes agreed to with DRUP in July 2011. In the July 2011 action, DRUP included a Warning regarding Xgeva and Prolia containing the same active ingredient. DBOP did not recommend inclusion of this Warning in Xgeva product labeling as the (safety) risks of receiving a lower dose of Prolia (or Prolia in lieu of Xgeva) in addition to Xgeva were considered by review staff as low.

DRISK completed a review of the Medication Guide on August 16, 2011. DBOP and representatives of OSE (including DRISK) met on August 31, 2011 and agreed upon final changes to the Medication Guide. DBOP and OSE proposed the following additional changes to the Mediation Guide.

- Revise the following statement originally proposed by DRISK: "It is not known if Prolia is safe and effective in children" to "Prolia is not recommended for use in children." This change highlighted the DBOP and DRUP concerns regarding the use of denosumab in growing children.
- DBOP did not accept the DDMAC recommendation to change "Your doctor *may* prescribe calcium and vitamin D" to "Your doctor *will* prescribe vitamin D" because some patients may not benefit from calcium or vitamin D (for example, patients with hypercalcemia).
- DBOP agreed to include the DDMAC recommendations to include the italicized part of the following sentence to clarify the intended population: "Treat bone loss in women who have an increased risk for fractures and are receiving certain treatments for breast cancer *that has not spread to other parts of the body.*"
- DBOP considered the DDMAC recommendation to highlight the pregnancy information in the "Before taking Prolia...." section. DBOP and OSE agreed to include additional "white space" to better highlight this information.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This Cross Discipline Team Leader recommends approval of sBLAs STN 125320/5 and 125320/6 submitted under Section 351 of the Public Health Service Act (pending agreement on product labeling, the REMS modification plan, and the Medication Guide). All current review teams recommended approval (following Amgen's submission of additional data to support these supplements) or have reported that there were no findings that would prevent approval.

13.2 Risk-benefit assessment

This CDTL reviewer agrees with current review staff and recommends approval of this efficacy supplement (STN 125320/5 and 6) for the following indications:

> Prolia is indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.

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Prolia is indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

This CDTL reviewer agrees with review staff to not approve denosumab for the prevention of osteoporosis in patients with cancer. Ultimately, the benefit of denosumab in patients at high risk for fractures was demonstrated in the postmenopaual osteoporosis Trial 20030216 (216) that was reviewed by DRUP. This study demonstrated a reduction in the risk of fractures in postmenopausal women with osteoporosis (T-score between -2.5 and -4).

Using the WHO FRAX fracture risk assessment tool, a 65 year old woman [160 cm and 75 kg (mean values using NHANES data 1999-2002)] has an approximate 2.8% 10 year risk of hip fracture and a 12% risk of major osteoporotic fracture [http://usgovinfo.about.com/gi/o.htm?zi=1/XJ&zTi=1&sdn=usgovinfo&cdn=newsissues&tm=24&gps=157_137_1899_936&f=00&tt=2&bt=1&bts=0&zu=http%3A//www.cdc.gov/nchs/data/ad/ad347.pdf (accessed 8/31/2011). The risk increases dramatically for the same patient with a T score of -4.0: the 10 year risk of major osteoporotic fracture is 26% and hip fracture is 13%. These data are for non-smokers without a history of previous fracture, glucocorticoid use, rheumatoid arthritis, or secondary osteoporosis.

These two efficacy supplements (patients with prostate or breast cancer at high risk for fracture) largely relied on the benefits demonstrated in the postmenopausal osteoporosis trial. The two trials submittted in these efficacy supplements evaluated effects on bone mineral density (BMD) as a surrogate for beneficial effects on fractures. These two trials enrolled patients considered at high risk for fractures (osteopenic patients receiving therapies that hasten bone loss).

In the clinical study report for Trial 135, Amgen cited data from the ATAC trial (ATAC Trialists' Group, Lancet 2002) citing an increased fracture risk for patients receiving anastrazole compared to tamoxifen (5.9% versus 3.7% after a median follow-up of 33.3 months). Other studies also confirmed an increased risk of fractures in women receiving aromatase inhibitors compared to tamoxifen (Pant S, Shapiro, Drugs, 2008).

In the clinical study report for Trial 138, Amgen cited data regarding bone loss related to androgen deprivation from orchiectomy or medical hormonal suppression. Amgen cited two reports citing an increased fracture risk among men undergoing androgen deprivation therapy [Shahinian et al., NEJM, 2005 (SEER database and Medicare database) and Smith et al., JCO, 2005 (claims database)]. One report (Shahinian et al., 2005) stated that the risk of fractures increased from 12.6 to 19.4% over four years.

Based on these reports, aromatase inhibitor therapy and androgen deprivation therapy appear to result in an increased risk for fractures. Trials 135 and 138 were smaller trials than the primary post-menopausal osteoporosis trial. Nevertheless, Trial 138 showed a reduced risk for vertebral fractures at three years in men with prostate cancer receiving androgen deprivation therapy. Both trials demonstrated that denosumab increased bone mass compared to placebo in the two patient populations. This increase in bone mass was considered by the review team

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as an acceptable surrogate for fracture reduction for patients at high risk for fracture only because of the demonstrated reduction in fractures observed in the postmenopausal osteoporosis study, along with the supportive effect on vertebral fractures in the prostate cancer population.

Overall denosumab was well tolerated by patients in Trials 135 and 138. Most adverse events were comparable in incidence rates to the placebo arm. The most common adverse reactions reported with denosumab in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer were arthralgia, back pain, pain in the extremity, and musculoskeletal pain. An increased incidence rate of cataracts was observed in men in Trial 138; however, this finding was not replicated in two other trials of denosumab (as Xgeva) in prostate cancer. Osteonecrosis of the jaw remains a concern; however, this risk remains low among patients treated with denosumab as Prolia. This risk is higher in patients treated with denosumab as Xgeva (higher dose).

The benefits of denosumab appear favorable only for patients at high risk for fractures (postmenopausal osteoporosis or *certain* patients receiving adjuvant aromatase inhibitor therapy for breast cancer or androgen deprivation therapy for prostate cancer). Because the benefits of denosumab have not been established using the surrogate markers of bone mineral density in patients at normal or low risk for fractures, this drug should not be approved for the *prevention* of osteoporosis.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The Agency notified Amgen of the need for a REMS consisting of a Medication Guide and a Communication Plan regarding the risks of serious infections, dermatologic toxicity, and over-suppression of bone on October 2, 2009 prior to the original approval of denosumab for the treatment of women with osteoporosis (as Prolia). In the complete response safety update, Amgen submitted a plan to modify the Communication Plan, largely to update new prescribers. Amgen also proposed a modification of the goal of the REMS as follows: (b) (4)

(b) (4)

DRISK completed an assessment of the REMS modification plan on July 29, 2011 and a joint meeting between representatives of DBOP, DRUP, and DRISK occurred on August 5, 2011. Agreement was reached during the meeting regarding the major provisions of the REMS. DBOP communicated the following recommendations to Amgen on August 5, 2011.

- Revise the REMS goal so that it continues to describe the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover. Osteonecrosis of the jaw was added to the goal statement.
- Revise the REMS so that a Dear Health Care Provider Letter (DHCPL) will be sent to new prescribers including oncologists and urologists.
- Revise the REMS to include the website for Amgen's Prolia Post-Marketing Active Safety Surveillance Program in the DHCPL.

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Amgen responded to FDA recommendations to the DHCP letter, Webpage document, and REMS document on August 15, 2011. Amgen agreed to the FDA recommendations; however, requested that FDA not include the following additional sentence in the Serious Infections section of the DHCP letter. (b) (4) Amgen stated that this statement is theoretical and is not appropriate for inclusion in the letter.

DBOP and DRISK met on August 31, 2010 to discuss Amgen's proposal. OSE recommended inclusion of the information because the information remains in product labeling. However, to address Amgen's concerns, DRISK and DBOP agreed to include this information at the end of the Serous Infections section of the DHCP letter and to include the additional information included in the product label to put this statement into context: (b) (4) ."

Agreement regarding final changes to the REMS modification plan and the final language in the Medication Guide has not been reached at this time. Refer to Section 12.4 for further discussion of the Medication Guide, a part of the REMS.

13.4 Recommendation for other postmarketing requirements and commitments

DBOP identified no additional postmarketing requirements as necessary following the review of these two efficacy supplements. Postmarketing requirements and commitments to further characterize safety, including effects on overall survival, are ongoing and were part of the original approval of denosumab on 6/1/2010 and the approval of the Advanced Cancer efficacy supplement (STN 125330/7) on 11/18/2010.

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Signature:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA (post-CR resubmission)
Application Numbers	125320/5 and 125320/6 (formerly BLAs 125332/00 and 125333/00)
Priority or Standard	6-month
Submit Date	March 18, 2011
Received Date	March 18, 2011
PDUFA Goal Date	September 19, 2011
Division / Office	Division of Biologic Oncology Products/Office of Oncology Drug Products
Reviewer Name(s)	Shan Pradhan, MD
Review Completion Date	August 22, 2011
Established Name	Denosumab
(Proposed) Trade Name	Prolia
Therapeutic Class	Human monoclonal antibody
Applicant	Amgen, Inc.
Formulation	Single use pre-filled syringes and vials containing 60 mg/mL
Dosing Regimen	60 mg subcutaneously every 6 months
Proposed Indication(s)	Treatment and prevention of

	bone loss associated with hormone ablation therapy in patients with breast or prostate cancer
Intended Population(s)	Patients with non-metastatic breast and non-metastatic prostate cancer receiving hormone ablation therapy

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

Refer to section 1 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of supplemental Biologic License Application (sBLA) 125320/5/65 for the the *treatment* of bone loss in patients at high risk for fracture who are receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer.

It is the recommendation of this reviewer to deny approval of the applicant's proposed indications for the *prevention* of bone loss in men with prostate cancer receiving androgen deprivation therapy and for the *prevention* of bone loss in women with breast cancer receiving adjuvant aromatase inhibitor therapy. Refer to section 1, pages 10-11, of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko for further discussion regarding the proposed prevention indications.

Regarding the basis of the treatment indications portion of this application, refer to section 1.1 of the initial clinical review of BLAs 125332 and 125333 (completed 2009) by S. Demko. In addition, the review states that future consideration of the application should be predicated on demonstration that there are no detrimental effects of Prolia on cancer outcomes based on analyses of data from completed and ongoing clinical trials in patients with metastatic cancers.

See section 2.5 below regarding subsequent regulatory activity related to the submission including details of the Complete Response letter issued October 19, 2009; the applicant's subsequent proposal to submit results from pivotal Xgeva skeletal-related event (SRE) Trials 20050103, 20050136, and 20050244 to fulfill the deficiencies outlined in the CR letter; and the Agency's agreement that the response proposal would meet expectations regarding the BLA 125332 and 125333 clinical deficiencies. All three denosumab SRE trials were designed to prospectively evaluate time-to-disease progression and overall survival (OS) cancer outcomes. As Xgeva Trials 20050103, 20050136, and 20050244 were initially submitted and reviewed under sBLA 125320/7, refer to the sBLA 125320/7 clinical and statistical reviews for full discussion of overall survival and progression-free survival results. Overall survival and progression-free survival were similar between arms in each of the three trials and similar also in a pooled analysis, demonstrating no detrimental effect of denosumab on time-to-disease progression or OS cancer outcomes, adequately addressing the BLA 125332 and 125333 clinical deficiencies.

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1.2 Risk Benefit Assessment

Refer to section 1.2 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko for a full risk-benefit discussion. The review states that additional data was required to assess effects on cancer outcomes for patients treated with denosumab, the basis for the October 2009 CR action. Refer to section 1.1 above and the clinical and statistical reviews for sBLA 125320/7 regarding the overall survival and progression-free survival data submitted under sBLA 125320/7 for pivotal Xgeva SRE Trials 20050103, 20050136, and 20050244; overall survival and progression-free survival were similar between arms in each of the three trials and similar also in a pooled analysis.

This reviewer concludes that denosumab has an acceptable risk-benefit profile for treatment of bone loss in patients at high risk for fracture who are receiving androgen deprivation therapy for prostate cancer or aromatase inhibitor therapy for breast cancer.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

In this resubmission the applicant proposed a REMS modification including changes to the Medication Guide, DHCP letter, and Prolia REMS website. See section 9.1 for this reviewer's recommendations regarding the Medication Guide. See also the DRISK REMS modification review under separate cover. At this time, the REMS modification remains under review and negotiations with the applicant are ongoing.

1.4 Recommendations for Postmarket Requirements and Commitments

None. Of note, however, is a postmarketing requirement under Xgeva sBLA 125320/7 for the applicant to submit a final report that includes updated overall survival results for Trials 200501013, 20050136, and 20050244. The final report submission date for this PMR is October 1, 2012.

2 Introduction and Regulatory Background

Refer to section 2 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

2.1 Product Information

Refer to section 2.1 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

2.2 Tables of Currently Available Treatments for Proposed Indications

Refer to section 2.2 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues With Consideration to Related Drugs

Refer to section 2.4 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Refer to sections 1 and 2.5 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

A Complete Response (CR) letter, stating that data submitted was inadequate to determine if Prolia has detrimental effects on breast or prostate cancer outcomes since the trials were not adequately designed to compare disease-free survival and overall survival between treatment arms, and recommending that the applicant provide results from adequate and well-controlled clinical trials demonstrating that Prolia has no detrimental effects on either time-to-disease progression or overall survival, was issued October 19, 2009, for both BLAs 125332 and 125333.

In a response proposal summary submitted February 18, 2010, the applicant proposed to submit results from pivotal Xgeva skeletal-related event (SRE) Trials 20050103, 20050136, and 20050244 to fulfill the above BLA 125332 and 1252333 deficiencies.

On March 2, 2010, the DBOP clinical review team issued a memorandum regarding the applicant's Complete Response proposal, stating that the overall proposal to provide results from Trials 20050103 and 20050136, with supporting data from Trial 20050244, was adequate in meeting the Agency's expectations with regard to the BLA 125332 and 125333 clinical deficiencies.

2.6 Other Relevant Background Information

Since issuing the CR letter for Prolia BLAs 125332 and 125333 in October 2009, FDA has granted marketing approval for denosumab under the Prolia and Xgeva tradenames, with two distinct product labels and dosing regimens. Denosumab was approved by DRUP in June 2010 as Prolia for the treatment of women with

postmenopausal osteoporosis (PMO) at high risk for fracture, and by DBOP in November 2010 as Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

Also refer to section 2.6 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

3 Ethics and Good Clinical Practices

Refer to section 3 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

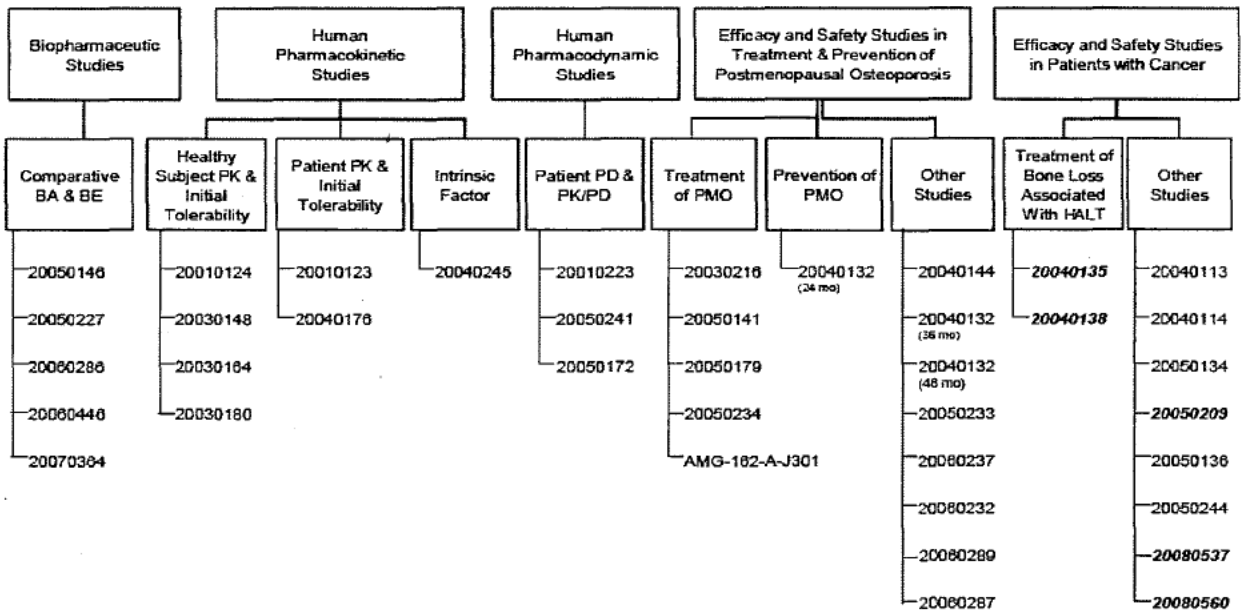
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Refer to section 4 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko. No additional issues related to other review disciplines with regard to these supplements have been identified.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Figure 1 Denosumab Clinical Trials (copied from Amgen's submission: HALT CR response, module 2.7.4)



BA = bioavailability; BE = bioequivalence; HALT = hormone ablation therapy; PD = pharmacodynamics; PK = pharmacokinetics; PMO = postmenopausal osteoporosis

bold italic text: data from this study provided in this Safety Update; plain text: no data from this study provided in this Safety Update.

Refer to section 5 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko for a full discussion of pivotal HALT Trials 20040135 and 20040138.

Amgen included extended follow-up data from pivotal HALT Trials 20040135 and 20040138 in the HALT CR safety update. Data from other studies in patients receiving hormone ablation for cancer (Studies 20050209, 20080537, and 20080560) are included in the submission; these studies are ongoing, vary in design, and include one open-label study and two that remain blinded.

As results from Xgeva SRE Trials 20050103, 20050136, and 20050244 form the basis of the HALT CR response submission, discussion of these trials is included in section 5.3 below. Refer also to the the Xgeva sBLA 125320/7 clinical and statistical reviews.

5.2 Review Strategy

The initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko includes the primary safety review of pivotal HALT trials 20040135 and 20040138. Data from the safety follow-up periods of these two trials, a portion of which was included in the initial HALT 120-day safety update submission, is included in the HALT CR resubmission and is the focus of the present safety review. Safety data including CRFs, case narratives, and electronic datasets were reviewed. The safety review also included investigations for submission-specific safety concerns.

As results from Xgeva SRE Trials 20050103, 20050136, and 20050244, initially submitted and reviewed under sBLA 125320/7, form the basis of the current HALT CR response submission (as detailed in earlier sections of this review), refer to the the Xgeva sBLA 125320/7 clinical and statistical reviews.

5.3 Discussion of Individual Studies/Clinical Trials

HALT Trials 20040135 (breast) and 20040138 (prostate)

Refer to section 5 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko for a complete discussion of pivotal HALT Trials 20040135 and 20040138.

In Trial 20040135, all patients who received at least one dose of investigational product (IP) and completed the 24-month treatment phase were asked to participate in the safety followup period (months 25-48). Data from the 24-month safety period were included in the HALT CR resubmission. Investigational product was not administered in the safety followup period.

In Trial 20040138, all patients who completed the 36-month treatment phase were asked to participate in the safety followup period (months 37-60) or were offered enrollment in an open-label extension study. Data from the 24-month safety period were included in the HALT CR resubmission. Investigational product was not administered during the safety followup period.

SRE Trials 20050103, 2005136, and 2005244

Trials 20050103, 20050136, and 20050244 (hereon Trials 103, 136, and 244) are international, randomized, double-blind, double-dummy trials of parallel design. The

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trials encompass different tumor types and were initially submitted in support of the single proposed indication for the treatment of patients with bone metastases from solid tumors.

Table 1 Trials 103, 136, and 244

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

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

- Primary
  - Time to first on-study SRE ***(non-inferiority)***

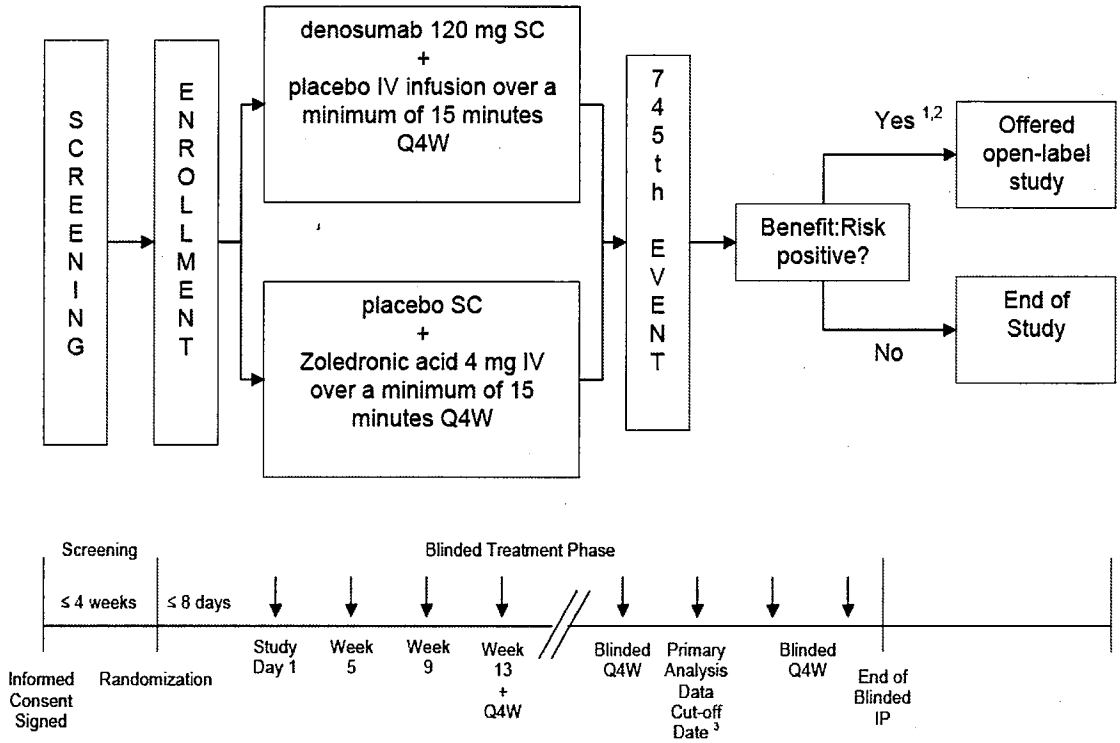
- Secondary (tested only if denosumab was found to be non-inferior to zoledronic acid with respect to time to first on-study SRE)
  - Time to first on-study SRE ***(superiority)***
  - Time to first-and-subsequent on-study SRE
    - Multiple event analysis
    - To be considered a subsequent event, the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

- Exploratory endpoints included OS and PFS

A skeletal-related event (SRE) was defined as any of the following:
- Pathologic fracture (vertebral or non-vertebral)
- Radiation therapy to bone (including the use of radioisotopes)
- Surgery to bone
- Spinal cord compression

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

Figure 2 Treatment Schema for Trials 103, 136, and 244 (adapted from sBLA 125320/7)



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

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

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Table 2 Trial Initiation/Cutoff Dates

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

Randomization was stratified within each trial as shown below.

Table 3 Randomization Stratification

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

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

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

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

Important Inclusion Criteria (modified from the protocols)

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

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

Important Exclusion Criteria (modified from the protocols)

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

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

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

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

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

Concomitant Therapies

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

Prohibited Therapies

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

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

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

Figure 3 Schedule of Assessments

(copied from the BLA)

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

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	Blinded Treatment Period[3] in weeks (Visits every 4 weeks)																
*Informed Consent must be obtained before any study assessments are performed unless it is standard of care	W53	W57	W61	W65	W69	W73	W77	W81	W85	W89	W93	W97	W101	W105	W109	End of Study Visit[19]	Follow Up[20] (Q12W)
Medical History[4]																	
Physical Examination[5] and ECOG Assessment			x			x			x			x			x	x	
Oral Examination[6]						x						x				x	
CENTRAL LABORATORY																	
Serum Chemistry[7]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Hematology[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Pregnancy Test[9]																	
Urine Collection[10]																x	
Bone Specific Alk. Phos.																x	
Anti-Denosumab Antibody												x				x	x[21]
Denosumab Concentration (subset of 150 subjects)						x						x				x	
LOCAL LABORATORY																	
Serum Creatinine[11]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
INVESTIGATIONAL PRODUCT ADMINISTRATION[12] - Subcutaneous injection is to be administered before IV infusion																	
Denosumab/placebo (SC)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Zoledronic acid/placebo (IV)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
IMAGING																	
Skeletal Survey (X-rays)[13]			x			x			x			x			x	x	
OTHER ASSESSMENTS																	
Skeletal Event Recording[14]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Event Collection[15]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medications[16]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
PROs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Healthcare Utilization	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Survival Data																	x

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

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

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Skeletal-Related Events

- Skeletal surveys were sent from the site to the central imaging vendor for central reading. See Section 6 of the sBLA 125320/7 clinical review for further details regarding the central imaging review and IRC.
- Surgery to bone included procedures used to set or stabilize a fracture or to prevent an imminent fracture or cord compression.
- Radiation therapy to bone included radiation for pain control, to treat or prevent pathologic fractures, or to treat or prevent cord compression.
- Cord compression events were to be confirmed using MRI or CT scans which were to be submitted to the central imaging reader for review.
- All scheduled and non-scheduled x-rays were to be submitted to the central imaging vendor for review.

Disease Progression

- Overall disease progression in these double-blind placebo-controlled trials was to be assessed and documented by the investigator on the CRF based on clinical observations.

Statistical Considerations

- See the sBLA 125320/7 clinical and statistical reviews for discussion of the statistical analysis plans including sample size assumptions and analysis of primary and secondary endpoints.
- Early stopping
  - No trial was to be stopped early based on evidence of non-inferiority.
  - For superiority, no trial was to be stopped unless a p-value of 0.0005 was achieved.
- The protocol specified that the Applicant would monitor the rate of SREs by treatment group and if this was lower than expected, may choose to modify the sample size.

Important Protocol Amendments

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

6 Review of Efficacy

Refer to section 6 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

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7 Review of Safety

Safety Summary

Refer to section 7 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko for a summary of the primary safety review of HALT Trials 20040135 and 20040138 (hereon Trials 135 and 138), including a list of key safety issues pertinent to the application.

The initial (October 2009) clinical review of BLAs 125332 and 125333 highlights a concern regarding the potential for tumor promotion in drugs being considered as supportive care in the oncology setting, i.e. the potential for a supportive care drug to act as a tumor promoter to already existing cancers or to negatively impact the efficacy of concomitant cancer therapy. Neither Trial 135 nor 138 included prespecified, defined plans to evaluate for potential treatment effects on time-to-disease-progression, and though overall survival (OS) was a designated exploratory endpoint, an insufficient number of events was expected to occur and neither trial was powered to detect a meaningful decrement in OS. Therefore, it could not be determined from the data submitted whether denosumab has an impact on time-to-disease progression or overall survival cancer outcomes. This was the basis of the Agency's October 2009 Complete Response letter to the applicant requesting results from adequate and well-controlled clinical trials demonstrating that Prolia has no detrimental effects on either time-to-disease progression or overall survival. In March 2010, the applicant submitted a proposal, to which the Agency agreed, to submit results from pivotal Xgeva SRE Trials 103, 136, and 244 in response to this clinical deficiency. Though the populations in these trials were at a later stage of disease than those in Trials 135 and 138, sample sizes were chosen to meet non-inferiority boundaries not based on the intended PFS or OS analyses, patients were treated at a higher dose than in the HALT trials, and exposure and duration of treatment varied among trials, it was determined that these primary analysis data would be adequate to answer the question of whether denosumab has any detrimental effects on cancer outcomes. The trials were initially submitted to and reviewed under sBLA 125320/7; refer to the sBLA 125320/7 clinical and statistical reviews for full discussion of the SRE trial PFS and OS results. Both OS and PFS were similar between arms in each trial, and in pooled analysis, demonstrating no detrimental effect of denosumab on time-to-disease progression or OS cancer outcomes. Additionally, the three Xgeva trials were designed to prospectively evaluate tumor outcomes. Under an sBLA 125320/7 postmarketing requirement, the applicant will submit updated OS results from Trials 103, 136, and 244 in 2012.

Other safety evaluations in this resubmission relevant to the proposed indication included data from the 24-month extended follow-up phases of HALT Trials 135 and 138. One hundred eighty-six patients completed the 24-month treatment phase of Trial 135 and participated in the extended follow-up phase (96 in the prior denosumab group,

90 in the prior placebo group). Eight hundred two patients completed the 36-month treatment phase of Trial 138 and participated in the extended follow-up phase (417 in the prior denosumab group, 385 in the prior placebo group). This safety update review includes summaries of deaths and of common, serious, and significant adverse events (AEs) and AEs resulting in dropout from study. In addition, AEs of special interest based on the antibody target or on safety signals identified either during development or from experience with other anti-resorptive agents are summarized.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Adverse event analyses were conducted using data from the extended follow-up phases of Trials 135 and 138. The safety analysis population in the Trial 135 extended follow-up phase consisted of 96 patients who received denosumab in the treatment phase and 90 who received placebo. The safety analysis population in the Trial 138 extended follow-up phase consisted of 417 patients who received denosumab in the treatment phase and 385 who received placebo.

Electronic datasets were submitted in CDISC format as requested by the Division.

7.1.2 Categorization of Adverse Events

Adverse events were coded in the extended follow-up phase of Trial 135 using version 12.0 of the MedDRA dictionary. In the extended follow-up phase of Trial 138, adverse events were coded using version 13.0 of the MedDRA dictionary.

Adverse events from a subset of case report forms and case narratives for the extended follow-up phase of Trials 135 and 138 were reviewed and compared to the datasets in order to confirm adequacy of the data transfer. To confirm the overall adequacy of AE coding, a comparison of verbatim terms to corresponding MedDRA lower level terms was performed. In this evaluation, this reviewer found no substantial deficiencies that would preclude further review.

Toxicity grading was based on the NCI CTCAE version 3.0.

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

For this resubmission safety update review, the extended follow-up phase of Trial 135 and the extended follow-up phase of Trial 138 were analyzed individually due to basic differences in design between Trials 135 and 138, including in trial population, duration, and exposure.

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7.2 Adequacy of Safety Assessments

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

Only patients who completed the 24-month treatment phase of Trial 135 and patients who completed the 36-month treatment phase of Trial 138 participated in the respective 24-month extended follow-up phases. Investigational product was not administered during either extended follow-up phase.

Table 4 Demographics Summary by Trial

	Trial 135 (Breast) Extended Followup		Trial 138 (Prostate) Extended Followup	
	Denosumab	Placebo	Denosumab	Placebo
	n=96	n=90	n=417	n=385
	n (%)	n (%)	n (%)	n (%)
Age (years)				
Mean	59.7	60.0	74.4	74.1
Min	38	42	48	52
Median	59	58	75	74
Max	84	81	92	90
Sex				
F	96	90	0	0
M	0	0	417	385
Race				
American Indian/ Alaska Native	1 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Asian	1 (1.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Black or African American	1 (1.0%)	0 (0.0%)	18 (4.3%)	13 (3.4%)
Hispanic or Latino	4 (4.2%)	1 (1.1%)	47 (11.3%)	51 (13.2%)
Japanese	1 (1.0%)	0 (0.0%)	0 (0.0%)	3 (0.8%)

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	Trial 135 (Breast) Extended Followup		Trial 138 (Prostate) Extended Followup	
	Denosumab	Placebo	Denosumab	Placebo
	n=96	n=90	n=417	n=385
	n (%)	n (%)	n (%)	n (%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (1.1%)	0 (0.0%)	2 (0.5%)
Other	2 (2.1%)	0 (0.0%)	350 (84.1%)	315 (81.6%)
White or Caucasian	86 (89.6%)	88 (97.8%)	0 (0.0%)	2 (0.5%)

There were no significant differences in demographic characteristics between the extended follow-up phase safety populations and the safety analysis populations described in Section 7 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009).

Patient demographics were balanced between prior treatment groups in the extended follow-up phase of each trial.

7.2.2 Explorations for Dose Response

The dosing regimen in Trials 135 and 138 was the labeled Prolia regimen of 60 mg administered subcutaneously every 6 months. Planned treatment duration was 2 years (4 doses) in trial 135 and 3 years (6 doses) in Trial 138. The following table summarizes the number of doses received by patients in the extended-phase safety population in each trial, during the treatment phase. The majority of the patients in the extended follow-up phase of Trial 135 received the planned 4 doses and the majority of the patients in the extended follow-up phase of Trial 138 received the planned 6 doses.

Figure 4 Trials 135 and 138 – Denosumab Exposure

	Number of doses	Trial 135	Trial 138
		n=96 (ext. followup)	n=417 (ext. followup)
		n (%)	n (%)
Denosumab 60 mg SC q6M	1	2 (2.1%)	3 (0.7%)
	2	1 (1.0%)	0 (0.0%)
	3	4 (4.2%)	1 (0.2%)
	4	89 (92.7%)	0 (0.0%)
	5	0 (0.0%)	2 (0.5%)
	6	0 (0.0%)	410 (98.6%)

7.2.3 Special Animal and/or In Vitro Testing

None. Refer to section 7.2.3 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

7.2.4 Routine Clinical Testing

Not applicable to this resubmission safety update as the focus of safety analyses in this review is the extended follow-up phase of Trials 135 and 138.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable to this resubmission safety update as the focus of safety analyses in this review is the extended follow-up phase of Trials 135 and 138. Refer to section 7.2.5 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko and the clinical review of Xgeva sBLA 125320/7.

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

Refer to section 7.2.6 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

7.3 Major Safety Results

7.3.1 Deaths

A total of 56 fatal adverse events occurred during the extended follow-up phases of Trials 135 and 138. Numbers of fatal events were balanced between prior treatment groups in each trial, as shown in the table below.

Table 5 Fatal Adverse Events (per patient incidence)

Trial 135 Extended Followup		**Trial 138 Extended Followup**	
Denosumab	**Placebo**	**Denosumab**	**Placebo**
n=96	**n=90**	**n=417**	**n=385**
n (%)	**n (%)**	**n (%)**	**n (%)**
2 (2.2%)	2 (2.3%)	26 (6.2%)	26 (6.8%)

Trial 135

During the extended follow-up phase of Trial 135 a total of 4 patients died, 2 in each prior treatment group. Review of case report forms and narrative listings for each of the 4 patients confirmed that breast cancer disease progression was the cause of death in each case.

Trial 138

In general, causes of death during the extended follow-up phase of Trial 138 were expected in the patient population being studied, men with a median age of 75 and 91% of patients above age 65 at enrollment. The table below summarizes all fatal events that occurred during the extended follow-up phase of Trial 138, by MedDRA system organ class (SOC) and preferred term (PT). A review of CRFs was performed to evaluate stated causes of death and in general, the causes of death described in the reports accurately reflect the patient histories.

Table 6 Trial 138 Extended Follow-up Phase - Deaths by SOC and PT

SOC	PT	Denosumab n=417 n (%)	Placebo n=385 n (%)
Blood and lymphatic system disorders	Anaemia	0 (0.0%)	1 (0.3%)
Cardiac disorders	Cardiac failure	0 (0.0%)	3 (0.8%)
	Cardiopulmonary failure	0 (0.0%)	2 (0.5%)
	Cardio-respiratory arrest	1 (0.2%)	0 (0.0%)
	Cardiovascular insufficiency	1 (0.2%)	0 (0.0%)
General disorders and administration site conditions	Death	6 (1.4%)	2 (0.5%)
	General physical health deterioration	0 (0.0%)	1 (0.3%)
	Sudden cardiac death	0 (0.0%)	1 (0.3%)
	Thrombosis in device	0 (0.0%)	1 (0.3%)
Metabolism and nutrition disorders	Failure to thrive	1 (0.2%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute lymphocytic leukaemia	1 (0.2%)	0 (0.0%)
	Brain neoplasm malignant	0 (0.0%)	1 (0.3%)
	Colorectal cancer metastatic	1 (0.2%)	0 (0.0%)
	Lung neoplasm malignant	0 (0.0%)	1 (0.3%)
	Metastases to bone	1 (0.2%)	2 (0.5%)
	Pancreatic carcinoma	1 (0.2%)	0 (0.0%)
	Prostate cancer	4 (1.0%)	2 (0.5%)

SOC	PT	Denosumab n=417 n (%)	Placebo n=385 n (%)
	Prostate cancer metastatic	3 (0.7%)	1 (0.3%)
	Rectal cancer metastatic	1 (0.2%)	0 (0.0%)
	Tongue neoplasm malignant stage unspecified	1 (0.2%)	0 (0.0%)
Nervous system disorders	Cerebrovascular accident	2 (0.5%)	1 (0.3%)
Renal and urinary disorders	Urogenital haemorrhage	0 (0.0%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	0 (0.0%)	1 (0.3%)
	Pneumonia aspiration	0 (0.0%)	1 (0.3%)
	Pulmonary embolism	0 (0.0%)	2 (0.5%)
	Respiratory failure	1 (0.2%)	1 (0.3%)
Vascular disorders	Aortic aneurysm rupture	0 (0.0%)	1 (0.3%)
	Arteriosclerosis	1 (0.2%)	0 (0.0%)

7.3.2 Serious Adverse Events

A total of 160 patients experienced serious adverse events in the extended follow-up phases of Trials 135 and 138. The analyses of SAEs are summarized in the tables below. Case report forms or case narratives were reviewed for selected cases.

Table 7 Serious Adverse Events (per patient incidence)

Trial 135 Extended Followup		Trial 138 Extended Followup	
Denosumab	**Placebo**	**Denosumab**	**Placebo**
n=96	**n=90**	**n=417**	**n=385**
n (%)	**n (%)**	**n (%)**	**n (%)**
9 (9.4%)	4 (4.4%)	78 (18.7%)	69 (17.9%)

Trial 135

The following table summarizes the analyses of SAEs for the extended follow-up phase of Trial 135. The case of pneumonia occurred in a 76 year old patient. The case of

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lobar pneumonia occurred in a patient with a history of repeated bouts of pneumonia. The patient who experienced a fibula fracture also fractured her tibia after a fall.

Table 8 Trial 135 Extended Follow-up Phase - SAEs by SOC and PT

SOC	PT	Denosumab n=96 n (%)	Placebo n=90 n (%)
Blood and lymphatic system disorders	Febrile neutropenia	0 (0.0%)	1 (1.1%)
Cardiac disorders	Myocardial infarction	1 (1.0%)	0 (0.0%)
Gastrointestinal disorders	Colonic stenosis	1 (1.0%)	0 (0.0%)
	Diverticulum intestinal	2 (2.1%)	0 (0.0%)
	Gastritis	1 (1.0%)	0 (0.0%)
	Haemorrhoids	1 (1.0%)	0 (0.0%)
Hepatobiliary disorders	Hepatic failure	0 (0.0%)	1 (1.1%)
	Jaundice	1 (1.0%)	0 (0.0%)
Infections and infestations	Cellulitis	0 (0.0%)	1 (1.1%)
	Clostridium difficile colitis	0 (0.0%)	1 (1.1%)
	Lobar pneumonia	1 (1.0%)	0 (0.0%)
	Pneumonia	1 (1.0%)	0 (0.0%)
Injury, poisoning and procedural complications	Fibula fracture	1 (1.0%)	0 (0.0%)
	Overdose	0 (0.0%)	1 (1.1%)
	Tibia fracture	2 (2.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Arthralgia	1 (1.0%)	0 (0.0%)
	Muscular weakness	1 (1.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma pancreas	1 (1.0%)	0 (0.0%)
	Breast cancer	0 (0.0%)	1 (1.1%)
	Breast cancer in situ	0 (0.0%)	1 (1.1%)
	Breast cancer metastatic	2 (2.1%)	1 (1.1%)
	Metastases to bone	1 (1.0%)	0 (0.0%)
Nervous system disorders	Syncope	1 (1.0%)	0 (0.0%)
Psychiatric disorders	Depression	0 (0.0%)	1 (1.1%)

Trial 138

A MedDRA SOC level analysis was performed for the extended follow-up phase of Trial 138. The overall per-patient incidence of SAEs was balanced between prior treatment groups. The following table summarizes the analysis of SAEs for the extended follow-up phase of Trial 138. Overall there were no clinically meaningful differences between

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prior treatment groups. The higher overall rate of SAEs as compared to the extended follow-up phase of Trial 135 likely reflects the age and associated comorbidities of the population studied in Trial 138.

Table 9 Trial 138 Extended Follow-up Phase - SAEs by SOC

SOC	Denosumab n=417 n (%)	Placebo n=385 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (5.3%)	14 (3.6%)
Gastrointestinal disorders	15 (3.6%)	10 (2.6%)
Infections and infestations	15 (3.6%)	14 (3.6%)
Cardiac disorders	14 (3.4%)	12 (3.1%)
General disorders and administration site conditions	12 (2.9%)	7 (1.8%)
Nervous system disorders	10 (2.4%)	13 (3.4%)
Renal and urinary disorders	9 (2.2%)	14 (3.6%)
Respiratory, thoracic and mediastinal disorders	9 (2.2%)	8 (2.1%)
Blood and lymphatic system disorders	6 (1.4%)	4 (1.0%)
Injury, poisoning and procedural complications	6 (1.4%)	7 (1.8%)
Musculoskeletal and connective tissue disorders	6 (1.4%)	5 (1.3%)
Vascular disorders	5 (1.2%)	8 (2.1%)
Metabolism and nutrition disorders	3 (0.7%)	6 (1.6%)
Surgical and medical procedures	3 (0.7%)	1 (0.3%)
Hepatobiliary disorders	2 (0.5%)	1 (0.3%)
Ear and labyrinth disorders	1 (0.2%)	0 (0.0%)
Psychiatric disorders	1 (0.2%)	0 (0.0%)
Skin and subcutaneous tissue disorders	1 (0.2%)	0 (0.0%)
Congenital, familial and genetic disorders	0 (0.0%)	1 (0.3%)

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SOC	Denosumab n=417 n (%)	Placebo n=385 n (%)
Eye disorders	0 (0.0%)	2 (0.5%)
Reproductive system and breast disorders	0 (0.0%)	1 (0.3%)

7.3.3 Dropouts and/or Discontinuations

No patients withdrew from Trial 135 due to an adverse event during the extended follow-up period.

Five patients withdrew in the prior denosumab group and no patients in the prior placebo group in the extended follow-up period of Trial 138. Four patients withdrew due to events related to progression of prostate cancer; the fifth patient withdrew due to worsening Alzheimer's disease.

7.3.4 Significant Adverse Events

In addition to discussion in Section 7.4.1 Common Adverse Events, CTCAE Grade 3-5 adverse events were analyzed at each level of the MedDRA hierarchy for the extended follow-up periods of Trials 135 and 138:

Trial 135

At the PT level, most terms occurring in the prior denosumab group occurred in a single patient. Terms occurring at higher incidence in the prior denosumab group compared to the prior placebo group were lumbar vertebral fracture, meniscus lesion, thoracic vertebral fracture, and tibia fracture, each occurring in 2 patients. Similarly, no HLT term occurred in more than 2 patients in the prior denosumab group. At the HLGT level, only 'Bone and joint injuries' occurred in more than 2 patients in the prior denosumab group, occurring in 7 patients in the prior denosumab group compared to 1 patient in the prior placebo group. Preferred terms subsumed under this HLGT included meniscus lesion (2 patients), radius fracture (1 patient), thoracic vertebral fracture (2 patients), tibia fracture (2 patients), and fibula fracture (1 patient). Review of cases revealed that at least 3 fracture events were due to trauma and the patient who experienced fibula fracture also experienced a tibia fracture after a fall. In addition, at least one vertebral fracture event was also due to trauma. Only SOC terms 'Injury, poisoning, and procedural complications' (7 patients vs. 2 patients) and 'Musculoskeletal and connective tissue disorders' occurred in more than 2 patients each in the prior denosumab group. 'Injury, poisoning, and procedural complications' included the PT terms listed above under the PT analysis, and 'Musculoskeletal and connective tissue disorders' included PTs arthralgia, osteoarthritis, muscular weakness, neck pain, pain in

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extremity, and synovial cyst, each occurring in a single patient. Arthralgia, musculoskeletal pain, and pain in extremity are included in the Prolia labeling; see section 7.4.1 and labeling recommendations.

Trial 138

At the PT, HLT, HLGT, and SOC levels, no term occurred at greater than 2% increased incidence in the prior denosumab group compared to the prior placebo group.

7.3.5 Submission Specific Primary Safety Concerns

Refer to section 7.3.5 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

Osteonecrosis of the Jaw

No patient experienced an event of osteonecrosis of the jaw (ONJ) during the extended follow-up phases of Trials 135 and 138.

Cataracts in Trial 138

Refer to section 5.3 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko. In the extended follow-up phase of Trial 138, four patients in the prior denosumab group and seven patients in the prior placebo group experienced an adverse event of cataract. Refer also to the clinical safety review of Xgeva SRE sBLA 125320/7; in Xgeva SRE Trials 103, 136, and 244, which utilized the labeled Xgeva dosing regimen of 120 mg denosumab administered every 4 weeks, there were no safety signals concerning for increased risk of cataract.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Consistent with the common adverse event (AE) search criteria applied by S. Demko in the initial clinical review of BLAs 125332 and 125333, this reviewer defined common AEs, for the purpose of presentation below (highlighted), as events occurring at a per patient incidence of > 5% with >5% difference favoring the prior denosumab treatment group. The labeling proposed by the applicant includes adverse reactions reported in 10% or more of Prolia-treated patients and this reviewer is in agreement with this labeling proposal.

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Trial 135

Table 10 AEs by PT (>5% per patient incidence in the prior denosumab group)

PT	Denosumab n=96 n (%)	Placebo n=90 n (%)
Arthralgia	11 (11.5%)	4 (4.4%)
Back pain	6 (6.3%)	5 (5.6%)
Dyspepsia	6 (6.3%)	1 (1.1%)
Insomnia	6 (6.3%)	0 (0.0%)
Pain in extremity	6 (6.3%)	4 (4.4%)

Arthralgia has been included in the Prolia labeling.

Table 11 AEs by HLT (>5% per patient incidence in the prior denosumab group)

HLT	Denosumab n=96 n (%)	Placebo n=90 n (%)
Musculoskeletal and connective tissue pain and discomfort	16 (16.7%)	12 (13.3%)
Joint related signs and symptoms	11 (11.5%)	5 (5.6%)
Upper respiratory tract infections	10 (10.4%)	7 (7.8%)
Urinary tract infections	7 (7.3%)	3 (3.3%)
Disturbances in initiating and maintaining sleep	6 (6.3%)	0 (0.0%)
Dyspeptic signs and symptoms	6 (6.3%)	1 (1.1%)
Pain and discomfort NEC	6 (6.3%)	2 (2.2%)

The HLT 'Joint related signs and symptoms' includes the PT arthralgia.

Table 12 AEs by HLGT (>5% per patient incidence in the prior denosumab group)

HGLT	Denosumab n=96 n (%)	Placebo n=90 n (%)
Infections - pathogen unspecified	18 (18.8%)	14 (15.6%)
Bone and joint injuries	16 (16.7%)	8 (8.9%)
Musculoskeletal and	16 (16.7%)	13 (14.4%)

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HGLT	Denosumab n=96 n (%)	Placebo n=90 n (%)
connective tissue disorders NEC		
Joint disorders	14 (14.6%)	8 (8.9%)
Gastrointestinal signs and symptoms	13 (13.5%)	6 (6.7%)
General system disorders NEC	10 (10.4%)	10 (11.1%)
Bone disorders (excl congenital and fractures)	6 (6.3%)	7 (7.8%)
Gastrointestinal motility and defaecation conditions	6 (6.3%)	6 (6.7%)
Sleep disorders and disturbances	6 (6.3%)	0 (0.0%)
Epidermal and dermal conditions	5 (5.2%)	7 (7.8%)
Injuries NEC	5 (5.2%)	5 (5.6%)
Physical examination topics	5 (5.2%)	1 (1.1%)
Respiratory disorders NEC	5 (5.2%)	10 (11.1%)
Synovial and bursal disorders	5 (5.2%)	0 (0.0%)
Urinary tract signs and symptoms	5 (5.2%)	4 (4.4%)

The HLGT 'Bone and joint injuries' includes fracture PTs addressed in section 7.3.4 above. 'Joint disorders' includes the PT arthralgia. 'Gastrointestinal signs and symptoms' includes disparate GI PTs already included in the Prolia labeling.

Table 13 AEs by SOC (>5% per patient incidence in the prior denosumab group)

SOC	Denosumab n=96 n (%)	Placebo n=90 n (%)
Musculoskeletal and connective tissue disorders	33 (34.4%)	24 (26.7%)
Infections and infestations	22 (22.9%)	17 (18.9%)
Injury, poisoning and procedural complications	18 (18.8%)	13 (14.4%)
Gastrointestinal disorders	17 (17.7%)	12 (13.3%)
Psychiatric disorders	13 (13.5%)	6 (6.7%)

SOC	Denosumab n=96 n (%)	Placebo n=90 n (%)
General disorders and administration site conditions	12 (12.5%)	11 (12.2%)
Investigations	11 (11.5%)	4 (4.4%)
Nervous system disorders	9 (9.4%)	13 (14.4%)
Respiratory, thoracic and mediastinal disorders	9 (9.4%)	12 (13.3%)
Reproductive system and breast disorders	8 (8.3%)	4 (4.4%)
Skin and subcutaneous tissue disorders	8 (8.3%)	8 (8.9%)
Vascular disorders	7 (7.3%)	5 (5.6%)
Metabolism and nutrition disorders	6 (6.3%)	9 (10.0%)
Renal and urinary disorders	6 (6.3%)	4 (4.4%)

The SOC 'Musculoskeletal and Connective Tissue Disorders' includes PTs arthralgia, back pain, and musculoskeletal pain, which are included in the Prolia labeling. The SOC 'Investigations' includes a number of disparate laboratory PTs mostly occurring in 1-2 patients each.

Trial 138

Table 14 AEs by PT (>5% per patient incidence in the prior denosumab group)

PT	Denosumab n=417 n (%)	Placebo n=385 n (%)
Arthralgia	21 (5.0%)	14 (3.6%)

No PT occurred at greater than 5% per patient incidence in the prior denosumab group.

Table 15 AEs by HLT (>5% per patient incidence in the prior denosumab group)

HLT	Denosumab n=417 n (%)	Placebo n=385 n (%)
Musculoskeletal and connective tissue pain and discomfort	33 (7.9%)	20 (5.2%)
Bladder and urethral symptoms	26 (6.2%)	21 (5.5%)

HLT	Denosumab n=417 n (%)	Placebo n=385 n (%)
Joint related signs and symptoms	22 (5.3%)	14 (3.6%)

Table 16 AEs by HLGT (>5% per patient incidence in the prior denosumab group)

HLGT	Denosumab n=417 n (%)	Placebo n=385 n (%)
Infections - pathogen unspecified	45 (10.8%)	33 (8.6%)
Musculoskeletal and connective tissue disorders NEC	36 (8.6%)	23 (6.0%)
Urinary tract signs and symptoms	33 (7.9%)	31 (8.1%)
Joint disorders	28 (6.7%)	19 (4.9%)
Gastrointestinal motility and defaecation conditions	27 (6.5%)	13 (3.4%)
Gastrointestinal signs and symptoms	25 (6.0%)	19 (4.9%)
General system disorders NEC	24 (5.8%)	20 (5.2%)

Table 17 AEs by SOC (>5% incidence in the prior denosumab group)

SOC	Denosumab n=417 n (%)	Placebo n=385 n (%)
Musculoskeletal and connective tissue disorders	72 (17.3%)	51 (13.2%)
Infections and infestations	55 (13.2%)	46 (11.9%)
Gastrointestinal disorders	53 (12.7%)	42 (10.9%)
Renal and urinary disorders	48 (11.5%)	49 (12.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	43 (10.3%)	28 (7.3%)
Nervous system disorders	33 (7.9%)	38 (9.9%)
General disorders and	31 (7.4%)	25 (6.5%)

SOC	Denosumab n=417 n (%)	Placebo n=385 n (%)
administration site conditions		
Respiratory, thoracic and mediastinal disorders	30 (7.2%)	26 (6.8%)
Cardiac disorders	25 (6.0%)	27 (7.0%)
Injury, poisoning and procedural complications	24 (5.8%)	27 (7.0%)
Metabolism and nutrition disorders	23 (5.5%)	20 (5.2%)
Vascular disorders	22 (5.3%)	24 (6.2%)

7.4.2 Laboratory Findings

No laboratory evaluations were collected in the extended follow-up phases of Trials 135 and 138.

7.4.3 Vital Signs

No vital sign data were collected in the extended follow-up phases of Trials 135 and 138.

7.4.4 Electrocardiograms (ECGs)

No ECGs were collected in the extended follow-up phases of Trials 135 and 138.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted.

7.4.6 Immunogenicity

Samples for detecting antidenosumab antibodies were not collected during the extended follow-up phases of Trials 135 and 138.

7.5 Other Safety Explorations

Refer to section 7.5 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko and the clinical review of Xgeva sBLA 125320/7.

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7.6 Additional Safety Evaluations

Refer to section 7.6 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko and the clinical review of Xgeva sBLA 125320/7.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Initial marketing approval of Prolia was granted in June 2010 and marketing approval of Xgeva was granted in November 2010. To date, postmarketing experience with denosumab has identified no new safety signals or risks not already recognized during clinical development.

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9 Appendices

9.1 Literature Review/References

Refer to section 9.1 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

9.2 Labeling Recommendations

This reviewer recommended the following key labeling changes, including changes to the medication guide as below.

Indications and Usage

- Change the indication from "the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer" to the following two indications (for clarity and for consistency with the PMO sections of the labeling):
  - treatment to increase bone mass in men at high risk for fracture who are also receiving androgen deprivation therapy for nonmetastatic prostate cancer
  - treatment to increase bone mass in women at high risk for fracture who are also receiving adjuvant aromatase inhibitor therapy for breast cancer
- Removal of the prevention of bone loss indication, as above [see section 1.1 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko], and removal of all related language in the sections below

Warnings and Precautions

- A July 2011 labeling supplement approved by DRUP included addition of the following warning: "Patients receiving Prolia should not receive Xgeva."
  - As noted in section 9.2 of the Clinical Review of sBLA 125320/7 (Xgeva), there is no evidence that inadvertently receiving an extra 60 mg dose of denosumab would acutely harm cancer patients receiving Xgeva, therefore removal of the "Drugs with Same Active Ingredient" warning from the Xgeva label was recommended in the sBLA 125320/7 review, along with inclusion of a statement in the Xgeva Patient Counseling Information Section that Xgeva is also marketed as Prolia and that patients should inform their healthcare provider if they are taking Prolia.

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Adverse Reactions

- Replacement of [redacted] (b) (4) with "receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer" (for clarity and consistency)
- Removal of [redacted] (b) (4) (occurred with similar incidence in the denosumab and placebo arms) from and the addition of pain in extremity and musculoskeletal pain to the list of most common adverse reactions reported with Prolia in the HALT study populations
- Removal of a statement regarding [redacted] (b) (4)

Clinical Trials

- Inclusion of absolute risk reduction and relative risk reduction with regard to effect on vertebral fractures in men with prostate cancer
- Inclusion of demographic information for the study populations, includinmean baseline lumbar spine BMD T-scores and vertebral fracture rates (for consistency with the PMO sections of the labeling)
- Inclusion of the stratification factors in each trial
- Removal of figures (to remove redundant information or information not pertinent to the benefits, risks, or use of denosumab)
- [redacted] (b) (4) results in the prostate cancer trial, as there was no plan for alpha allocation beyond the key secondary endpoint
- [redacted] (b) (4) results in the breast cancer trial, as there was no plan for alpha allocation beyond the primary endpoint
- Removal of BMD results for sites other than the lumbar spine, total hip, femoral neck (for consistency with the PMO sections of the labeling)
- Removal of selected subgroup analyses from statements regarding [redacted] (b) (4) [redacted] (b) (4) (for consistency with the PMO sections of the labeling)
- Editorial changes for consistency with the PMO sections of the labeling

Medication Guide

- Removal of language regarding prevention of bone loss
- Changes regarding the most common side effects of Prolia, for consistency with the recommendations above under the Adverse Reactions section of the labeling
- Removal of statements regarding treatments for breast or prostate cancer [redacted] (b) (4)

9.3 Advisory Committee Meeting

Refer to section 9.3 of the initial clinical review of BLAs 125332 and 125333 (completed October 2009) by S. Demko.

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125332/00 and 125333/00
Priority or Standard	Standard
Submit Date	December 19, 2008
Received Date	December 19, 2008
GRMP Goal Date	August 19, 2009
PDUFA Goal Date	October 19, 2009
Reviewer Name(s)	Suzanne Demko 10/09/2009
Review Completion Date	October 7, 2009
Established Name	Denosumab
(Proposed) Trade Name	Prolia™
Therapeutic Class	Human monoclonal antibody
Applicant	Amgen
Formulation(s)	Single use pre-filled syringes and vials containing 60 mg/mL
Dosing Regimen	60 mg subcutaneously every 6 months
Indication(s)	Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate or breast cancer
Intended Population(s)	Patients with non-metastatic breast and non-metastatic prostate cancer receiving hormone ablation therapy

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1 Recommendations/Risk Benefit Assessment

The application under review included four separate proposed indications, only two of which pertain to patients with cancer, i.e., prevention and treatment of patients with breast cancer receiving aromatase inhibitor therapy, and prevention and treatment of men with prostate cancer receiving androgen deprivation therapy. For the purposes of this section of the review, the treatment and prevention indications will be discussed separately. In addition, reference will be made to the postmenopausal osteoporosis indications sought by this application, i.e., treatment of women with postmenopausal osteoporosis, and prevention of osteoporosis in post-menopausal women, only as they apply to the trials submitted in support of the cancer indications.

1.1 Recommendation on Regulatory Action

Treatment

It is the recommendation of this reviewer to deny the approval of these original Biological License Applications (BLA), STN 125332/00 and STN 125333/00, for denosumab (Prolia™) for the treatment of patients with bone loss associated with hormone ablation therapy (HA) administered to patients with breast and prostate cancers. Any future consideration of this application is predicated on a demonstration that there are no detrimental effects on cancer outcomes from analyses of data from completed and ongoing clinical trials in patients with metastatic cancers. The data should be submitted to the agency for review and demonstrate neutral or positive effects on cancer outcomes for patients treated with denosumab. In addition, should Amgen secure approval for denosumab for these cancer indications in the future, treatment should be limited to patients who are at high risk for fracture, patients who are refractory to bisphosphonates, or patients who are intolerant of bisphosphonates.

These recommendations are based on the analyses of efficacy and safety data submitted from two randomized, placebo-controlled trials, Trial 20040135 (135) and Trial 20040138 (138). Trial 135 studied bone mineral density as the primary endpoint. Bone mineral density (BMD) is not accepted as a regulatory endpoint for anti-resorptive agents. Skeletal related events, including incidence of new vertebral fractures is an accepted regulatory endpoint for this class of products. As a result, demonstration of clinical benefit for Trial 135 is based upon the efficacy data submitted for Trial 20030216 (216) which supported the primary indication for the treatment of postmenopausal osteoporosis (PMO). The primary efficacy endpoint in Trial 216 was reduction of new vertebral fractures. For trial 135, BMD is a surrogate endpoint while reduction of new vertebral fractures is considered clinical benefit for regulatory purposes. The data from Trial 138 does not rely on another study to confirm clinical benefit.

[Data from Trial 216 were reviewed in the Division of Reproductive and Endocrinology Products (DRUP).]

Trial 135 was a multinational, multicenter, double-blind, placebo-controlled trial involving 252 patients with non-metastatic breast cancer receiving adjuvant aromatase inhibitor (AI) therapy following definitive local therapy. Patients were randomized 1:1 to denosumab (127) or placebo (125) once every 6 months for a total of 4 doses during the treatment period of 24 months. All patients received daily calcium ($\geq$ 1 g) and vitamin D ($\geq$ 400 IU) supplementation throughout the trial. Randomization was stratified by the duration of aromatase inhibitor therapy ($\leq$ 6 months vs.

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> 6 months). A 24 month safety follow-up period was ongoing at the time the BLA was submitted. The primary efficacy endpoint was percentage change in lumbar spine bone mineral density (BMD) from baseline to month 12. Key secondary endpoints were percentage change in lumbar spine bone mineral density (BMD) from baseline to month 6, and percentage change in total hip and femoral neck BMD from baseline to months 6 and 12. There were no neoplastic disease assessments specified as part of the trial and such data was not captured during the conduct of the trial. Survival rate at month 24 was an exploratory endpoint.

There was a statistically significant increase in lumbar spine BMD between denosumab and placebo treated groups at 12 months (denosumab + 4.8%, placebo – 0.7%) based on a least square mean estimate. The treatment difference between the groups was 5.5% (95% CI: 4.8, 6.3). Consistent effects on lumbar spine bone mineral density were observed regardless of baseline age, duration of aromatase inhibitor therapy, weight/bone mass index (BMI), prior chemotherapy, prior selective estrogen receptor modulator (SERM) use, and time since menopause. The treatment differences in total hip and femoral neck BMDs from baseline to month 12 were also statistically significant ($p<0.0001$). Trial 135 did not include an evaluation of skeletal related events and relied on the outcome of Trial 216 to demonstrate clinical benefit. All cause mortality included 2 deaths (1%) for each treatment group at 24 months.

Trial 216 was a multinational, multicenter, randomized, double-blind placebo-controlled trial to investigate the safety and efficacy of denosumab on the reduction of new vertebral fractures in 7808 postmenopausal women with osteoporosis after 3 years of treatment. Subjects were randomized (1:1) to receive either denosumab (3902) or placebo (3906). All patients received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation throughout the trial. Randomization was stratified by age at study entry: 60 to 64 years, 65 to 69 years, 70 to 74 years, and ≥ 75 years. BMD T-scores were required to be ≤ - 2.5 and ≥ - 4.0 at baseline. The last scheduled dose of investigational product was administered at month 30, and patients were followed until month 36 at which time they were offered the opportunity to enroll in an extension trial. The primary efficacy endpoint was the incidence of new vertebral fractures during the 36-month treatment period. Key secondary endpoints were time to first nonvertebral fracture and time to first hip fracture.

There was a statistically significant reduction in the risk of new vertebral, nonvertebral, and hip fractures for denosumab when compared with placebo based on a prespecified sequential testing procedure. The risk reduction for new vertebral fractures at month 36 was 68% (95% CI: 0.26, 0.41; $p < 0.0001$). Risk reductions for nonvertebral fractures and hip fractures were 20% (95% CI: 0.67, 0.95; $p = 0.0106$) and 40% (95% CI: 0.37, 0.97; $p = 0.0362$), respectively. Consistent effects were observed in subgroups at higher fracture risk defined by other baseline characteristics: subjects with ≥ 2 prevalent vertebral fractures or having prevalent vertebral fractures which were moderate or severe, subjects with femoral neck T score ≤ - 2.5 and subjects with age ≥ 75 years. Body weight did not affect the incidence of vertebral fracture or lumbar spine BMD levels.

Trial 138 was a multinational, multicenter, double-blind, placebo-controlled trial involving 1468 men with nonmetastatic prostate cancer following definitive local therapy receiving androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonists or following

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orchiectomy. Approximately 10% of the study population underwent orchiectomy. Patients were randomized 1:1 to either denosumab (734) or placebo (734) once every 6 months for a total of 6 doses over a 36-month treatment period. All patients received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation throughout the trial. Randomization was stratified by age group (< 70 years vs. ≥ 70 years) and duration of ADT at trial entry (≤ 6 months vs. > 6 months). Upon completion of the 36-month treatment period, patients were either continued on trial for 24 months during which no investigational product was administered, or were offered enrollment in a 2-year extension trial. The primary efficacy endpoint was the percent change in lumbar spine BMD from baseline to month 24. Key secondary endpoints were percentage change in femoral neck BMD and total hip BMD from baseline to month 24, percentage change in lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36, subject incidence of any fracture, and subject incidence of new vertebral fracture over the 36-month treatment period. Neoplastic disease assessments consisted of bone scans at baseline and month 36 and PSA levels every 6 months during the treatment phase of the trial. In addition, there were exploratory analyses to assess effects on cancer outcomes based on periodic bone scans or PSA results. Survival rate at 36 months was also an exploratory endpoint.

There was a statistically significant increase in lumbar spine BMD between denosumab and placebo treated groups at 2 years (denosumab + 5.6%, placebo -1%) based on a least square mean estimate. The treatment difference was 6.7% (95% CI: 6.2, 7.1), favoring denosumab. Consistent effects on lumbar spine BMD were observed regardless of baseline age, race, geographical region, weight/BMI, BMD, level of bone turnover, duration of androgen deprivation therapy, and presence of vertebral fracture. The treatment differences from baseline to month 24 in femoral neck BMD were 3.9% (95% CI: 3.5, 4.4, $p < 0.0001$) and total hip BMD 4.8% (95% CI: 4.4, 5.1. $p < 0.0001$). There was a statistically significant reduction in the incidence of new vertebral fractures at 36 months, denosumab 1.5%, placebo 3.5% (OR: 0.37, 95% CI: 0.18, 0.78: p=0.0125). At month 24, the incidence of any fracture was not statistically significant, 45/734 (6.1%) in the placebo group and 32/734 (4.4%) in the denosumab group (p=0.1282). At month 36, the incidence of any fracture was also not statistically significant, 53/734 (7.2%) in the placebo group and 38/734 (5.2%) in the denosumab group (p=0.1048). The PSA and bone scan data were inadequate to provide any meaningful conclusions regarding progression of pre-existing prostate cancer. All cause mortality was 5.9% for both treatment groups at 36 months.

The evaluation of clinical safety for this application was based on analyses of the experiences of 14,000 patients in 30 clinical trials with up to 5 years of exposure. These trials included patients with normal or low bone density, as well as those with bone density in the osteoporotic range. In addition to separate analyses of the two randomized, placebo controlled trials for the hormone ablation therapy (HA) indications (135 and 138), safety data from trials 135, 138 as well as two randomized, placebo controlled trials (216 and 132) for the post-menopausal osteoporosis (PMO) indications were pooled and analyzed to assess overall safety. The most common adverse events (patient incidence of ≥ 5%, and denosumab group > placebo) were back pain, arthralgia, extremity pain, osteoarthritis, constipation, musculoskeletal pain, hypercholesterolemia, dizziness, peripheral edema, and upper respiratory tract infection. The most serious adverse events were cardiac disorders, nervous system disorders, infections, and gastrointestinal disorders. Adverse events identified as important by the applicant and the FDA review teams

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were infections (including serious skin infections in PMO Trial 216), tumor promotion (i.e., growth of pre-existing tumors in response to stimulation by a drug or biologic), new primary malignancies, hypocalcemia, suppression of bone remodeling, osteonecrosis of the jaw, and cataracts (in Trial 138 only).

All key trials submitted with this application met their efficacy endpoints. When compared to placebo, treatment with denosumab increases bone mineral density in both women with breast cancer treated with aromatase inhibitors (AIs) and men with prostate cancer treated with androgen deprivation therapy (ADT). In addition, treatment with denosumab significantly decreases the risk of vertebral fractures in women with postmenopausal osteoporosis (PMO) and men with prostate cancer receiving ADT. There is a need for drugs for the treatment of patients with osteoporosis who are at high risk for fractures. While there are currently approved therapies for the treatment and prevention of osteoporosis (see Table 2), not all patients receive benefit from these drugs and other patients become refractory to their effects. In addition, there are patients who are intolerant to these therapies because they can have major gastrointestinal and other severe toxicities. Over half of women who start bisphosphonates (BP) therapy discontinue treatment based on side effects and intolerability within one year. Mortality rates for women with osteoporosis in the first year after a hip or vertebral fracture are significantly higher than in the general population, and approximately 20% of women die within a year of hip fracture. There is also a need for agents to treat patients with bone loss associated with hormone ablation (HA) therapies. At the present time, there are no FDA approved agents for the HA indications; although, it is the accepted practice of medicine to treat with bisphosphonates for these indications.

The overall safety profile for denosumab is unacceptable for women with breast cancer receiving aromatase inhibitors, and men with prostate cancer receiving androgen deprivation therapy because neither trial submitted in support of these indications was designed to evaluate neoplastic disease. Additional data from well-designed, controlled clinical trials is needed to determine if denosumab plays a role in stimulating tumor growth in pre-existing tumors. Although it is notable that the most common adverse events observed with denosumab were not serious, or are amenable to mitigation, there are a number of safety issues requiring further study and experience to determine their relevance and importance. While there were no confirmed cases of osteonecrosis of the jaw (ONJ) in this application, data from ongoing and recently completed trials in patients with advanced cancers indicate that ONJ remains a safety concern. Because denosumab inhibits the signaling of RANK on activated T-cells and dendritic cells by binding RANK ligand, and an increase in the incidence of infections was noted throughout the development program for denosumab, the effects of denosumab on the immune system will also require additional study. Likewise, the effects of denosumab on the development of new malignancies will require further assessment and experience as will long term outcomes resulting from the significant suppression of bone remodeling observed with denosumab. Finally, the increased incidence of cataracts observed in prostate cancer patients (Trial 138) will require additional study.

Prevention

It is also the recommendation of this reviewer to deny approval for the applicant's proposed indications for the prevention of bone loss in women with breast cancer receiving aromatase

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inhibitors and for the prevention of bone loss in men with prostate cancer receiving androgen deprivation therapy. This recommendation is based on the following: In Trial 135, although the breast cancer patients studied were individuals with low and normal bone mass, the trial was never intended to stand alone in support of approval because the primary endpoint is not accepted as a measure of clinical benefit for regulatory purposes. Reduction in fractures is the accepted primary endpoint for regulatory purposes and the trial in patients with breast cancer (Trial 135) relied upon the PMO prevention trial (Trial 132) for confirmation of clinical benefit. Trial 132 enrolled women with low bone mass who were at relatively low risk of fracture based on an estimated 10-year risk of hip fracture (0.8%) and an estimated 10-year risk of major osteoporotic-related fractures (9.5%) for the overall study population in the pivotal prevention trial. Although the trial met its primary efficacy endpoints, the submitted data does not indicate how to identify patients who would benefit from administration of denosumab for a prevention indication in women with breast cancer on aromatase inhibitors. Since it is not possible to identify these patients for therapy, and many of the risks associated with denosumab therapy are serious or unknown, the administration of denosumab in a prevention population is not justified. This same logic applies to patients with prostate cancer receiving ADT. The data submitted does not indicate how to identify patients with prostate cancer on ADT who would benefit from a prevention strategy. Baseline lumbar spine BMD T-scores for trial enrollees included 61% with normal bone mass, 29% with low bone mass, and 9% with osteoporosis. It should be noted that Trial 138 included a measure of clinical benefit as part of the trial, i.e., the incidence of new vertebral fractures at 36 months, which was statistically significantly decreased for patients in the denosumab group. In spite of this result, the risk: benefit ratio for prostate cancer patients receiving ADT with normal or low bone mass is unfavorable at this time. Since the benefits of osteoporosis prevention are not well defined for either group of patients studied to support the prevention indications, the potential safety signals identified for denosumab are serious enough to warrant additional study in these patients in order to identify who would benefit from administration of denosumab for any prevention indication.

1.2 Risk Benefit Assessment

The risks identified in this review outweigh the benefits of approving a new biologic agent for a population of patients who are at increased risk for fractures associated with hormone ablation therapies. Patients with postmenopausal osteoporosis (PMO) have many approved agents for the indications sought in this application, and while there are no other approved agents for the specific indications sought for the breast and prostate cancer populations, other agents are in common use by the medical community in both populations. The distinction between the osteoporosis and cancer populations, however, is somewhat artificial if one considers the fact that bone loss associated with hormone ablation therapies is no different from bone loss associated with other drugs, e.g., corticosteroids, or other causes of hypogonadism. The need for health care provider administration could increase oncologist oversight and enhance participation in promoting the bone health of patients, a stated goal of the American Society of Clinical Oncologists. Because it is given subcutaneously, denosumab may be easier to take than some of the oral bisphosphonates, and is not subject to the serious upper gastrointestinal toxicity caused by them. The dose frequency proposed for labeling (every 6 months) may be beneficial to patients by improving compliance; however, the dose frequency is by no means unique. There are a number of approved bisphosphonates with infrequent dosing regimens. For patients who exhibit significant bone loss, the immediate pharmacodynamic effects observed with denosumab

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are of benefit in rapidly increasing bone density. In addition, unlike bisphosphonates, denosumab's effects on bone resorption cease almost immediately upon discontinuation. This could be of benefit to some patients, e.g., women of childbearing age who plan to become pregnant. (Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm, e.g., skeletal and other abnormalities, if a woman becomes pregnant even after completing a course of bisphosphonate therapy.) It must also be remembered that not all patients respond to other approved treatments for osteoporosis, and some patients are intolerant of the gastrointestinal side effects.

As with any new product, not all of the associated risks can be known prior to marketing approval. The potential safety signals identified in this application require close observation of postmarketing adverse event reporting. Previously unknown risks may also be identified during the postmarketing period. The risks observed during the clinical development of denosumab to date include a number of important toxicities. Discussions of these specific safety signals follow.

Tumor Promotion: For supportive care agents administered to patients with cancer, the risk/benefit analysis must take into consideration the potential for the agent to stimulate growth of pre-existing tumors or to negatively impact the efficacy of concomitant cancer therapy. There is a growing body of evidence suggesting that promotion of tumor growth may exist for drugs in which there is no demonstrable direct relationship between receptors and tumor proliferation. Neither of the hormone ablation (HA) trials included rigorous prespecified plans to evaluate potential treatment effects on time-to-event endpoints or overall survival. The data that was analyzed with regard to tumor promotion for both HA trials are subject to a number of caveats for consideration in decision making. Because disease progression data were obtained as part of the overall safety data and were not based upon pre-specified, scheduled assessments of breast or prostate cancer, there is the strong potential for ascertainment bias in the results. In addition, because the trials were relatively small and not powered for time-to-event or survival endpoints, the confidence intervals around the safety data obtained are wide.

Limited data on cancer progression are available for patients with breast cancer in Trial 135. A tabulation of adverse events of metastasis and an exploratory analysis of OS are the only data available for analyses involving progressive disease in patients with breast cancer. As noted previously, the adverse event data tabulated for events of metastasis were not confirmed by prespecified imaging assessments and are prone to ascertainment bias. The exploratory OS analysis in Trial 135 was not statistically meaningful because there were not enough events (1% for each treatment group), and not enough events would be expected in this population of breast cancer patients to perform a meaningful analysis. With regard to patients with prostate cancer, in Trial 138, the adverse events data tabulated for events of metastasis are also prone to ascertainment bias. However, of note in the 138 Trial, exploratory analyses of the OS, PSA and bone scan data provided positive evidence that was contrary to the findings in the adverse events tabulated data. Although exploratory, these analyses demonstrated denosumab was no worse

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than placebo with regard to measures of tumor progression. These analyses have been interpreted as reassuring; however, the trial was not designed appropriately to measure these outcomes. Additional data from well designed, blinded trials (which include time-to-event endpoints and are powered for survival), are required before any conclusions about the effect of denosumab on tumor progression can be reached.

Infections: Patients in the denosumab group were observed to have an increased incidence of serious infections. There were more serious infections of the skin, ear, abdominal system and urinary tract. Also, endocarditis, infective arthritis and skin ulcers were observed more commonly in denosumab treatment groups. However, there was no increase in opportunistic infections observed in patients treated with denosumab. RANKL, the target for denosumab, is involved in signaling pathways that play a role in immune function, either directly via activated T-cells and dendritic cells, or indirectly via TNF-related activation-induced cytokine (TRANCE). Activated T-cells express TRANCE, a differentiating factor of osteoclasts. In the adult immune system, TRANCE also modulates immunity via dendritic cells which are required to initiate T-cell mediated immunity. Disruption of the RANKL/RANK pathway over time may lead to unforeseen consequences with regard to immune dysregulation; therefore, the long-term immune effects of denosumab should be studied in new or ongoing trials.

Malignancy: In the postmenopausal osteoporosis (PMO trials), patients in the denosumab group were observed to have an increased incidence of breast cancer, pancreatic cancer, gastrointestinal cancer and reproductive cancers. Breast cancer was the most common adverse event that led to discontinuation of investigational product in patients with PMO. However, the incidence rates for the common cancers observed were small, < 1%, and the overall incidence of cancers in the PMO trials were balanced between the treatment groups (approximately 4%). These findings also require further study to determine their significance.

Skin and soft tissue disorder: Patients treated with denosumab were more likely to develop skin and soft tissue related adverse events. These excluded infections. There were more bullous conditions, pruritic conditions, skin rashes, dermatitis and eczema related adverse events in the denosumab group compared to placebo. For other specific events, the incidence rates were balanced between the treatment groups.

Bone biopsy histomorphometry: Bone histomorphometry results demonstrated a degree of bone remodeling suppression not previously observed with other antiresorptive agents. Additional data is required to determine the long term consequences of this finding.

Hypocalcemia: Hypocalcemia associated with the administration of denosumab was transient (nadir at day 8-11), resolved spontaneously after discontinuation, and there were no serious clinical sequelae observed. Adequate calcium and Vitamin D supplementation was required in the key clinical trials.

Osteonecrosis of the jaw (ONJ): No cases of ONJ were positively adjudicated in the key clinical trials. This included cases identified by the applicant and adjudicated by the independent ONJ committee. An FDA analysis of the integrated safety database identified possible additional cases. These cases were reviewed by subject matter experts in the Division of Dermatology and Dental Products and based on accepted diagnostic criteria were not confirmed. However, at least ten confirmed cases of ONJ have been reported in other ongoing or completed trials conducted by the applicant in patients with multiple myeloma and metastatic cancers.

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Severe and End-stage Renal Disease: In a single dose, open label trial to assess PK, safety and tolerability in patients with both normal and abnormal renal function not receiving calcium or vitamin D supplementation, it was concluded that the PK of denosumab is not influenced by renal dysfunction of any severity. However, in patients with severe (creatinine clearance < 30 mL/min) or end-stage renal disease, an increased incidence and severity of hypocalcemia was observed.

Although the trials submitted as part of this application have met their efficacy endpoints, approval for both of the cancer treatment indications should be denied. Based on the available data provided for denosumab as a part of this application, the risk:benefit analysis cannot be completed. There is no reliable data to support the contention that this antibody causes no detrimental effects on tumor outcomes, and additional data from ongoing and recently completed trials in patients with metastatic cancers, designed with specific cancer related endpoints, should be submitted to FDA for review prior to consideration for approval. Should future approval be granted, the approval should be limited to well-defined patient populations who are at high risk for fracture, or who have failed or are intolerant to other treatment alternatives. While the majority of the safety concerns identified are not severe, some of the potential safety signals previously identified and discussed have serious ramifications for patients and must be evaluated further. This is especially true with regard to the possibility of detrimental effects on cancer outcomes. Any approval must be predicated on data from adequately designed and well-conducted clinical trials demonstrating that treatment with denosumab results in no detrimental effects on cancer outcomes. Such data is lacking in this application. Additional data is required to assess effects on cancer outcomes for patients treated with denosumab.

1.3 Recommendations for Postmarket Risk Management Activities

None.

1.4 Recommendations for Postmarket Studies/Clinical Trials

None.

2 Introduction and Regulatory Background

Denosumab is an IgG_2, fully human monoclonal antibody to receptor activator for nuclear factor-kB ligand (RANKL). RANKL is a 38kD, 316 amino acid protein with extracellular domains that self-associate as a trimer. RANKL expression is modulated by various cytokines, glucocorticoids, and parathyroid hormone and is produced by cells of osteoblastic lineage and activated T cells. RANKL stimulates its specific receptor, RANK, initiating intracellular signaling cascades which promote osteoclast formation, fusion, differentiation, activation, and survival, leading to enhanced bone resorption and bone loss. Denosumab blocks the binding of RANKL to RANK. RANK is a widely expressed 616 amino acid, type I transmembrane protein that associates at the cell surface as a trimer. RANK can be induced by CD40L stimulation on dendritic cells and via T cell receptor engagement (+ TGF-b, IL-4) on T cells. RANK also prevents terminal differentiation and activation of osteoclasts. Denosumab binds specifically to RANKL and does not bind to TNFα, TNFβ, TNF-related apoptosis-inducing ligand (TRAIL), or CD40L.

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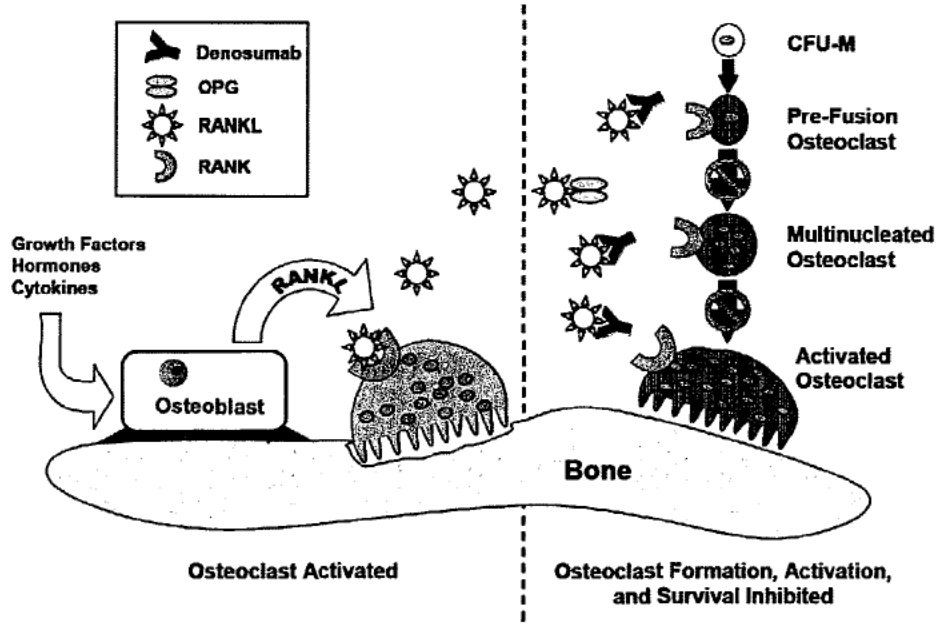
Figure 1 OPG/RANK/RANKL Pathway (excerpt from Clinical Overview)



CFU-M - colony-forming unit-macrophage; OPG = Osteoprotegerin; RANK = receptor activator of nuclear factor-κB; RANKL = RANK ligand

In the United States (US), breast cancer is the most common cancer in women and the second most common cause of cancer deaths. US breast cancer deaths for 2008 are estimated at over 40,000, with an estimated overall incidence of approximately 182,000. Similarly, for prostate cancer in the US, deaths are estimated at approximately 28,000 for 2008 with an overall incidence of approximately 186,000[1]. Hormone depletion is a primary treatment modality for estrogen receptor positive breast cancer as well as prostate cancer. For women with breast cancer, aromatase inhibitor (AI) therapy has been shown to be beneficial for postmenopausal women with ER+ breast cancer. The American Society of Clinical Oncology (ASCO) has concluded that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen.[2] The main consequence of AI therapy is reduction in estrogen levels. It is well recognized that bone loss is associated with estrogen deficiency in postmenopausal women. Postmenopausal bone loss may be accelerated with further reductions in estrogen levels by aromatase inhibition. Bone loss in postmenopausal women occurs at a rate of approximately 1% per year. In the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial, treatment with the aromatase inhibitor Arimidex alone resulted in a median percent change in lumbar spine bone

1.Jemal A, Siegel R, Ward E et. al. Cancer statistics, 2008. Cancer J Clin. 2008 Mar-Apr;58(2):71-96. Epub 2008
2 Winer EP, Hudis C, Burstein HJ et.al. American society of clinical oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005 Jan 20;23(3):619-29. Epub 2004 Nov 15

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mineral density of -2.3% at one year and -4.0% at two years. In addition to the changes in BMD, these women are at increased risk for fractures.[3]

Prostate cancer is the most commonly diagnosed cancer among men in the United States accounting for approximately 29% of all new cancers reported. For men with prostate cancer, short course androgen deprivation therapy (ADT) is commonly prescribed as monotherapy or in combination with external beam radiation for men with early stage disease. ADT lowers both testosterone and estrogen in men with prostate cancer by decreasing the availability of testosterone for conversion to estrogen. A loss of BMD can occur after only 6 to 9 months of ADT and the longer the duration of therapy, the greater the risk for osteoporosis and skeletal fractures[4].

Although there is no FDA approved treatment for the specific cancer-related indications sought in this application, there are numerous trials, including trials with bisphosphonates[5], demonstrating increased bone density and decreased fractures for therapies affecting bone resorption for both women receiving AIs and men receiving ADT. Lifestyle modifications, including smoking cessation, regular exercise, and supplementation with calcium and Vitamin D are the treatments most commonly recommended.

Osteoporosis is a systemic skeletal disease characterized by low bone mass as well as microarchitectural changes in bone tissue. These changes result in fragile bones and an increase in susceptibility to fracture. The risk of osteoporotic fractures for both men and women is dependent upon factors other than decreased bone mass. Age, prior factures, a family history of hip fractures, high bone turnover, low body mass index, tobacco use, and alcohol abuse, are among the most important factors. Genetic and nutritional factors (e.g. calcium and vitamin D intake) also play significant roles.

Antiresorptive agents alter three-dimensional trabecular bone architecture that do not necessarily depend upon changes in BMD, making cancellous bone more plate-like and denser, with increased and thicker trabeculae. With bisphosphonates, the trabecular architecture becomes more isotropic providing protection against fracture risk in falls that may stress the bone in unusual directions. The fracture risk reduction seen in the first year of treatment with antiresorptive agents seems to be most prominent at trabecular bone sites. Antiresorptive agents have little effect on cortical bone geometry. Consequently, increased strength of cortical bone probably occurs through increased tissue mineralization and/or decreased cortical porosity rather than through geometric changes.

3 Eastell R, Adams JE, Coleman RE et.al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination, trial 18233230. J Clin Oncol. 2008 Mar 1;26(7):1052-8.
4 Shahinian VB, Kuo YF, Freeman JL, et. al. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005 Jan 13;352(2):154-64.
5 Smith MR, Eastham J, Gleason DM, et. al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol 2003 Jun;169(6):2008-12

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In general, the primary endpoint for osteoporosis treatment trials is the incidence of morphometric vertebral fractures. The key trial submitted in support of the breast cancer indication was not designed to evaluate fracture events. However, Trial 216, the key trial for the PMO indication, was designed to evaluate the incidence of morphometric vertebral fractures in postmenopausal women. FDA agreed that the primary endpoint for the trial in patients with breast cancer would be an acceptable surrogate for clinical benefit based upon a demonstration of decreased incidence of fractures in Trial 216. Trial 138 included both a primary endpoint of increase in BMD and key secondary endpoints of vertebral and all fractures.

It is important to note that it has been the practice of the Office of Oncology Drug Products (OODP) and it's predecessors in CDER and CBER to examine *in vitro* and *in vivo* nonclinical proof-of-concept and available clinical data for evidence of adverse effects on tumor outcomes prior to marketing approval, with the requirement for clinical studies to investigate possible adverse risks by conducting post-marketing studies. In cases where pharmacodynamic or nonclinical data suggested the potential for stimulation of tumor growth, such as the receptor for a growth factor being present on tumor cells, and clinical studies were lacking in specific tumor types expressing the receptor, the indication for the product was restricted until such studies were performed (e.g., initial approval for granulocyte colony stimulating factors was limited to patients with non-myeloid malignancy). In addition, there is a growing body of medical literature suggesting that promotion of tumor growth may exist for drugs in which there is no demonstrable direct relationship between receptors and tumor proliferation. In these instances, drugs used to palliate cancer treatment-related toxicity may not only bind directly to tumor cells with consequent alterations in known signal transduction pathways, but may also stimulate tumor growth through binding to receptors in non-malignant components of the tumor microenvironment, or through activation of other signal transduction pathways not directly or intentionally targeted. Many aspects of tumor progression are still not well understood. However, there is now evidence that some agents administered to palliate cancer treatment-toxicity may enhance tumor growth. OODP currently requires that supportive care drugs and biologics which may affect tumor growth directly or indirectly be evaluated in studies designed to identify detrimental effects on cancer outcomes (i.e., time-to-event endpoints such as progression free survival or overall survival).

2.1 Product Information

Table 1 Denosumab Product Information

Generic Name:	Denosumab
Trade Name:	PROLIA™
Pharmacological Category:	Receptor activator for nuclear factor-kB ligand (RANKL) antagonist
Original BLA:	Yes
Drug Class:	Recombinant humanized monoclonal antibody
Route of Administration:	Subcutaneous injection
Dose and Regimen:	60 mg SQ once every 6 months
Populations Studied:	Patients with non-metastatic breast and prostate cancer receiving hormone ablation therapy Women with postmenopausal osteoporosis

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2.2 Tables of Currently Available Treatments for Proposed Indications

Approved products available for the treatment and prevention of osteoporosis are listed below in Table 2 which was adapted from the clinical review conducted by the Division of Reproductive and Urologic Products (DRUP).

Table 2 Approved Products for Osteoporosis Prevention and Treatment

Class	Drug	Prevention	Treatment
Bisphosphonate	Fosamax	•	•
	Fosamax PlusD		•
	Actonel	•	•
	Actonel with Calcium	•	•
	Boniva	•	•
	Reclast	•	•
Estrogen Agonist/Antagonist	Evista	•	•
PTH analog	Forteo		•
Calcitonin	Miacalcin	**both***	
	Fortical	**both***	
Estrogen and Estrogen/Progestin combination products	Premarin	•	
	Premphase	•	
	Prempro	•	
	Climara	•	
	Climara Pro	•	
	Prefest	•	
	Femhrt	•	
	Activella	•	
	Vivelle	•	
	Alora	•	
	Menostar	•	
	Vivelle Dot	•	
* Original Approval based on BMD, not fracture efficacy			

2.3 Availability of Proposed Active Ingredient in the United States

Denosumab is not marketed in the United States currently. The current application is an original BLA.

2.4 Important Safety Issues with Consideration to Related Drugs[6]

In general in patients with cancer, bisphosphonates are administered to treat bone loss associated with the malignancy or its treatment. The most common toxicities experienced with bisphosphonate therapy are tolerated by patients after appropriate treatment. However, several complications associated with bisphosphonates are serious and require careful attention and monitoring, specifically, hypocalcemia, renal toxicity, and osteonecrosis of the jaw (ONJ).

6 Dunstan CR, Felsenberg D, Seibel MJ. Therapy insight: the risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease. Nat Clin Pract Oncol. 2007 Jan;4(1):42-55.

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Hypocalcemia can occur in patients treated with bisphosphonates when the compensatory mechanisms of the body, most importantly secretion of parathyroid hormone, are dysfunctional because of a history of parathyroidectomy, low levels of Vitamin D, and/or hypomagnesemia. Periodic monitoring of serum magnesium, calcium and phosphate during therapy is essential. Nephrotoxicity for patients receiving bisphosphonates is both dose and infusion-time dependent and may require treatment and dose modifications as appropriate. ONJ with bisphosphonate therapy is most common in patients with underlying malignancies. Risk factors include dental extraction, poor dental hygiene during treatment, monthly sequential therapy with pamidronate/zometa, longer periods of follow-up, older age at diagnosis, and certain concomitant medications (e.g., corticosteroids). Both prevention and conservative treatment strategies (limited debridement, antibiotics, and good oral hygiene) are recommended for ONJ.

In addition to the foregoing, RANKL inhibition has immune system effects because RANK is expressed on dendritic cells and activated B and T cells. Treatment with denosumab could lead to an increased risk of susceptibility to infections, especially in certain high risk groups of patients (e.g., patients receiving chemotherapy).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 3 Regulatory Activity

July 17, 2001	INDs 9837 and 9838 may proceed letters issued
April 21, 2004	Type B Pre-IND (11709)/Pre Phase III meeting
May 14, 2004	Original IND 11709 submission (Protocols 20040135 and 20040138)
March 14, 2005	SAP acceptable
September 20, 2005	Pre-Phase 3 meeting
December 8, 2006	Type C CMC meeting
February 5, 2008	Type C teleconference to discuss structure and content of marketing application
July 8, 2008	Pre-BLA CMC meeting
July 29, 2008	Pre-BLA CMC follow-up teleconference
October 21, 2008	Type B Pre-BLA Clinical meeting
December 19, 2008	BLA application submitted (under BLA STN 125320/0)
January 14, 2009	Application administratively divided
May 15, 2009	120 Day Safety Update received

2.6 Major Clinical Regulatory Agreements

The history with regard to products developed for osteoporosis includes FDA involvement in the design and review of trials that established the regulatory precedent for the aggregate endpoint, skeletal related events (SRE). It was determined that SREs represented an adequate efficacy measure for new drug approval and that a decrease in the number of SREs represented clinical benefit. In the current application, the primary endpoints for the HA indications, change in BMD from baseline to a fixed time point, are not regarded as representative of clinical benefit. Rather, proof of clinical benefit relies on the outcome of the larger PMO trial for Trial 135 (see summary

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of agreements, 21 April 2004 Type B Meeting below), and fracture reduction (a secondary endpoint) in Trial 138.

The following major clinical regulatory agreements were made regarding the conduct of the trials submitted to support both the breast and prostate cancer indications.

21 April 2004 Type B Meeting
FDA and the applicant agreed:

- Approval for denosumab for the treatment of bone loss associated with hormone ablation therapy would be contingent upon adequate anti-fracture efficacy being demonstrated in the three year postmenopausal osteoporosis treatment trial. This trial would then validate that denosumab-induced increases in BMD are associated with anti-fracture efficacy

- The phase 2 trial (20010223) supported the selected dose of 60 mg denosumab administered SC once every 6 months for the Phase 3 trials.

- The design of the two phase 3 trials in breast cancer and prostate cancer would support registration in this indication, provided adequate anti-fracture efficacy is demonstrated in the 3-year PMO treatment trial.

FDA did not agree that the phase 3 trial in prostate cancer (b) (4) (b) (4)

14 March, 2005 FDA Letter Comments
FDA and the applicant agreed:

- The proposed SAP was acceptable.
- The primary analysis of BMD percent change would be from baseline to the last scheduled time point (at month 12) using either an ANOVA or ANCOVA with the baseline measurement as a covariate.
- Missing data should be kept to a minimum and imputation should be done by the last observation carried forward (LOCF) method.
- A repeated measures analysis can be used as a supportive analysis.

2.7 Other Relevant Background Information

May, 2004 Medical Products Agency (Sweden); AFSSAPS (France); Medicines Evaluation Board (Netherlands)
Scientific advice from these agencies regarding the phase 3 clinical trials was integrated into the denosumab development program. The two phase 3 trials to treat bone loss associated with hormone ablation therapy in non-metastatic breast and prostate cancer (Trials 20040135 and 20040138 respectively) were considered appropriate designs to evaluate changes in BMD and potential reduction in fracture risk (latter in prostate cancer only). The recommendation to evaluate fractures in the breast cancer population was not incorporated into the phase 3 trial (20040135).

June, 2008 EMEA

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A single RMP for denosumab was requested by EMEA. EMEA stated that it should include discussion of any other indications (adult and pediatric) in the development program with regard to risk minimization in the context of potential off-label use. In addition, the introduction of adherence aids such as reminder stickers was requested for inclusion in the RMP.

October, 2008 EMEA
The EMEA issued a decision related to denosumab: Pediatric Investigation Plan under Article 25 of Regulation (EC) No. 1901/2006 as amended for PIP (EMEA-000145-PIP01-07). There were no recommendations to conduct pediatric trials related to HA associated bone loss in breast or prostate cancer (Product Specific Waiver).

3 Ethics and Good Clinical Practice

3.1 Submission Quality and Integrity

This application was submitted in CDISC format. In general, the quality of the submission was adequate for review of the trials pertaining to both the HA and PMO indications. However, analyses of the specific key trial databases revealed a large number of database errors. Specifically, each database was compared to the CDISC SDTM and ADaM standards and reports were generated of all instances where the data did not conform to the standards. In a review of the specific errors identified, the majority were noted to be minor noncompliance with the controlling standards which are not expected to affect the quality of the submission or the conduct of this review. Other divergences from specific controlling data standards and/or regulations will be discussed under the headings to which they apply.

3.2 Compliance with Good Clinical Practices

On March 5, 2009 in response to FDA's questions regarding on site trial monitoring activities, the applicant submitted to the file an amendment discussing the monitoring procedures for Trials 20040135 (Trial 135) and 20040138 (Trial 138). Provided was a detailed report of the monitoring plan and execution of the plan for the aforementioned trials. In general, the applicant audited a minimum of 5% of the investigator sites for each trial (4 sites for Trial 135 and 10 sites for Trial 138) as well as 2 of the top 10 enrolling sites for Trial 135 and 5 of the top 10 enrolling sites for Trial 138. Sites were selected for audit based on pre-specified criteria, i.e., enrollment, feedback received from applicant clinical trial teams, protocol deviations, serious adverse events (SAEs), investigators' experience, use of contracted monitors, and site location (region). The majority of site audits were conducted during the enrollment phase of the trial. The fourteen site audits included a review of compliance with the protocol, informed consent process, SAE reporting, accuracy and integrity of trial data, investigational product (IP) management, trial master file, support services (e.g. imaging facilities), and sponsor oversight of trial conduct. The assessment of trial activities/processes was accomplished through a review of trial documentation and interviews with the principal investigator and key trial staff. In addition to audits during the enrollment phase, sites were audited every 8 – 12 weeks during the treatment phase with the option to increase the monitoring frequency if warranted. One hundred percent (100%) source document verification was specified for the informed consent; eligibility criteria; DXA, X-ray, and fracture reports; adverse events; concomitant medications; and trial drug

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administration. The applicant's efforts to manage compliance with good clinical practices in these trials were adequate.

Analyses of the data for each of the HA trials were performed by this reviewer to identify sites of interest for DSI inspection. Protocol deviations were identified and evaluated by site. In addition, data for the primary endpoints were analyzed to evaluate if any site or sites were the main contributors to the efficacy results. Based on these analyses, a DSI consult was requested for sites 159 (Port Lucie, FL) and 183 (Wichita, KS) in Trial 135 and sites 129 (Waterbury, CT) and 188 (Myrtle Beach, SC) in Trial 138.

As DSI attempted to make arrangements to inspect the bone density data at the clinical trial sites, information regarding the verification of efficacy data became available. DSI was informed that trial sites do not retain a copy of the scans and there are no reports to verify as part of subject records. It was verified at the clinical sites that scans were performed at the required time points. In addition, the applicant was contacted in an effort to determine how the bone density data could be verified. DSI was informed that there was little they could do to verify the data, since the process of generating this data were mostly if not entirely electronic. The scans obtained at clinical sites were burned onto CDs and sent to (b) (4) the independent radiologic vendor for the trials, which then: (1) checked the CDs for meeting quality specifications, (2) removed CDs/images that did not meet quality standards from the pool to be analyzed, (3) selected the portion of the image on which bone density measurements were to be made, (4) "ran" the program which generated bone density data, and (5) uploaded the data to a central server shared with the applicant. Amgen then accessed the server to down load the data for creating bone density data sets and line listings. The typical material that is inspected to verify efficacy endpoint data (i.e., case report forms and source documents) were never generated. Some procedural aspects of converting the images into bone density results were available for verification at the CRO (b) (4), and selected portions of this information could be made available to the applicant, upon request. The DSI inspection concluded that the procedures employed by the applicant and the applicant's CRO (b) (4) were adequate.

In addition, the applicant noted in their clinical study report that there were GCP violations for Trial 216. Site 803, Lithuania, was reported as having a significant number of violations including enrollment of patients without informed consent or without meeting eligibility criteria, under reporting of serious adverse events, and other study conduct violations. The applicant excluded all subjects from this site, N=60, from the efficacy and safety analyses. Based upon this information, it is unlikely that bias was introduced into the analyses of the trial data as a result of theses violations.

3.3 Financial Disclosures

As required by 21 CFR 54.4(a) (1), the applicant provided listings of investigators who participated in each trial as well as completed forms FDA 3454 and 3455. In addition, the applicant submitted lists of investigators having disclosable financial arrangements, investigators who had no arrangements or financial interests requiring disclosure, and investigators who did not provide financial disclosure information. A review of these lists and information was undertaken. In the majority of cases, investigators had no arrangements or financial interests that

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required disclosure. Investigators who reported disclosable financial interest in the applicant are summarized in Table 4. For investigators who disclosed financial interests in the applicant, a Statement of Actions to Minimize Bias was completed and the actions taken were reviewed and are acceptable.

Table 4 Investigators with Disclosable Financial Arrangements or Interests (All Trials)

Investigator	Study	Site	Financial Information - Category	No. subjects enrolled
(b) (6)	20030216 20040132	(b) (6)	2,175 shares of Amgen stock	0/7868 1/332
	20050134		Owns Amgen stock (undisclosed amount)	0/96
	20040113 20040114		Stock valued in excess of $50,000	2/255 0/111
	20040135		Approx. $35,000 in lecture honoraria in (b) (6)	3/252
	20040138		Research grant from Amgen (undisclosed amt)	2/1468
	20040135		1,000 shares of Amgen stock	0/252
	20050134		Preceptorship	0/96
	20040113		$50,000 to conduct preclinical studies	0/255
	20050141		Contract with Amgen to fund a study (undisclosed amount)	6/1189
	20040144		Compensation for consultation and honoraria (undisclosed amt)	0/227
	20030216		Amgen provided research support: AUS $56,756, AUS $11,350 and AUS $50,000.	17/7868
	20040138		Each of his (b) (6) children own 800 shares of Amgen stock	6/1468
	20040138		Amgen stock worth $109,400	12/1468
	20030216		Amgen provided research support in the amount of $100,000.	51/7868
	20040114		Amgen has several grants with his institution (b) (6) (undisclosed amount)	0/111
	20040114		Owns Amgen stock (undisclosed amount)	0/111
	20050234		Undisclosed amt of stock (held for > 10 years)	5/504
	20050134		Other Amgen sponsored trials	0/96
	20040113		Research grant (undisclosed amount)	1/255
	20030216 20060289		Amgen subsidized a study – $85,350.	1/7868 1/4900
	20040138		Grant or research (undisclosed amount)	5/1468
	20030216 20050141 20040144		1,200 or 5,000 shares of Amgen stock	13/7868 8/1189 14/227
	20050134		Grants to support research (undisclosed amt)	0/96
	20040138		Owns equity interest exceeding $50,000	1/1468
	20040138		Undisclosed significant equity interest	8/1468
	20040144		Funding for clinical project (undisclosed amt)	0/227

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

This submission was reviewed by the Division of Biologic Oncology Products (DBOP), Division of Reproductive and Urology Products (DRUP), the Office of Pharmacoepidemiology and Statistical Science, Office of Pharmaceutical Science/Office of Biotechnology Products/Division of Monoclonal Antibodies, Office of Biostatistics Review; the Office of Clinical Pharmacology; Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group, the Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies. Separate archived reviews for offices/divisions other than DBOP are available in the FDA document file and are referenced herein as appropriate.

4.1 Chemistry Manufacturing and Controls

The following discussion relies on the original review performed by the product quality team in the Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies. A separate archived review is available in the FDA document file.

Denosumab is a full length IgG_2 kappa human mAb against RANKL that is produced in a CHO cell line. It recognizes an epitope (b) (4) in the D-E loop of human RANKL within the receptor binding portion of the ligand. There is diminished ADCC and CDC activity because denosumab is constructed as an IgG_2 antibody. The mechanism of action for the antibody is ligand-binding which blocks the subsequent interaction of the ligand with its receptor. The antibody is manufactured using standard mAb manufacturing procedures and controls. There have been no clinically significant changes to manufacturing processes or product comparability during phase 2 and 3 trials. A facilities inspection was conducted for the drug substance manufacturing site at Boerhringer Ingelheim Pharma GmbH & Co., Biberach an der Riss, Germany. A contaminated harvest was revealed in the manufacture of drug substance lot 76003. It was recommended that the inspection be classified VAI. An additional facilities inspection was conducted for the drug substance manufacturing site at the Amgen, Inc. Lake Centre Facility in Boulder, Colorado. The results of this inspection are pending. The Amgen Manufacturing, Ltd. drug product manufacturing site in Juncos, Puerto Rico was last inspected April 9, 2007. A surveillance inspection was planned for June, 2009; however a report of this inspection was not yet available.

4.2 Clinical Microbiology

Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed by Dr. Suvarna from the Division of Manufacturing and Product Quality (DMPQ), Biotech Manufacturing Team (BMT). There were at least 6 amendments to the BLA based on information requests. The drug substance aspect of the BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective. Important CMC microbiology and product quality aspects of the drug substance are summarized below. These were excerpted from the DRUP clinical review.

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1. The ACO facility was inspected by a team of investigators (Kalavati Suvarna, Ph.D., Sarah Kennett, Ph.D, Nancy Schmidt, Kimberley Hoefen, and Maan Abduldyaem) from June 8, 2009 to June 12, 2009. No FDA form 483 was issued at the end of inspection (No violations found). The manufacturing process is microbially controlled at the ACO site. Hold time for all in process intermediates at the ACO site has been adequately validated for microbial control.

2. The BI Pharma facility was inspected by a team of investigators (Kalavati Suvarna, Ph.D., Chana Fuchs, Ph.D and Sarah Kennett, Ph.D.) from May 11, 2009 to May 19, 2009. A 1-item FDA form 483 was issued at the end of inspection. A contaminated harvest lot was processed further. A recommendation was made to classify this inspection as voluntary action indicated (VAI). The sponsor has responded to this observation. This response is being evaluated by the international compliance team within DMPQ, Office of Compliance and a final decision is pending.

3. The bioburden procedure for denosumab process was adequately qualified. The endotoxin procedure for denosumab drug substance analysis was adequately validated. The applicant was asked to provide calculation of the endotoxin limit based on worst-case minimal patient weight of 50 kg and the maximum single human dose for denosumab to determine the safety margin for the proposed endotoxin specification. The endotoxin drug substance specification for the postmenopausal osteoporosis indication is (b) (4) EU/mL, which is well below the threshold of human pyrogenic response. The endotoxin results for batches manufactured at ACO site (b) (4) varied from that manufactured at BI Pharma (b) (4) Although the endotoxin results from the two sites varied at the two sites, the results at both sites were within the acceptance criteria and well below the threshold of human pyrogenic response.

4. Section 3.2.P of the BLA pertains to drug product manufacture and was reviewed by Dr. Don Obenhuber from the Division of Manufacturing and Product Quality (DMPQ). The drug product manufacturing was found to be satisfactory; no major issues of concern were identified.

4.3 Preclinical Pharmacology/Toxicology

The following discussion relies on the original reviews performed by the Pharmacology/ Toxicology review teams in the Office of Oncology Drug Products, Division of Biologic Oncology Products and the Division of Reproductive and Urology Products. Separate archived reviews are available in the FDA document file.

The applicant performed a number of preclinical studies. In a one month study of cynomolgus monkeys administered doses of 0, 0.1, 1, and 10 mg SC once weekly with a 3 month recovery period, the expected pharmacological effects were observed, i.e., increased cortical bone mineral density, dose-dependent reduction in bone biomarkers, reductions of alkaline phosphatase and fluctuations of serum calcium levels without end organ toxicities. In addition, 28 out of 30 non-human primates observed were positive for anti-denosumab antibodies. In 6 and 12 month non-human primate studies, doses of 0, 1, 10, and 50 mg/kg SC once monthly were administered with a 3 month recovery. Observed were increases in cortical and trabecular BMD (radius, tibia, and femur) in the 10 and 50 mg/kg dose cohorts in females and in the 50 mg/kg dose cohort in males.

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In addition, dose-dependent decreases in bone markers, i.e., osteocalcin, serum C-telopeptide, urine N-telopeptide, were observed. Four females developed abscesses of the teeth or jaw at doses exceeding 10 mg/kg. In addition, two unscheduled deaths were observed in the male 50 mg/kg dose cohort, one found dead at week 11 and the other sacrificed moribund at week 42. The probable causes of death were acute renal failure secondary to infection. While both control and treated animals exhibited protozoal infections, it is possible that the treated animals were immunosuppressed resulting from treatment and, therefore, succumbed to infection. In addition, one animal exhibited cardiac histopathology consisting of minimal multifocal acute myocarditis and focal acute pericarditis

Reproductive toxicology studies were also performed. In the female reproductive toxicology study, no effects on cycle length, mating performance, or hormone levels were observed at doses up to 12.5 mg/kg SC weekly. The NOAEL in this study was > 12.5 mg/kg. Effects on embryo-fetal development included increased fetal spleen weight; however there was no histopathological correlate observed. In addition, there was a trend toward delayed ossification, including incidence of shortened, isolated, rudimentary and/or vestigial cervical ribs, and misaligned vertebrae. However, the trend was not deemed clinically relevant. In the male non-human primate reproductive toxicology study, no toxicity to spermatogenesis or male reproductive organs were observed following 12 months of monthly exposure at doses up to 50 mg/kg.

The potential for carcinogenicity was not evaluated in long term animal studies. However, there was no evidence for carcinogenicity in the 12 month non-human primate toxicology study or in the 12 or 16 month non-human primate pharmacology studies. There are no recommendations for carcinogenicity studies based on the intended HA clinical indications. Mutagenicity was not evaluated.

The potential safety issues suggested by the nonclinical studies, i.e., RANK -/- and RANKL -/- knockout transgenic mice failed to lactate because of impaired mammary gland development or impaired lactation, and RANKL knockout mice exhibited impaired lymph node formation during early development, are both addressed in labeling. Denosumab is not recommended for pregnant or breast feeding women, or for pediatric patients. No other nonclinical safety concerns were identified.

4.4 Clinical Pharmacology

The following discussions of the clinical pharmacology analyses undertaken for denosumab rely on the original review performed by the Office of Clinical Pharmacology, Divisions of Clinical Pharmacology 3 and 5. A separate archived review is available in the FDA document file.

4.4.1 Mechanism of Action

Denosumab binds with high affinity (Kd 3 x 10-12 M) and specificity to the soluble and cell-membrane-bound forms of human RANKL. Binding prevents activation of RANK and inhibits the formation, activation, and survival of osteoclasts. End effects are reduction in the number and function of osteoclasts, and decrease in bone resorption as well an increase in cortical and trabecular bone mass, volume, and strength. Denosumab is highly specific, binding only to

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RANKL and not binding to other members of the TNF family, including TNFα, TNFβ, TNF-related apoptosis-inducing ligand, or CD40 ligand.

4.4.2 Pharmacodynamics

The pharmacodynamic effects of denosumab were evaluated over the life of the development program. All key trials required scheduled evaluation of bone turnover markers, specifically serum C-telopeptide (CTx) and serum N-terminal propeptide type I procollagen (P1NP). Denosumab administration resulted in significant inhibition of bone resorption, as assessed by reductions in serum levels of Type 1 C-telopeptide (CTX1). Treatment with 60 mg of denosumab resulted in rapid reduction in the bone resorption marker serum CTX1 within 6 hours of SC administration by approximately 70% (Trials 216 and 132), with reductions of approximately 85% occurring by 3 days (Trial 223). Serum CTX1 reductions in bone turnover were maintained throughout the dosing interval (6 months). At the end of the dosing cycle, some attenuation of bone resorption inhibition was observed, indicating that reduction of bone turnover associated with denosumab administration is reversible when serum concentrations of denosumab diminish. Bone mineral density (BMD) continuously increased during treatment.

4.4.3 Pharmacokinetics

Pharmacokinetics (PK) of denosumab were studied broadly over the course of the development program. A validated sandwich enzyme-linked immunosorbent assay was utilized to quantify serum antibody concentrations. The assay methods relied upon securing denosumab and RANKL bound to the assay plate and detecting the antibody with labeled RANKL or anti-denosumab antibody. Serum concentrations timed data were analyzed using non-compartmental PK analysis methods. In patients with cancer, the PK analysis key trials were Trials 123 and 176. Trial 123 was a randomized, double-blind, active controlled, single dose, Phase I trial that evaluated the safety and tolerability of denosumab in patients with cancer-related bone metastases. A total of 54 subjects were enrolled in this two phase trial. Trial 176 was an open label, ascending dose, single and multiple dose trial that evaluated safety, PK and PD in 19 Japanese women with breast cancer and bone metastases. In the patients evaluated in Trial 176, PK characteristics were measured as follows: mean PK AUC0-t was 351 mcg d/mL (SD 144); mean Cmax was 7.7 mcg/mL (SD 3.1); mean Tmax was 8 days with a median range of 7 to 28 days; and mean $T^{1/2}$ was 24.7 days (SD 2.44).

Whether subject type affected denosumab PK parameters was also analyzed and there appeared to be no difference in PK when comparing healthy subjects to women with postmenopausal osteoporosis, women with breast cancer, and men with prostate cancer.

In addition to characterization of PK, the effects of renal impairment on the PK of denosumab were evaluated. PK was not influenced by renal dysfunction, regardless of the severity.

5 Sources of Clinical Data

Amgen submitted clinical data in eCTD and SDTM format for trials in support of both the HA and PMO indications as noted in Figure 2 below. Separate analyses of each trial were performed and a CSR was submitted for each key trial. Case report forms (CRF) were submitted for each

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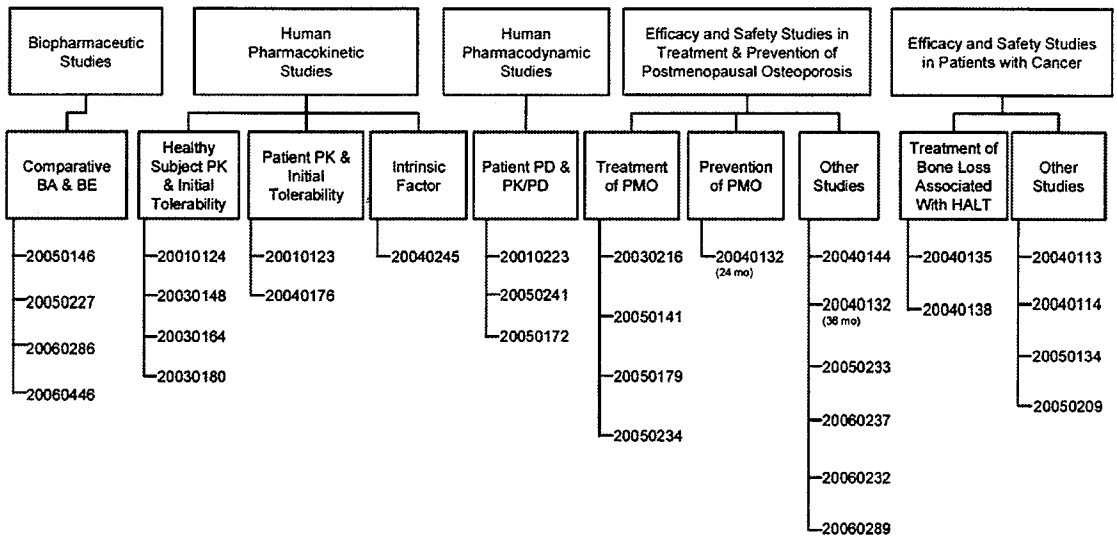
patient who died while receiving investigational product (IP), who had serious adverse events, those terminating study drug prematurely, and those categorized as other, lost to follow up, physician decision to terminate study drug, or patient decision to terminate study drug. A 120 day safety update was also submitted, as were follow-up data requested by FDA for further analysis of emerging safety issues identified during the review of this application.

5.1 Tables of Studies/Clinical Trials

Figure 2 Denosumab Clinical Trials (excerpt from CSR)



BA = bioavailability; BE = bioequivalence; HALT = hormone-ablative therapy; PD = pharmacodynamics; PK = pharmacokinetics; PMO = postmenopausal osteoporosis

5.2 Review Strategy

Clinical data from 1705 patients who received at least one dose of investigational product (IP) during the conduct of Trials 135 and 138 were submitted in support of the HA indications. These patients comprise the safety analysis population evaluated for this indication. Trial 135 included data from 249 patients receiving either denosumab (129) or placebo (120). There were six patients in the trial who did not receive the treatment to which they were randomized. Trial 138 included data from 1456 patients receiving either denosumab (731) or placebo (725). These two trials were the primary focus of this review. Each trial was reviewed separately for both efficacy and safety. Also reviewed were supporting Trials 113, 114, 134, and 209. Each clinical study report was reviewed to determine if the results demonstrated for the supporting trials were consistent with the primary analyses of the registrational trials. However, no formal comparisons to Trials 135 and 138 were performed. A random subset of approximately 10% of all case report forms and case narrative listings were reviewed for Trials 135 and 138 and compared to one or more of the datasets in order to confirm the adequacy of the data transfer. In addition, each trial was reviewed for adverse events of interest (e.g. hypocalcemia, infections, and osteonecrosis of the jaw). There were no major discrepancies identified during this review.

In addition to analyses of the key trials supporting the HA indication, data from the four key trials (132, 135, 138, and 216) submitted in support of all indications for this application were

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pooled and reviewed. Where necessary to further investigate a safety concern, CRFs and narrative line listings for Trials 132 and 216 were reviewed. In addition, the applicant's summary reports for certain adverse events of interest were reviewed and compared and contrasted to the independent safety analyses performed by this and other reviewers. The results of these reviews are discussed at length as part of the pooled analyses.

A number of SDTM data tabulation and ADaM datasets provided by the applicant were utilized to accomplish this safety review. These are discussed separately under the headings to which they apply below. In addition, the safety database was analyzed at all levels of the MedDRA hierarchy and by Standard MedDRA Queries in order to identify safety signals.

5.3 Discussion of Individual Clinical Trials

5.3.1 A Randomized, Phase III, Double-blind, Placebo-controlled Trial to Evaluate AMG 162 in the Treatment of Bone Loss in Patients Undergoing Aromatase Inhibitor Therapy for Nonmetastatic Breast Cancer (Trial 135)

Trial Summary: This was a multicenter (3), double-blind, placebo-controlled trial conducted in the US and Canada from October 4, 2004, when the first patient was enrolled, to May 11, 2007, when the last patient completed their end of study visit. Randomized were 252 patients (208 patients were planned) with nonmetastatic breast cancer who had received definitive local therapy and who were receiving aromatase inhibitor therapy. Patients were randomized (1:1) and received either 60 mg denosumab (129) or placebo (120) SC once every 6 months for a total of 4 doses during the treatment period of 24 months. Randomization was stratified by the duration of aromatase inhibitor therapy ($\leq$ 6 months vs. > 6 months). The primary endpoint was percentage change in lumbar spine bone mineral density (BMD) from baseline to month 12. All patients received daily calcium and vitamin D supplements. Adverse events, the incidence of fractures, and concomitant medications were evaluated prior to treatment and at months 1, 3, 6, 12, 15, 18, and 24 after initiation of investigational product or at the early-termination visit; clinical laboratory parameters and vital signs were measured at the same time points, with the exception of months 3 and 15. Dual x-ray absorptiometry (DXA) of the spine, femoral neck, and total hip was performed at baseline, months 1, 3, 6, and 12, and at the early-termination/month-24 visit; DXA of the total body and radius was performed at baseline, month 12, at the early termination/month-24 visit; x-rays were taken at baseline and month 24. Bone turnover markers were assessed at baseline, at months 1, 6, and 12, and at the early-termination/month-24 visit. Serum samples were obtained before and during the treatment period for assessment of denosumab concentrations, anti-denosumab antibodies, and exploratory biomarkers. An external data monitoring committee (DMC) monitored patient safety on an ongoing basis for the duration of the 24-month treatment period.

Eligibility Criteria: Eligible patients met the following criteria:

- Women $\geq$ 18 years of age with the ability to provide informed consent who had histologically or cytologically confirmed early-stage, estrogen-receptor-positive adenocarcinoma of the breast;
- Eastern Cooperative Oncology Group (ECOG) score of 0 or 1;
- no distant metastases;

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- completed treatment pathway (surgery, chemotherapy, radiation, and/or hormone therapy); currently on or initiating aromatase inhibitor therapy for the duration of the trial;
- no evidence of current unstable systemic disease, organic or psychiatric disorder, or inadequate organ function that could have interfered with completion of the trial or interpretation of results;
- no recent exposure to bisphosphonates or other medications known to influence bone metabolism;
- were not receiving concurrent anti-neoplastic agents;
- did not have recurrent disease;
- had not experienced fracture after the age of 25;
- lumbar spine, total hip, and/or femoral neck BMD T-score of -1.0 to -2.5 (low bone mass);
- none of the anatomic sites could have been in the BMD range corresponding to a T-score of < -2.5;
- ≥ 2 evaluable vertebrae for DXA assessments.

Endpoints:

- Primary: Percentage change in lumbar spine bone mineral density (BMD) from baseline to month 12.
- Secondary: Effect of denosumab compared with placebo on the BMD of the lumbar spine at 6 months, the total hip and femoral neck at 6 and 12 months, safety, and pharmacokinetics
- Exploratory: During 24 months of denosumab administration:
  - Assess BMD of the distal 1/3 radius (left forearm) and total body
  - Assess bone resorption and formation as measured by serum type 1 C-telopeptide (CTX1) and procollagen type 1 N-terminal peptide (P1NP)
  - Assess the effect of denosumab compared with placebo on vertebral and nonvertebral fracture incidence
  - Assess overall survival at month 24

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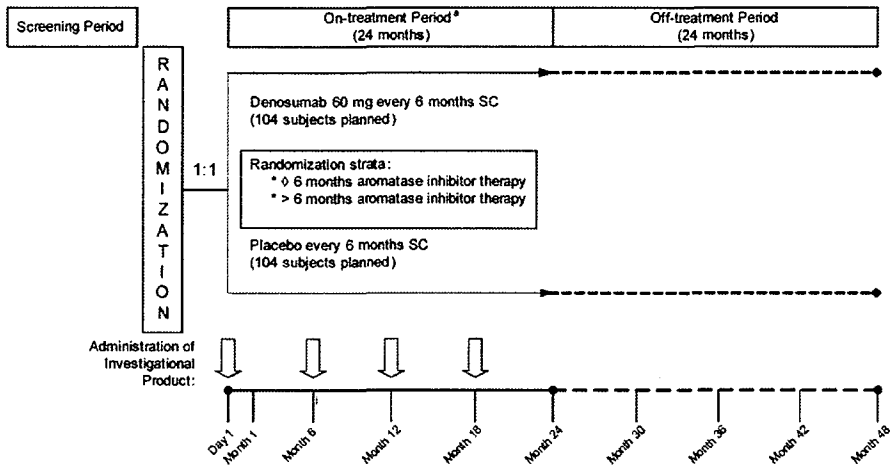
Trial Design:

Figure 3 Trial 135 Trial Design Schema (excerpt from CSR)



SC = subcutaneous

* BMD of the lumbar spine was assessed at screening and at all planned study visits except day 1 and months 15 and 18; the assessment obtained during screening was used as the baseline assessment of the BMD of the lumbar spine.

Treatments: Patients received 60 mg denosumab or placebo subcutaneously once every 6 months for a total of 4 doses during the treatment period of 24 months. This was planned as a 48-month trial to include the treatment period (with last dose administered at month 18) and a 24-month safety follow-up period that is ongoing.

Trial Sites and Enrollment:
See Appendix 9.4, Table 48.

Trial Populations:

- Efficacy: Full analysis set (all randomized patients), primary efficacy subset (patients with endpoints requiring reference to baseline), per protocol set (primary efficacy subset who were compliant with protocol), subgroup analysis subsets (age group, duration of aromatase treatment at trial entry, baseline BMI, prior chemotherapy, prior SERM use, race, baseline weight).
- Safety: The subset for safety included all randomized patients who received at least one dose of investigational product.

Demographics:
Summarized in Table 5 below are the patient demographics for this trial. Trial 135 enrolled 252 women with non-metastatic breast cancer, 127 randomized to the denosumab treatment group and 125 randomized to placebo. Of note are 2 patients randomized to denosumab who received placebo and 4 patients randomized to placebo who received denosumab. Most patients were white or Caucasian (denosumab 91%, placebo 95%), and most were treated in the US (denosumab 96%, placebo 97%). Other baseline demographics were also balanced between treatment groups.

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Table 5 Trial 135 Patient Demographics

Demographic	Denosumab n (%)	Placebo n (%)
COUNTRY		
CAN	5 (4)	4 (3.2)
USA	122 (96)	121 (97)
SEX		
F	127	125
AGE		
Min	38	35
Median	59	60
Max	84	81
Mean	59.2	59.7
≥ 65	35 (28)	41 (33)
≥ 75	6 (5)	9 (7)
RACE		
American Indian or Alaska Native	1 (0.8)	0
Asian	2 (2)	0
Black or African American	1 (0.8)	1 (0.8)
Hispanic or Latino	5 (4)	3 (2.4)
Japanese	0	1 (0.8)
Native Hawaiian or Other Pacific Islander	0	1 (0.8)
Other	2 (2)	0
White or Caucasian	116 (91)	119 (95)

Disease Characteristics and Concomitant Drugs: The majority of women enrolled in the trial had infiltrating ductal carcinoma as their tumor histology (86% denosumab, 74% placebo) with a lymph node status of N0 (68% denosumab, 57% placebo). Early stage of disease (i.e., stages I and IIA) was also prevalent. As expected, the majority of women were estrogen receptor positive (98% denosumab, 99% placebo), and progesterone receptor positive (87% denosumab, 78% placebo). Sixty-eight (68%) of denosumab treated women and 62% of placebo treated women were also HER2Neu negative, while HER2Neu status was unknown for 16% of women who received denosumab and 18% of women who received placebo. The mean number of years since patients were diagnosed with cancer was balanced between the treatment arms as was the mean number of years since last menstrual period. ECOG performance status for the majority of women was zero. At baseline, women who reported having received radiation included 68% for denosumab and 64% for placebo; reports of prior chemotherapy included 68% for denosumab and 59%; reports of prior hormone therapy included 51% for denosumab and 43% for placebo; reports of prior tamoxifen therapy included 47% for denosumab and 41% for placebo; and reports of prior selective estrogen modulator therapy (SERM) included 49% for denosumab and 41% for placebo. There was no prior IV bisphosphonate treatment reported and oral bisphosphonates were reported in only 2% of women who received denosumab and 6% of women who received placebo. Table 6 below summarizes the disease characteristics of patients

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at baseline for this trial. It is unlikely that the minimal differences observed between treatment arms for certain characteristics had an impact on the outcome of this trial.

Table 6 Study 135 Disease Characteristics at Baseline (all randomized patients)

Characteristic		Denosumab N=127 n (%)	Placebo N=125 n (%)
Tumor Type	**Stage**		
INFILTRATING DUCT CARCINOMA	I	47 (37)	39 (31.2)
	IIA	39 (30.7)	28 (22.4)
	IIB	13 (10.2)	18 (14.4)
	IIIA	10 (7.9)	6 (4.8)
	IIIB	0	1 (0.8)
	IIIC	1 (0.8)	0
INFILTRATING LOBULAR CARCINOMA	I	5 (3.9)	7 (5.6)
	IIA	3 (2.4)	4 (3.2)
	IIB	3 (2.4)	3 (2.4)
	IIIA	2 (1.6)	1 (0.8)
	IIIB	0	1 (0.8)
OTHER	I	3 (2.4)	7 (5.6)
	IIA	3 (2.4)	2 (1.6)
	IIB	1 (0.8)	3 (2.4)
	IIIA	1 (0.8)	1 (0.8)
Lymph Node Status			
N0		86 (67.7)	71 (56.8)
N1		37 (29.1)	45 (36)
N2		7 (5.5)	5 (4)
N3		1(0.8)	0
Estrogen Receptor Status			
NEGATIVE		3 (2.4)	1(0.8)
POSITIVE		124 (97.6)	124 (99.2)
Progesterone Receptor Status			
NEGATIVE		18 (14.2)	23 (18.4)
POSITIVE		111 (87.4)	98 (78.4)
UNKNOWN		2 (1.6)	0
HER2NEU Status			
NEGATIVE		87 (68.5)	78 (62.4)
POSITIVE		24 (18.9)	20 (16)
UNKNOWN		20 (15.7)	23 (18.4)
Years Since LMP	Mean	12.87	13.02
Years Since Diagnosis	Mean	3.23	3.22
ECOG PS			
0		117 (92.1)	102 (81.6)
1		13 (10.2)	14 (11.2)
History of Radiation		86 (67.7)	80 (64)
History of Chemo		87 (68.5)	74 (59.2)
History of Hormone Therapy		65 (51.2)	54 (43.2)
History of Tamoxifen Therapy		60 (47.2)	51 (40.8)
History of Selective Estrogen Receptor Modulator Therapy (SERM)		62 (48.8)	51 (40.8)
History of PO Bisphosphonates		3 (2.4)	7 (5.6)

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Characteristic		Denosumab N=127 n (%)	Placebo N=125 n (%)
History of Estrogens		3 (2.4)	8 (6.4)
Any Fracture		38 (29.9)	45 (36)
Vertebral Fracture		2 (1.6)	3 (2.4)
Non-vertebral Fracture		34 (26.8)	40 (32)
Lumbar BMD	Mean	1.007	1.018
Lumbar T-score	Mean	-1.125	-0.983

Patient Disposition: Table 7 below summarizes patient disposition by event at the end of treatment for Trial 135. Overall disposition of patients was balanced between treatment groups. A greater number of patients completed the trial for the denosumab group. However, a greater number of patients randomized to denosumab withdrew consent, were ineligible, or had their disposition noted as "other". Deaths were excluded from this analysis. There were two deaths during the treatment period for this trial, one for each treatment group. A more in-depth discussion of these cases is included separately as part of the safety analysis below.

Table 7 Trial 135 Patient Disposition by Event

Disposition Term	Denosumab N=127 n (%)	Placebo N=125 n(%)
ADVERSE EVENT	0	3 (2)
COMPLETED	111 (86)	103 (82)
CONSENT WITHDRAWN	11 (9)	9 (7)
DISEASE PROGRESSION	2 (1)	3 (2)
INELIGIBILITY DETERMINED	5 (4)	4 (3)
INFORMED CONSENT SIGNED	129 (101)	126 (101)
LOST TO FOLLOW-UP	0	3 (2)
NONCOMPLIANCE	4 (3)	4 (3)
OTHER	3 (2)	3 (2)
PROTOCOL DEVIATION	1 (0.7)	1 (0.8)
RANDOMIZED	129 (101)	126 (101)
SUBJECT REQUEST	1 (0.7)	1 (0.8)

Patient Exposure: Table 8 and Figure 4 are summaries of the exposure and disposition of all patients on Trial 135. Nearly 80% of patients received all four doses of denosumab, which was not appreciably different from the percentage of patients who received placebo.

Table 8 Trial 135 Exposure by Dose Number (intent to treat population)

Number of Doses	Denosumab n (%)	Placebo n (%)
0	2 (1.5)	1 (0.8)
1	10 (7.6)	14 (11.5)
2	7 (5.3)	7 (5.8)
3	8 (6.1)	5 (4.1)
4	104 (79.4)	94 (77.7)

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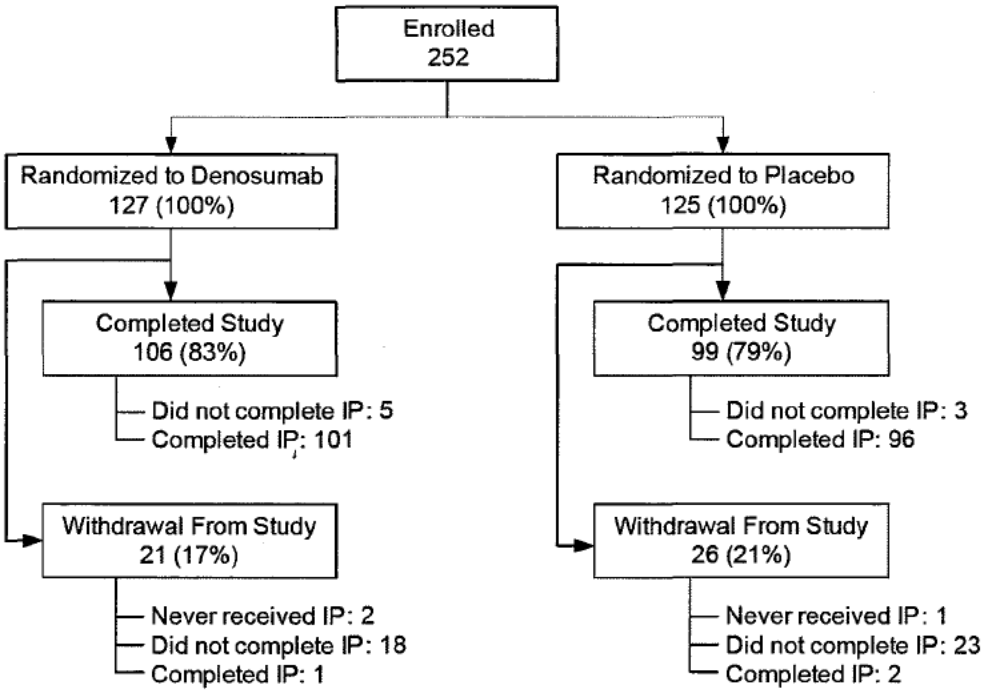
Figure 4 Trial 135 Disposition for All Randomized Patients (excerpt from CSR)



Protocol Deviations: Protocol violations pertaining to eligibility criteria occurred in < 10% of patients (denosumab 10, 8%; placebo 11, 9%) and were balanced between treatment groups. Overall, 5% of women were included in the trial who did not meet the criteria for BMD t-score, and 7% of women had inadequate organ function to be included in the trial. In addition, this trial pre-defined protocol deviations as important if a patient did not meet eligibility criteria, missed more than 2 doses of investigational product while on trial, received the first dose of investigational product > 72 hours after randomization, missed assessments for the primary endpoint, received certain proscribed medications, received the incorrect treatment assignment, or did not withdraw from the trial after meeting trial withdrawal criteria. Table 9 below summarizes the incidence of these pre-defined violations. All protocol violations pertaining to the conduct of the trial were balanced between the treatment arms and were unlikely to have a major effect on the efficacy or safety outcomes of this trial.

Table 9 Trial 135 Protocol Deviations All Randomized Patients (excludes eligibility deviations)

Protocol Deviation	Denosumab N=127	Placebo N=125
	n (%)	n (%)
Investigational Product	14 (5.6)	10 (4.0)
Exclusionary medication taken on trial	6 (2.4)	7 (2.8)
Off-schedule trial procedures	5 (2.0)	5 (2.0)
Missing data	3 (1.2)	1 (0.4)

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Non Withdrawal	1 (0.4)	1 (0.4)
Total	25 (9.9)	23 (9.1)

Efficacy Summary

For the complete summary of efficacy, see section 6 Review of Efficacy.

Safety Summary

Categorization of Adverse Events (AE): Adverse events were coded utilizing MedDRA version 9 and for certain analysis datasets, MedDRA version 11. The safety subset in the datasets utilized for analysis consists of 129 patients who received denosumab and 120 patients who received placebo. For the majority of the adverse event analyses that follow, the denominators used for calculations are the numbers of patient who actually received the IP to which they were randomized. Any divergence from this will be noted in the text preceding the analysis or table containing the change.

Adverse events were presented to include all five levels of the MedDRA hierarchy, and event grading was performed utilizing NCI CTCAE version 3. A side by side comparison of verbatim term to MedDRA Lower Level Term (LLT) was performed to verify the accuracy of the coding process. This included a review of approximately 957 AE line listings for Trial 135. Coding was deemed appropriate in the majority of cases. The cases where the judgment of this reviewer differed from the coder were not clinically meaningful and did not have a meaningful impact on the safety results of the trial. Table 10 below is a summary of adverse events for Trial 135. Overall, adverse events were balanced between treatment groups. Of the patients receiving denosumab, 91% experienced at least one AE, as well as 90% of patients receiving placebo. There was a slight imbalance for denosumab with regard to SAEs (denosumab 15%, placebo 9%). Deaths were balanced between treatment groups (1%); however this trial was not powered to evaluate survival adequately. The incidence of withdrawal from the trial for AEs was greater for the placebo group (denosumab 2%, placebo 4%). Common AEs occurring in > 10% of patients who were treated with denosumab, included arthralgia, pain (extremity, back, muscle, and headache), fatigue, constipation, and cough. Except for cough where the denosumab rate was nearly double that of the placebo group, the incidence rates for the most common AEs were relatively balanced between treatment groups. Specific AEs that were a concern based on actual or theoretical risks associated with denosumab are discussed in detail in section 7 of this review. Laboratory results demonstrated expected decreases in calcium, phosphorous, and alkaline phosphatase, the majority of which were not clinically meaningful. Only 2% of patients treated with denosumab developed binding antibodies that were non-neutralizing and one patient treated with placebo had pre-existing denosumab antibodies.

Table 10 Trial 135 Summary of AEs (safety population)

	Denosumab N=129 n (%)	**Placebo N=120 n (%)**
AEs All Grades	117 (90.7)	108 (90)

Reference ID: 3168397

	Denosumab N=129 n (%)	Placebo N=120 n (%)
AEs Grade 3 – 4	30 (23.3)	27 (22.5)
Any SAE	19 (14.7)	11 (9.2)
AE resulting in IP withdrawal	2 (1.6)	5 (4.2)

Adequacy of Safety Assessments: All testing reasonably applicable to this population were conducted to assess the overall safety profile of denosumab. When the results of this trial were pooled with the data from the PMO trials, there are adequate numbers for a meaningful analysis of short term safety.

Major Safety Results:

Deaths: In Trial 135, fatal events were reported for deaths occurring at any time during the 24 month treatment period regardless of temporal association to the investigational product. The 120 day safety report will update these data to include any deaths reported during the 24 month safety follow-up period. Only 2 deaths were reported during the 24 month treatment period, one for each treatment group. The case report forms and narrative listings for each subject who experienced a fatal event on this trial confirmed that disease progression was the cause of death in each case.

Nonfatal Serious Adverse Events (SAE): The AAE ADaM dataset was the primary source for analyses of SAEs. Patients who had received at least one dose of the investigational product and experienced any AE coded (by the investigator) in the AAE dataset as serious, life threatening, resulting in death, or requiring or prolonging hospitalization were analyzed. Table 11 summarizes the results of the analyses performed during this review. There were 26 separate SAEs experienced by 19 patients who received denosumab and 18 SAEs experienced by 11 patients who received placebo. A case report form (CRF) review of the patients who experienced an SAE subsumed under the Neoplasms SOC was undertaken. In each case, there was either progression from a known diagnosis of cancer, or an evolving or stable pre-existing cancer diagnosis. CRFs for patients who experienced infections were also reviewed. In the case of pneumonia reported, the patient had pre-existing COPD and was at increased risk for pneumonia. For the remaining cases (i.e. labrynthitis, cellulitis, and diverticulitis), there were no apparent commonalities based on history and no pattern could be discerned based on causative organisms because none were collected routinely in the trial. Specifically in the case of diverticulitis, the applicant suggested that a history of abdominal surgery may have pre-disposed the patient to having diverticular disease, and subsequently diverticulitis. The medical literature does not support this view. Most notable in a review of the data is the minor incidence of SAEs on this study overall and that patients treated with denosumab reported the majority of cases.

Reference ID: 3168397

Table 11 Trial 135: SAE Incidence by MedDRA SOC and PT

MedDRA SOC	MedDRA PT	Denosumab		Placebo	
		n	%	n	%
Cardiac disorders	Acute myocardial infarction	1	0.8	0	0
	Atrioventricular block second degree	1	0.8	0	0
	Myocardial infarction	1	0.8	0	0
	Atrial fibrillation	0	0	1	0.8
	Cardiac failure congestive	0	0	1	0.8
	Myocardial ischaemia	0	0	1	0.8
Endocrine disorders	Goitre	0	0	1	0.8
Gastrointestinal disorders	Colitis ischaemic	1	0.8	0	0
	Diverticulum	1	0.8	0	0
	Gastrointestinal haemorrhage	1	0.8	0	0
	Small intestinal obstruction	1	0.8	0	0
	Faecaloma	0	0	1	0.8
	Large intestine perforation	0	0	1	0.8
General disorders and administration site conditions	Pelvic mass	1	0.8	0	0
Hepatobiliary disorders	Cholecystitis	1	0.8	1	0.8
	Cholelithiasis	0	0	2	1.7
Infections and infestations	Cellulitis	1	0.8	0	0
	Diverticulitis	1	0.8	0	0
	Labyrinthitis	1	0.8	0	0
	Pneumonia	0	0	1	0.8
Injury, poisoning and procedural complications	Fracture	1	0.8	0	0
	Femoral neck fracture	0	0	1	0.8
	Incisional hernia	0	0	1	0.8
Musculoskeletal and connective tissue disorders	Osteoarthritis	2	1.5	0	0
	Arthritis	1	0.8	1	0.8
	Intervertebral disc protrusion	1	0.8	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Benign ovarian tumour	1	0.8	0	0
	Breast cancer in situ	1	0.8	0	0
	Colon adenoma	1	0.8	0	0
	Malignant pleural effusion	1	0.8	0	0
	Metastatic neoplasm	1	0.8	0	0
	Uterine leiomyoma	1	0.8	0	0
	Benign breast neoplasm	0	0	1	0.8
	Metastases to bone	0	0	1	0.8

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MedDRA SOC	MedDRA PT	Denosumab		Placebo	
		n	%	n	%
Nervous system disorders	Transient ischaemic attack	1	0.8	1	0.8
Reproductive system and breast disorders	Rectocele	1	0.8	0	0
Respiratory, thoracic and mediastinal disorders	Respiratory failure	1	0.8	0	0
	Chronic obstructive pulmonary disease	0	0	1	0.8
	Pneumonitis	0	0	1	0.8

Dropouts/Discontinuations:
In Trial 135 at the end of treatment, 2 patients in the denosumab treatment group, and 5 patients in the placebo group withdrew from the trial for an adverse event. Consent was withdrawn for 9 (3.6%) patients treated with denosumab and 6 (2%) patients treated with placebo. No patients who were treated with denosumab were lost to follow up, while 2 (0.8%) treated with placebo were so designated. Overall for this trial, the numbers of patients who discontinued therapy or withdrew from trial were balanced between treatment groups.

Significant Adverse Events:
During the development of denosumab, safety concerns were identified based on the target of the antibody, literature-described effects on the signal transduction pathway, as well as cellular effects. A safety concern of particular interest to the applicant was hypocalcemia. The applicant also identified the following other AEs as significant: cardiovascular (CV) events (focused on Trials 216 and 138 only) and osteonecrosis of the jaw (ONJ) and related events (all events adjudicated for all trials). During the conduct of this review, all of the safety concerns identified by the applicant were reviewed in detail. In addition, increased incidence rates of infection were identified occurring in all phases of development for denosumab during this review and were analyzed in detail.

Submission Specific Primary Safety Concerns:
A pooled analysis of the data from the four key trials submitted in support of this application is discussed below in 7.3.5 Submission Specific Primary Safety Concerns.

Supportive Safety Results: In order to examine the data at a depth of granularity sufficient to detect all important safety signals, adverse events were analyzed at each level of the MedDRA hierarchy. Analyses were performed using the defined safety populations and analysis datasets (AAE) from the trial. These data were then analyzed for the AE totals by trial, and incidence rates by grade and treatment group. In addition, Standardized MedDRA Queries (SMQ) were performed and analyzed. SMQs are groupings of terms from one or more MedDRA SOCs relating to a defined medical condition or area of interest. The results of SMQ level analyses can highlight areas for further inquiry. The results from these analyses can be found in Appendix 9.4 Tables Referenced in Text. Terms in the relevant tables are grouped as either broad or narrow in scope and these correlate to sensitivity and specificity.

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Common Adverse Events: For the analyses of common adverse events (AE), the ADaM dataset AAE was utilized as the primary dataset. This dataset contained all AEs experienced during the conduct of the trial reported as one record per subject per AE per visit. The incidence rates discussed below were derived from a subset of the AAE dataset containing one row per subject per AE and grouped by maximum toxicity. These data were then tabulated and analyzed. By trial design, no laboratory abnormalities will appear in the following tables unless they are associated with a symptom. The protocol required that only abnormal labs associated with a symptom were to be considered an adverse event. A full analysis of the range of laboratory abnormalities during the trial is discussed later in this review. The safety population for Trial 135 was defined as any patient who received ≥ 1 dose of IP and consisted of 249 patients (129 denosumab, 120 placebo) who experienced a total of 1332 separate events. For patients treated with denosumab, 117 (93.6%) experienced at least one AE during the trial, and there were 756 events; for patients receiving placebo, 108 (87%) experienced at least one AE during the trial, and there were 576 events. Adverse events occurring at an incidence of > 5% and at an increased incidence of >5% in the denosumab treatment group, the search criteria utilized by this reviewer to identify common AEs, were cough (denosumab 10%, placebo 4%), myalgia (denosumab 9%, placebo 4%), shoulder pain (denosumab 9%, placebo 3%), sinusitis (denosumab 7%, placebo 3%), and vulvovaginal dryness (denosumab 7%, placebo 3%). Table 49 - Table 54 in Appendix 9.4 summarize all AEs for Trial 135 at each level of the MedDRA hierarchy and by Standardized MedDRA Queries (SMQ). All tables were derived utilizing the safety population.

Vital Signs: For Trial 135, vital signs, including temperature, diastolic and systolic blood pressure, pulse, weight, and BMI were reported for each treatment group at baseline, day 1, and months 1, 6, 12, 18, and 24. The analysis dataset AVS was utilized for all vital sign explorations. Analyses of temperature, diastolic and systolic blood pressure, pulse, weight, and BMI distributions by treatment group at baseline and each protocol mandated measurement time point demonstrated no clinically significant differences between treatment groups. In addition, comparisons of vital sign changes from baseline to each protocol mandated measurement time point demonstrated no statistically significant or clinically meaningful changes between treatment groups.

Laboratory Findings: Data for the four key registrational trials were pooled and the laboratory findings are discussed under section 7.4.2 Laboratory Findings below.

Immunogenicity: Of the 252 patients enrolled in the trial, 246 (98%) provided samples for antibody testing. There were three subjects who tested positive for the development of anti-denosumab antibodies. Patient (b) (6), treated in the placebo group, tested positive for binding antibodies at baseline through month 18, and the end of trial sample at month 24 was negative. Patients (b) (6) and (b) (6) were both treated in the denosumab group. Patient (b) (6) tested positive for antibodies on day 30 and at month 12. Samples at months 6 and 24 were negative. Patient (b) (6) tested positive for antibodies at month 18, but all other samples were negative. When compared to other patients in the trial, all three patients who tested positive for antibodies exhibited similar efficacy and safety profiles as patients who were antibody negative.

Reference ID: 3168397

5.3.2 A Randomized, Double-blind, Placebo-controlled Trial to Evaluate AMG 162 in the Treatment of Bone Loss in Patients Undergoing Androgen-deprivation Therapy for Nonmetastatic Prostate Cancer (Trial 138)

Trial Summary:
This was an international, multicenter, randomized, double-blind, placebo-controlled trial in 1468 patients with nonmetastatic prostate cancer who were undergoing androgen deprivation therapy (ADT). Patients were randomized (1:1) to receive either placebo or denosumab 60 mg subcutaneously (SC) once every 6 months for a total of 6 doses over a 36-month treatment period. Randomization was stratified by age group (< 70 years vs. ≥ 70 years) and duration of ADT (gonadotropin-releasing hormone (GnRH) agonists or orchiectomy) at trial entry (≤ 6 months vs. > 6 months). All received daily supplemental calcium (≥ 1 g) and vitamin D (≥ 400 IU). Bone mineral density assessments by dual x-ray absorptiometry (DXA) for the lumbar spine, total hip, femoral neck, and trochanter were obtained, and BMD of the total body and 1/3 distal radius performed in a subset of patients (N = 309). A blinded central image reader identified or confirmed all vertebral and nonvertebral fractures. An independent Data Monitoring Committee monitored patient safety on an ongoing basis for the duration of the 36-month treatment period. Upon completion of the 36-month treatment period, patients were continued on trial for 24 months during which no investigational product was administered, or were offered enrollment in a 2-year extension trial (20080537).

Eligibility Criteria:
- Men ≥ 70 years with histologically confirmed prostate cancer, or men < 70 years with histologically confirmed prostate cancer and a history of osteoporotic fracture or BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 (using the normative male database)
- BMD T-score at the lumbar spine, total hip or femoral neck not < -4.0
- have undergone bilateral orchiectomy or initiated ADT with GnRH agonists and are expected to continue on with ADT for at least 12 months
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- No distant metastases
- No evidence of current unstable systemic disease, organic or psychiatric disorder, or inadequate organ function that could have interfered with completion of the trial or interpretation of results
- No recent exposure to bisphosphonates or other medications known to influence bone metabolism

Endpoints:
- Primary: the percent change in lumbar spine BMD from baseline to month 24.
- Secondary
  - The percentage change of femoral neck BMD and total hip BMD from baseline to month 24; percentage change of lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36; patient incidence of any fracture and patient incidence of new vertebral fracture over the 36-month treatment period;

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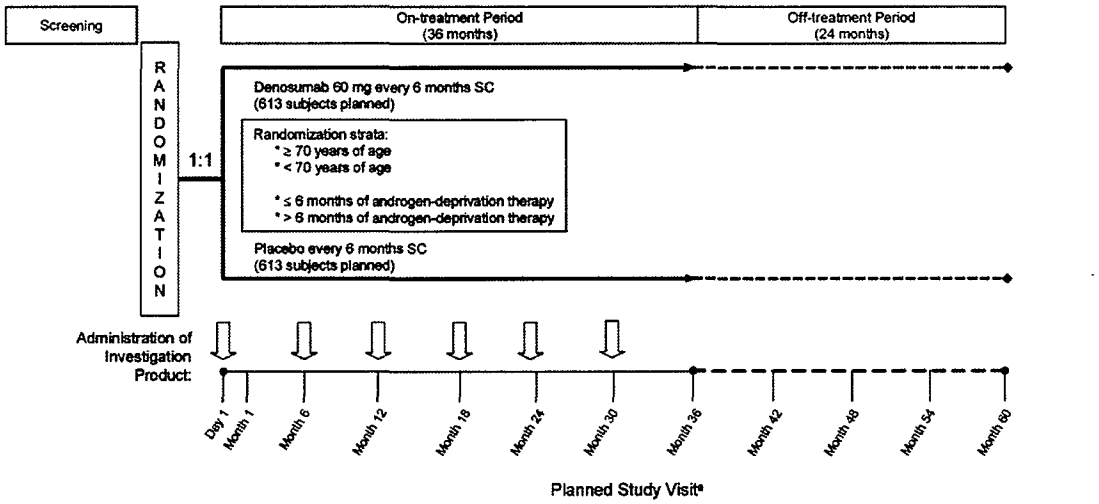
time to first clinical fracture over the 36-month treatment period; patient incidence of any fracture over the 24-month treatment period

- Assess the safety and pharmacokinetics of denosumab over the 36-month treatment period.

- Exploratory: Effect of denosumab on prostate-specific antigen (PSA), overall survival, and patient-reported outcomes.

Trial Design Schema:

Figure 5 Trial 138: Trial Design Schema (excerpt from CSR)



SC = subcutaneous
[a] BMD of the lumbar spine was assessed at screening and at all planned study visits except day 1 and month 18; the assessment obtained during screening was used as the baseline assessment of lumbar spine BMD.

Treatments: Patients were randomized to receive either 60 mg denosumab subcutaneously every 6 months (day 1 and months 6, 12, 18, 24, and 30) or placebo. Patients were also required to take 1 g of calcium and 400 IU of vitamin D daily.

Trial Sites and Enrollment: Because of the size of the trial, a table of specific sites was deemed lengthy and impractical. The table below summarizes patient enrollment by country. The USA and Canada accounted for the majority of patients enrolled on the trial. Based on the distribution of patients per site, it is unlikely that any one site influenced the efficacy outcome of the trial.

Table 12 Trial 138: Sites and Enrollment by Country

Country (number of sites)	Denosumab	Placebo
Canada (35)	192	200
Switzerland (3)	6	6
Czech Republic (8)	46	46
Finland (2)	14	12
Hungary (6)	41	52
Mexico(9)	70	69
Netherlands (6)	16	16

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Country (number of sites)	Denosumab	Placebo
Poland (10)	55	46
USA (87)	291	278

Trial populations:
Efficacy:

- Full analysis set (all randomized patients)
- BMD analysis subset (all randomized patients with baseline and ≥ 1 post-baseline measurement at or before the time under consideration
- vertebral fracture analysis subset (all randomized patients with baseline and ≥ 1 post-baseline measurement at or before the time under consideration)
- per protocol set (primary efficacy subset who were compliant with protocol)
- subset for subtrial (randomized patients in the subtrial [DXA total body and distal 1/3 radius] who have a baseline and ≥ 1 postbaseline measurement of the endpoint of interest at or prior to the time point under consideration)
- observed data analysis set (randomized and have observed values of the endpoint at the time point under consideration)
- repeated measures analysis set (randomized having a baseline and at least one post baseline measurement of the endpoint of interest)

Safety: Subset for safety (all randomized patients who received at least one dose of investigational product)

Demographics: Trial 138 enrolled 1468 men, 734 randomized to each treatment group. Most patients were Caucasian (denosumab 84%, placebo 83%) and most were treated in the US and Canada (denosumab 66%, placebo 66%). As summarized in Table 13 below, other baseline demographics were also balanced between treatment groups.

Table 13 Trial 138 Patient Demographics (all randomized patients)

Demographic	Denosumab n (%)	Placebo n (%)
COUNTRY		
CAN	192 (26)	202 (27)
CHE	6 (0.8)	6 (0.8)
CZE	46 (6)	46 (6)
FIN	14 (2)	12 (1.7)
HUN	40 (5)	53 (7)
MEX	69 (9)	70 (9)
NLD	17 (2.3)	16 (2.1)
POL	55 (7.5)	46 (6)
USA	295 (40)	283 (39)
SEX		
M	734	734
AGE		
Min	48	50
Median	76	76

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Demographic	Denosumab n (%)	Placebo n (%)
Max	92	97
Mean	75.3	75.5
≥ 65	685 (93.3)	679 (92.5)
≥ 75	415 (56.5)	424 (57.8)
RACE		
American Indian or Alaska Native	0	2 (0.3)
Asian	5 (0.7)	3 (0.4)
Black or African American	36 (4.9)	32(4.4)
Hispanic or Latino	77 (10.5)	81 (11)
Japanese	1 (0.1)	4 (0.5)
Other	0	3 (0.4)
Caucasian	615 (84)	609 (83)

Disease Characteristics and Concomitant Drugs: The analysis dataset ASLBASE was utilized for the analysis of disease characteristics. The majority of patients had stage II (74% denosumab, 73% placebo) or stage III disease (19% denosumab, 22% placebo). Gleason scores for most patients were ≤ 7 (68% denosumab, 73% placebo) and the majority of patients also had a relapse risk that was low or intermediate (60% in both groups). Prostate cancer treatments (i.e., radiation and/or surgery, chemical or surgical castration) were balanced between treatment groups. Fifty-two percent of patients received no primary therapy, 26% received radiation, and 19% received surgery. Most patients at baseline (93%) were receiving therapy for androgen deprivation (ADT); and 9% were surgically castrated. The majority of patients were on ADT for > 6 months (79% denosumab, 78% placebo). The mean duration of ADT was 31 months in the denosumab group and 30 months in the placebo group. ECOG performance status was balanced with a median score of 0; and 1 patient (0.1%) in the placebo group had an unknown ECOG score. Baseline mean lumbar BMD T-scores were -0.3 in the denosumab group and –0.4 in the placebo group. Prior history of bisphosphonate use was similar between treatment groups as was substance use (caffeinated beverages, alcoholic beverages, and tobacco). The minimal differences observed between treatment groups for specific disease characteristics did not have an impact on the outcome of this trial.

Table 14 Study 138 Baseline History (all randomized patients)

Characteristic		Denosumab N=734 n (%)	Placebo N=734 n (%)
Tumor Stage			
II		544 (74.1)	524 (71.4)
III		135 (18.4)	158 (21.5)
IV		52 (7.1)	43 (5.9)
Gleason Scores			
<7		498 (67.8)	534 (72.8)
8 - 10		164 (22.3)	138 (18.8)
Years from dx	Mean	4.97	4.88
Relapse Risk			
HIGH		210 (28.6)	214 (29.1)

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Characteristic		Denosumab N=734 n (%)	Placebo N=734 n (%)
INTERMEDIATE		263 (35.8)	240 (32.7)
LOW		174 (23.7)	198 (27)
VERY HIGH		84 (11.4)	73 (9.9)
ECOG	Median	0	0
History of Radiation		244 (33.2)	247 (33.7)
History of Chemo		1 (0.14)	3 (0.42)
Months of ADT	Mean	31.4	30.4
History IV Bisphosphonates		1 (0.14)	2 (.27)
History PO Bisphosphonates		9 (1.2)	7 (1)
Surgical Castration		77 (11)	60 (8.2)
Chemical Castration		676 (92.1)	677 (92.2)
Lumbar BMD	Mean	1.136	1.126
Lumbar T-score	Mean	-0.318	-0.408
Any Fracture		246 (33.5)	268 (36.5)
Vertebral Fracture		14 (2)	19 (2.6)
Osteoporotic Fractures		162 (22.1)	194 (27)
Non-vertebral Fractures		153 (21)	181 (25)

Patient Disposition: Deaths will be analyzed separately as part of the safety summary, see Table 19. For Trial 138, the number of fatal events was balanced between treatment groups, 46 patients (6.3%) treated with placebo and 44 patients (6.0%) treated with denosumab. Figure 6 below summarizes the disposition for all randomized patients in the trial. However, the discrepancies were unlikely to have a major effect on the efficacy or safety outcomes of this trial.
Figure 6 Trial 138 Patient Disposition (excerpt from CSR)

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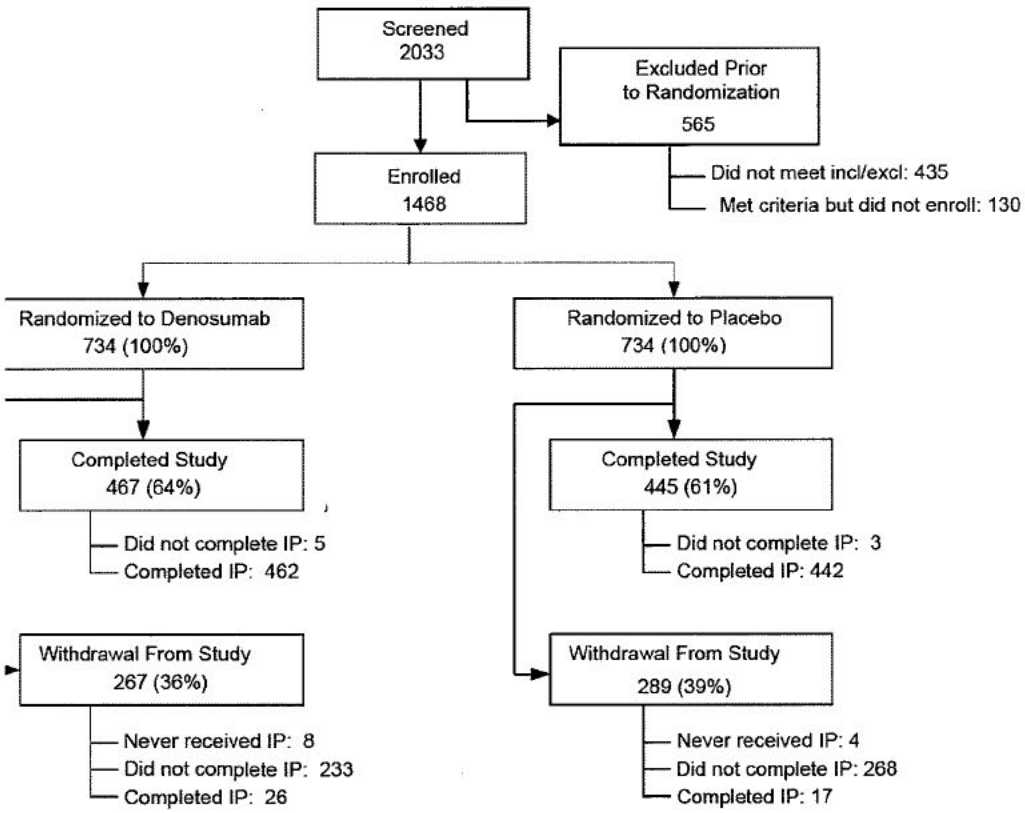

(Figure appears in the original as shown)

Table 15 summarizes patient disposition in relation to the investigational product (IP) at the end of study for all patients enrolled in Trial 138. Of the 734 patients randomized to the denosumab group, 472 patients (64%) completed the trial. The reasons for the drop out rate of 36% were varied. Ineligibility was determined in 0.8% of patients, while 2.3% were lost to follow up, and "other" was cited in 1.2% of cases. Adverse events were the reason for the dropout of about 4% of patients, and 16.8% withdrew consent. Issues of disease progression and treatment were responsible for 3.7% of dropouts. As a result of the relatively high dropout rate, a review of the patient data from a sample of cases was undertaken. There were a number of cases where the reason for dropout from the trial was miscoded. For example, patient (b) (6) had "administrative decision" given as the reason for trial dropout; however this patient experienced rash and erythema with administration of the IP and was advised by his physician to withdraw participation. This event should have been coded as an AE. Patient (b) (6) was designated as "lost to follow-up"; however the patient was ill, likely as a result of disease progression. With regard to patients whose end of study designation was "other", patients (b) (6) (b) (6), and (b) (6) all experienced disease progression. These discrepancies in the data speak to the conduct of the trial and are notable as such. However, the discrepancies were unlikely to have a major effect on the efficacy or safety outcomes of this trial.

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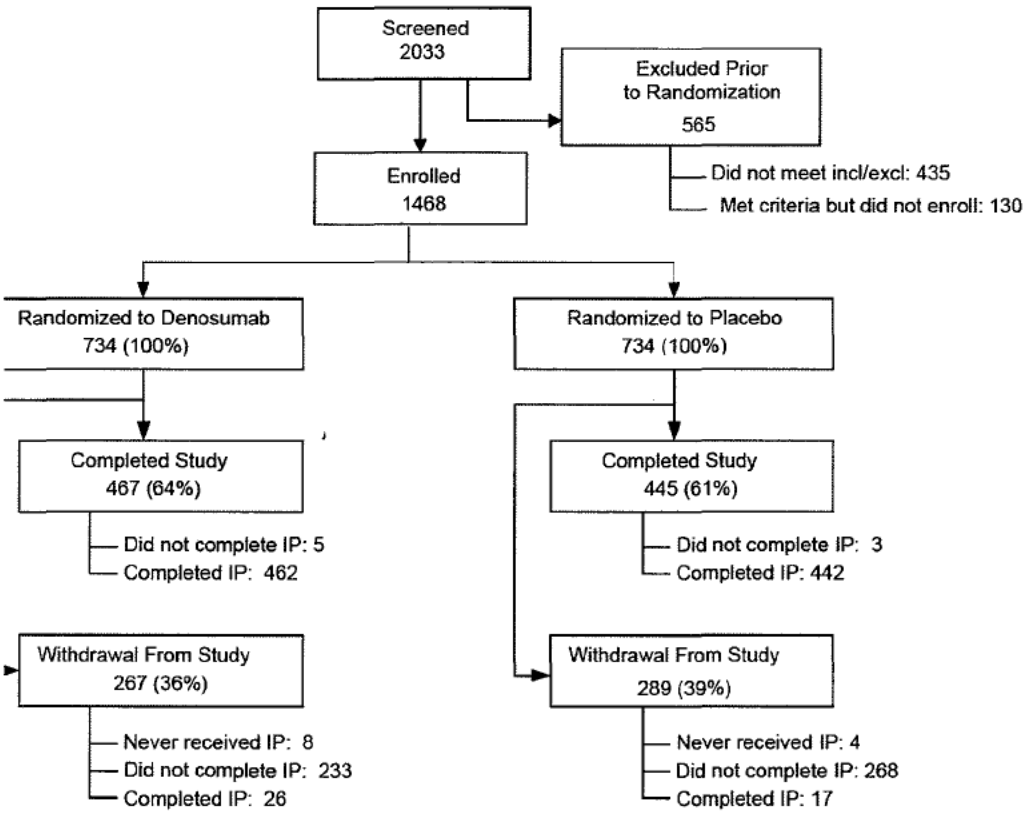
Figure 6 Trial 138 Patient Disposition (excerpt from CSR)



(Figure appears in the original as shown)

Table 15 Trial 138 Patient Disposition (all randomized patients)

Disposition	Denosumab	Denosumab %	Placebo	Placebo %
Completed	472	64	440	60
Consent Withdrawn	123	17	142	19
Adverse Event	29	4	23	3
Disease Progression	23	3	21	3
Lost to Follow-up	17	2	21	3
Other	9	1	5	0.7
Ineligibility Determined	6	0.8	5	0.7
Alternative Therapy	4	0.5	14	1.9
Noncompliance	3	0.4	7	0.9
Administrative Decision	2	0.3	4	0.5

Protocol Violations: There were 257 patients (35%) who received denosumab and 233 patients (32 %) who received placebo having protocol violations reported for this trial. The largest categories of protocol violations were missing data, investigational product administration, and

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other. The category labeled as "other" represented incorrect stratification of patients on the trial. Except for the missing data category, where there were more patients with missing data who received denosumab (12% denosumab, 8% placebo), the protocol violations were balanced between treatment groups. The incidence of violations and missing data in this large trial are of concern with regard to the conduct of the trial; however it is unlikely that the missing data had an impact on the efficacy or safety outcomes of the trial.

Table 16 Trial 138 Protocol Violations (all randomized patients)

Protocol Deviation	Denosumab N=734 n (%)	Placebo N=734 n (%)
Missing data	85 (11.6)	57 (7.8)
Others	65 (8.9)	73 (9.9)
Investigational product administration	64 (8.7)	66 (9.0)
Off-schedule study procedures	30 (4.1)	20 (2.7)
Non Withdrawal	7 (0.9)	3 (0.4)
Exclusionary medication taken	6 (0.8)	14 (1.9)
Total	257 (35)	233 (32)

Efficacy Summary:
For the complete summary of efficacy, see section 6 Review of Efficacy.

Safety Summary

Categorization of Adverse Events (AE): Adverse events for this trial were coded utilizing MedDRA version 9 and for certain ADaM datasets, MedDRA version 11. Adverse events were presented to include all five levels of the MedDRA hierarchy, and event grading was performed utilizing NCI CTC version 3. A side by side comparison of verbatim term to MedDRA Lower Level Term (LLT) was performed to verify the accuracy of the coding process. This included a review of approximately 4051 AE line listings for Trial 138. Coding was deemed appropriate in the majority of cases. The cases where judgment of this reviewer differed from that of the coder were not clinically meaningful and did not have a meaningful impact on the safety results of the trial had they been coded correctly. Table 17 is a summary of adverse events for Trial 138. Overall, about 87% of patients experienced an adverse event during the conduct of this trial. Grades 3 to 5 AEs, SAEs, withdrawals because of AEs, and deaths were balance between the treatment groups.

Table 17 Summary of AEs in Trial 138 (safety population)

	Denosumab N=731 n (%)	Placebo N=725 n (%)
AEs All Grades	638 (87.3)	627 (86.5)

Reference ID: 3168397

	Denosumab N=731 n (%)	Placebo N=725 n (%)
AEs Grade 3 – 5	269 (36.8)	244 (33.7)
Any SAE	253 (34.6)	222 (30.6)
AE resulting in IP withdrawal	49 (6.7)	47 (6.5)

Adequacy of Safety Assessments:
All testing applicable to the population studied were conducted to assess the overall safety profile of denosumab. Table 18 summarizes patient exposure based on number of injections received as well as total dose received. The trial required that denosumab be administered for 6 doses of 60 mg each over a similar period of months. Each patient who completed the trial per protocol should have received a total of 360 mg. It is notable that the totals differ for number of doses received as compared to mgs received. This may be explained by the fact that 11 patients who were randomized to placebo actually received denosumab.

Table 18 Trial 138: Patient Exposure to Investigational Product

Number of Doses	Denosumab n (%)	Placebo n (%)
1	45 (6.2)	54 (7.4)
2	31 (4.2)	44 (6.1)
3	40 (5.5)	43 (5.9)
4	97 (13.3)	99 (13.7)
5	28 (3.8)	35 (4.8)
6	490 (67.0)	450 (62.1)
Total Dose (in mg)		
0	0	725 (100)
60	50 (6.8)	0
120	31 (4.2)	0
180	41 (5.6)	0
240	97(13.3)	0
300	30 (4.1)	0
360	482 (65.9)	0
Wrong IP Received		
N	720 (98.5)	725 (100)
Y	11 (1.5)	0

Major Safety Results:

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Deaths: In Trial 138, the numbers of fatal events were balanced between treatment groups, 46 patients (6.3%) treated in the placebo group and 44 patients (6.0%) treated in the denosumab group. In general, causes of death are representative of the patient population being studied where the median age for both treatment groups was 76 years and 93% of men enrolled were ≥ 65 years. Table 19 summarizes all fatal events by SOC and PT in Trial 138. A review of approximately 10% of the case report forms (CRF) was undertaken to evaluate stated causes of death. In general, the causes of death reported accurately reflect the patient histories. Of interest, while there are no apparent cases of death as a result of an infection-related event for denosumab in a search of the AAE database, in one case, patient [redacted] (b) (6), the CRF review revealed that this 93 year old male developed aspiration pneumonia for which he was hospitalized and treated. During the hospitalization, a second aspiration event occurred which did not respond to treatment and the patient died.

Cardiovascular events for this trial were subject to adjudication by an independent review committee. These events will be discussed separately in section 7.3.5 Submission Specific Primary Safety Concerns.

Table 19 Trial 138, Deaths per Treatment Group by SOC and PT

SOC	PT	Denosumab N=731 (%)	Placebo N=725 (%)
Cardiac disorders	Cardiac arrest	3 (0.4)	2 (0.3)
	Cardiac failure	2 (0.3)	1 (0.4)
	Cardiac failure congestive	1 (0.1)	0
	Cardiogenic shock	2 (0.3)	1 (0.4)
	Cardio-respiratory arrest	2 (0.3)	0
	Cardiovascular disorder	1 (0.1)	1 (0.4)
	Myocardial infarction	4 (0.5)	7 (.9)
Gastrointestinal disorders	Gastrointestinal haemorrhage	0	1 (0.4)
	Intestinal obstruction	1 (0.14)	0
General disorders and administration site conditions	Death	2 (0.3)	5 (0.7)
	Hypothermia	0	1 (0.4)
	Sudden death	1 (0.1)	1 (0.4)
Hepatobiliary disorders	Hepatic failure	1 (0.1)	0
	Hepatitis alcoholic	1 (0.1)	0
Infections and infestations	Gastrointestinal gangrene	0	1 (0.4)
	Pneumonia	0	2 (0.3)
	Sepsis	0	2 (0.3)
	Septic shock	0	1 (0.4)
Injury, poisoning and procedural complications	Injury	0	1 (0.4)
	Subdural	0	1 (0.4)

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SOC	PT	Denosumab N=731 (%)	Placebo N=725 (%)
	haemorrhage		
Metabolism and nutrition disorders	Hypoglycaemia	1 (0.1)	0
	Metabolic acidosis	1 (0.1)	0
Neoplasms benign, malignant and unspecified Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer metastatic	0	1 (0.4)
	Gastric cancer	1 (0.1)	1 (0.4)
	Lung neoplasm malignant	0	2 (0.3)
	Malignant glioma	0	1 (0.4)
	Metastases to abdominal cavity	1 (0.1)	0
	Metastases to bone	0	3
	Metastases to liver	1 (0.1)	0
	Metastases to pleura	1 (0.1)	1 (0.4)
	Metastatic renal cell carcinoma	1 (0.1)	0
	Pancreatic carcinoma	1 (0.1)	0
Nervous system disorders	Brain injury	1 (0.1)	0
	Cerebral haemorrhage	1 (0.1)	0
	Cerebrovascular accident	4 (.5)	2 (0.3)
	Haemorrhage intracranial	1 (0.1)	0
	Haemorrhagic stroke	0	1 (0.4)
	Hypoxic encephalopathy	1 (0.1)	0
Renal and urinary disorders	Renal failure	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	2 (0.3)	1 (0.4)
	Dyspnoea	1 (0.1)	0
	Lung disorder	0	1 (0.4)
	Pneumonia aspiration	2 (0.3)	1 (0.4)
	Respiratory failure	3 (0.4)	1 (0.4)
Vascular disorders	Cardiovascular insufficiency	0	1 (0.4)

Nonfatal Serious Adverse Events (SAE): A MedDRA SOC level analysis was performed for Trial 138 which identified SAEs occurring in 253 (35%) patients treated with denosumab and 222 (31%) treated with placebo. The SAEs most commonly reported were in the cardiac disorders SOC with 9.4% reported in the denosumab group and 10% reported in the placebo group. Other SAEs reported commonly were in the nervous system disorders, and infections

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and infestations SOCs, 6.8% for denosumab, 4.8% for placebo and 5.9% for denosumab, 4.6% for placebo respectively. Overall, there were no statistically significant or clinically meaningful differences between treatment groups in the incidence of SAEs for this trial. The relatively high rate of SAEs is most likely a reflection of the age of the population studied (median 76 years) whose co-morbid conditions can often correlate with a higher incidence of toxicities overall.

Table 20 Trial 138: SAE Incidence by MedDRA SOC

	Denosumab n=731 (%)	Placebo n=725 (%)
Total	**253** (34.6)	**222** (30.6)
Cardiac disorders	69 (9.4)	75 (10.3)
Gastrointestinal	23 (3.1)	33 (4.6)
Musculoskeletal	17 (2.3)	12 (1.7)
Infection	43 (5.9)	33 (4.6)
Neoplasms	37 (5.1)	42 (5.8)
Injury, poisoning	32 (4.4)	24 (3.3)
Nervous system	50 (6.8)	35 (4.8)
Respiratory	27 (3.7)	16 (2.2)
Hepatobiliary	12 (1.6)	5 (0.7)
Other*	117 (16.0)	77 (10.6)

Dropouts/Discontinuations

In Trial 138, at the end of treatment for patients treated with denosumab, 27 (1.9%) dropped out of the trial or discontinued treatment for AEs, 102 (7%) withdrew consent, 13 (0.9%) were lost to follow up, and 22 (1.5%) withdrew for disease progression. For patients having taken placebo, 25 (1.7%) withdrew consent, 16 (1.1%) were lost to follow up, and 19 (1.3%) withdrew for disease progression. Overall in this trial, the numbers of patients who discontinued therapy or withdrew from trial were balanced between treatment groups.

Significant Adverse Events

Of particular note in Trial 138 was an imbalance in the incidence of cataracts, denosumab 34 (4.7%), placebo 4 (0.5%). A statistically oriented safety analysis performed by the Quantitative Safety and Pharmacoepidemiology Group (QSPG) computed the following statistical values for this finding: 95% confidence interval (CI): 1.81, 7.85, $p = 0.0004$. This analysis utilized categorical data analysis methods which are exploratory in nature. The confidence intervals and p-values are not intended for statistical inference and should be interpreted as demonstrating the magnitude and strength of the relationship between the treatment group and placebo group. This potential safety signal was not observed in other trials and, in fact, when safety data were pooled, the overall incidence of cataracts was greater for the placebo group. The applicant has submitted Protocol 20080560, A Double-Blind, Placebo-controlled Study to Evaluate New or Worsening Lens Opacifications in Subjects with Non-metastatic Prostate Cancer Receiving Denosumab for Bone Loss due to Androgen-Deprivation Therapy, a non-inferiority trial, to further evaluate this finding. While it is agreed that this safety finding warrants further study in the postmarketing

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period, the protocol as submitted is inadequate. See 1.4 Recommendations for Postmarket Studies/Clinical Trials, for a full discussion of the deficiencies and remedies.

Submission Specific Primary Safety Concerns
A pooled analysis of the data from the four key trials submitted in support of this application is discussed below and the safety concerns associated with this trial are discussed at length in section 7.3.5 Submission Specific Primary Safety Concerns.

Supportive Safety Results: Adverse events were analyzed at each level of the MedDRA hierarchy. Analyses were performed using the defined safety populations and analysis datasets submitted. In addition, Standardized MedDRA Queries (SMQ) were performed and analyzed. SMQs are groupings of terms from one or more MedDRA SOCs relating to a defined medical condition or area of interest. The results of SMQ level analyses can highlight areas for further inquiry.

Common Adverse Events: For the analyses of common adverse events (AE), the analysis dataset AAE was utilized as the primary dataset. This dataset contained all AEs experienced during the conduct of the trial reported as one record per subject per AE per visit. The incidence rates discussed below were derived from a subset of the AAE dataset containing one row per subject per AE and grouped by maximum toxicity. These data were then tabulated and analyzed. By trial design, no laboratory abnormalities will appear in the following tables unless they are associated with a symptom. The protocol required that only abnormal labs associated with a symptom were to be considered an adverse event. A full analysis of the range of laboratory abnormalities during the trial is discussed later in this review.

The safety population for this trial was defined as any patient who received $\geq$ 1 dose of IP and consisted of 1456 patients, 731 in the denosumab group and 725 in the placebo group. In Trial 138, over 85% of patients receiving denosumab (638/87%) or placebo (627/86%) experienced at least one AE. In the majority of cases AEs were reported as grades 1 or 2 (65% denosumab, 62% placebo). Grades 3 or 4 events were reported less frequently (19% denosumab, 17% placebo). There were 3,831 events experienced by denosumab treated patients and 3,470 events experienced by patients receiving placebo. There were no AEs occurring at an incidence of > 5% with >5% difference favoring the denosumab treatment group, which was the search criteria applied by this reviewer for common AEs. In general, incidence rates for AEs were low and relatively balanced between the treatment groups. Summaries of AEs at all levels of the MedDRA hierarchy can be found in Appendix 9.4, Tables 28 - 33.

Laboratory Findings: Data for the four key registrational trials were pooled and the laboratory findings are discussed under section 7.4.2 Laboratory Findings.

Vital Signs: For Trial 138, vital signs, including temperature, diastolic and systolic blood pressure, pulse, weight, and BMI were reported for each treatment group at baseline, day 1, and months 1, 6, 12, 18, and 24. The analysis dataset AVS was utilized for all vital sign explorations. Analyses of temperature, diastolic and systolic blood pressure, pulse, weight, and BMI distributions by treatment group at baseline and each protocol mandated measurement time point demonstrated no clinically significant differences between treatment groups. In addition,

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comparisons of vital sign changes from baseline to each protocol mandated measurement time point demonstrated no statistically significant or clinically meaningful changes between treatment groups.

Immunogenicity: Assays for antibodies against denosumab were evaluated for a total of 1448 patients in this trial. Four patients tested positive for binding antibodies, two patients in the placebo group at baseline (0.3%) and one patient from each treatment group during treatment (0.1%). All antibodies were transient (absent upon retesting one month later) and non-neutralizing. There were no indications that the presence of antibodies had effects on efficacy, safety, pharmacokinetics, or pharmacodynamic parameters during the trial.

6 Review of Efficacy

Efficacy Summary

The efficacy conclusions for this application are based on the analyses of efficacy data submitted from two randomized, placebo-controlled trials, Trial 20040135 (135) and Trial 20040138 (138). Trial 135 studied bone mineral density as the primary endpoint. Bone mineral density (BMD) is not accepted as a regulatory endpoint for anti-resorptive agents. Skeletal related events, including incidence of new vertebral fractures is an accepted regulatory endpoint for this class of products. The primary endpoint in Trial 216 was reduction of new vertebral fractures over the three year treatment period. As a result, demonstration of clinical benefit for Trial 135 is based upon the efficacy data submitted for Trial 216 which supported the primary indication for the treatment of postmenopausal osteoporosis (PMO). For trial 135, BMD is a surrogate endpoint while reduction of new vertebral fractures is considered clinical benefit for regulatory purposes. Data from Trial 216 were reviewed in the Division of Reproductive and Endocrinology Products (DRUP).

Trial 135 was a multinational, multicenter, double-blind, placebo-controlled trial involving 252 patients with non-metastatic breast cancer receiving adjuvant aromatase inhibitor therapy following definitive local therapy. Patients were randomized 1:1 to denosumab (127) or placebo (125) once every 6 months for a total of 4 doses during the treatment period of 24 months. All patients received daily calcium ($\geq$ 1 g) and vitamin D ($\geq$ 400 IU) supplementation throughout the trial. Randomization was stratified by the duration of aromatase inhibitor therapy ($\leq$ 6 months vs. > 6 months). A 24 month safety follow-up period was ongoing at the time the BLA was submitted. The primary efficacy endpoint was percentage change in lumbar spine bone mineral density (BMD) from baseline to month 12. Key secondary endpoints were percentage change in lumbar spine bone mineral density (BMD) from baseline to month 6, and percentage change in total hip and femoral neck BMD from baseline to months 6 and 12. There were no neoplastic disease assessments specified as part of the trial and such data was not captured during the conduct of the trial. Survival rate at month 24 was an exploratory endpoint.

There was a statistically significant increase in lumbar spine BMD between denosumab and placebo treated groups at 12 months (denosumab + 4.8%, placebo – 0.7%) based on a least square mean estimate. The treatment difference between the groups was 5.5% (95% CI: 4.8, 6.3). Consistent effects on lumbar spine BMD were observed regardless of baseline age, duration of aromatase inhibitor therapy, weight/bone mass index (BMI), prior chemotherapy, prior selective estrogen receptor modulator (SERM) use, and time since menopause. The treatment differences

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in total hip and femoral neck BMDs from baseline to month 12 were also statistically significant ($p<0.0001$). Trial 135 did not include an evaluation of skeletal related events and relied on the outcome of Trial 216 to demonstrate clinical benefit. All cause mortality included 2 deaths (1%) for each treatment group at 24 months.

Trial 216 was a multinational, multicenter, randomized, double-blind placebo-controlled trial to investigate the safety and efficacy of denosumab on the reduction of new vertebral fractures in 7808 postmenopausal women with osteoporosis after 3 years of treatment. Subjects were randomized (1:1) to receive either denosumab (3902) or placebo (3906) for 3 years. All patients received daily calcium ($\geq$ 1 g) and vitamin D ($\geq$ 400 IU) supplementation throughout the trial. Randomization was stratified by age at study entry: 60 to 64 years, 65 to 69 years, 70 to 74 years, and $\geq$ 75 years. BMD T-scores were required to be $\leq$ - 2.5 and $\geq$ - 4.0. The last scheduled dose was administered at month 30, and patients were followed until month 36 at which time they were offered the opportunity to enroll in an extension trial. The primary efficacy endpoint was the incidence of new vertebral fractures during the 36-month treatment period. Key secondary endpoints were time to first nonvertebral fracture and time to first hip fracture.

There was a statistically significant reduction in the risk of new vertebral, nonvertebral, and hip fractures for denosumab when compared with placebo based on a prespecified sequential testing procedure. The risk reduction for new vertebral fractures at month 36 was 68% (95% CI: 0.26, 0.41; $p < 0.0001$). Risk reductions for nonvertebral fractures and hip fractures were 20% (95% CI: 0.67, 0.95; $p = 0.0106$) and 40% (95% CI: 0.37, 0.97; $p = 0.0362$), respectively. Consistent effects were observed in subgroups at higher fracture risk defined by other baseline characteristics: subjects with $\geq$ 2 prevalent vertebral fractures or having prevalent vertebral fractures with moderate or severe severity, subjects with femoral neck T score $\leq$ - 2.5 and subjects with age $\geq$ 75 years. Body weight did not affect the incidence of vertebral fracture or lumbar spine BMD levels.

Trial 138 was a multinational, multicenter, double-blind, placebo-controlled trial involving 1468 patients with nonmetastatic prostate cancer following definitive local therapy receiving androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonists or following orchiectomy. Approximately 10% of the study population underwent orchiectomy. Patients were randomized 1:1 to either denosumab (734) or placebo (734) once every 6 months for a total of 6 doses over a 36-month treatment period. All patients received daily calcium ($\geq$ 1 g) and vitamin D ($\geq$ 400 IU) supplementation throughout the trial. Randomization was stratified by age group ($<$ 70 years vs. $\geq$ 70 years) and duration of ADT at trial entry ($\leq$ 6 months vs. $>$ 6 months). Upon completion of the 36-month treatment period, patients were continued on trial for 24 months during which no investigational product was administered, or were offered enrollment in a 2-year extension trial. The primary efficacy endpoint was the percent change in lumbar spine BMD from baseline to month 24. Key secondary endpoints were percentage change in femoral neck BMD and total hip BMD from baseline to month 24, percentage change in lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36, subject incidence of any fracture, and subject incidence of new vertebral fracture over the 36-month treatment period. Neoplastic disease assessments consisted of bone scans at baseline and month 36 and PSA levels every 6 months during the treatment phase of the trial. There were no pre-specified analyses to

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assess effects on cancer outcomes based on bone scan or PSA results. Survival rate at 36 months was an exploratory endpoint.

There was a statistically significant increase in lumbar spine BMD between denosumab and placebo treated groups at 2 years (denosumab + 5.6%, placebo -1%) based on a least square mean estimate. The treatment difference was 6.7% (95% CI: 6.2, 7.1), favoring denosumab. Consistent effects on lumbar spine BMD were observed regardless of baseline age, race, geographical region, weight/BMI, BMD, level of bone turnover, duration of androgen deprivation therapy, and presence of vertebral fracture. The treatment differences from baseline to month 24 in femoral neck BMD were 3.9% (95% CI: 3.5, 4.4, $p < 0.0001$) and total hip BMD 4.8% (95% CI: 4.4, 5.1. $p < 0.0001$). There was a statistically significant reduction in the incidence of new vertebral fractures at 36 months, denosumab 1.5%, placebo 3.5% (OR: 0.37, 95% CI: 0.18, 0.78: p=0.0125). At month 24, the incidence of any fracture was 45/734 (6.1%) in the placebo group and 32/734 (4.4%) in the denosumab group (p=0.1282). At month 36, the incidence of any fracture was 53/734 (7.2%) in the placebo group and 38/734 (5.2%) in the denosumab group (p=0.1048). All cause mortality was 5.9% for both treatment groups at 36 months.

Indication

The indications proposed for this application are treatment and prevention of bone loss in patients undergoing hormone ablation (HA) for prostate or breast cancer and treatment and prevention of postmenopausal osteoporosis (PMO). By design, the HA breast cancer indication is dependent upon the outcome of the trial in support of the PMO treatment indication to demonstrate clinical benefit. There is regulatory precedent establishing that the aggregate endpoint, skeletal related event (SRE), represents an adequate efficacy measure and that decreasing the number of SREs constitutes clinical benefit. For this reason, HA Trial 135 relies on the PMO treatment trial to confirm clinical benefit. Trial 138 conducted in men with prostate cancer has both BMD and skeletal related events as endpoints and does not rely on other data to confirm clinical benefit. The results of the analyses of efficacy for the trials submitted in support of the HA indications are discussed herein, as is a brief discussion of the efficacy findings supporting the primary PMO indication, Trial 216.

6.1.1 Methods

The efficacy discussions that follow rely in part on original reviews conducted by the Office of Biostatistics Review.

Summaries of the key HA trials are found in Figure 7 below. **Figure 8** summarizes the efficacy endpoints from the key clinical trials supporting the HA indications.

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Figure 7: Hormone Ablation Indications Key Trials (excerpt from CSR)

Study No.	Study Design	Study Population	Study Objectives	Region	Number of Randomized Subjects	Duration of Treatment
20040135	Phase 3 randomized, double-blind, study of denosumab versus placebo	Women with nonmetastatic breast cancer receiving AIT who had low bone mass (T-score of -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck).	To evaluate whether denosumab compared with placebo preserved lumbar spine BMD after 12 months of treatment To evaluate the effect of denosumab compared with placebo on BMD of the total hip and femoral neck and the safety and pharmacokinetics of denosumab	United States and Canada	252 (127 denosumab 60 mg Q6M, 125 placebo)	24 months (4 doses total), followed by 24-month safety follow-up
20040138	Phase 3 randomized, double-blind study of denosumab versus placebo	Men with nonmetastatic prostate cancer receiving ADT who were < 70 years of age and who had a history of osteoporotic fracture or a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0; men ≥ 70 years did not have to meet these latter requirements. Men with BMD-T scores of < -4.0 at lumbar spine, total hip, or femoral neck were excluded.	To evaluate whether denosumab compared with placebo preserved lumbar spine BMD after 24 months of treatment To evaluate the effect of denosumab compared with placebo on BMD of the total hip and femoral neck; subject incidence of any (osteoporotic) fracture, subject incidence of new vertebral fracture, time to first clinical fracture; and the safety and pharmacokinetics of denosumab	United States, Europe, Canada, and Mexico	1468 (734 denosumab 60 mg Q6M, 734 placebo)	36 months (6 doses total), followed by 24-month safety follow-up or 2-year extension study (20080537)

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Figure 8 Efficacy Endpoints for Trials, Hormone Ablation Indications (excerpt from CSR)

Endpoint	Study 20040135	Study 20040138
BMD		
Percentage change from baseline in lumbar spine BMD	Primary	Primary
Percentage change from baseline in total hip BMD	Secondary	Secondary
Percentage change from baseline in femoral neck BMD	Secondary	Secondary
Percentage change from baseline in trochanter BMD	Exploratory	Exploratory
Percentage change from baseline in distal 1/3 radius BMD[a]	Exploratory	Exploratory
Percentage change from baseline in total body (excluding the head) BMD[a]	Exploratory	Exploratory
Fracture		
Subject incidence of any (osteoporotic) fracture	-	Secondary
Subject incidence of new vertebral fracture	Exploratory	Secondary
Time of first clinical fracture	-	Secondary
Subject incidence of new and worsening vertebral fractures	-	Exploratory
Subject incidence of multiple new vertebral fractures	-	Exploratory
Time to first nonvertebral fracture	Exploratory	Exploratory
Time to first major nonvertebral fracture	-	Exploratory
Subject incidence of multiple any fracture	-	Exploratory
Subject incidence of nonvertebral fracture	Exploratory	-
Bone Turnover Markers		
Percentage change from baseline in bone markers (serum CTX1, P1NP, TRAP5b[b])	Exploratory	Exploratory

[a] Distal 1/3 radius and total body (excluding the head) evaluated in Study 20040138 as a substudy.
[b] TRAP5b evaluated in Study 20040138 only.

6.1.2 Demographics

See the tables and discussions of patient demographics above under section 5.3 Discussion of Individual Clinical Trials.

6.1.3 Patient Disposition

See the tables and discussions of patient disposition above under section 5.3 Discussion of Individual Clinical Trials.

6.1.4 Analysis of Primary Endpoint(s)

Trial 135 (Patients with breast cancer)

The primary efficacy endpoint was the percentage change in lumbar spine bone mineral density (BMD) from baseline to month 12. Randomized were 252 patients, 127 to denosumab and 125 to

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placebo. The eligibility criteria allowed enrollment of women with BMD T-scores between -1.0 and -2.5. These scores are consistent with low bone mass, but are not diagnostic of osteoporosis. Approximately 37% of patients randomized had baseline BMD T-scores out of this range (36% had normal bone mass, and 1% were osteoporotic). BMD assessments by dual x-ray absorptiometry (DXA) were performed at baseline, on day 30, then at months 3, 6, 12, and 24 (or off trial). The same DXA machine was to be used for all procedures for a particular patient and the scans included the L1 through L4 vertebrae. The sample size of 252 patients was chosen to provide adequate power to detect a 2% difference between the groups. Table 21 summarizes the primary efficacy results.

Missing BMD scores were 9% and 15% at months 12 and 24 for the denosumab treated group and 15% and 19% at the same time points for the placebo group. Missing data at month 12 were imputed using the last-observation-carried-forward method. This is the traditional method of data imputation for trials intended to support BMD and fracture endpoints. However, during the development program for denosumab, FDA informed the applicant that missing post-baseline values imputed using the last-observation-carried-forward (LOCF) method could increase the treatment effect and recommended that other imputation methods and sensitivity analyses be proposed (see Meeting Summary, April 21, 2004). In response to this the applicant performed their statistical analyses of the efficacy data using both the LOCF and mean of the other group (MOTH) imputation methods.

Table 21 Trial 135 Percent Change in Lumbar Spine BMD from Baseline to Month 12

Denosumab n=123	Placebo n=122	Treatment effect	p-value
4.8	-0.7	5.5 (CI:4.8, 6.3)	< 0.0001

Based on ANCOVA model adjusting for stratification variable, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction.

The mean changes from baseline BMD to month 12 were 4.8% (95% CI 4.3, 5.4) for denosumab treated patients and -0.7% (95% CI -1.3, -0.1) for placebo treated patients. The treatment difference between denosumab and placebo at month 12 was statistically significant, 5.5% (95% CI 4.8, 6.3) with a p-value < 0.0001. Stratification by duration of aromatase inhibitor therapy (≤ 6 months vs. > 6 months) had no effect on the observed results. Both the DXA T-scores and percent change from baseline were statistically significant between treatment groups. Sensitivity analyses were also performed and included an ANCOVA model using mean-of-the-other-group (MOTH) imputation for missing 12-month BMD values; an ANCOVA model using the per-protocol analysis set with no imputation of missing values; an ANCOVA model with LOCF imputation using the actual strata rather than the as-randomized (if > 5% error); and a likelihood-based repeated-measures model that included treatment group, stratum, baseline BMD value, machine type, baseline BMD value and machine type interaction, visit, and visit-by treatment interaction as fixed effects. These analyses demonstrated no significant effects on the observed results and confirm the results are robust.

It is noteworthy that while demonstrating a statistically significant difference with regard to the efficacy endpoint studied, this trial cannot stand alone to support a demonstration of clinical benefit. As previously noted, in order to determine if the changes in BMD observed in this trial correlate to clinical benefit, the results are dependent upon a demonstration of a positive effect

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on fracture risk as observed in the trial submitted in support of the PMO treatment indication. Trial 216, A Trial to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis: FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months), was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of 7808 postmenopausal women with osteoporosis, 3902 randomized to receive denosumab and 3906 randomized to receive placebo. The primary efficacy endpoint of the trial was incidence of new vertebral fractures during the 36 month treatment period. Denosumab demonstrated a statistically significant decrease in new vertebral fractures (2.3%) vs. placebo (7.2%) with a risk ratio of 0.32 and a p-value < 0.0001. The risk reduction for new fractures at 36 months was 68%. The efficacy result in the current trial (135) was accepted as a surrogate for decreased risk of fracture as determined for the data in Trial 216. The results from Trial 216 were supportive of a claim of clinical benefit in Trial 135.

Analyses of the data for the exploratory fracture incidence endpoint in Trial 135 demonstrated no vertebral fractures during the 24 month treatment period for this trial, and an incidence of nonvertebral fractures of 6% (8 patients) for both treatment groups. While these exploratory data are not supportive of the primary findings in the trial, the exploratory nature of the analysis, the size of the trial, and the duration of treatment preclude any meaningful analysis.

Trial 138 (Patients with prostate cancer)
The primary efficacy endpoint for this trial was the percentage change in lumbar spine BMD from baseline to month 24. Patients enrolled had histologically confirmed prostate cancer and were ≥ 70 years, or were < 70 years with either low baseline BMD (defined as a T-score at the lumbar spine, total hip, or femoral neck < -1) or a history of osteoporotic fracture. BMD was assessed by DXA of the lumbar spine at screening and months 1, 3, 6, 12, 34, and 36. The same DXA machine type (either Hologic or GE Lunar) was to be used for all procedures for a particular patient and the scans included L1 through L4. There was central monitoring and reading of all imaging. The sample size of 1226 patients was chosen to provide adequate power to detect a 2% difference in lumbar spine BMD between groups at an alpha of 0.05 (2-sided) and 80% power to detect a 45% incidence in fracture reduction at 24 months. A Cochran-Mantel-Hanzel test was applied by estimating a 10% expected lost to follow-up rate per year for DXA assessments. The primary analyses of the data were conducted when all patients completed the 36 month treatment period. At 24 months for patients in the denosumab group exhibited a 5% increase in lumbar spine BMD compared to a decrease of 1% in the placebo group. The treatment effect was 6.7% with 95% CI 6.2, 7.1 and p < 0.0001. Table 22 summarizes the primary efficacy results.

Sensitivity analyses for the primary endpoint included a repeated measures model, an ANCOVA model using the per protocol analysis set, an ANCOVA model using actual stratum, and univariate and multivariate covariate analyses using planned covariates, i.e., baseline lumbar BMD T-score, vertebral fracture prevalence, age, race, baseline BMI, and baseline weight. Each of these analyses resulted in statistically significant results (all p-values < 0.0001). The efficacy results in this trial were dependent upon a demonstration of a positive effect on secondary endpoints of fracture risk to demonstrate efficacy.

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Table 22 Trial 138 Percent Change in Lumbar Spine BMD from Baseline to Month 24

Denosumab n=714	Placebo n=716	Treatment effect	p-value
5.6	-1.0	6.7 (CI:6.2, 7.1)	< 0.0001

Based on ANCOVA model adjusting for stratification variable, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction.

Trial 216 As noted above, the efficacy results from this trial were viewed as a demonstration of clinical benefit for Trial 135. The results of the primary efficacy analysis (patient incidence of new vertebral fractures) for Trial 216 are summarized in Table 23 Trial 216 Primary Efficacy Outcomes through Month 36. Based on the analysis, there was a statistically significant reduction in the number of subjects with new vertebral fractures through each of months 12, 24, and 36.

Table 23 Trial 216 Primary Efficacy Outcomes through Month 36

Time Point	Incidence Placebo (N= 3902)	Incidence Denosumab (N=3906)	Relative risk reduction%, 95% CI	Risk Ratio (95% CI)	P value
0-1 year	82/3691 (2.2%)	32/3702 (0.9%)	61 (42,74)	0.39 (0.26, 0.58)	<0.0001
0-2 years	183/3691 (5.0%)	53/3702 (1.4%)	71 (61,79)	0.29 (0.21, 0.39)	<0.0001
0-3 years	**264/3691 (7.2%)**	**86/3702 (2.3%)**	**68 (59,74)**	**0.32 (0.24,0.51)**	**<0.0001**

P value is based on Mantel-Haenszel method adjusting for age stratification variable

A statistically significant decrease in the risk of new vertebral fracture at month 36 ($p < 0.0001$) was observed in all subgroups of baseline characteristics examined (age (≥75 years, >65 years, <75 years), geographic region, body weight, BMI, lumbar spine BMD T-score, total hip BMD T-score, fracture risk assessed by the World Health Organization, fracture risk assessment tool (FRAX), prior use of medication for osteoporosis and serum CTX1). Consistent results were also observed when the data were analyzed by prevalent vertebral fracture or non-vertebral fracture at baseline. For a complete discussion of the efficacy results in this trial, please see the original clinical review performed by DRUP in the FDA document file.

6.1.5 Analysis of Secondary Endpoints(s)

Trial 135

The secondary efficacy endpoints were percentage change in lumbar spine BMD from baseline to month 6, and percentage changes in total hip and femoral neck BMD from baseline to months 6 and 12. All results for these endpoints were at statistically significant levels. Lumbar BMD at month 6 increased by 3.7% for patients in the denosumab group and decreased by 0.6% for patients in the placebo group. This represents a treatment difference of 4.3% with a 95% CI: 3.6, 5.0 and p-value <0.0001. For patients in the denosumab group, total hip BMD at 6 and 12

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months increased by 2.3% and 3.1% respectively and decreased by 0.4% and 0.7% respectively for patients in the placebo group. These results were both statistically significant with p-values <0.0001. For patients in the denosumab group, femoral neck BMD at 6 and 12 months increased by 1.2% and 1.9% respectively and decreased by 0.9% and 0.6% respectively for patients in the placebo group. These results were both statistically significant with p-values <0.0001.

Trial 138

Secondary efficacy endpoints included percentage change in femoral neck BMD and total hip BMD from baseline to month 24. The secondary efficacy endpoints analyses were contingent on rejection of the primary null hypothesis at a level of 0.05 and used the Hochberg procedure to adjust for multiplicity at a level of 0.05. The treatment differences from baseline to month 24 in femoral neck BMD were 3.9% (95% CI: 3.5, 4.4, $p < 0.0001$) and total hip BMD 4.8% (95% CI: 4.4, 5.1. $p < 0.0001$). There was a reduction in incidence of new vertebral fractures of 1.5% for denosumab compared to placebo of 3.5% at 36 months (OR: 0.37, 95% CI: 0.18, 0.78: p=0.0125). At months 24 and 36, the incidences of any fracture were not statistically significant, 6.1% in the placebo group and 4.4% in the denosumab group at 24 months (p=0.1282), and 7.2% in the placebo group and 5.2% in the denosumab group at month 36 (p=0.1048).

Trial 216

Secondary efficacy endpoints included time to first non-vertebral fracture, and time to first hip fracture, both assessed at the time of the 36-month analysis. Nonvertebral fractures were those excluding the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges. In addition, fractures associated with high trauma severity and pathologic fractures were excluded from this category. Nonvertebral fractures were required to be confirmed either by radiographs or other diagnostic images, or by documentation in a radiology report, surgical report, or discharge summary.

There was a statistically significant reduction in the risk of nonvertebral fracture compared to placebo ($p = 0.0106$). The incidence of nonvertebral fractures at Month 36 (based on Kaplan-Meier estimates) was 8% in the placebo group and 6.5% in the denosumab group. The relative risk reduction was 20%, with a hazard ratio of 0.80 (95% CI: 0.67, 0.95) at Month 36.

There was a statistically significant reduction in the risk of hip fracture compared to placebo. The incidence of hip fractures at month 36 (based on Kaplan-Meier estimates) was 1.2% in the placebo group and 0.7% in the denosumab group, resulting in an unadjusted absolute risk reduction of 0.5% (95% CI: 0.0%, 0.9%). The relative risk reduction was 40%, i.e., a hazard ratio of 0.60 (95% CI: 0.37, 0.97) at month 36.

6.1.6 Other Endpoints

PFS was not an endpoint in either the breast cancer or prostate cancer trials and neither trial included defined, prespecified, rigorous plans to evaluate disease progression. There were no routine neoplastic disease assessments included in the protocol for Trial 135. In Trial 138, the protocol included disease assessments only as related to metastatic disease to bone (i.e., bone scan at baseline and month 36) and disease specific markers (i.e., PSA, at pre-specified time points during the treatment phase of the trial). Descriptive statistics for PSA and percent change in PSA from baseline by treatment group were calculated as part of the safety analyses as were

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the proportion of patients experiencing a rise in PSA (defined as ≥ 50% increase from on-study nadir to an absolute PSA value ≥ 5.0 ng/mL) while having castrate levels of serum testosterone (< 50ng/dl). The incidence of PSA rise was compared between treatment groups based on an analysis of covariants approach (ANCOVA) adjusting for baseline PSA level (high vs. low where high was defined as PSA > 0.5 ng/mL and ADT > 1 month, or PSA > 5.0 ng/mL and ADT ≤ 1 month; otherwise, the value was considered low), age group (< 70 years vs. ≥ 70 years), duration of ADT (≤ 6 months vs. > 6 months), and prostate cancer recurrence risk level as the covariates. PSA mean levels at baseline were similar between treatment groups (denosumab 0.86/SD 2.48, placebo 0.81/SD 2.58). (Table 24 summarizes the results of this analysis which was performed by the statistical reviewer for this application, Kyung Yul Lee, Ph.D.) Mean PSA levels from month 0 to month 18 were almost identical for both groups. Higher mean PSA levels were reported for the denosumab group at month 24, but for the placebo group at months 30 and 36. During the follow-up safety phase of each trial there were no specific instructions contained in either protocol related to the assessment of disease status. As a result of the design of these trials with regard to neoplastic disease assessments, FDA cannot determine the impact denosumab has on neoplastic disease progression in either patient population. In addition, a determination cannot be made if treatment with denosumab has an inhibitory effect on the efficacy of anticancer therapy.

Table 24 Trial 138 Least Square Mean PSA Months 6 to 36

	PSA			Difference from Placebo		
	n	LS mean	95% CI	LS mean	95% CI	p-value*
Month 6						
Placebo	688	1.229	(0.66, 1.79)			
Denosumab 60 mg Q6M	706	1.055	(0.49, 1.62)	-0.174	(-0.80, 0.45)	0.582
Month 12						
Placebo	667	2.825	(0.87, 4.78)			
Denosumab 60 mg Q6M	673	2.746	(0.80, 4.69)	-0.079	(-2.26, 2.10)	0.943
Month 18						
Placebo	600	1.231	(0.26, 2.21)			
Denosumab 60 mg Q6M	625	1.533	(0.55, 2.51)	0.302	(-0.79, 1.39)	0.588
Month 24						
Placebo	534	2.350	(-1.92, 6.62)			
Denosumab 60 mg Q6M	560	3.694	(-0.60, 7.98)	1.344	(-3.50, 6.19)	0.586
Month 30						
Placebo	463	3.369	(-0.08, 6.82)			
Denosumab 60 mg Q6M	499	2.771	(-0.69, 6.23)	-0.598	(-4.54, 3.35)	0.766
Month 36						
Placebo	451	8.048	(2.79, 13.30)			
Denosumab 60 mg Q6M	475	6.358	(1.05, 11.67)	-1.690	(-7.74, 4.36)	0.584
Month 6 - Month 36*						
Placebo		3.879	(1.72, 6.04)			
Denosumab 60 mg Q6M		4.077	(1.92, 6.23)	0.198	(-2.24, 2.64)	0.874

*: Proc mixed model (repeated measures) was used adjusting for baseline PSA level, age group (< 70 years vs. ≥ 70 years), duration of ADT (≤ 6 months vs. > 6 months), and prostate cancer recurrence risk level

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In both trials, overall survival (at month 24 in Trial 135 and month 36 in Trial 138) was a designated **exploratory** endpoint. However, neither trial was powered to adequately assess overall survival. Case report forms required collection of survival data at various time points during the treatment and safety follow up phases for each trial, and each statistical plan included a survival analysis. However, no OS analysis was performed in Trial 135 because the small number of deaths (one in each group) precluded meaningful results. In the analysis of OS performed for Trial 138, depicted in Table 25 below, there was no difference in overall survival between denosumab and placebo. The proportion of subjects who were alive at 36 months (94%) and the Kaplan-Meier estimates of survival were identical. The hazard ratio for the difference in survival at month 36 was 0.97 with a 95% confidence interval of 0.64 - 1.49 and p-Value 0.904. A hazard ratio of 0.97, if true, demonstrates that the result observed is among the possible outcomes. The upper bound of the confidence interval indicates that versus placebo, there could be a survival decrement with denosumab of up to 49%. As a result of the design of these trials with regard to overall survival, FDA cannot determine the impact denosumab has on survival in either patient population.

Table 25 Trial 138 Overall Survival Analysis

Statistic	Denosumab n = 734	Placebo n = 734
Number of Patients With OS Event	43 (5.9%)	43 (5.9%)
Number of Patients Without OS Event	691 (94.1%)	691 (94.1%)
Median Duration of OS months (95% CI)	NA	NA
Mean Duration (SE)	37.23 (0.22)	37.37 (0.22)
Hazard Ratio (95% CI)	0.97 (0.64- 1.49)	
P-Value (Stratified Log-Rank test)	0.904	

6.1.7 Subpopulations

In both study populations, subgroup analyses demonstrated no detrimental effects on the efficacy outcomes reported.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Trial 223 was a Phase II dose finding study examining 7 different subcutaneous doses of denosumab and one cohort each of placebo or weekly oral alendronate in postmenopausal women with low bone mass. The denosumab cohorts were given double-blind study drug as a subcutaneous injection of 6 mg, 14 mg, or 30 mg every 3 months; or 14 mg, 60 mg, 100 mg, or 210 mg every 6 months for the first 24 months of the study. There were approximately 40 subjects per dosing cohort, for a total of 412 subjects (319 denosumab, 46 placebo, 47 alendronate). The study design was adequate to assess dose response.

One dose, 60 mg subcutaneously every 6months, was chosen for administration in the four Phase 3 trials for treatment of postmenopausal osteoporosis (216), prevention of postmenopausal osteoporosis (132), bone loss associated with hormone ablation for prostate cancer (138), and bone loss associated with hormone ablation for breast cancer (135). The rationale for this dose included the fact that doses higher than 60 mg did not result in greater increases in BMD despite more prolonged effects on reducing markers of bone resorption;

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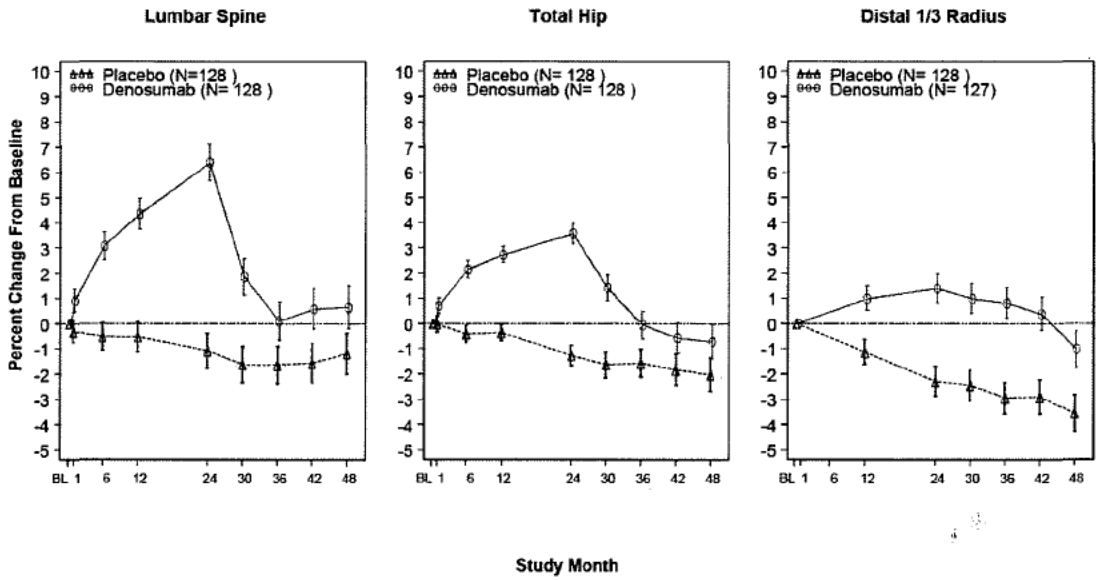
doses of 30 mg every 3 months were equivalent in PD activity to the 60 mg every 6 months dosing regimen (the 6 month dose interval was selected for patient convenience and the potential for increased compliance); and the 60 mg dose was at least as effective as alendronte 70 mg once weekly. The rationale for dose selection is regarded as somewhat arbitrary based on the data available. Why lower, equally pharmacodynamic doses were not chosen for these trials is being investigated by the reviewers in DRUP. Additional data and analyses have been requested from the applicant and are pending.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The effects of denosumab treatment on BMD persist while patients are on continuous treatment and the effects are reversible upon treatment discontinuation. This was demonstrated in Trial 132, submitted in support of the PMO prevention indication, and can be observed in Figure 9. Treatment in this trial was discontinued at month 24.

Figure 9 Trial 132 BMD by DXA Percent Change from Baseline by Visit (Least Squares Means and 95% CI from Repeated Measures Model)



6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues identified or analyses performed during the conduct of this review.

7 Review of Safety

Safety Summary

The applicant presented data from over 13,000 subjects (11,000 women with low BMD or osteoporosis, 252 women with nonmetastatic breast cancer receiving AI therapy, and 1468 men with nonmetastatic prostate cancer receiving androgen deprivation therapy) who participated in

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33 clinical trials with the majority of patients exposed to denosumab for up to 3 years. There were also a small number of patients, <200, with exposure for up to 5 years. The Integrated Summary of Safety (ISS) was focused on the analyses of patients who received the denosumab dosing regimen proposed for labeling, 60 mg subcutaneously every 6 months. Analyses of the hormone ablation (HA) safety databases were performed to analyze the individual HA trials, and pooled safety data was analyzed for the four key HA and PMO trials. Drug exposure and overall safety were evaluated to include summaries of deaths and common, serious, or significant adverse events. In addition, adverse events of special interest based on the antibody target, safety signals identified during development, or safety signals identified from experience with other bone resorptive agents were summarized. Safety laboratory evaluations were also performed at regular intervals and summaries of the data were compiled. In general, the approach taken by the applicant and the analyses of the data utilized to identify the safety profile for this antibody were adequate.

Following is a list of safety issues pertinent to this application. These issues are discussed in full in section 7.3.5 Submission Specific Primary Safety Concerns:

- Tumor Promotion: For supportive care agents administered to patients with cancer, the risk/benefit analysis must take into consideration the potential for that agent to act as a tumor promoter to already existing cancers or to negatively impact the efficacy of concomitant cancer therapy. There is a growing body of evidence suggesting that promotion of tumor growth may exist for drugs in which there is no demonstrable direct relationship between receptors and tumor proliferation. Neither of the HA trials included prespecified, defined, rigorous plans to evaluate for potential treatment effects on time-to-disease progression. There were no routine assessments for neoplastic disease status in the protocol for Trial 135. In Trial 138, the protocol included disease assessments only for metastatic disease to bone (i.e., bone scan at baseline and month 36) and disease-specific markers (i.e., PSA, at pre-specified time points during the treatment phase of the trial). During the follow-up safety phase of each trial, there were no specific instructions contained in either protocol related to the assessment of disease status. In both trials, overall survival (at month 24 in Trial 135 and month 36 in Trial 138) was a designated exploratory endpoint. However, not enough events were expected to occur and neither trial was powered to detect a clinically meaningful decrement in overall survival.

  It cannot be determined whether denosumab has an impact, either adverse or favorable, on time-to-event tumor outcomes in either patient population. It is the recommendation of this reviewer that data from studies designed to identify detrimental effects on cancer outcomes relating to tumor progression (i.e., time-to-event endpoints such as progression free survival or overall survival) be submitted to FDA for review to confirm the safety of denosumab with regard to the potential for tumor promotion.

- Infections: Overall, patients in the denosumab group had a slightly increased incidence of serious infections. There were more serious infections of the skin, ear, abdominal system and urinary tract. Also, endocarditis, infective arthritis and skin ulcers occurred more commonly in denosumab groups. There was no increase in opportunistic infections

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observed in denosumab treated patients. Deaths as a result of infections were more common in the placebo group for the HA trials.

- Malignancy: Overall, patients in the denosumab group in the Primary PMO safety population had a minimally increased incidence of breast cancer, pancreatic cancer, gastrointestinal cancer and reproductive cancers. There was an imbalance noted for breast cancer among the adverse events that led to discontinuation of investigational product in the Primary PMO safety population (denosumab 20 patients, placebo 10 patients). This fact engendered lengthy discussion during the advisory committee meeting; however the relevance of these cases are negated by the overall incidence of breast cancer in the PMO trials, which was balanced (4% each arm).

- Skin and soft tissue disorder: Patients treated with denosumab were more likely to develop skin and soft tissue related adverse events. There were more bullous conditions, pruritic conditions, skin rashes, dermatitis and eczema related adverse events in the denosumab group compared to placebo.

- Bone biopsy histomorphometry: Bone histomorphometry results demonstrate a degree of bone remodeling suppression not previously observed with other agents having effects on bone resorption. The denosumab group had markedly suppressed osteoclast and osteoblast counts compared to placebo and alendronate. Dynamic bone formation parameters such as activation frequency, bone formation rate and mineralizing surface were also markedly suppressed.

- Hypocalcemia: Hypocalcemia is a known class effect of antiresorptive drugs. Denosumab-induced hypocalcemia appears to be transient (nadir at day 8-11) with spontaneous resolution and without any serious clinical sequelae observed.

- ONJ: No cases of ONJ have been positively adjudicated in the PMO and Hormone Ablation trials under review. However, at least ten confirmed case of ONJ have been reported in other trials conducted by the Applicant in patients with multiple myeloma and metastatic cancer.

- Severe and End-stage Renal Disease: In a Phase I, single dose, open label trial to assess PK, safety and tolerability in patients with both normal and abnormal renal function not receiving calcium or vitamin D supplementation, it was concluded that the PK of denosumab is not influenced by renal dysfunction of any severity. However, in patients with severe (creatinine clearance < 30 mL/min) or end-stage renal disease, there is an increased incidence and severity of hypocalcemia.

7.1 Methods

Clinical data from the denosumab trials submitted in support of the HA indications were reviewed individually and analyzed to assess the overall safety of each trial. See section 5.3 Discussion of Individual Clinical Trials, for an in-depth analysis of safety for Trials 135 and 138. In order to improve the precision of incidence estimates, data from the key HA and PMO trials (132, 135, 138, and 216) were pooled to perform additional safety analyses utilizing a larger

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population. These four trials were chosen in order to attempt to confirm the analyses of the applicant in the integrated summary of safety (ISS), and because of the homogeneity of design elements, including demographics, endpoints, IP dose and duration. The ISS data analysis datasets were utilized for the review. Patients from each of the key studies were identified and subsets of their pooled data were utilized for analyses. In addition to the foregoing, targeted safety analyses utilizing the entire ISS databases (i.e., 27 separate trials consisting of 12, 363 patients) was undertaken to confirm and contrast the results obtained from all other safety analyses. However, these analyses were limited by the differences in trial design, dose, dose regimen, and comparators among the studies which made any conclusions subject to numerous qualifications.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For a complete summary of the trials examined by the applicant during the safety evaluation of the trials submitted with this application, see section 5.1 Tables of Studies/Clinical Trials. For the purposes of this review, and for the reasons stated above, the safety analyses will be limited to the key trials submitted in support of both the PMO and HA indication, i.e., Trials 216, 132, 135, and 138. A total of 9796 patients were enrolled in the four key trials, 4929 received ≥ 1 dose of denosumab and 4867 received ≥ 1 dose of placebo. For the PMO indications, 4041 patients were exposed to denosumab and for the HA indications 860 patients were exposed to denosumab.

7.1.2 Categorization of Adverse Events (AE)

For the key trials, adverse events were coded utilizing MedDRA versions 9 and 11 and were presented to include all five levels of the MedDRA hierarchy. Event grading for the HA trials was performed utilizing NCI CTC version 3, while the PMO trials used a system corresponding to grades of mild, moderate, severe, life threatening and fatal, which were then coded into a numbered scale of 1 through 5. A side by side comparison of verbatim term to MedDRA Lower Level Term (LLT) was performed to verify the accuracy of the coding process. Coding was deemed appropriate in the majority of cases. The cases where the judgment of this reviewer differed from that of the coder were not clinically meaningful.

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

Data from the key trials supporting the PMO (Trials 132 and 216) and HA indications (Trials 135 and 138) were pooled and analyzed. The numerator events and denominators for each trial were combined. No formal weighting methods were employed. Pooling the data provided a database of 9796 patients for the comparative safety analyses and other explorations of the safety profile for denosumab. This approach was taken because these trials were the key trials submitted in support of safety and efficacy and, as noted previously, there was relative homogeneity of design. It has been noted that the safety data from the HA and PMO trials were graded using different grading systems. While the PMO trials used a system corresponding to grades of mild, moderate, severe, life threatening and fatal, the HA trials utilized NCI CTCAE version 3. This is noteworthy because the greater granularity and specificity of the NCI CTCAE coding system. However, both of these scales were then coded using a numbered scale of 1

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through 5; see Table 26. Because of the identical coding and similarities in the corresponding scales, data pooling and adverse event analyses for these key trials are deemed appropriate.

Table 26 Severity Coding for PMO and HA Trials

Code	PMO Trials Text	HA Trials NCI CTCAE Text
01	MILD	GRADE 1
02	MODERATE	GRADE 2
03	SEVERE	GRADE 3
04	LIFE THREATENING	GRADE 4
05	FATAL	GRADE 5

7.2 Adequacy of Safety Assessments

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

For the four key trials submitted in support of this application, the dosing regimens were identical to the dose suggested for labeling, i.e., 60 mg subcutaneously every 6 months. A total of 4867 patients received at least one dose of denosumab during the conduct of the four key trials. Each trial utilized the dosing regimen proposed for labeling with a maximum duration of exposure of 3 years (Trials 216 and 138) and a minimum exposure of 2 years (Trials 132 and 135). Patient demographics for Trials 135 and 138 can be reviewed in section 5.3 Discussion of Individual Clinical Trials. Patient demographics for the PMO trials, 132 and 216, follow in Table 27 below. Demographic characteristics were balanced between treatment groups for the pooled data in the PMO trials.

Table 27 PMO Trials 216 and 132 Demographics

Demographic		Denosumab n (%)	Placebo n (%)
AGE	Mean	71.8	71.8
	Min	46	43
	Median	72	72
	Max	90	91
SEX			
F		4080 (100)	4070 (100)
RACE			
AMERICAN INDIAN/ ALASKA NATIVE		1 (0.02)	0
ASIAN		16 (0.4)	14 (0.3)
BLACK OR AFRICAN AMERICAN		38 (0.9)	33 (0.8)
HISPANIC OR LATINO		250 (6.1)	244 (5.9)
JAPANESE		9 (0.2)	6 (0.1)
NATIVE HAWAIIAN OR OTHER PACIFIC		0	2 (0.05)

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Demographic	Denosumab n (%)	Placebo n (%)
ISLANDER		
OTHER	7 (0.17)	6 (0.1)
CAUCASIAN	3759 (92)	3765 (92)
COUNTRY[7]		
ARG	235 (5.8)	240 (5.9)
BRA	232 (5.7)	220 (5.4)
CAN	117 (2.9)	98 (2.4)
CZE	263 (6.4)	250 (6.1)
DNK	625 (15.3)	619 (15.2)
ESP	101 (2.5)	105 (2.6)
EST	227 (5.6)	199 (4.9)
GBR	401 (9.8)	388 (9.5)
HUN	120 (2.9)	113 (2.8)
ITA	115 (2.8)	103 (2.5)
POL	473 (11.6)	476 (11.7)
USA	271 (6.6)	306 (7.5)

7.2.2 Explorations for Dose Response

Overall, there were 30 separate denosumab dosing regimens studied during the development program; and there were 27 clinical trials involving over 14,000 subjects (12,129 females, 1956 males). In the entire denosumab trial database, there were 5065 patients who received the dose intended for labeling. Table 28 summarizes the number of doses received. The majority of patients received 6 doses (70.7%), which represents per patient exposure of 360 mg over 3 years.

Table 28 ISS Denosumab Exposure at 60 mg SC q 6M

	Number of doses	n (%)
Denosumab 60 mg SC q6M	1	271 (5.4)
	2	334 (6.6)
	3	220 (4.3)
	4	457 (9.0)
	5	200 (3.9)
	6	3583 (70.7)

7.2.3 Special Animal and/or In Vitro Testing

The nonclinical safety data was limited to non-human primates based on species specificity and RANKL tissue distribution. Denosumab is not pharmacologically active in rodents.

7.2.4 Routine Clinical Testing

Overall, routine clinical and laboratory assessments of patients enrolled in denosumab clinical trials were adequate to determine both efficacy and safety. However, more frequent monitoring of Vitamin D levels, which were assessed at baseline and end of study only, would have allowed for a more in-depth analysis designed to evaluate the effects of Vitamin D levels on adverse

7 Countries with < 100 patients enrolled are not represented in this table.

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events and outcomes. Cardiovascular (CV) safety was identified early in development as a theoretical concern because of conflicting evidence in the medical literature identifying both cardio-protective and cardiac-inciting effects for RANKL inhibition on levels of osteoprotegrin (OPG). As a result throughout the development program, evaluation of cardiovascular data (including ECGs, QTc effects, CV AEs and SAEs, and aortic calcifications) were included in all clinical trials. In addition, an independent committee was utilized for Trials 216 and 138 to evaluate all CV-related SAEs, including deaths. OPG levels were evaluated in a bone marker substudy of Trial 216.

7.2.5 Metabolic, Clearance, and Interaction Workup

Because denosumab is a monoclonal antibody and is not eliminated via cytochrome P450 [CYP] enzymes, hepatic impairment and drug interaction studies (e.g., with CYP inhibitors or inducers) were not considered appropriate and were not conducted by the applicant. However, a study including transition from a bisphosphonate to denosumab was conducted which allowed for an indirect evaluation of drug interactions when compared to results from other trials. The PK of denosumab was not altered in patients who transitioned from bisphosphonates to denosumab. As noted previously in this review, a renal impairment evaluation was also conducted in patients with normal, mild, moderate, severe, and end-stage renal disease. No relationship was observed between denosumab PK and renal function and it was concluded by the applicant that no dose adjustment is necessary in patients with renal impairment. However, because of the effects of denosumab on serum calcium in patients with severe renal dysfunction (creatinine clearance <30 mL/min) and end-stage renal disease, denosumab should be used with extreme caution in these patients.

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

Potential safety issues were identified early in the development program for denosumab. During the Phase III trials, strategies were developed by the applicant to assess and mitigate safety issues of particular concern. Targeted were hypocalcemia, cardiovascular events, malignancy, infections, ONJ, hypersensitivity, and fracture healing complications. In an attempt to mitigate hypocalcemia, calcium and Vitamin D supplementation was required for patients in the trials. During data analyses, specific searches and analyses of the data were performed in order to ensure that symptoms of hypocalcemia were identified in addition to laboratory values. An independent ONJ adjudication committee was utilized to evaluate suspected cases of ONJ, and make a diagnosis based upon pre-defined criteria. In addition, a panel of independent cardiologists was utilized for adjudication of all cases of cardiovascular SAEs and deaths.

The known safety issues with other agents having antiresorptive effects were a consideration of this review. The analyses which follow were performed to confirm assertions of the applicant pertaining to adverse events of particular interest.

7.3 Major Safety Results

7.3.1 Deaths

Deaths occurring in Trials 135 and 138 are discussed in section 5.3 Discussion of Individual Clinical Trials, above.

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Deaths occurring in key PMO Trial 216 included 70 (1.7%) patients in the denosumab group and 90 (2.2%) patients in the placebo group. All fatal events occurring during this trial were reviewed and adjudicated by a Cardiovascular Adjudication Committee. Deaths were then classified by cause as cardiovascular or non-cardiovascular. All deaths were presumed cardiovascular unless another cause was identified (e.g., accidental death, disease progression). The causes of death were balanced between treatment groups for Trial 216.
No deaths occurred in Trial 132 through the 24 month treatment period or during the first 12 months of the off-treatment period.

Table 29 summarizes the causes of death by MedDRA System Organ Class (SOC) for the key trials.

Table 29 Causes of Death by MedDRA SOC for Key Trials in the ISS

MedDRA SOC	Trial 216 (PMO Treatment)		Trials 135 & 138 (Hormone Ablation)	
	Placebo n (%) N = 4041	Denosumab n (%) N= 4050	Placebo n (%) N = 845	Denosumab n (%) N = 860
Cardiac	23 (0.6)	18 (0.4)	12 (1.4)	15 (1.7)
Endocrine	0	1 (< 0.1)	0	0
Gastrointestinal	2 (< 0.1)	4 (0.1)	1 (0.1)	1 (0.1)
General disorders & admin. site conditions	6 (0.1)	4 (0.1)	7 (0.8)	3 (0.3)
Hepatobiliary	1 (< 0.1)	1 (< 0.1)	0	1 (0.1)
Infections & infestations	6 (0.1)	6 (0.1)	6 (0.7)	0
Injury, poisoning & proc. complications	3 (0.1)	1 (< 0.1)	2 (0.2)	0
Metabolism & nutrition	1 (< 0.1)	0	0	2 (0.2)
Neoplasms benign, malignant & unspec	26 (0.6)	20 (0.5)	10 (1.2)	7 (0.8)
Nervous system	11 (0.3)	6 (0.1)	3 (0.4)	8 (0.9)
Renal and urinary	0	1 (< 0.1)	1 (0.1)	0
Respiratory, thoracic & mediastinal	11 (0.3)	6 (0.1)	4 (0.5)	8 (0.9)
Social circumstances	0	1 (< 0.1)	0	0
Vascular disorders	0	3 (0.1)	1 (0.1)	0
Total	**90 (2.2)**	**70 (1.7)**	**47 (5.6)**	**45 (5.2)**

7.3.2 Nonfatal Serious Adverse Events (SAE)

Serious Adverse Events (SAEs) occurring in Trials 135 and 138 are discussed in section 5.3 Discussion of Individual Clinical Trials. For the PMO trials, nonfatal serious adverse events were generally balanced across treatment groups, and are summarized in Table 30 ISS Trials 216 and 132 Serious Adverse Events by MedDRA SOC below.

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Table 30 ISS Trials 216 and 132 Serious Adverse Events by MedDRA SOC

MedDRA SOC	Placebo n (%)	Denosumab n (%)
Blood and lymphatic system disorders	22 (0.6)	20 (0.5)
Cardiac disorders	142 (3.8)	181 (4.8)
Congenital, familial and genetic disorders	1 (0.03)	0 (0)
Ear and labyrinth disorders	15 (0.4)	24 (0.6)
Endocrine disorders	6 (0.2)	5 (0.1)
Eye disorders	45 (1.2)	39 (1)
Gastrointestinal disorders	102 (2.7)	143 (3.8)
General disorders & administration site conditions	30 (0.8)	34 (0.9)
Hepatobiliary disorders	33 (0.9)	29 (0.8)
Immune system disorders	1 (0.03)	1 (0.03)
Infections and infestations	130 (3.5)	162 (4.3)
Injury, poisoning and procedural complications	191 (5.1)	126 (3.4)
Investigations	9 (0.2)	5 (0.1)
Metabolism and nutrition disorders	14 (0.4)	20 (0.5)
Musculoskeletal and connective tissue disorders	151 (4)	169 (4.5)
Neoplasms benign, malignant and unspec	123 (3.3)	152 (4)
Nervous system disorders	120 (3.2)	125 (3.3)
Pregnancy, puerperium and perinatal conditions	0	0
Psychiatric disorders	14 (0.4)	20 (0.5)
Renal and urinary disorders	19 (0.5)	20 (0.5)
Reproductive system and breast disorders	38 (1)	32 (0.9)
Respiratory, thoracic and mediastinal disorders	76 (2)	80 (2.1)
Skin and subcutaneous tissue disorders	7 (0.2)	10 (0.3)
Social circumstances	0	0
Surgical and medical procedures	0	1 (0.03)
Vascular disorders	71 (1.9)	71 (1.9)

7.3.3 Dropouts and/or Discontinuations

Analysis of the pooled data from the key PMO and HA Trials demonstrated that the number of patients discontinuing investigational product was higher in subjects receiving placebo, with only 74% of placebo and 79% of denosumab patients completing all scheduled doses of investigational product. The reasons for ending investigational product were balanced across treatment groups. Trial specific reasons for discontinuation in Trials 135 and 138 can be

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reviewed in section 5.3 Discussion of Individual Clinical Trials, above. Table 31 Reasons for Discontinuation of IP, summarizes the reasons for discontinuation for Trials 216 and 132.

Table 31 Reasons for Discontinuation of IP in Trials 216 and 132

Reason	Placebo n (%)	Denosumab n (%)
Administrative decision	5 (0.1)	9 (0.2)
Adverse event	209 (5.6)	197 (5.2)
Consent withdrawn	258 (6.9)	213 (5.7)
Death	58 (1.5)	38 (1)
Disease progression (PMO)	61 (1.6)	10 (0.3)
Ineligibility determined	7 (0.2)	4 (0.1)
Lost to follow-up	26 (0.7)	26 (0.7)
Noncompliance	13 (0.3)	10 (0.3)
Other	33 (0.9)	29 (0.7)
Protocol deviation	24 (0.6)	21 (0.6)
Requirement for alternative therapy	63 (1.7)	28 (0.7)
Subject request	85 (2.3)	85 (2.3)

7.3.4 Significant Adverse Events

All significant AEs related to the HA trials have been discussed under previous headings or are discussed in section 7.3.5 Submission Specific Primary Safety Concerns, below.

7.3.5 Submission Specific Primary Safety Concerns

Tumor Promotion: For supportive care agents administered to patients with cancer, the risk/benefit analysis must take into consideration the potential for any agent to act as a tumor promoter for pre-existing cancers or to negatively impact the efficacy of concomitant cancer therapy. There is a growing body of evidence suggesting that promotion of tumor growth may exist for drugs in which there is no demonstrable direct relationship between receptors and tumor proliferation. In these instances, drugs used to palliate cancer treatment-related toxicity may not only bind directly to tumor cells with consequent alterations in known signal transduction pathways, but may also stimulate tumor growth through binding to receptors in non-malignant components of the tumor microenvironment, or through activation of other signal transduction pathways not directly or intentionally targeted. Many aspects of tumor promotion for pre-existing cancers are still not well understood.

Neither of the HA trials included prespecified, defined, rigorous plans to evaluate for potential treatment effects on time-to-disease progression. There were no routine assessments for neoplastic disease status in the protocol for Trial 135. In Trial 138, the protocol included disease assessments only as related to metastatic disease to bone (i.e., bone scan at baseline and month 36) and disease specific markers (i.e., PSA, at pre-specified time points during the treatment phase of the trial). Descriptive statistics for PSA and percent change in PSA from baseline by treatment group were calculated as part of the safety analyses as were the proportion of patients

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experiencing a rise in PSA (defined as ≥ 50% increase from on-study nadir to an absolute PSA value ≥ 5.0 ng/mL) while having castrate levels of serum testosterone (< 50ng/dl). The incidence of PSA rise was compared between treatment groups based on an analysis of covariants approach (ANCOVA) adjusting for baseline PSA level (high vs. low where high was defined as PSA > 0.5 ng/mL and ADT > 1 month, or PSA > 5.0 ng/mL and ADT ≤ 1 month; otherwise, the value was considered low), age group (< 70 years vs. ≥ 70 years), duration of ADT (≤ 6 months vs. > 6 months), and prostate cancer recurrence risk level as the covariates. PSA mean levels at baseline were similar between treatment groups (denosumab 0.86/SD 2.48, placebo 0.81/SD 2.58). (Table 24 summarizes the results of this analysis which was performed by the statistical reviewer for this application, Kyung Yul Lee, Ph.D.) Mean PSA levels from month 0 to month 18 were almost identical for both groups. Higher mean PSA levels were reported for the denosumab group at month 24, but for the placebo group at months 30 and 36. In addition, as shown in Table 32, the incidence rise in PSA at 36 months was similar between treatment groups. During the follow-up safety phase of each trial there were no specific instructions contained in either protocol related to the assessment of disease status. As a result of the design of these trials with regard to neoplastic disease assessments, FDA cannot determine the impact denosumab has on neoplastic disease progression in either patient population. In addition, a determination cannot be made if treatment with denosumab has an inhibitory effect on the efficacy of anticancer therapy.

Table 32 Incidence of PSA Rise at 36 Months for trial 138 (safety population)

	Crude Incidence		Odds Ratio[a]		
	n/N1	%	Pt Est	(95% CI)	p-value
Through Month 12					
Placebo (N = 725)	40/703	5.7			
Denosumab 60 mg Q6M (N = 731)	42/719	5.8	1.00	(0.62, 1.62)	0.9949
Through Month 24					
Placebo (N = 725)	74/707	10.5			
Denosumab 60 mg Q6M (N = 731)	73/719	10.2	0.94	(0.65, 1.36)	0.7422
Through Month 36					
Placebo (N = 725)	92/708	13.0			
Denosumab 60 mg Q6M (N = 731)	98/720	13.6	1.05	(0.75, 1.46)	0.7889

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N = Number of subjects who received ≥ 1 dose of investigational product
N1 = Number of subjects with an evaluation during the time point of interest
Values < 1 for odds ratio favor denosumab.
PSA rise defined as a rise by ≥ 50% from the previous on-study PSA nadir to an absolute PSA ≥ 5.0 ng/mL while in a castrate state (serum testosterone level < 50 ng/dl)
[a]Based on logistic regression model adjusting for age group, duration of ADT at study entry, PC recurrence risk level, and the baseline PSA level

In both trials, overall survival (at month 24 in Trial 135 and month 36 in Trial 138) was a designated exploratory endpoint. However, neither trial was powered to detect a clinically meaningful decrement in overall survival because not enough events were expected to occur in these patient populations. Case report forms required collection of survival data at various time points during the treatment and safety follow up phases for each trial, and each statistical plan included a survival analysis. An analysis of OS

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was not performed in Trial 135 because the small number of deaths (one in each group) precluded meaningful results. An analysis of 3-year survival rates was performed for Trial 138, see Table 33 below. There was no difference in overall survival between denosumab and placebo in this trial with 94% of patients alive at 36 months in both groups. The hazard ratio for the difference in survival at month 36 was 0.97 with a 95% confidence interval of 0.64 - 1.49 and p-value 0.90 (stratified log-rank test).

As a result of the design of these trials with regard to disease assessments as well as the designs and limited number of events with regard to overall survival, it cannot be determined whether denosumab has an impact, either adverse or favorable, on disease progression or survival in either patient population. It is the recommendation of this reviewer that prior to approval of this application, data from studies designed to identify detrimental effects on cancer outcomes (i.e., time-to-event endpoints such as progression free survival or overall survival) be submitted to FDA for review to confirm the safety of denosumab with regard to the potential for the promotion of pre-existing tumors.

Table 33 Trial 138 Overall Survival at Month 36

OS	Denosumab N = 734	Placebo N = 734
Patients with OS Event	43 (5.9%)	43 (5.9%)
Patients without OS Event	691 (94.1%)	691 (94.1%)
Median duration OS (months)	NA	NA
Mean duration OS(SE)	37.23 (0.22)	37.37 (0.22)
Hazard ratio (95% CI)	0.97 (0.64 - 1.49)	
p-value (stratified log-rank test)	0.90	

Stratification factors: age group (< 70 years vs. ≥ 70 years), duration of ADT at study entry (≤ 6 months vs. > 6 months).

Hypocalcemia:
The analyses in this section rely in part on the original DRUP clinical review and the statistical review performed by the Quality Safety and Pharmacoepidemiology Group (QSPG).

Calcium and Vitamin D are necessary elements of normal skeletal homeostasis. Studies demonstrate that calcium balance is related to calcium intake, and negative balance can be reversed with appropriate intake. Calcium balance becomes positive in premenopausal women at approximately 1000 mg/day and in menopausal women at 1500 mg/day. Calcium levels can be reduced as a consequence of a decreased rate of bone resorption and hypocalcemia can be associated with a number of clinical manifestations. With mild hypocalcemia, few, if any, symptoms may be evident while severe hypocalcemia can lead to life threatening seizures, heart failure, or laryngospasm. Based on the known target and effects of denosumab, hypocalcemia was an anticipated toxicity during clinical development. The applicant included in their key trials preventative measures to mitigate potential hypocalcemia as well as safety assessments evaluating both corrected and uncorrected serum calcium levels. All patients received both supplemental calcium and vitamin D (calcium 1 g daily, vitamin D ≥ 400 IU vitamin D daily or ≥ 800 IU vitamin D daily dependent upon baseline vitamin D level), and regular laboratory

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assessments were performed. The analyses conducted by the applicant for the incidence of hypocalcemia included a review of all laboratory data and a search of the adverse events database for events that could result from hypocalcemia. Specifically searched were the MedDRA preferred terms hypoesthesia, oral hypoesthesia, parasthesia, oral parasthesia, and tetany. Based on evaluations of both the laboratory and adverse events data, the applicant concluded that there were no clinically significant adverse events of hypocalcemia related to laboratory results, although decreased calcium levels (corrected for albumin) were noted.

Data from the pooled HA and PMO trials were analyzed individually for events of hypocalcemia. The applicant provided data for three measures of serum calcium: serum calcium, serum calcium corrected for albumin, and serum calcium corrected for albumin if albumin was less than 4 g/dL. All serum calcium samples were assessed at a central laboratory and uniform lower limits of normal were fixed at 8.5 mg/dl for the two key PMO trials (132 and 216) and 8.4 mg/dl for the two key HA trials (135 and 138). Serum calcium levels consistent with hypocalcemia were not recorded as adverse events unless they were associated with clinical symptoms; however changes in calcium levels requiring new or adjusted therapy were considered to be AEs.

There were no deaths attributable to hypocalcemia. Four patients experienced five SAEs related to hypocalcemia; but these events were balanced between treatment groups. In PMO Trial 216, an 80 year old woman (USUBJID 20030216 (b) (6)) receiving placebo was reported to have an AE related to hypocalcemia for which she was hospitalized. No further information on the outcome of this event is known. In HA Trial 138, three individuals experienced hypocalcemia SAEs. An 83-year old man (USUBJID 20040138 (b) (6) receiving placebo, experienced dysesthesias of the right and left hands, was hospitalized and removed from the trial. A 75-year old man (USUBJID 20040138 (b) (6) receiving denosumab had two separate symptoms associated with hypocalcemia (dysesthesias of the left arm and right hand) lasting for three days, for which he was hospitalized. An 83-year old man (USUBJID 20040138- (b) (6)) receiving denosumab experienced hypocalcemia occurring 12 days after the most recent dose and lasted for 9 days. The patient was hospitalized and removed from the trial.

A review of the analysis datasets for the HA and pooled PMO trials was performed. The search included MedDRA PT terms indicating both actual hypocalcemia events and other events that had the potential of being the sequelae of hypocalcemia. Table 34 and Table 35 include the terms utilized during the search. For the pooled PMO trials, Table 36 demonstrates that there were no coded AEs of hypocalcemia in the denosumab group and 2 in the placebo group and overall, potential clinical effects of hypocalcemia resulting from the expanded search were balanced between the treatment groups, denosumab 112 (2.77%) and placebo 110 (2.72%). In HA Trial 138, there was one patient receiving denosumab who reported a hypocalcemia event, and no patients receiving placebo, Table 37. Potential clinical effects of hypocalcemia resulting from the expanded search in this trial demonstrated a slightly higher incidence of parasthesias and hypoestheisas for denosumab than placebo, 32 (3.0%) vs. 15 (2.0). In HA Trial 135, there were no patients with hypocalcemia in either treatment group, and the potential clinical effects of hypocalcemia resulting from the expanded search were relatively balanced between treatment groups, Table 38.

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Subgroup analyses of hypocalcemia based on baseline vitamin D levels, and baseline renal function were also performed. For the pooled PMO and HA Trial 138 data, the incidences of hypocalcemia across the treatment groups were balanced when stratified for vitamin D levels. In HA Trial 135, among women whose vitamin D levels were between 12 ng/mL and 20 ng/mL, there was an increased incidence of hypocalcemia in patients in the denosumab group compared to patients in the placebo group, 6 (9.7%) and zero respectively. It is unknown why this group of women appears to be more susceptible to hypocalcemia when treated with denosumab compared to women in the PMO trials.

In addition to the searches of the databases described above, baseline and subsequent corrected calcium levels for the pooled data for the PMO trials and the individual data from the HA trials were analyzed. The PMO trials defined hypocalcemia as a value < 8.5 mg/dL and the HA trials defined hypocalcemia as < 8.4 mg/dL. The majority of laboratory results that were consistent with these definitions of hypocalcemia were balanced between the treatment groups. There was a < 1% incidence of grade 3 hypocalcemia in the PMO trials and none in the HA trials. Of interest is labeling submitted by the applicant with regard to hypocalcemia; it is proposed to include data based on a definition of hypocalcemia that uses 7.5 mg/dL as the value below which the incidence rates of hypocalcemia are noted. Doing so would underestimate the incidence of hypocalcemia. It is the opinion of this reviewer that the cutoffs for defining hypocalcemia used in the clinical trials should also be used in labeling.

Table 34 FDA Hypocalcemia MedDRA Preferred Terms

Hypocalcemia MedDRA PT
Hypocalcaemia
Blood calcium decreased
Calcium ionized decreased
Calcium deficiency
Paraesthesia
Paraesthesia oral
Hypoaesthesia
Hypoaesthesia oral
Tetany
Hypoparathyroidism
Blood parathyroid hormone decreased
Hypomagnesemia
Magnesium deficiency
Blood magnesium decreased
Hyperphosphatemia
Calcium phosphate product increased
Blood phosphorus increased
Vitamin D decreased
Vitamin D deficiency

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Table 35 Clinical Manifestations of Hypocalcemia

Acute Hypocalcemia
Neuromuscular irritability (Tetany)
Paresthesias (peri-oral, extremities)
Muscle twitching
Carpopedal spasm
Trousseau's sign
Chvostek's sign
Seizures
Laryngospasm
Bronchospasm

Table 36 Hypocalcemia Events by MedDRA PT for Pooled PMO Trials

MedDRA PT	Denosumab N=4050 n (%)	Placebo N=4041 n (%)
TOTAL	112 (2.77)	110 (2.72)
Hypocalcaemia	0 (0.00)	2 (0.05)
Paraesthesia	65 (1.60)	60 (1.48)
Paraesthesia oral	1 (0.02)	2 (0.05)
Hypoaesthesia	42 (1.04)	42 (1.04)
Hypoaesthesia oral	1 (0.02)	1 (0.02)
Hypoparathyroidism	1 (0.02)	0 (0.00)
Blood magnesium decreased	1 (0.02)	0 (0.00)
Vitamin D deficiency	1 (0.02)	1 (0.02)

Table 37 Hypocalcemia Events by MedDRA PT for Trial 138

MedDRA PT	Denosumab N=731 n (%)	Placebo N=725 n (%)
TOTAL	22 (3.01)	16 (2.21)
Hypocalcaemia	1 (0.14)	0 (0.00)
Paraesthesia	6 (0.82)	6 (0.83)
Hypoaesthesia	16 (2.19)	9 (1.24)
Vitamin D deficiency	0 (0.00)	1 (0.14)

Table 38 Hypocalcemia by MedDRA PT for Trial 135

MedDRA PT	Denosumab N=129 n (%)	Placebo N=120 n (%)

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MedDRA PT	Denosumab N=129 n (%)	Placebo N=120 n (%)
TOTAL	8 (6.20)	4 (3.33)
Paraesthesia	2 (1.55)	2 (1.67)
Paraesthesia oral	1 (0.78)	0 (0.00)
Hypoaesthesia	6 (4.65)	4 (3.33)

Osteonecrosis of the Jaw: The analyses in this section rely in part on the original DRUP clinical review as well as a consult review performed by the Division of Dermatology and Dentistry Products (DDDP)

Osteonecrosis, or avascular necrosis of the jaw (ONJ) is a pathological process associated with pain, swelling, exposed bone, local infection, and pathologic fracture of the jaw. Risk factors for developing ONJ include treatment with bisphosphonates, duration of bisphosphonate exposure, cancer and anti-cancer therapy, dental extractions, dental implants, poorly fitting dentures, glucocorticoids, smoking, and pre-existing dental disease. The mechanism by which osteonecrosis develops in relationship to treatment with bisphosphonates is not well understood. Bisphosphonates inhibit osteoclastic bone resorption by integrating into the bone matrix, especially areas of bone undergoing active resorption. When osteoclasts begin to resorb bone that is impregnated with bisphosphonate, the bisphosphonate released during resorption impairs the ability of the osteoclasts to adhere to the bony surface, and to produce the protons necessary for continued bone resorption. ONJ presents as an infection and exposed necrotic bone typically involving the maxilla or mandible. It is especially common in patients with malignancies being treated with high potency, intravenous bisphosphonates. It is not known whether ONJ is the primary process that becomes secondarily infected; if ONJ represents primary osteomyelitis, exacerbated by the use of bisphosphonates; or if it is the consequence of a combination of events, including the use of bisphosphonates, poor dental hygiene, and/or a dental procedure or condition. It is also uncertain if the presence of actinomyces, noted commonly in ONJ lesions, actively contributes to the development or progression of ONJ, or is related to the presence of necrotic bone in an anaerobic environment.

The true incidence and risk of ONJ related to treatment with denosumab is unknown; however based on its antiresorptive effects, there is a recognized risk that patients treated with denosumab have the potential to develop ONJ. As a result, the applicant included during development a plan to specifically evaluate patients for ONJ signs and symptoms. This was accomplished through formation of an adjudication committee, the Osteonecrosis of the Jaw Adjudication Committee (ONJAC), and developing prespecified MedDRA terms which would trigger cases of potential ONJ to be reviewed by the committee. A review of the ONJAC and its processes, procedures, and findings was undertaken. The definition of ONJ used by the applicant (a lesion occurring in the oral cavity as an area of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found, associated with non-healing after appropriate care by 8 weeks in a patient without prior history of radiation to the head, face or mouth, the lesion can be asymptomatic, or oral/orofacial fistulas suspicious for underlying ONJ can be present) was accurate and consistent with the current medical literature and the definitions developed by the American Dental Association and the American Society of Bone Mineral Research. In addition, the PT terms chosen by the applicant (Table 39 below) were appropriate and reasonably complete. The

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applicant's search identified 21 potential cases of ONJ. The ONJAC reviewed all 21 of the cases and concluded that none that were positive for meeting the criteria. The applicant submitted a listing of the cases, but not a rationale for eliminating them from an ONJ diagnosis.

A review of MedDRA PTs was also performed which determined that there were a number of potential terms that could be associated with ONJ that were not included in the applicant's list of search terms (Table 40 below). It was concluded that a more detailed search utilizing these terms would not likely yield new cases for adjudication. However, a search of the AAE database was performed utilizing the expanded list of PTs. A list of 21 new subjects was compiled who met the expanded criteria, and case report forms were reviewed. The applicant was asked to send further information about the involved patients. The applicant submitted additional information which included case narratives, follow-up documentation from the treating dentists, and photographs. These materials were reviewed by a consultant in the Division of Dermatology and Dentistry who concluded that none of the events in the expanded list met the requirements for the diagnosis of ONJ. Table 41 is a listing of the potential new cases of ONJ and the comments of the DDDP consultant.

Noteworthy with regard to the adjudication process are the meeting minutes and adjudicator contact logs submitted with this application. In a review of the logs, it is noted that one of the adjudicators expressed concerns that the adjudicators were being unblinded to patients' treatment assignments as a result of information contained in the adjudication packets; and that ONJ was being under diagnosed because some of the adjudication packets were insufficient for adjudicators to make a diagnosis of ONJ. However, even in light of this criticism, it appears that the conduct of the ONJAC was appropriate.

The procedures utilized by the applicant for identifying cases of ONJ were reasonable and appropriate. However, an expanded list of search terms for data analyses from future trials should be considered. In addition, because data from completed and ongoing trials under IND 9838 have demonstrated positively adjudicated cases of ONJ, the label should contain appropriate precautionary language to alert both prescribers and patients to the risk.

Table 39 MedDRA Preferred Terms for ONJ Adjudication by Applicant

Applicant ONJ Search Terms	
Abscess jaw	Oral cavity fistula
Abscess oral	Oral surgery
Alveolar osteitis	Oroantral fistula
Bone debridement	Osteitis
Bone erosion	Osteomyelitis
Bone fistula	Osteomyelitis acute
Bone infarction	Osteomyelitis chronic
Dental fistula	Osteomyelitis drainage
Dental necrosis	Osteonecrosis
Gingival abscess	Pain in jaw
Gingival erosion	Periodontal destruction
Gingival ulceration	Periodontal infection
Jaw lesion excision	Periodontal Operation
Jaw operation	Primary sequestrum
Loose tooth	Secondary sequestrum
Maxillofacial operation	Sequestrectomy

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Necrosis	Tertiary sequestrum

Table 40 Expanded MedDRA Preferred Terms for ONJ Identification by FDA

FDA ONJ Expanded Search Terms	
Biopsy bone abnormal	Jaw fracture
Bone abscess	Musculoskeletal pain
Bone disorder	Imaging abnormal
Bone lesion	Oral infection
Bone Pain	Osteomyelitis bacterial
Bone scan abnormal	Osteomyelitis fungal
Bone swelling	Osteomyelitis viral
Buccal mucosal roughening	Osteoradionecrosis
Dental alveolar abnormality	Palatal dysplasia
Exostosis	Resorption bone increased
Face and mouth x-ray abnormal	Septic necrosis
Failure of implant	Tooth abscess
Impaired healing	Tooth infection
Implant expulsion	Ulcer
Implant site reaction	X-ray abnormal

Table 41 ONJ Expanded Search Cases Identified with DDDP Consultant Comments

USUBJID	MedDRA PT	DDDP Comments
(b) (6)	Bone disorder	Bone graft successfully placed after routine extraction of non-restorable tooth with local infection
	Dental prosthesis user	Dental implant placed with resultant normal healing
	Dental prosthesis user	Routine dental implant
	Post procedural infection	Localized infection immediately after extraction
	Tooth abscess	Infected tooth, resulting from decay
	Tooth abscess	Local periodontal infection
	Dental implantation	Routine dental implant
	Dental prosthesis user	Routine dental implant for missing tooth
	Dental prosthesis user	Routine dental implant
	Post procedural infection	Local infection immediately following tooth extraction
	Tooth abscess	Routine extraction with complete healing
	Dental implantation	Routine dental extraction followed by implant placement (See next row – two separate reports for same subject; one for extraction and one for implant placement)

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USUBJID	MedDRA PT	DDDP Comments
(b) (6)	Dental operation	Routine dental extraction, following by implant placement
	Bone graft	Periodontal surgery with bone grafting and complete healing
	Dental operation	Dental implant successfully placed
	Dental prosthesis user	Dental implant successfully placed
	Postoperative wound infection	Verbatim term should be "extraction", not "traction." The post-extraction infection healed, and there was no exposed bone.
	Bone lesion	Implant placed in edentulous patient for denture retention. Post-placement infection, which resolved completely with no exposed bone.
	Tooth abscess	Endodontically caused infection; resolved after extraction of tooth.
	Mastication disorder	Two individual implants placed without incident.
	Post procedural infection	Transient infection during healing of multiple facial fractures - left mandibular ramus and left maxillary sinus. Infection resolved.

Fracture Healing Complications: The discussion in this section relies in part on the original DRUP clinical review as well as a statistical analysis performed by QSPG.

The concern for fracture healing complications with denosumab arose from nonclinical findings in denosumab treated genetically modified mice vs. placebo who exhibited increased bone callus size and consistency during healing after induced closed femoral fractures. This finding was thought to have an effect on bone mobility, but not bone strength. While all four of the key trials submitted in support of the PMO and HA indications included some data for nonvertebral fracture healing, the data may not be sufficient to answer all questions with regard to dysregulation of fracture healing because of the lengths of the trials (up to 36 months when it can take up to 5 years to observe fracture complications) as well as the numbers of events. In fact, only PMO Trial 216 had enough data on fracture healing outcomes for a meaningful analysis (more than 1 subject with a complication per group) because of a focused substudy evaluating healing of distal radius fractures. In all of the key trials, however, the observed fracture healing complications were balanced between the treatment groups; see Table 42. More data over longer time periods is needed to address the issue of fracture healing complications.

Table 42 Fracture Healing Outcomes in PMO and HA Key Trials

Complication	Denosumab n (%)	Placebo n (%)
Trial 216		
Delayed Healing	2 (0.7)	2 (0.6)

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Complication	Denosumab n (%)	Placebo n (%)
Malunion	3 (1.0)	3 (0.9)
Nonunion	0	1 (0.3)
Chronic Pain	7 (2.3)	11(3.1)
Other	10 (3.3)	7 (2.0)
Patients with nonvertebral fx/patients in tx group	303/3886	354/3876
Trial 132		
Delayed healing	1 (7.7)	0
Number of nonvertebral fx/patients in tx group	13/164	15/165
Trial 135		
Delayed healing	0	1 (11.1)
Number of nonvertebral fx/patients in tx group	10/129	9/120
Trial 138		
Chronic pain	1 (2.3)	0
Other	0	1 (2.3)
Number of nonvertebral fx/patients in tx group	44/731	44/725

Infections: The analyses in this section rely in part on the original DRUP clinical review as well as a consult performed by the Division of Anti-infectives and Ophthalmology Products (DAIOP).

Because RANK is expressed on activated B and T cells and RANKL inhibition has been reported to have immune system effects (e.g., regulation of the developing immune system, B-cell, T-cell, and dendritic cell activation and signaling, generation and maintenance of T lymphocyte tolerance), there is biological plausibility that treatment with denosumab could lead to an increased incidence of infections. Infection events assessed during the denosumab development program were reviewed; overall, the incidence of infections was balanced between treatment groups.

The DAIOP consultant provided a background review of the TNF-related activation-induced cytokine (TRANCE)-RANK-osteoprotegrin (OPG) signaling pathway on which denosumab exerts its effects. The background review is reproduced here in part in order to provide a scientific rationale and foundation for the review of the trial data.

The bone microenvironment is critical for the development of hematopoietic stem cells (HSCs); and bone plays a role in adaptive immunity beyond lymphocyte development. Activated T cells express the TNF superfamily member TRANCE which is a key differentiating factor for osteoclasts (OCs). Receptor activator of nuclear factor-Kβ (RANK) is the signaling receptor for TRANCE. Pathogenic stimuli or self antigens are phagocytosed and presented to naive T cells by dendritic cells (DCs). T cells provide activating signals to DCs through CD40L and in return receive optimal activating and costimulatory signals. The activated T cells are induced to express TRANCE, which provides further activating and survival signals to DCs. The DCs may negatively regulate TRANCE-RANK signaling through upregulation of the TRANCE decoy

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receptor, osteoprotegerin (OPG). Denosumab binds and inhibits RANKL in a manner similar to OPG. Inflammatory cytokines (IL-I, TNF-a.) produced during successful T cell immune responses, as well as calciotropic factors (PGE2 or VitD3), induce TRANCE expression by osteoblasts (OBs), which cooperate with effector T cells to induce osteoclast (OC) differentiation by providing TRANCE to OC precursors. TRANCE signaling in mature OCs induces bone-resorbing function. OBs block TRANCE binding through secretion of OPG, whereas INF-y and IL-4 produced by effector T cells inhibit RANK signaling. Without proper regulation, excessive bone resorption leads to osteoporosis, arthritic joint erosion, and periodontal tooth loss.

RANK expression at the RNA level is detected in most cell types or tissues (e.g., skeletal muscle, thymus, liver, colon, small intestine, and adrenal gland). RANK signal transduction is mediated by adapter proteins, TNF receptor-associated factors (TRAFs). Of the six TRAFs, RANK interacts with 1, 2, 3, 5, and 6.

The significance of the TRANCE-RANK-OPG signaling axis in regulating the developing immune system is not entirely clear and continues to emerge in the medical literature. Studies of TRANCE and RANK- deficient mice demonstrate the importance of these signals for secondary lymphoid organ development, as these animals display a lack of peripheral lymph nodes and abnormalities in B cell follicle formation and marginal zone integrity in the spleen. In the adult immune system, TRANCE modulates immunity through dendritic cells (DCs). DCs are the most potent antigen presenting cells (APCs) in the human immune system and are required to initiate T-cell mediated immunity in vivo. DCs differentiate from the hematopoietic monocyte/macrophage progenitor cell lineage and are close relatives of osteoclasts (OCs). TRANCE signaling has also been implicated in the regulation of DC survival. Blockade of TRANCE signaling in vivo results in a slightly reduced CD4+ T cell response to lymphocytic choriomeningitis virus (LCMV) infection, although the response is severely inhibited in the absence of CD40 signaling. TRANCE-RANK and CD40L-CD40 function may overlap. TRANCE-RANK signaling may be more important during the waning phases of an immune response to ensure that T cell memory formation is established and then to wind down remaining T cell-DC interactions, possibly through OPG interference with TRANCE signaling. In addition, enforced autocrine TRANCE-RANK signaling but not CD40L-CD40 signaling on DCs may enhance antitumor immunity. TRANCE may also be important for the survival of interstitial DCs engaged in antigen surveillance during the interim period separating immune responses. Human CD34+ immature DCs express both TRANCE and RANK and can therefore provide an autocrine survival signal. Peripheral maturation of these DCs leads to down-regulation of TRANCE, suggesting a requirement for an independent source of TRANCE to validate DC activation. TRANCE signaling may also be involved in the generation and maintenance of T lymphocyte tolerance. TRANCE signaling has been directly implicated in the induction of oral tolerance to food antigens in mice. It has also been demonstrated that TRANCE-mediated signaling is required to prevent the onset of autoimmune disease in a TNF-a-inducible mouse model of diabetes and that blockade of TRANCE-RANK interactions were associated with decrease in CD4+CD25+ regulatory lymphocytes, which is necessary to prevent cytotoxic T lymphocyte (CTL)-mediated islet cell destruction.

Additionally, the TRANCE-RANK-OPG axis appears to regulate B cell maturation, proliferation, and the development of efficient antibody responses. In OPG-deficient mice there

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is an expansion of pro-B cells in the bone marrow, whereas the opposite has been observed in TRANCE- or RANK-deficient mice.

Table 43 below summarizes the incidences of infection for the key trials submitted in support of this application. In HA Trial 135, there were no deaths in either group resulting from infection events. In HA Trial 138, there were 2 deaths on the denosumab group for patients who had infection events. Reported were 2 patients with pneumonia, USUBJIDs 20040138-(b) (6) and 20040138-(b) (6) the former developed aspiration pneumonia in the setting of progressive disease to which he succumbed, and the latter was a 93 year old male who developed aspiration pneumonia which was treated, a second aspiration event occurred while the patient was still recovering from the first event. The second aspiration pneumonia did not respond to therapy and the patient succumbed.

In PMO Trials 216 and 132, serious infections due to bacteria or unspecified pathogens were balanced between the treatment groups (denosumab 4%, placebo 3%) as were the incidence of bacterial infections overall (denosumab 53%, placebo 55%). However, there was an imbalance in serious skin infections. Serious streptococcal infections occurred in 7 denosumab (0.2%) and 1 placebo (0.03%) patients in the key PMO trials. In addition, there were 7 denosumab (0.2%) and no placebo subjects who had serious events of erysipelas; and there was an imbalance in infected skin ulcers with 4 denosumab (0.1%) and 1 placebo (0.03%) subjects developing an event of infected skin ulcer. The increased incidence of dermatologic events (discussed below) could account for the increases seen in infections of the skin, at least in part.

Table 43 SAEs and All Infection Rates in the ISS

	Placebo n (%)	**Denosumab n (%)**
SAEs, Study 216	133 (3.4)	159 (4.1)
SAEs, Study 132	1 (0.6)	8 (4.9)
SAEs, Study 135	1 (0.8)	3 (2.3)
SAEs, Study 138	33 (4.6)	43 (5.9)
AEs, Study 216	2108 (54.4)	2055 (52.9)
AEs, Study 132	101 (61.2)	99 (60.4)
AEs, Study 135	38 (31.7)	47 (36.4)
AEs, Study 138	226 (31.2)	257 (35.2)

In phase 1 Trials 146 and 148, 3 healthy volunteers developed pneumonia. In Trial 146, a 33 year old male ((b) (6)) required hospitalization for pneumonia for 13 days, and a 24 year old male (b) (6) required hospitalization for 4 days on day 74 of the trial both after receiving one dose of denosumab 60 mg. The applicant was unable to confirm these events with

the site investigator and with the hospitals where the subjects reported having received treatment. In Trial 148, subject ID1 (b) (6) reported developing pneumonia on day 242 after receiving one dose of denosumab 3.0 mg/kg. Notable in this case is a 40 pack year history of smoking, a history of chronic bronchitis, and a subsequent lung cancer diagnosis. Although two of the three cases are not well documented, these three cases of pneumonia occurred following a single 100 mg dose of denosumab. One subject was a smoker with bronchitis who was subsequently diagnosed with lung cancer. The other 2 subjects were young, healthy volunteers and did not appear to have risk factors for the development of pneumonia.

The incidence of infections in the key trials required comprehensive analysis because disturbances in the RANKL/RANK signaling pathway have been reported to have immune system effects. While there is no overall safety signal for infections identified in this application; there are specific safety signals of concern. In both ongoing trials and in the postmarketing period, continued careful scrutiny of cases of infection is recommended. In addition, special attention should be paid to categorizing the infections observed; therefore investigators should be instructed to obtain the identification of the causative organism for all infections.

Dermatologic events: An imbalance in skin and soft tissue disorders was identified in HA Trial 135; specifically, there was an imbalance in skin related events noted at the MedDRA HLGT level in "Epidermal and dermal conditions", denosumab 22 (17%), placebo 15 (13%). Because of the small numbers in this trial, an analysis of the larger PMO trials was undertaken to identify any similar imbalances.

In the two PMO trials (216 and 132), the incidence of skin related AEs in the denosumab group was 616, 16% and in the placebo group 507, 13%. The imbalance was also noted at the MedDRA HLGT level in "Dermal and Epidermal Conditions", 450 denosumab vs. 343 placebo. Table 45 displays the incidence of events using the MedDRA HLGT levels of the hierarchy. The events listed are not specific to injection site. Table 45 displays the incidence of events contributing to the imbalance by MedDRA HLT.

Table 44 Selected Dermatologic HLGT (PMO safety population)

MedDRA HLGT	Denosumab N-=3765	Placebo N=3769
Angioedema and urticaria	31	32
Cornification and dystrophic skin disorders	22	23
Cutaneous neoplasms benign	9	5
Epidermal and dermal conditions	**450**	**343**
Pigmentation disorders	4	6
Skin and subcutaneous tissue disorders NEC	45	38
Skin appendage conditions	90	100
Skin vascular abnormalities	12	13

Table 45 Selected Adverse Event High Level Terms Mapping to HLGT Epidermal and Dermal Conditions (PMO safety population)

MedDRA HLT	Denosumab N-=3765	Placebo N=3769

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MedDRA HLT	Denosumab N-=3765	Placebo N=3769
Bullous conditions	**9**	**3**
Connective tissue disorders	1	1
Dermal and epidermal conditions NEC	**69**	**56**
Dermatitis and eczema	**148**	**83**
Dermatitis ascribed to specific agent	6	1
Erythemas	19	17
Exfoliative conditions	1	3
Granulomatous and deep cutaneous inflammatory conditions	2	1
Papulosquamous conditions	6	12
Photosensitivity conditions	**6**	**1**
Pruritus NEC	**112**	**97**
Psoriatic conditions	16	13
Rashes, eruptions and exanthems NEC	**116**	**91**
Skin injuries and mechanical dermatoses	2	4
Total Subjects	**450**	**343**

The imbalances noted in the HA and PMO trials were small. More experience with denosumab is needed in order to further evaluate this finding. In addition, the increases in skin-related AEs could, in part, help to explain the corresponding increase in the incidence of skin infections.

Cardiovascular events:
The analyses in this section rely in part on the original DRUP clinical review and the statistical review performed by the Quality Safety and Pharmacoepidemiology Group (QSPG).

During the denosumab development program, a possible mechanism was identified for treatment with denosumab to lead to atherosclerosis. This was based on reports in the published literature regarding a possible association between OPG levels and arterial (aortic) wall calcification, cardiovascular disease and mortality, and the possibility that inactivation of RANKL by denosumab could result in elevated levels of osteoprotegerin (OPG) via an unopposed feedback mechanism. Because the target populations for treatment with denosumab supported by this application could conceivably receive treatment with denosumab for many years, and are at risk for development of cardiovascular disease, the applicant established an independent review panel to adjudicate cardiovascular events. Two phase 3 trials, one in postmenopausal women (Trial 216) and one in men (Trial 138) were chosen to accomplish the adjudication. In addition, an analysis of changes in abdominal aortic calcification (as assessed using lateral lumbar spine radiographs) was also conducted in a subset of study subjects in Trial 216.

The adjudication process for review of cardiovascular events included:

- Committee members were independent Cardiologists not associated with the study.
- All deaths were reviewed. Serious adverse events (SAEs) were identified for adjudication using pre-selected MedDRA preferred terms
- The committee categorized serious adverse events as one of the following:
    - Acute coronary syndrome/revascularization

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  - Congestive heart failure
  - Stroke/transient ischemic attacks
  - Cardiac arrhythmias
  - And other vascular disorders/revascularization
- Deaths were categorized as cardiovascular or non-cardiovascular;

Baseline cardiovascular risk factors such as myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, diabetes, smoking, hypertension, and high cholesterol were similar in both treatment groups in Trials 20030216 and 20040138.

Submitted to the panel for adjudication in Trial 216 were 526 events in the placebo group and 572 in the denosumab group. The incidence of positively adjudicated events in Trial 216 included 233(44%) for the placebo group and 247(43%) for denosumab. In Trial 138, 203 events were submitted for adjudication in the placebo group and 236 events in the denosumab group. The incidence of positively adjudicated events included 105(52%) for the placebo group and 118 (50%) for denosumab.

The point estimate for the cardiovascular death hazard ratio was 0.7 (CI: 0.4, 1.2) in Trial 216 and 0.97 (CI: 0.7, 1.3) in Trial 138. The hazard ratio for any adjudicated event in either trial was approximately 1. A time to event analysis of time to first adjudicated cardiovascular event did not suggest worsening outcomes over time for both low cardiovascular risk and high cardiovascular risk patients. The incidence of any adjudicated CV serious adverse event (SAE), CV death, acute coronary syndrome, stroke/transient ischemic attack, congestive heart failure and other vascular disorders was balanced across treatment groups (Table 46).

Table 46 Cardiovascular-related Serious Adverse Events Adjudicated in Trials 216 and 138

	PMO 216			**HA 138**		
Incidence at 36 Months	Placebo (N = 3876)	Denosumab (N = 3886)	Hazard ratio (95%CI)	Placebo (N = 725)	Denosumab (N = 731)	Hazard ratio (95%CI)
	n (%)	n (%)		n (%)	n (%)	
Any adjudicated positive CV SAE	178 (4.6)	186 (4.8)	**1.02** (0.8,1.2)	80(11)	80(10.9)	**0.97** (0.7,1.3)
CV death	31 (0.8)	23 (0.6)	**0.72** (0.4,1.2)	21(2.9)	19(2.6)	**0.9** (0.5,1.6)
Stroke / transient ischemic attack	54 (1.4)	56 (1.4)	**1.17** (0.8,1.8)	17(2.3)	21(2.9)	**1.2** (0.6,2.3)
Acute coronary syndrome	39 (1.0)	47 (1.2)	**1.02** (0.7,1.5)	27(3.7)	18(2.5)	**0.67** (0.4,1.2)
Congestive heart failure	22 (0.6)	27 (0.7)	**1.19** (0.7,2.1)	11(1.5)	8(1.1)	**0.7** (0.2,1.7)
Other vascular event	30 (0.8)	31 (0.8)	**1** (0.6,1.6)	12(1.7)	18(2.5)	**1.44** (0.6,2.9)
Arrhythmia	45 (1.2)	52 (1.3)	**1.13** (0.8,1.7)	15(2.1)	19(2.6)	**1.23** (0.6,2.4)

The effect of treatment with denosumab on osteoprotegerin levels was evaluated at baseline, day 1 and months 1, 6, 12, 24 and 36 in a subset of subjects (denosumab 96, placebo 64) enrolled in a

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bone marker sub study of Trial 216. There was no statistically significant increase in osteoprotegerin levels for denosumab compared to placebo-treated patients.

Patients in Trial 216 were also assessed for an aortic calcification score if they were considered high risk according to modified RUTH criteria (Table 47). The 2363 patients assessed for an aortic calcification score were similar to the overall study population with regard to disposition, baseline body composition and baseline BMD T-scores. The distribution of baseline scores was balanced between the two treatment groups. The mean change from baseline in aortic calcification scores for both treatment groups was not statistically significant or clinically meaningful (0.1 at one year, 0.2 at 2 years and 0.4 at 3 years in both groups).

Table 47 Modified RUTH Criteria for Defining High Risk Population for Cardiovascular Events

Cardiovascular Risk Factor Points
Prior myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery 4
Diabetes mellitus 3
Age ≥ 70 years 2
Age 65 to 69 years 1
Former/current smoker [a] 1
Hypertension [a] 1
High cholesterol [a] 1

a An extra point is added if all 3 criteria (former/current smoker, hypertension, and high cholesterol) were met (total of 4 points).

Overall, evaluations of cardiovascular events performed by the applicant during development of denosumab were adequate to identify cardiovascular safety signals in the populations studied.

Bone Biopsy Histomorphometry: The results of bone histomorphometry, reviewed by the DRUP medical team, raise concerns about the degree of bone remodeling suppression noted with denosumab. For a full discussion of the results, see the original primary review of the DRUP Medical Officer. Quantitative histomorphometry parameters demonstrated that treatment with denosumab reduced bone remodeling to a level not seen with previous anti-resorptive agents. The denosumab group had markedly suppressed osteoclast and osteoblast counts compared to placebo and alendronate. In Trial 216, the osteoblast-osteoid interface was 25% for placebo vs. 0% for denosumab at month 36; and osteoclast number was 7/100 mm for placebo vs. 0 for the denosumab group. When compared to alendronate in trial 20050234, the osteoblast-osteoid interface was 9.7% for the alendronate group vs. 0% for denosumab. The osteoclast number was 10/100 mm for alendronate vs. 2 for the denosumab group at month 12. Dynamic bone formation parameters such as activation frequency, bone formation rate and mineralizing surface were also markedly suppressed. Dynamic bone formation parameters provide information about bone formation during the labeling interval (between 2 dosing periods of tetracycline). Tetracycline gets deposited in the newly mineralized bone, so absence of label means that during the tetracycline dosing period there was no new bone mineralization. Across all studies, all subjects

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in the placebo group had double label, however, only 31-60% subjects in the denosumab group had any double label. Absence of label suggests suppressed bone formation.

These findings raise the possibility that with long term use, suppression of bone remodeling may lead to complications such as delayed fracture healing, ONJ, or atypical fracture. Additional experience and data are needed to evaluate these findings.

Injection-related reactions: It is a well known that administration of monoclonal antibodies can result in cytokine release and subsequent reactions that mimic hypersensitivity and anaphylaxis. This appears to be especially true for intravenous administration. NCI CTCAE version 3 criteria do not include terms in their coding dictionary to adequately capture the diverse events that can be related to antibody administration. However, MedDRA includes terms in its coding dictionary that are sufficient for the identification of these types of reactions.

Denosumab was administered subcutaneously in all four of the key studies submitted in support of this application. In an analysis of the ISS database for signs and symptoms of injection-related reactions (e.g., hypotension, hypertension, rash, pain, pyrexia) temporally associated with the administration of denosumab, there were no imbalances noted.

7.4 Supportive Safety Results

Adverse events were analyzed at each level of the MedDRA hierarchy. Analyses were performed using the defined safety populations and ADaM datasets from pooled data of the key trials. In addition, Standardized MedDRA Queries (SMQ) were performed and analyzed.

7.4.1 Common Adverse Events

Adverse events for the ISS dataset were grouped and analyzed. Common adverse events were defined by this reviewer as any event occurring at $\geq$ 5% or if there was a > 5% difference between the groups in favor of denosumab. In addition, search criteria were utilized for selected adverse events, which were defined as events occurring with 5-fold greater frequency in the denosumab treatment group. Table 55 through Table 60 in Appendix 9.4 represent the results of these analyses.

There were no AEs occurring at an incidence of > 5% and at an increased incidence of >5% in the denosumab treatment group. In addition, the incidences of grades 3 and 4 events were under 2%. Analyses at other levels of the MedDRA hierarchy demonstrate relative balance between the treatment groups overall.

7.4.2 Laboratory Findings

The laboratory data obtained from the HA and PMO trials were considered and analyzed separately. Incidence rates were calculated for patients having laboratory values outside the upper and lower limits of normal for CBC, including total neutrophils and lymphocytes, and sodium, potassium, magnesium, phosphorus, creatinine, aspartate amino transferase, alanine amino transferase, alkaline phosphatase, total bilirubin and glucose. Analyses of central tendencies to identify outlier results were also analyzed. In addition, minimum, maximum, median, and mean baseline and on treatment laboratory results were analyzed utilizing the paired t-test. This test compares results for the chosen variable at different time points, usually before

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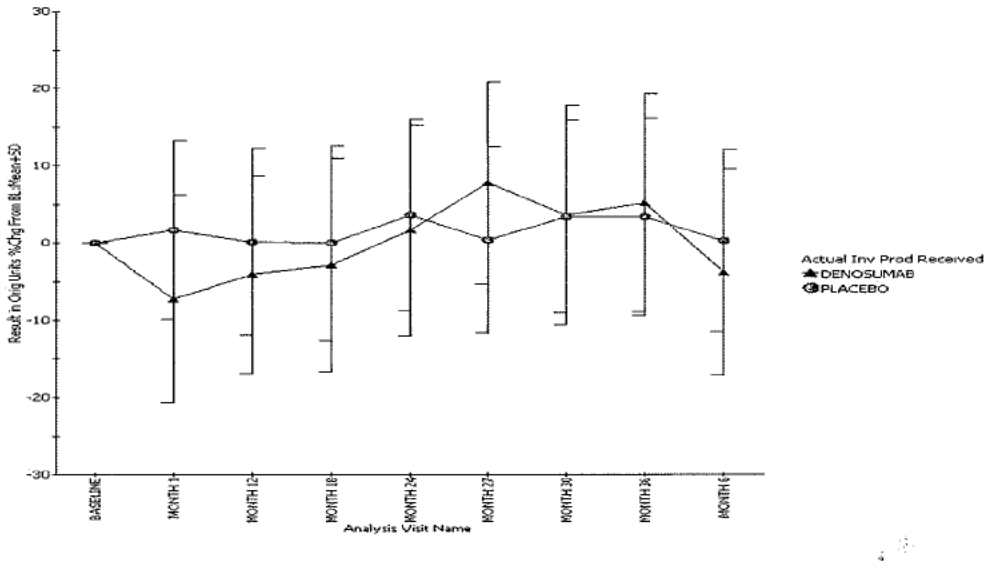
and after an event, in this case, treatment with denosumab. The analysis of central tendency for the HA and PMO clinical laboratory results revealed few outliers and infrequent grade 3 and 4 toxicities. For the HA trials, four patients (0.5%) treated with denosumab experienced grade 3 or 4 hypophosphatemia compared to zero for the placebo group. For the PMO trials, there was an incidence of hypophosphatemia for 7 patients (0.2%) treated with denosumab compared to zero for the placebo group. These laboratory findings were transient and were not associated with adverse events for either population of patients (PMO and HA). Analyses of the results at the one month time point demonstrated a higher incidence of hypocalcemia and hypophosphatemia (see Figure 10, excerpted from DRUP clinical review) for denosumab treated patients which was transient. This finding was expected since earlier in the development of denosumab a nadir for both calcium and phosphorus was observed between days 8 and 11. In addition, there were no statistically significant or clinically meaningful differences between baseline and on study laboratory results for the HA or PMO trials.

Figure 10 Serum Phosphorus Mean % Change from Baseline in PMO Trials



7.4.3 Vital Signs

Vital signs including systolic and diastolic blood pressures, pulse rate, body temperature, body weight, and BMI were assessed at each visit in all phase 3 clinical trials. On days when the investigational product was administered, there were no requirements for pre and/or post administration vital sign assessments. Overall for the four key trials, denosumab did not have an effect on mean values, mean changes from baseline, or overall incidences of outliers for all vital signs measured. In addition, an analysis of adverse events demonstrated no difference in the incidence of associated clinical events (e.g., hypotension, hypertension, tachycardia, bradycardia, and pyrexia) between treatment groups.

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7.4.4 Electrocardiograms (ECGs)

Of the four key trials, only Trial 132, submitted in support of the PMO prevention indication, included ECG assessments. ECGs were obtained pre-dose, and at months 1, 6, 12, 18 and 24. Calcium supplementation was administered as part of the protocol and serum calcium levels were obtained at the same time points as ECGs. There were 332 patients in this trial from whom ECG data were obtained. There was a central, blinded reading of all ECGs in this trial. There was no difference between treatment groups in ECG measurements over the 24 month treatment period and there were no patients in either group who had a > 60 msec change in QTc from baseline. The post-baseline maximum change in QTc between the treatment groups was a mean of 9.5 msec for placebo and 10.3 msec for denosumab.

7.4.5 Special Safety Studies/Clinical Trials

Renal Function and PK: Trial 245 was a single dose (60 mg subcutaneously), open label trial to assess PK, safety and tolerability in 46 patients with both normal and abnormal renal function. Patients with renal dysfunction were stratified into normal (n=12) mild (n=10), moderate (n=10), severe (n=7), and end stage renal disease (ESRD, n=7) cohorts and standard PK parameters were analyzed. The results of this trial demonstrated that denosumab PK is not influenced by renal dysfunction of any severity. However, the trial also demonstrated the most common and severe AE experienced by patients in this trial was hypocalcemia. Adverse events of hypocalcemia were greater in patients with severe and ESRD. As a result of this finding, calcium and Vitamin D supplementation were added and this intervention mitigated the risk by decreasing the incidence of hypocalcemia, see Figure 11 and Figure 12. This is demonstrated in the figures below by the upper graph line connecting the circles. Although the numbers of patients in this study were small, the comparative findings demonstrated before and after calcium and Vitamin D supplementation are persuasive. It is recommended that the findings from this trial be included in labeling along with precautionary language regarding the need for supplementation in these patient populations.

Figure 11 Adjusted Serum Calcium over Time in Trial 245 - Severe Renal Disease

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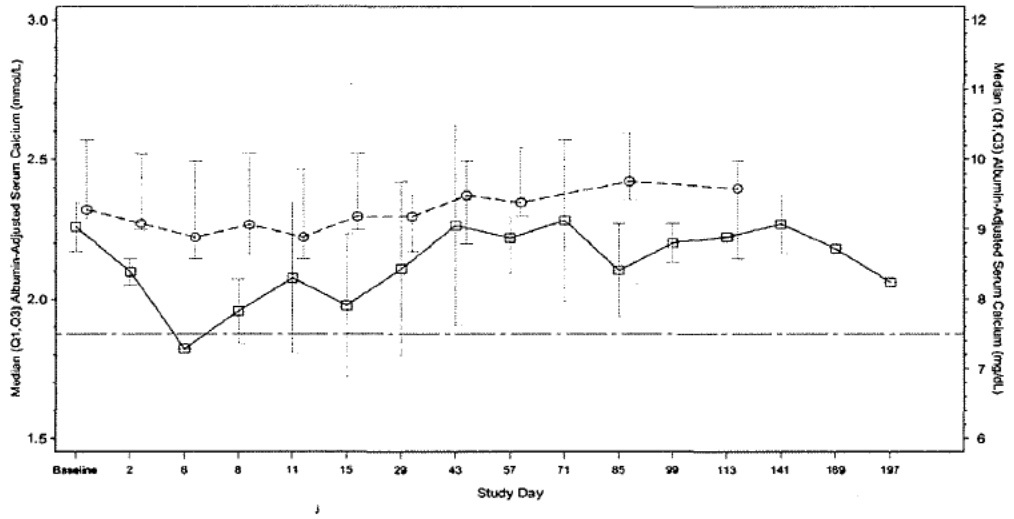
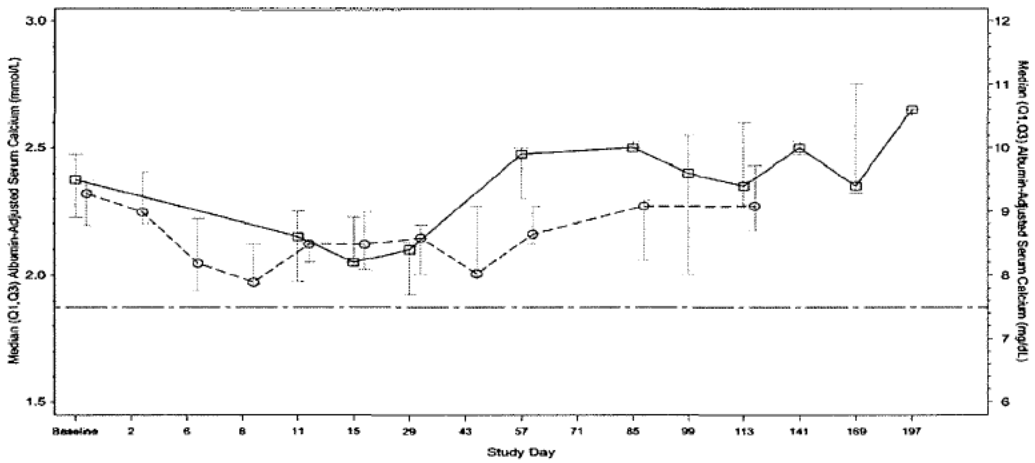


Figure 12 Adjusted Serum Calcium over Time in Trial 245 - End Stage Renal Disease



Bone Biopsies and Bone Histomorphometry: The following section was excerpted from the DRUP clinical review.

Evaluation of bone biopsies was performed in 3 clinical trials.

- Trial 20030216 was the randomized, double-blind, placebo-controlled fracture trial in postmenopausal women. One hundred-three subjects consented to participate in the substudy, 92 subjects (45 placebo, 47 denosumab) received ≥1 dose of investigational product and had ≥1 evaluable biopsy, and 23 subjects (17 placebo, 6 denosumab) underwent sequential biopsy evaluation. The mean age of enrollees in this bone biopsy substudy was 71 years. It should be noted that one subject in the month 36 denosumab group was excluded from the Agency's analysis because the patient had discontinued study drug after month 12.

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- Study 20010223 was the randomized, placebo and active-controlled, dose-finding study in postmenopausal women with low bone mineral density. At baseline, biopsies were obtained from 39 subjects, of which 37 were evaluable (31 denosumab, 5 placebo, and 1 alendronate). At 12 months, biopsies were obtained from 51 subjects, 49 of which were evaluable (41 denosumab, 4 placebo, and 4 alendronate). The mean age of enrollees in the bone biopsy substudy was 60 years.
- Study 20050234 was a double-blind, double-dummy, active-controlled, parallel-group study in postmenopausal women with low BMD (T-score between -2.0 and -4.0) who had received alendronate (70 mg weekly or equivalent) for at least 6 months preceding study entry. At study entry, subjects were randomized to either continue on alendronate 70 mg once weekly or switch to denosumab 60 mg q 6 months. Bone biopsies were obtained from 36 subjects (21 alendronate, 15 denosumab) at month 12. The mean age of enrollees in the bone biopsy substudy was 67.6 years.

Histology

In general, there was evidence of normal lamellar bone and normal mineralization in all treatment groups. In addition, there was no evidence of osteomalacia or woven bone in these studies. In study 20030216, normal osteoid was present in all placebo (62/62) and denosumab (48/53, 91%) subjects. Five subjects in the denosumab-treated group at month 24 did not have osteoid that could be visualized. This could be due to suppressed bone turn over. One denosumab treated subject (6613015), who received all doses of denosumab, was determined to have normal histology at month 24 and cortical trabecularization at month 36. Cortical-endosteal resorption ("trabecularization" of the cortical bone) is one of the major determinants of reduced bone strength. In study 20050234, one subject treated with alendronate had evidence of marrow fibrosis on biopsy.

Histomorphometry

Bone histomorphometry is the only method that allows the measurement of mineralization rate and the study of bone formation at the cell, remodeling unit and tissue levels. In order to assess ongoing bone remodeling, subjects participating in the bone biopsy substudies were treated with two courses of either demeclocycline or tetracycline with 10-14 day interval between the two courses. Tetracycline is incorporated into mineralizing bone and fluoresces under ultraviolet light. Therefore, in active bone, the time-spaced lines of tetracycline can be used for calculation of new bone formation and mineralization rates and absence of label means that during the tetracycline dosing period there was no new bone mineralization.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling and formation. Trabecular bone, the most active site of bone remodeling, is the usual site of evaluation of tetracycline labeling. Across all studies, all subjects in the placebo groups had double label, however, only 31-60% subjects in the denosumab group had any double label. Absence of label suggests suppressed bone formation. In subjects treated with denosumab, 21% had no tetracycline label present at a month 12 biopsy, 35% had no label present at month 24 biopsy and 38% had no label present at month 36 biopsy. One subject treated with alendronate had no label present at month 12 biopsy. While a sporadic biopsy specimen with absence of double label is not unusual, the number of patients treated with

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denosumab who exhibit absence of double labeling is striking. The clinical consequences of these findings are unclear. One concern is that absence of double label may suggest over suppression of bone turnover.

In subsequent sections, Placebo controlled trials (20030216 and 20010223) are discussed separately from active control trial (20050234).

In study 20030216, the number of biopsies evaluable for analysis of all histomorphometry parameters at month 24 was 31 placebo, 5 denosumab; and at month 36 was 22 placebo and 2 denosumab (One subject who only received denosumab for 1 year and had a biopsy at month 36 was excluded, since effect of denosumab is expected to reverse in one year based on BMD data from trial 20040132). To be able to evaluate all histomorphometric parameters, a double label in the trabecular bone is necessary. There were 23 subjects (17 placebo, 6 denosumab) who underwent sequential biopsy evaluation. Paired evaluation can provide insight into the progressive effect of denosumab on bone with increasing duration. However, due to limited number of evaluable biopsies, this evaluation could not be performed.

Activation frequency is the most important regulator of bone turn over. It is defined as the rate at which the bone remodeling units are formed. Suppression is evident at month 12 and by month 36 it was severely suppressed and virtually zero in the denosumab group.

Bone formation rate per bone surface: Bone formation rate per bone surface represents the volume of bone formed per unit of trabecular surface. Treatment with denosumab decreased bone formation rate.

Eroded surface/Bone surface and Osteoid surface / Bone surface: Eroded surface represents the fraction of trabecular bone surface where osteoclasts have eroded or are eroding bone. Denosumab inhibits osteoclast recruitment. Treatment with denosumab resulted in decreased number of osteoclast sites. The osteoid surface presents the fraction of trabecular bone surface where osteoid is present. Osteoblast lays down the osteoid matrix. Treatment with denosumab resulted in decrease in osteoid surface suggesting suppression of new bone formation.

Mineral apposition rate: Mineral Apposition Rate (MAR) is an important parameter assessing mineralized bone accrual at remodeling sites. Treatment with denosumab decreased MAR. No change or small increases in MAR during treatment with study medication would suggest that the mineralization of newly formed bone is not affected by the therapy. Decreases in MAR can be seen with a reduction in bone turnover.

Mineralization Lag Time (days): Mineralization lag time is a sensitive measure of mineralization abnormalities and represents the time interval between deposition of osteoid and its mineralization, averaged over the life of the osteoid seam. The increase in MLT in denosumab treated patients at month 24 is driven by 3 subjects with mineralization lag time greater than 100 days. In each of these subjects, activation frequency and other dynamic parameters were very low. These elevations in mineralization lag time could represent artifact due to the calculation which is based on other parameters.

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Osteoid thickness and Osteoid volume: Increases in osteoid thickness and osteoid volume would be expected in the setting of a mineralization defect. Treatment with denosumab did not result in increased osteoid thickness or volume. This could also happen in cases of severely suppressed bone formation.

In trial 20010223, 7 doses of denosumab were evaluated. Evaluation of dose response relationship suggested no clear relationship, however, the number of subjects with an evaluable biopsy in each dose group were too limited to reach any conclusions.

Trial 234 (subjects switched from alendronate to denosumab or continued on alendronate) provides a comparison to active control (alendronate) and offers important safety information for patient who may be switched from bisphosphonate to denosumab. The results demonstrated further decreases in bone turnover with denosumab compared with continued alendronate. Activation frequency, eroded surfaces and osteoid volume were further suppressed with initiation of denosumab treatment, compared to continued alendronate therapy. Mineralization lag time and osteoid thickness were not appreciably increased with denosumab therapy, as compared to alendronate by month 12.

Correlation to clinical findings and reversibility:
The relationship between percent change in BMD at month 36, incident fractures, and degree of reduced remodeling, as reflected by label status, was explored in trial 20030216. Those subjects with less prominent tetracycline labeling showed the greatest gains in BMD at the total hip and lumbar spine at month 36. Among subjects with no label, 2 sustained fractures, 1 of which was a patellar fracture that occurred less than 6 months after the first dose of denosumab (USUBJIDs (b) (6) and (b) (6)). One subject with single label uptake sustained both a radial and ulnar fracture 6.5 months after first dose of denosumab (USUBJID (b) (6), and 6 subjects with double label uptake, all of whom received placebo, sustained fractures (USUBJIDs (b) (6), (b) (6)).

The applicant argues that long-term reduction in bone remodeling, as reflected by the small number of tetracycline labels in bone biopsy samples, did not translate into an increase in fracture risk. However, decrease in bone remodeling is expected to increase BMD with relatively short term use (up to 3 years). The risk of complications related to continuously suppressed bone remodeling is expected to increase after long term use (7-10 years).

In summary, bone histology evaluations did not identify any major concerns. However, bone histomorphometry results raise significant concerns about the degree of bone remodeling suppression. The denosumab treated groups had markedly suppressed bone remodeling compared to placebo and alendronate. Absence of label suggests suppressed bone remodeling. Dynamic bone formation parameters such as activation frequency, bone formation rate and mineralizing surface were also markedly suppressed.

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7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose ranging studies were undertaken during denosumab's development. Trial 223 was a randomized, double-blind, placebo-controlled, multidose trial evaluating nine dosing cohorts (6 mg, 14 mg, or 30 mg every 3 months; or 14 mg, 60 mg, 100 mg, or 210 mg every 6 months) with the dose administered subcutaneously. Of the 293 patients enrolled, nearly all experienced AEs (denosumab 93%, placebo 94%). SAEs were experienced by 18% of patients in the denosumab group and 11% in the placebo group. There were 4 fatal AEs in this trial in patients in denosumab treatment groups. The causes of death included gastric cancer, lung cancer, brain neoplasm, and CVA. All three of the newly diagnosed cancers were observed in the denosumab 100 mg dose cohort. When the adverse event, laboratory parameters and physical findings were analyzed based on cumulative yearly denosumab dose, there were no observed increases in adverse events.

7.5.2 Time Dependency for Adverse Events

There were no differences in the incidence and severity of adverse events identified with durations of treatment up to five years. However, a trend of progressive suppression of bone remodeling was noted at 12, 24 and 36 months in the PMO trials.

7.5.3 Drug-Demographic Interactions

There were few discrepancies in the incidence or severity of toxicities noted with denosumab among subgroups. Adequate safety and efficacy was reported in the key trials for patients <75 and ≥ 75 years of age. The overall incidences of adverse events were also balanced across geographic regions and between treatment groups within each regional subgroup.

7.5.4 Drug-Disease Interactions

As noted previously, patients with reduced renal function were studied in Trial 245. The results of this study demonstrate that patients with severe renal disease (creatinine clearance < 30mL/min) and end stage renal disease are at increased risk for hypocalcemia during treatment with denosumab. Although no dose reduction is recommended, it is the opinion of this reviewer that special mention of these populations and risks be included in labeling.

7.5.5 Drug-Drug Interactions

There were no formal drug-drug interaction studies performed during the development of denosumab.

7.6 Additional Safety Evaluations

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7.6.1 Human Carcinogenicity

The potential for human carcinogenicity was not specifically evaluated in the denosumab development program. However, the potential for tumor promotion of pre-existing cancers was a primary focus of this review for the HA cancer trials. No safety signal suggestive of tumor promotion was identified during this review, although the number of patients treated is small, the duration of follow-up is short and the trials were not designed to evaluate cancer related endpoints. As experience with this agent accumulates, analyses of ongoing and recently completed trials conducted in patients with metastatic cancers that have skeletal related event and time-to-event endpoints (PFS, OS) will be required to confirm the present finding.

7.6.2 Human Reproduction and Pregnancy Data

During the denosumab development program, there were no trials conducted that enrolled pregnant or breastfeeding women. A total of four subjects became pregnant while on denosumab trials. In study 20050227, a healthy volunteer who received a single dose of 60 mg became pregnant within 3 months of receiving denosumab. She gave birth to an apparently healthy infant. Of note is the fact that the father of the child was also enrolled in the same study; he received a single 78 mg dose. In study 20060286, a healthy volunteer became pregnant within 2 months of receiving a single 60 mg dose of denosumab. The pregnancy was ongoing at the time the data was reported. In study 20050146, two healthy volunteers became pregnant within 6 months of receiving a single 60 mg dose of denosumab. Both of these women were reported by the applicant to be lost to follow-up; therefore no data exist with regard to the course and outcome of either pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

There were no studies conducted with denosumab in pediatric patients; therefore, there is no data to report on the use of the antibody in this population, or its effects on human growth. However, based on the target of the antibody, and findings noted in nonclinical studies, there exists a potential for the inhibition of bone growth and tooth eruption. Denosumab should not be administered to children except in cases where it may be medically necessary, or until such time as appropriate studies have been completed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no overdoses reported for denosumab during the development program. There is no data to suggest that treatment with denosumab leads to dependence; therefore, the potential for abuse of this antibody is low and there are no known associated withdrawal effects.
The potential for rebound decrease in bone mineral density below baseline was evaluated. While the effects of denosumab were reversible over a period of 12 months after ceasing treatment, there were no data suggesting associated adverse effects.

7.7 Additional Submissions

A 120 day safety update was submitted by the applicant on April 14, 2009. This amendment included materials and data as agreed upon between FDA and the applicant on October 21, 2008. Pursuant to the agreements made, the data in this submission were not integrated into the data

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submitted in the original BLA. For the HA indications, the submission included cleaned and source verified safety data for Trials 135 and 138 up to the cut-off date of December 2, 2008. This data pertained to the safety follow-up period for each of the studies and includes information on patients who were no longer receiving denosumab. Pertaining to the PMO indications, submitted were BMD and safety data from the off-treatment phase of Trial 132 up to the final study visit (month 48) in January 2009, and interim analysis of Trial 289 (open-label extension phase to study 216 up to the cut-off of December 2, 2008. In addition, new and updated narratives and case report forms were submitted. Where necessary to further inform the analyses of overall safety, the data submitted as part of this safety update were analyzed separately and integrated into the findings of this review.

8 Postmarket Experience

To date, there has been no postmarket experience with denosumab; and no postmarket data from either US or foreign safety assessments were submitted for review with this application.

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9 Appendices

9.1 Literature Review/References

The applicant submitted an extensive list of references as a part of this application. The references were reviewed by FDA. In addition, selective searches of the medical literature relevant to specific issues and topics of concern pertaining to this application were performed. Relevant references are as follows:

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Eastell R, Adams JE, Coleman RE et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol. 2008 Mar 1;26(7):1051-7.

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Jemal A, Siegel R, Ward E; et al. Cancer statistics, 2008 Cancer J Clin. 2008 Mar-Apr;58(2):71-96. Epub 2008 Feb 20

Johnell,O, Kanis,JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporos. Int 2004;15: 897-902.

Powles TJ, McCloskey E, Paterson AH, et al. Oral clodronate and reduction in loss of bone mineral density in women with operable primary breast cancer. *J Natl Cancer Inst.* 1998;90:704-708.

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Smith M, Morton RA, Wallace H, et al. A phase III randomized controlled trial of toremifene to prevent fractures and other adverse events of androgen therapy in men with prostate cancer [abstract]. In: Proceedings of the 99th Annual Meeting of the American Association for Cancer Research; 2008 Apr 12-16; San Diego, CA. Philadelphia (PA): AACR; 2008. Abstract LB-241.

Weycker,D, Macarios,D, Edelsberg,J, Oster,G. Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos. Int 2006;17: 1645-1652.

Winer EP, Hudis C, Burstein HJ et al. American society of clinical oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005 Jan 20;23(3):619-29. Epub 2004 Nov 15

9.2 Labeling Recommendations

There are no final labeling recommendations.

9.3 Advisory Committee Meeting

A meeting of the Advisory Committee for Reproductive Health Drugs was held on August 13, 2009. Representative on the committee were oncologists expert in the areas of breast and prostate cancer, endocrinologists, infectious disease specialists, dermatologists, statisticians, a consumer representative, patient representative, and an industry representative. The committee heard presentations from the applicant, and FDA, as well as comments from the public. Prior to voting on the questions presented, a discussion among the committee, FDA and the applicant took place during which time questions from the committee with regard to the data presented were answered. A summary of the recommendations made by the committee follows:

- Approve for treatment of post menopausal osteoporosis (PMO); but limit to high risk patients
- Do not approve for prevention of PMO
- Do not approve for treatment or prevention of bone loss in patients with breast cancer receiving aromatase inhibitor therapy
- Approve for treatment of bone loss in men with prostate cancer receiving androgen deprivation therapy
- Do not approve for prevention of bone loss in men with prostate cancer receiving androgen deprivation therapy
- Include a Risk Evaluation and Mitigation Strategy (REMS) as a condition of approval

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9.4 Tables Referenced in Text

Table 48 Trial 135: Sites and Enrollment

SITEID	COUNTRY	DENOSUMAB	PLACEBO	TOTAL
101	USA	0	2	2
102	USA	3	4	7
103	USA	3	2	5
104	USA	0	2	2
106	USA	2	1	3
107	USA	4	2	6
108	USA	4	5	9
109	USA	0	1	1
111	USA	2	1	3
112	USA	0	1	1
115	USA	1	1	2
116	USA	4	3	7
120	USA	3	1	4
121	USA	5	5	10
125	USA	0	2	2
126	USA	2	1	3
127	USA	2	2	4
129	USA	6	4	10
133	USA	9	3	12
137	USA	1	1	2
138	USA	1	4	5
139	USA	0	4	4
141	USA	0	2	2
152	USA	2	3	5
153	USA	4	2	6
154	USA	4	5	9
155	USA	1	1	2
156	USA	4	6	10
157	USA	2	2	4
159	USA	10	9	19
162	USA	2	4	6
163	USA	1	0	1
164	USA	1	4	5
167	USA	1	1	2
168	USA	2	0	2
170	USA	3	0	3
173	USA	1	2	3
177	USA	9	7	16
183	USA	6	8	14

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SITEID	COUNTRY	DENOSUMAB	PLACEBO	TOTAL
185	USA	3	2	5
187	USA	0	1	1
200	CAN	4	3	7
202	CAN	0	1	1
203	CAN	1	0	1
233	USA	0	1	1
234	USA	3	2	5
238	USA	1	2	3
239	USA	0	1	1
333	USA	8	2	10
334	USA	0	1	1
434	USA	1	0	1
437	USA	0	1	1
533	USA	1	0	1

Table 49 Trial 135 AE Incidence by MedDRA PT (> 5% or > 5 fold difference between groups)

MedDRA PT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Arthralgia	31	24.0	30	25.0	1	0.8	2	1.7
Pain in extremity	19	14.7	14	11.7	1	0.8	0	0.0
Back pain	18	14.0	15	12.5	0	0.0	1	0.8
Fatigue	17	13.2	17	14.2	1	0.8	2	1.7
Constipation	15	11.6	11	9.2	0	0.0	0	0.0
Cough	13	10.1	5	4.2	1	0.8	0	0.0
Insomnia	12	9.3	14	11.7	0	0.0	1	0.8
Headache	11	8.5	9	7.5	0	0.0	0	0.0
Myalgia	11	8.5	5	4.2	0	0.0	0	0.0
Shoulder pain	11	8.5	4	3.3	0	0.0	0	0.0
Nausea	10	7.8	11	9.2	0	0.0	1	0.8
Rash	10	7.8	6	5.0	0	0.0	0	0.0
Upper respiratory tract infection	10	7.8	6	5.0	0	0.0	0	0.0
Sinusitis	9	7.0	4	3.3	1	0.8	1	0.8
Vulvovaginal dryness	9	7.0	3	2.5	0	0.0	0	0.0
Anxiety	8	6.2	6	5.0	2	1.6	0	0.0
Oedema peripheral	8	6.2	5	4.2	0	0.0	0	0.0
Vomiting	8	6.2	6	5.0	0	0.0	0	0.0
Depression	7	5.4	11	9.2	0	0.0	1	0.8
Dyspnoea	7	5.4	5	4.2	0	0.0	0	0.0
Hot flush	7	5.4	8	6.7	0	0.0	0	0.0
Hypoaesthesia	7	5.4	4	3.3	0	0.0	0	0.0
Muscle spasms	7	5.4	6	5.0	0	0.0	0	0.0
Musculoskeletal chest pain	7	5.4	6	5.0	0	0.0	1	0.8
Urinary tract infection	7	5.4	5	4.2	0	0.0	0	0.0

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Table 50 Trial 135 AE Incidence by MedDRA HLT (> 5% or > 3% difference between groups)

MedDRA HLT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Musculoskeletal and connective tissue signs and symptoms NEC	49	38.0	41	34.2	2	1.6	3	2.5
Upper respiratory tract infections	21	16.3	14	11.7	1	0.8	1	0.8
Pain and discomfort NEC	14	10.9	7	5.8	1	0.8	1	0.8
Coughing and associated symptoms	13	10.1	5	4.2	1	0.8	0	0
Muscle pains	12	9.3	5	4.2	0	0	0	0
Bladder and urethral symptoms	11	8.5	3	2.5	0	0	0	0
Oedema NEC	11	8.5	5	4.2	0	0	0	0
Paraesthesias and dysaesthesias	10	7.8	4	3.3	0	0	0	0
Upper respiratory tract signs and symptoms	9	7.0	2	1.7	0	0	0	0
Vulvovaginal signs and symptoms	9	7.0	3	2.5	0	0	0	0
Depressive disorders	7	5.4	11	9.2	0	0	1	0.8
Herpes viral infections	7	5.4	2	1.7	0	0	0	0
Diarrhoea (excl infective)	5	3.9	9	7.5	0	0	0	0
Vascular hypertensive disorders NEC	2	1.6	7	5.8	1	0.8	0	0

Table 51 Trial 135 AE Incidence by MedDRA HLGT (> 5% or > 3% difference between groups)

MedDRA HLGT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Musculoskeletal and connective tissue disorders NEC	50	38.8	41	34.2	2	1.6	3	2.5
Joint disorders	41	31.8	42	35.0	3	2.3	3	2.5
Infections - pathogen class unspecified	40	31.0	29	24.2	3	2.3	2	1.7
General system disorders NEC	39	30.2	29	24.2	2	1.6	3	2.5
Respiratory disorders NEC	24	18.6	10	8.3	1	0.8	0	0
Epidermal and dermal conditions	22	17.1	15	12.5	0	0	0	0
Gastrointestinal motility and defaecation conditions	21	16.3	26	21.7	0	0	0	0
Muscle disorders	21	16.3	12	10	0	0	0	0
Urinary tract signs and symptoms	14	10.9	4	3.3	0	0	0	0
Viral infectious disorders	13	10.1	8	6.7	0	0	0	0
Skin appendage conditions	12	9.3	6	5.0	0	0	0	0
Vulvovaginal disorders (excl infections and inflammations)	12	9.3	4	3.3	0	0	0	0
Depressed mood disorders and disturbances	7	5.4	11	9.2	0	0	1	0.8
Vascular hypertensive disorders	2	1.6	7	5.8	1	0.8	0	0

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Table 52 Trial 135 AE Incidence by MedDRA SOC (>5% or >3% difference between groups)

MedDRA SOC	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Infections and infestations	47	36.4	38	31.7	3	2.3	3	2.5
General disorders and administration site conditions	44	34.1	32	26.7	2	1.6	3	2.5
Nervous system disorders	35	27.1	25	20.8	3	2.3	1	0.8
Skin and subcutaneous tissue disorders	32	24.8	21	17.5	1	0.8	0	0
Reproductive system and breast disorders	27	20.9	14	11.7	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	19	14.7	10	8.3	4	3.1	5	4.2
Investigations	18	14.0	12	10	0	0	1	0.8
Metabolism and nutrition disorders	15	11.6	9	7.5	1	0.8	2	1.7
Renal and urinary disorders	15	11.6	6	5.0	0	0	0	0

Table 53 Trial 135 Standardized MedDRA Queries (Broad Scope)

p-Value*	SMQ	Denosumab	Placebo
0.0334	Noninfectious encephalopathy/delirium (SMQ)	9 (7.1%)	2 (1.6%)
0.0356	Guillain-Barre syndrome (SMQ)	17 (13.4%)	7 (5.6%)
0.0459	Optic nerve disorders (SMQ)	4 (3.1%)	0 (0.0%)
0.0542	Peripheral neuropathy (SMQ)	16 (12.6%)	7 (5.6%)
0.0585	Dementia (SMQ)	6 (4.7%)	1 (0.8%)
0.0631	Rhabdomyolysis/myopathy (SMQ)	25 (19.7%)	14 (11.2%)
0.0741	Angioedema (SMQ)	18 (14.2%)	9 (7.2%)
*** p-Values are derived from a Mantel-Haenszel test and are used for ranking purposes only. Not to be used for determining statistical significance.**			

Table 54 Trial 135 Standardized MedDRA Queries (Narrow Scope)

p-Value*	SMQ	Denosumab	Placebo
0.0845	Hyperglycaemia/new onset diabetes mellitus (SMQ)	3 (2.4%)	0 (0.0%)
0.1306	Dyslipidaemia (SMQ)	8 (6.3%)	3 (2.4%)
0.1598	Myocardial infarction (SMQ)	2 (1.6%)	0 (0.0%)
*** p-Values are derived from a Mantel-Haenszel test and are used for ranking purposes only. Not to be used for determining statistical significance.**			

Table 55 Trial 138 AE Incidence by MedDRA PT (> 5% or > 5 fold between groups)

MedDRA PT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%

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MedDRA PT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Arthralgia	92	12.5	80	10.9	4	0.5	5	0.7
Back pain	81	11.0	74	10.1	10	1.4	8	1.1
Constipation	73	9.9	75	10.2	1	0.1	9	1.2
Pain in extremity	66	9.0	51	6.9	0	0.0	3	0.4
Hypertension	57	7.8	51	6.9	7	1.0	5	0.7
Oedema peripheral	53	7.2	48	6.5	3	0.4	3	0.4
Nasopharyngitis	47	6.4	45	6.1	0	0.0	0	0.0
Fatigue	44	6.0	45	6.1	2	0.3	1	0.1
Musculoskeletal pain	41	5.6	26	3.5	5	0.7	3	0.4
Dizziness	41	5.6	31	4.2	0	0.0	2	0.3
Diarrhoea	40	5.4	39	5.3	3	0.4	1	0.1
Hot flush	38	5.2	32	4.4	3	0.4	0	0.0
Urinary tract infection	37	5.0	32	4.4	0	0.0	2	0.3

Table 56 Trial 138 AE Incidence by MedDRA HLT (>5% or >3% between groups)

MedDRA HLT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Musculoskeletal and connective tissue signs and symptoms NEC	175	23.9	150	20.7	20	2.7	13	1.8

Table 57 Trial 138 AE Incidence by MedDRA HLGT (>5% or >3% difference between groups)

MedDRA HLGT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Anterior eye structural change, deposit and degeneration	35	4.8	9	1.2	7	1.0	2	0.3

Table 58 Trial 138 AE Incidence by MedDRA SOC (>5% or >3% difference between groups)

MedDRA SOC	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Infections and infestations	257	35.2	226	31.2	43	5.9	30	4.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	117	16.0	86	11.9	49	6.7	42	5.8

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Table 59 Trial 138: Standardized MedDRA Queries (Broad Scope)

p-Value*	SMQ	Denosumab	Placebo
0.0046	Lens disorders (SMQ)	39 (5.3%)	18 (2.5%)
	Liver related investigations, signs and symptoms (SMQ)	6 (0.8%)	0 (0.0%)
0.0251	Infectious biliary disorders (SMQ)	5 (0.7%)	0 (0.0%)
0.0282	Hepatic disorders (SMQ)	13 (1.8%)	4 (0.5%)
	Possible drug related hepatic disorders - comprehensive search (SMQ)	13 (1.8%)	4 (0.5%)
0.0374	Gastrointestinal nonspecific inflammation (SMQ)	23 (3.1%)	11 (1.5%)
0.0479	Hostility/aggression (SMQ)	18 (2.5%)	8 (1.1%)
0.0512	Reproductive toxicity (SMQ)	10 (1.4%)	3 (0.4%)
0.0574	Malignant or unspecified tumours (SMQ)	103 (14.0%)	79 (10.8%)

*** p-Values are derived from a Mantel-Haenszel test and are used for ranking purposes only. Not to be used for determining statistical significance.**

Table 60 Trial 138: Standardized MedDRA Queries (Narrow Scope)

p-Value*	SMQ	Denosumab	Placebo
0.0002	Lens disorders (SMQ)	36 (4.9%)	11 (1.5%)
0.0251	Infectious biliary disorders (SMQ)	5 (0.7%)	0 (0.0%)
0.0453	Toxic-septic shock conditions (SMQ)	0 (0.0%)	4 (0.5%)
0.0570	Noninfectious encephalopathy/delirium (SMQ)	8 (1.1%)	2 (0.3%)
0.0574	Malignant or unspecified tumours (SMQ)	103 (14.0%)	79 (10.8%)
0.0583	Convulsions (SMQ)	1 (0.1%)	6 (0.8%)

*** p-Values are derived from a Mantel-Haenszel test and are used for ranking purposes only. Not to be used for determining statistical significance.**

Table 61 ISS AEs by MedDRA PT ≥ 5% or Denosumab ≥ 5 Fold

MedDRA PT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Back pain	1484	30.0	1471	29.9	265	5.4	265	5.4
Arthralgia	959	19.4	944	19.2	62	1.3	66	1.3
Hypertension	694	14.0	714	14.5	37	0.7	38	0.8
Pain in extremity	569	11.5	519	10.6	27	0.5	36	0.7
Osteoarthritis	488	9.9	482	9.8	63	1.3	61	1.2
Constipation	464	9.4	456	9.3	16	0.3	23	0.5
Musculoskeletal pain	369	7.5	337	6.9	19	0.4	27	0.5
Hypercholesterolaemia	301	6.1	251	5.1	2	0.0	3	0.1
Dizziness	273	5.5	264	5.4	5	0.1	9	0.2
Cataract	269	5.4	266	5.4	21	0.4	19	0.4

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Upper respiratory tract infection	254	5.1	221	4.5	7	0.1	4	0.1
Erectile dysfunction	8	0.2	1	0.0	2	0.0	0	0.0
Irritability	7	0.1	1	0.0	1	0.0	0	0.0
Libido decreased	7	0.1	1	0.0	0	0.0	0	0.0
Thrombocythaemia	6	0.1	1	0.0	0	0.0	0	0.0
Hepatomegaly	6	0.1	1	0.0	0	0.0	0	0.0
Tinea infection	6	0.1	1	0.0	0	0.0	0	0.0
Coronary artery stenosis	5	0.1	1	0.0	4	0.1	1	0.0
Gingival pain	5	0.1	1	0.0	0	0.0	0	0.0
Glossodynia	5	0.1	1	0.0	0	0.0	0	0.0
Haematemesis	5	0.1	1	0.0	0	0.0	1	0.0
Pancreatitis acute	5	0.1	1	0.0	2	0.0	0	0.0
Periodontal disease	5	0.1	1	0.0	0	0.0	0	0.0
Infected skin ulcer	5	0.1	1	0.0	2	0.0	0	0.0
Tooth injury	5	0.1	1	0.0	0	0.0	0	0.0
Metastases to spine	5	0.1	1	0.0	5	0.1	0	0.0
Peroneal nerve palsy	5	0.1	1	0.0	0	0.0	0	0.0
Arterial occlusive disease	5	0.1	1	0.0	1	0.0	0	0.0

Table 62 ISS AEs by MedDRA HLT ≥ 5% or Denosumab ≥ 5 fold

MedDRA HLT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Musculoskeletal and connective tissue signs and symptoms NEC	2108	42.7	2063	42.0	314	6.4	328	6.7
Osteoarthropathies	563	11.4	534	10.9	66	1.3	66	1.3
Gastrointestinal atonic and hypomotility disorders NEC	557	11.3	541	11.0	21	0.4	24	0.5
Asthenic conditions	339	6.9	322	6.6	14	0.3	20	0.4
Elevated cholesterol	301	6.1	251	5.1	2	0.0	3	0.1
Neurological signs and symptoms NEC	280	5.7	266	5.4	8	0.2	9	0.2
Depressive disorders	277	5.6	269	5.5	5	0.1	12	0.2
Cataract conditions	269	5.4	266	5.4	21	0.4	19	0.4
Oedema NEC	268	5.4	232	4.7	8	0.2	8	0.2
Erection and ejaculation conditions and disorders	8	0.2	1	0.0	2	0.0	0	0.0
Hepatobiliary signs and symptoms	7	0.1	1	0.0	0	0.0	0	0.0
Sexual desire disorders	7	0.1	1	0.0	0	0.0	0	0.0

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Dermatitis ascribed to specific agent	6	0.1	1	0.0	1	0.0	0	0.0
Photosensitivity conditions	6	0.1	1	0.0	0	0.0	0	0.0
Secondary thrombocythaemias	6	0.1	1	0.0	0	0.0	0	0.0
Gingival pains	5	0.1	1	0.0	0	0.0	0	0.0
Male reproductive tract infections	5	0.1	1	0.0	1	0.0	0	0.0

Table 63 ISS AEs by MedDRA HLGT ≥ 5% or Denosumab ≥ 5 fold

MedDRA HLGT	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Musculoskeletal and connective tissue disorders NEC	2129	43.1	2085	42.4	314	6.4	331	6.7
General system disorders NEC	807	16.3	768	15.6	54	1.1	52	1.1
Epidermal and dermal conditions	520	10.5	413	8.4	13	0.3	8	0.2
Muscle disorders	433	8.8	400	8.1	22	0.4	19	0.4
Lipid metabolism disorders	401	8.1	343	7.0	3	0.1	3	0.1
Cardiac arrhythmias	321	6.5	289	5.9	58	1.2	56	1.1
Depressed mood disorders and disturbances	307	6.2	289	5.9	7	0.1	12	0.2
Urinary tract signs and symptoms	283	5.7	257	5.2	19	0.4	12	0.2
Anterior eye structural change, deposit and degeneration	282	5.7	275	5.6	21	0.4	19	0.4
Coronary artery disorders	265	5.4	241	4.9	105	2.1	75	1.5
Bone disorders (excl congenital and fractures)	251	5.1	248	5.0	30	0.6	28	0.6
Sexual dysfunctions, disturbances and gender identity disorders	7	0.1	1	0.0	0	0.0	0	0.0
Renal and urinary tract neoplasms benign	5	0.1	1	0.0	0	0.0	1	0.0

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Table 64 ISS AEs by MedDRA SOC ≥ 5%

MedDRA SOC	Denosumab All Grades		Placebo All Grades		Denosumab Grades 3-4		Placebo Grades 3-4	
	n	%	n	%	n	%	n	%
Nervous system disorders	1356	27.4	1291	26.3	187	3.8	145	2.9
Skin and subcutaneous tissue disorders	726	14.7	601	12.2	24	0.5	17	0.3
Metabolism and nutrition disorders	704	14.2	620	12.6	38	0.8	24	0.5
Cardiac disorders	660	13.4	636	12.9	174	3.5	153	3.1
Psychiatric disorders	653	13.2	614	12.5	21	0.4	19	0.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	455	9.2	384	7.8	156	3.2	125	2.5
Investigations	258	5.2	307	6.2	10	0.2	14	0.3

Table 65 ISS SMQ Broad Scope

p-Value	SMQ Broad Scope MedDRA version 11.1	Denosumab	Placebo
0.0279	Malignant or unspecified tumours (SMQ)	306 (6.2%)	254 (5.2%)
0.0313	Rhabdomyolysis/myopathy (SMQ)	617 (12.5%)	545 (11.1%)
0.0323	Dyslipidaemia (SMQ)	428 (8.7%)	368 (7.5%)
0.0433	Biliary disorders (SMQ)	95 (1.9%)	124 (2.5%)
0.0547	Extravasation events (injections, infusions and implants) (SMQ)	47 (1.0%)	30 (0.6%)
0.0570	Malignancies (SMQ)	313 (6.3%)	267 (5.4%)
0.0576	Haemorrhage laboratory terms (SMQ)	5 (0.1%)	13 (0.3%)

Table 66 ISS SMQ Narrow Scope

p-Value	SMQ Narrow Scope MedDRA version 11.1	Denosumab N=4942	Placebo N=4916
0.0209	Extrapyramidal syndrome (SMQ)	39 (0.8%)	21 (0.4%)
0.0279	Malignant or unspecified tumours (SMQ)	306 (6.2%)	254 (5.2%)
0.0323	Dyslipidaemia (SMQ)	428 (8.7%)	368 (7.5%)
0.0407	Parkinson-like events (SMQ)	34 (0.7%)	19 (0.4%)
0.0570	Malignancies (SMQ)	313 (6.3%)	267 (5.4%)

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SIGNATURES PAGE

/Shan Pradhan, MD/
Shan Pradhan, MD
Clinical Reviewer
Division of Biologic Oncology Products
Office of Oncology Drug Products
OND/CDER

August 30, 2011
Date

/Steven Lemery, MD/
Steven Lemery, MD
Clinical Team Leader
Division of Biologic Oncology Products
Office of Oncology Drug Products
OND/CDER

August 30, 2011
Date

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125332 & 125333 **Applicant: Amgen** **Stamp Date: December 19, 2008**

Drug Name: Prolia **NDA/BLA Type: Standard**

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 in SDTM format
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		A redlined version was omitted?
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?		X		
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: 20050172 Study Title: Dose Response Study of AMG 162 (denosumab) in Subjects With Osteoporosis – A Randomized, Double-blind, Placebo-controlled, Dose Response Study of AMG 162 (denosumab) in Japanese Postmenopausal Osteoporotic Subjects Sample Size: 226 Arms: Denosumab 3 dose cohorts/placebo Location in submission: 5.3.4.2.1	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

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

Reference ID: 3168397

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1A: Randomized, Double-blind, Placebo-controlled Study to Evaluate AMG 162 in the Treatment of Bone Loss in Subjects Undergoing Aromatase Inhibitor Therapy for Nonmetastatic Breast Cancer **Indication:** Treatment of bone loss in patients undergoing aromatase inhibitor therapy for nonmetastatic breast cancer **Pivotal Study #2:** A Randomized, Double-blind, Placebo-controlled Study to Evaluate AMG 162 in the Treatment of Bone Loss in Subjects Undergoing Androgen-deprivation Therapy for Nonmetastatic Prostate Cancer **Indication:** Treatment of bone loss associated with hormone ablation therapy in subjects with prostate cancer				
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 a rationale in the submission; however, there are sufficient US sites for each registration study
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			
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			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

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

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
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		Not found in submission
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?				
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				Not found in submission
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			Follow up still ongoing
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			

[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).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

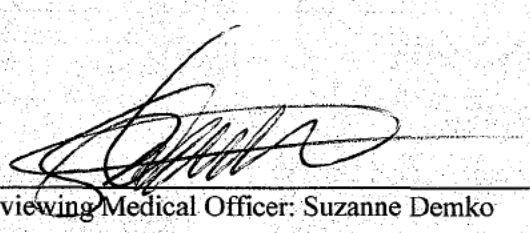
	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

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.

1. Narrative summaries for all deaths, dropouts due to adverse events, SAEs, and any cases adjudicated for possible diagnosis of osteonecrosis of the jaw should be submitted for the studies supporting the HALT indications.



January 28, 2009

Reviewing Medical Officer: Suzanne Demko Date

January 28, 2009

Clinical Team Leader: Jeff Summers Date

Reference ID: 3168397

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

CHEMISTRY REVIEW(S)

The Quality Team Leader's Executive Summary

From:	**Chana Fuchs, Ph.D., Team Leader** **Division of Monoclonal Antibodies (DMA)**
Through:	**Patrick Swann, Ph.D. Deputy Director, DMA**
Through:	**Kathleen A. Clouse, Ph.D., Director, DMA**
To:	**Theresa Kehoe, M.D. CDTL, DRUP, ODEIII** **Jeff Summers, M.D. CDTL, DBOP, OODP**

BLA Number:	**125320, 125331, 125332, 125333**
Product:	**Prolia™ (denosumab)**
Sponsor :	**Amgen**
Date of Review:	**September 15, 2009**

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this Biologics License Application support the conclusion that the manufacture of Prolia™ (denosumab) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. The Division of Monoclonal Antibodies recommends that Prolia™ (denosumab) be approved for human use (under conditions specified in the package insert).

B. Recommendation on Phase 4 (Post-Marketing) Commitments (PMC), Agreements (PMA), Requirements (PMR) and/or Risk Management Steps, if Approvable.

PMRs: none

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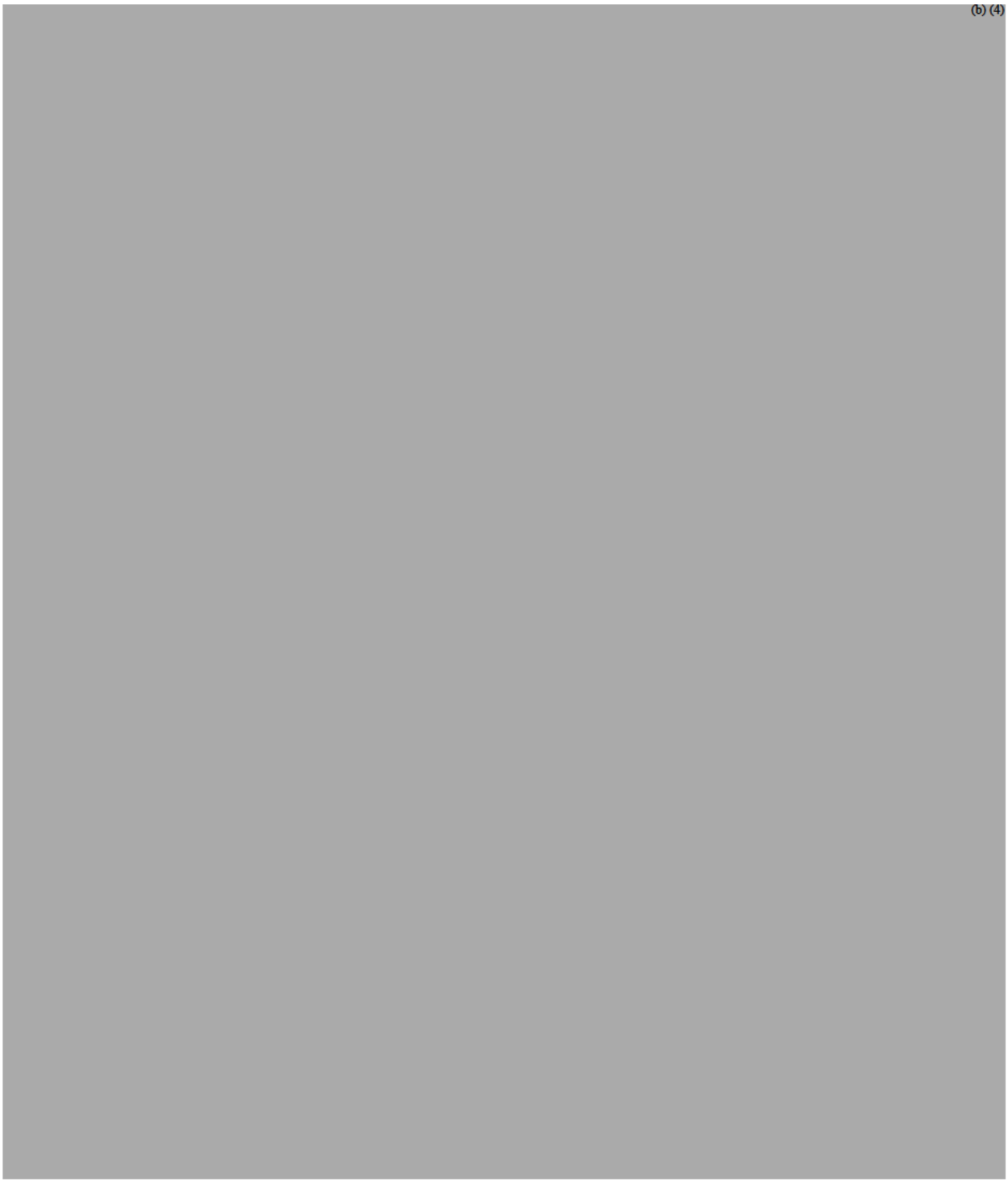

C. Description of How the Drug Product is Intended to be Used

- Prolia™ (denosumab) is indicated for the treatment and prevention of osteoporosis in postmenopausal women and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer

Reference ID: 3168397

- Prolia™ DP is currently provided as either single use vials or pre-filled syringes. Both vials and PFS contain 60 mg/ml denosumab.

- The recommended dose of Prolia™ is 60 mg every 6 months as a subcutaneous injection. Prolia is to be administered by a health care provider.

- Prolia™ formulation does not include preservatives, so any unused portion remaining in the vial must be discarded.

- Prolia™ (denosumab) DP is to be stored refrigerated (2°-8° C) inside the original carton to protect it from light.

D. Basis for Approvability or Not-Approval Recommendation

- Prolia (denosumab) is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Denosumab is manufactured consistently leading to a safe and effective product for the indications to be approved. Approval is recommended.

- Post marketing commitments described in the recommendations section above will provide additional information to assure the continued safety of the product.

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **August 21, 2009**
To: Administrative File, **STN 125320, 125331, 125332, 125333**
From: Donald C. Obenhuber, Ph.D., CDER/OC/DMPQ/MAPCB/BMT DCO 9/25/09
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT AL for PH 9/25/09
Subject: New Biologic License Application (BLA)
Applicant: Amgen, Inc.
US License: **1080**
Facility: Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos
Puerto Rico 00777 USA
FEI No. 1000110364
Product: Prolia (Denosumab)
Dosage: 60 mg (60 mg/mL), intervenus injection, vials and PFS
Indication: Treatment and prevention of osteoporosis in postmenopausal women and treatment and prevention of bone loss associated with HALT in patients with breast or prostate cancer
PDUFA date: 19 October 2009

Recommendation: The drug product part of this application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective. A separate evaluation of the drug product manufacture site at Amgen at Puerto Rico, will be conducted by the compliance officer at San Juan District Office.

Review Summary

Denosumab, a fully human IgG2 monoclonal antibody that inhibits receptor activator of nuclear factor kappa B ligand, for the treatment and prevention of osteoporosis in postmenopausal women and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. Denosumab drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial presentation with a 1.0 mL deliverable volume to support dosing of 60 mg every 6 months (Q6M). Each prefilled syringe contains: 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, 0.01 °Io polysorbate 20, sodium hydroxide for pH adjustment in Water for Injection, USP (pH of 5.2). Each vial contains: 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, sodium hydroxide for pH adjustment in Water for Injection, USP (pH of 5.2).

Assessment

Drug Product

Description of the Composition of the Drug Product (3.2.P.1):

Batch Formula

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[redacted]

Conclusion

I. The BLA is recommended for approval from a sterility assurance and product quality microbiology perspective.

II. Information and data in this submission not related to drug product sterility assurance was not evaluated and should be reviewed by an OBP reviewer.

III. A separate evaluation of the drug product manufacture site at Amgen at Puerto Rico, will be conducted by the compliance officer at San Juan District Office.

Cc: WO51: Obenhuber
WO51: Hughes
WO22: Celia Peacock
HFD-328, eCTD Blue Files (STN 125320, 125331, 125332, 125333)

Archived File: S:\archive\BLA \125320\STNI25320.rev.mem.BLA.09-23-09.doc
S:\archive\BLA\125331 \STNI25331.rev.mem.BLA.09-23-09.doc
S :\archive\BLA \125332\STNI25332.rev.mem.BLA.09-23-09 .doc
S:\archive\BLA \ 125333\STNI25333.rev.mem.BLA.09-23-09.doc

Reference ID: 3168397

Product Quality Review Data Sheet

1. **BLA#** STN 125320/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** 15-SEPT-2009

4. **REVIEWER(s):** Sarah Kennett, Ph.D.
Michele Dougherty, Ph.D.
Chana Fuchs, Ph.D., Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS TO DATE:**

Communication/Documents	Date
Pre-BLA meeting	05-FEB-2008
Pre-BLA meeting	08-JULY-2008
Pre-BLA meeting	29-JULY-2008
Pre-BLA meeting	21-OCT-2008
Filing Review (45 days)	28-JAN-2009
Boehringer Ingelheim 483 (BIP inspection)	20-MAY-2009
Information Request (74 day letter)	03-MAR-2009
Information Request	07-APR-2009
Information Request	20-APR-2009
Information Request	11-MAY-2009
Information Request	20-AUG-2009
Information Request	27-AUG-2009

6. **SUBMISSION(S) REVIEWED TO DATE:**

Submission(s) Reviewed	Document Date
STN 125320/0.1 (original submission)	19-DEC-2008
STN 125320/0.4	23-JAN-2009
STN 125320/0.6	13-FEB-2009
STN 125320/0.12	13-MAR-2009
STN 125320/0.13	16-MAR-2009
STN 125320/0.16	15-ARP-2009
STN 125320/0.18	23-APR-2009
STN 125320/0.21	01-MAY-2009
STN 125320/0.22 (labeling)	04-MAY-2009
STN 125320/0.24	19-MAY-2009
STN 125320/0.25 (labeling)	28-MAY-2009
STN 125320/0.29	25-JUNE-2009
STN 125320/0.32	21-JULY-2009
STN 125320/0.35 (labeling)	26-AUG-2009
STN 125320/0.36	26-AUG-2009

STN 125320/0.38	03-SEPT-2009
STN 125320/0.39	11-SEPT-2009
STN 125320/0.40 (labeling)	11-SEPT-2009
Response to 483	16-JUNE-2009

7. **NAME & ADDRESS OF APPLICANT:**
Name: Amgen, Inc.
Address: One Amgen Center Drive, Thousand Oaks, CA 91320-1799
Representative: Julie Lepin, Director, Regulatory Affairs
Telephone: (805) 447-3040
Fax: (805) 480-1330

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name:	Prolia™
Non-proprietary/USAN:	Denosumab
Code name:	AMG 162
Common name:	anti-human RANK ligand
Drug Review Status:	Standard
Chemical Type:	Recombinant human monoclonal antibody

9. **PHARMACOLOGIC CATEGORY:** Therapeutic recombinant human monoclonal antibody to RANK ligand

10. **DOSAGE FORM:** Injection, Solution (prefilled syringe)
Injection, Solution (vial)

11. **STRENGTH/POTENCY:**
a) The concentration of Prolia (denosumab) Drug Product is 60 mg/ml.
b) Potency is defined as percent inhibition of ligand binding relative to reference standard using a proprietary homogenous time resolved fluorescence assay.
c) Potency specification is (b) (4) of reference standard.
d) Dating period for vialed drug product is 30 months when stored at 2°C -8°C.
e) 60 mg of Denosumab is filled into either 3 ml glass vials or 1 ml glass syringes.

12. **ROUTE OF ADMINISTRATION:** Subcutaneous injection

13. **ACID (Animal Component Information Database)**
Section 3.2.A.2 lists starting materials of biological origin. No materials of direct animal origin are used in the current manufacturing process.

(b) (6)

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IV. ADMINISTRATIVE

A. Reviewers' Signatures

Product Quality Reviewer: Sarah Kennett, Ph.D. 9/14/09

Product Quality Reviewer: Michele Dougherty, Ph.D. 9/14/09

B. Endorsement Block

Product Division Team Leader: Chana Fuchs, Ph.D. 9/15/09

Product Division Deputy Director: Patrick Swann, Ph.D. 9/25/09

Product Division Director: Kathleen A. Clouse, Ph.D. 10/07/2009

C. cc Block

OBP Office Director: Steven Kozlowski, M.D.
Clinical Division Director (DRUP): Scott Monroe, M.D.
Clinical Division Director (DBOP): Patricia Keegan, M.D.
Division of Monoclonal Antibodies File: BLA STN 125320

Product Quality Assessment [Denosumab (Prolia), Amgen]
Reviewed by Sarah Kennett, Ph.D., Biologist (sk) Division of Monoclonal Antibodies, OBP/OPS/CDER/FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: August 1, 2009
To: Administrative File, STN 125320/0, STN 125331/0, STN 125332/0, STN 125333/0
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT PS 9/2/09
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PH 9/2/09
Subject: Original BLA
US License: #1080
Applicant: Amgen, Inc.
Mfg Facility: **For drug substance:** Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard, Boulder, CO 80301. USA.
FEI No. 3003072024

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany
FEI No. 3002806518

For drug product: Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA
FEI No. 1000110364.

Product: Prolia™ (Denosumab, AMG 162)
Dosage: Single-use, sterile, preservative-free solution for subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial.
Indication: Treatment and prevention of osteoporosis in postmenopausal women.
Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer or prostate cancer.
Due Date: October 19, 2009

Recommendation for Approvability: The drug substance section of the BLA, as amended, is recommended for approval from a microbiology product quality perspective.

SUMMARY:
Denosumab is a fully human IgG2 monoclonal antibody that inhibits the RANK ligand. It is derived from the Xeno-mouse™ technology and produced in CHO cells. The application contains information to support commercial production of denosumab drug substance at Amgen Colorado (ACO) located in Boulder, Colorado, and Boehringer Ingelheim Pharma (BIP), located in Biberach an der Riss, Germany, as well as drug product manufacture at Amgen Manufacturing Limited (AML), Puerto Rico. The BLA was submitted in eCTD format. This review covers the evaluation of the drug substance aspects of the application from a microbiology product quality perspective. The following amendments to quality section of the submission were reviewed in addition to the original application: eCTD sequence number 0004 dated 1/22/2009 (new in process controls/specifications), eCTD sequence number 0006 dated 2/12/2009 (production schedule), eCTD sequence number 0007 dated 2/27/2009 (authorized representatives change), eCTD sequence number 0017 dated 4/15/2009 (stability conclusion for drug substance), eCTD sequence number 0018 dated 4/23/2009 (response to informational request), and eCTD sequence number 0021 dated 5/1/2009 (endotoxin assay and validation).

ASSESSMENT:

This is a new BLA requesting approval of denosumab (AMG 162), a fully human IgG2 monoclonal antibody that inhibits the receptor activator of the nuclear factor kappa B (RANK) ligand, for the treatment and prevention of osteoporosis in postmenopausal women, and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. Denosumab is produced in the Chinese hamster ovary (CHO) cells. The application contains information to support commercial production of denosumab drug substance at Amgen Colorado (ACO) located in Boulder, Colorado, and Boehringer Ingelheim Pharma (BIP), located in Biberach an der Riss, Germany, as well as drug product manufacture at Amgen Manufacturing Limited (AML), Puerto Rico.

Denosumab drug product is supplied as a sterile, preservative-free solution for administration by subcutaneous injection. Amgen is seeking approval of a 60 mg/mL vial and 60 mg/mL prefilled syringe (PFS) presentations. The only difference in the formulations for these presentations is the addition of 0.01% (w/v) polysorbate to the formulation used for the PFS. A 70 mg/mL (1.7 mL deliverable volume) vial is also being developed. Amgen is not seeking approval of the 70 mg/mL vial in this application.

This assessment only covers the drug substance aspects of the application. For drug product aspects of the application, please see the review by Dr. Donald Obenhuber.

3.2.S. DRUG SUBSTANCE

3.2.S.1. GENERAL INFORMATION

Denosumab is a fully human IgG2 monoclonal antibody that inhibits the RANK ligand. It is derived from the Xeno-mouse™ technology and produced in CHO cells.

This section should be reviewed by OBP/DMA reviewer.

3.2.S.2. MANUFACTURE

3.2.S.2.1. MANUFACTURE(S)

The denosumab drug substance manufacturing process consists of (b) (4) (b) (4) stages. The denosumab drug substance manufacturing sites are (1) Amgen Inc. (ACO) located in Boulder, Colorado, and (2) Boehringer Ingelheim Pharma GmbH & Co. Kg (BIP) located in Biberach an der Riss, Germany.

The address and FEI numbers of the sites used for the manufacture of drug substance, raw material testing, storage of cell banks, contract testing laboratories, release and stability testing are listed below.

Manufacture, release and stability testing, and storage of drug substance and raw materials. Also, storage of working cell bank:
Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard Boulder, CO 80301. USA
FEI No. 3003072024

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 65 88397 Biberach an der Riss, Germany
FEI No. 3002806518

Storage of master cell bank, raw material testing and release, drug substance release and stability testing, and storage:
Amgen Inc. (ACO) Longmont Facility
4000 Nelson Road Longmont, CO 80503 USA
FEI No. 3002892484

Storage of master cell bank, working cell bank, raw materials and drug substance. Also, raw material testing and release:
Amgen Inc. (ATO)
One Amgen Center Drive Thousand Oaks, CA 91320 USA
FEI No. 2026154

Raw material testing and release, and drug substance storage, release and stability testing:
Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA
FEI No. 1000110364

(b) (4)

3.2.S.2.2. MANUFACTURING PROCESS AND PROCESS CONTROLS

The denosumab manufacturing process consists of (b) (4) (b) (4) stages. The BI Pharma and ACO sites use the same process except for facility specific differences. (b) (4) . The production bioreactor final working volume is approximately (b) (4) at ACO and (b) (4) at BI Pharma.

42 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications. You cannot have multiple indications under supplement submissions. If the sponsor submits multiple indications under a supplement, you must unbundle the submission.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN:125320/0; 125331/0; 125332/0; 125333/0 Product: Denosumab Applicant: Amgen, Inc.

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): Traditional (CTD)

Filing Meeting: Date _____ Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ____ Part A – RPM
  - __X__ Part B – Product/CMC/Facility Reviewer(s): Maan Abduldayem, Donald Obenhuber, Kalavati Suvarna, Bo Chi
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____ _____ _____ _____
- ☐ Memo of Filing Meeting

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	
❑ Novel Excipients	N	No novel excipients
❑ Executed Batch Records	Y	
❑ Method Validation Package	Y	
❑ Comparability Protocols	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y	OBP Lead
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y	OBP Lead
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	Y	Bioburden and endotoxin controls present. Phone call received from company to say that bioburden information was incorrectly filed and will be amended.
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	OBP Lead

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	OBP Lead
❑ characterization of drug substance	Y	OBP Lead
❑ control of drug substance o specification o justification of specs. o analytical procedures o analytical method validation o batch analyses o consistency (3 consecutive lots) o justification of specs.	Y	OBP Lead; Bioburden and endotoxin specification, analytical procedures and validation included.
❑ reference standards	Y	OBP Lead
❑ container closure system	Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	OBP Lead
Drug Product [3.2.P]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including (b) (4) processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
❑ control of drug product	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
(justification of specifications; analytical method validation) ❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s) ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y Y	
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent ❑ pharmaceutical development ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including (b) (4) processing & sterility assurance: o 3 consecutive lots o other needed validation data ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system o specifications (vial, elastomer, drawings)	 Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	Not applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
○ availability of DMF ○ closure integrity ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results	Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Y N Y N	Not applicable
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation and storage ○ sterilization of equipment and materials ○ procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients	Y Y Y N	OBP Lead No novel excipients, OBP Lead
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	Y Y Y N	OBP Lead
Literature references and copies [3.3]	Y	

Reference ID: 3168397

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable	Y Y Y Y Y Y Y	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	Y	
includes data demonstrating consistency of manufacture	Y	
includes complete description of product lots and manufacturing process utilized for clinical studies	Y	OBP Lead
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	OBP Lead
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y	OBP Lead
certification that all facilities are ready for inspection	Y	Drug substance manufacture at two sites: 1. Amgen Colorado facility (in operation early April 2009); 2. BI Pharma Germany (in operation early May 2009); Drug Product manufacture at Amgen, Juncos, Puerto Rico (in operation late April 2009).
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑	Y Y N Y	OBP Lead
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	
information and data supporting validity of sterilization processes for sterile products and (b) (4) manufacturing operations	Y	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	Not applicable

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Fileable

Recommendation (circle one): (File) RTF 1/22/09 01/22/09

Reviewer: Maan Abduldayem; Donald Obenhuber; Kalavati Suvarna, Bo Chi 01/22/09
(signature/ date)

Type (circle one): Product (Chair) (Facility (DMPQ))

Concurrence:
Branch/Lab Chief: 1/22/09
(signature/ date)

Division. Director:
(signature/ date) acting DD 1/26/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

PHARMACOLOGY REVIEW(S)

MEMORANDUM

TO: The file
CC: Patricia Keegan, M.D., Director, Division of Biologic Oncology Products (DBOP), Office of Oncology Drug Products (OODP), CDER
Jeffrey Summers, M.D., Deputy Director of Safety, DBOP, OODP, CDER
Michael S. Orr, Ph.D., D.A.B.T., Toxicology Reviewer, DBOP, OODP, CDER
Kimberly Hatfield, Ph.D., Division of Reproductive and Urologic Drug Products (DRUP), ODE-III, CDER
FROM: Anne M. Pilaro, Ph.D., Supervisory Toxicologist, Pharmacology/Toxicology Branch, Division of Biologic Oncology Products, OODP, CDER

STN BLA #: 125332/000/000 and 125333/000/000
SPONSOR: Amgen, Inc.
PRODUCT: recombinant, human monoclonal antibody directed against receptor activator of nuclear factor-κB (RANK) ligand (RANKL), denosumab (Prolia™)
AMENDMENT TYPE: original BLA submission
DATE: September 1, 2009

SECONDARY PHARMACOLOGY/TOXICOLOGY REVIEW:

Introduction: Amgen has submitted final study reports for nonclinical studies to evaluate the biologic activity, pharmacokinetics and safety of denosumab, in support of an original biologics licensing application (BLA). Denosumab is a novel, fully human IgG_2 monoclonal antibody, directed against an epitope present on the receptor activator of nuclear factor-κB (RANK) ligand (RANKL). RANKL binds to RANK on osteoclast precursors and mature osteoclasts, stimulates osteoclasts to resorb bone, and promotes differentiation of the precursor cells into osteoblasts. Binding of denosumab to RANKL inhibits interaction of the ligand with target receptors such as RANK, thereby neutralizing the effects of RANKL. Since RANKL binding to RANK is involved with the formation, function, and survival of cells that resorb bone such as osteoclasts, the inhibition of RANKL binding to RANK by denosumab leads to the suppression in osteoclast-mediated bone turnover.

This memorandum summarizes the principle nonclinical issues related to the approval of denosumab (proposed trade name, Prolia™), the reviewer's conclusions regarding the findings, and the appropriateness of the proposed labeling.

Summary: The pharmacology/toxicology reviewers, Dr. Michael Orr (DBOP) and Dr. Kimberly Hatfield (DRUP) have written reviews recommending approval of denosumab, based on safety and biologic activity data from nonclinical final study reports submitted with the original BLA application. Only the review conducted by Dr. Orr will be the subject of this secondary pharmacology/toxicology review; however, a brief summary of the nonclinical general toxicology data reviewed by Dr. Hatfield will be discussed in context of the pharmacology findings.

Pharmacology studies were reviewed by Dr. Michael Orr, and conducted by the sponsor in normal healthy, young adult cynomolgus monkeys, ovariectomized cynomolgus monkeys (as a model of bone loss following hormone ablation), and in transgenic mice that selectively express

the human RANKL (huRANKL) and RANK receptor. In a 12-month pharmacology study in ovariectomized (OVX) female cynomolgus monkeys bone biomarkers remained elevated in the vehicle control OVX females, and these animals developed mild osteopenia with increased bone turnover and loss of bone mass, based on bone densitometry measurements. By contrast, OVX female monkeys treated with denosumab alone, denosumab in combination with alendronate pretreatment, or alendronate alone showed significant reductions in biochemical markers of bone formation, accompanied by increased bone mineral density (BMD) in the whole body, lumbar spine, tibial diaphysis, and radial cortical diaphysis. Additionally, denosumab treatment with or without alendronate, or alendronate treatment alone prevented the OVX-induced BMD changes in both cortical and cancellous bone, and resulted in increased bone strength (force to fracture) as compared to the vehicle control, OVX animals.

The effects of denosumab and alendronate on fracture healing were compared using genetically engineered, huRANKL knock-in mice. Animals were treated with either agent or the combination of both following fracture of the right rear femur, and the antemortem effects on fracture healing and clinical signs), as well as post-mortem evaluation of fracture callus by histologic examination and tensile strength were recorded. The results showed that both alendronate and denosumab treatment delayed the removal of cartilage and remodeling of the fracture callus, and resulted in a distinct morphology of healed bone relative to control huRANKL mice with fractured femurs. However, the mechanical strength of the resulting healed bone was not negatively affected. Treatment with either denosumab or alendronate induced increases in strength and stiffness relative to the nonfractured control or vehicle control group. Overall, fractures took greater time to repair when the huRANKL mice were treated with denosumab or alendronate, as compared to the vehicle control.

Overall, the nonclinical pharmacology data demonstrate that denosumab is able to prevent bone loss due to reductions of estrogen in the OVX monkeys, and while the healing of fractured bone is delayed as compared to untreated control groups, the tensile strength and structure of the healed bone are not negatively impacted by denosumab treatment. Taken together, these data support the hypothesis that denosumab may prevent bone loss in human breast cancer patients that are undergoing hormone ablation therapy with subsequent bone loss. These findings were appropriately captured and discussed in Dr. Orr's review.

General and reproductive toxicology studies were reviewed by Dr. Hatfield in her review for the original BLA STN#125320, and are only briefly summarized here. All toxicology studies were conducted in cynomolgus monkeys, due to the species specificity of denosumab for human and non-human primate RANK ligand. The major effects following denosumab treatment in studies of 1 to 12 months duration were inhibition of bone turnover and dose-dependent reductions in serum osteocalcitonin and N-telopeptide accompanied by increased bone mineral density, which were evident after doses of 5 to up to 50-fold the recommended human dose, on a mg/kg basis. These effects are consistent with the expected pharmacodynamic effects of denosumab, and as such were considered tolerable toxicities for the indicated patient populations with bone loss secondary to hormone ablation therapy in breast or prostate cancer. There were no other, off-target toxicities reported. These findings were appropriately captured and discussed in Dr. Hatfield's review.

Conclusions: I concur with Dr. Orr's assessment of the nonclinical pharmacology and pharmacokinetic data submitted with the original BLA application, his recommendations for labeling, and his conclusion that these data support the approval of denosumab for the treatment of bone loss in patients with prostate or breast cancer undergoing hormone ablation treatment. There are no outstanding nonclinical issues, and no additional nonclinical studies are recommended or required to support this indication.

ADDENDUM

At the request of the Associate Director for Pharmacology and Toxicology, Office of Oncology Drug Products, scientific rationale is being provided for the decision to report the comparative animal vs. human denosumab exposure in the labeling on a mg/kg basis, as opposed to reporting as the cumulative area under the curve (AUC) values. Following a single dose of denosumab, the calculated $AUC_{0-\tau}$ in cynomolgus monkeys at the highest dose level tested of 50 mg/kg was approximately 25-fold greater than the human AUC-τ value obtained for the 60 mg fixed dose. To extrapolate the exposure measures to the 6-month treatment duration, the sponsor initially calculated the nonclinical exposure using the calculated AUC0-τ after the last exposure in cynomolgus monkeys and multiplied it by 6, to account for the animals receiving 6 monthly injections, or by 26 for those animals treated by weekly injections, while the human subjects were treated only once every 6 months. The tables and summary data presented below were provided by Dr. Kimberly Hatfield, as an addendum to her review.

In brief, the following table represents the values that the sponsor used for calculation:

Study	Dose	Cmax 1st dose (µg/mL)	Cmax last dose (µg/mL)	$AUC_{0-\tau}$ 1st dose (µg*hr/mL)	$AUC_{0-\tau}$ last dose (µg*hr/mL)
102090	50 mg/kg	853	666	343000	268000
103981	50 mg/kg	336	413	139000	171000
102842	12.5 mg/kg	122	291	16700	41400
20010223	60 mg	7.93	6.94	12072	10752

The following table was presented by the sponsor in the nonclinical overview as to how the exposure multiples were calculated and is abstracted from Dr. Hatfield's review:

Table 2. Calculated Exposure Multiples for Denosumab for the Recommended Dosea Relative to the NOAEL in the Pivotal Toxicology Studies

Study Type	NOAEL (mg/kg)	Cmax[b] (µg/mL) Mean (SD)	AUC_{0-tau}[b] (µg*hr/mL) Mean (SD)	Exposure Multiple Based on AUC[c]
12-month repeated-dose in cynomolgus monkeys (102090)	50	666 (156)	268000 (90300)	150
16-month repeated-dose in cynomolgus monkeys (103981)	50	413 (160)	171000 (72400)	95
Embryo-fetal toxicity in cynomolgus monkeys (102842)	12.5	282 (89.6)	41000 (10600)	99

[a] 60 mg, subcutaneously, once every 6 months. [b] At the end of dosing. Details of the multiple dose toxicokinetics are discussed in Module 2.6.4, Section 8.2.2. [c] Human C_{max} and $AUC_{0-6\ month}$ values (6.94 µg/mL and 10752 µg·hr/mL) were derived from Study 20010223. To take into account the differences in dosing frequency, the AUC for a 6 month interval in monkeys was approximated by multiplying by 26 and 6 for weekly (Study 102842) and monthly (Studies 102090 and 103981) dosing, respectively.

AUC = area under the plasma drug concentration-time curve; C_{max} = maximum observed concentration; NOAEL = no observed adverse effect level.

As summarized in Dr. Hatfield's review, the sponsor then used the following calculations, using 'approximated' doses in monkeys to account for the differences in dosing frequency (AUC times 6 for monthly dosing, and AUC times 26 for weekly dosing, and compared to the AUC after 2nd dose in humans):

102090 AUC after 13th dose = 268000 µg*hr/mL
268000 * 6 = 1608000 µg*hr/mL
1608000 / 10752 = **150** (exposure multiple)

103981 AUC after 15th dose = 171000 µg*hr/mL
171000 * 6 = 1026000 µg*hr/mL
1026000 / 10752 = **95** (exposure multiple)

102842 AUC after 5th dose = 41000 µg*hr/mL
41000 * 26 = 1066000 µg*hr/mL
1066000 / 10752 = **99** (exposure multiple)

Using the same AUC values, but not using the sponsor's multiplication factors of 6 and 26, Dr. Hatfield calculated the following exposure multiples based on AUC after 1st and last doses:

102090 AUC after 1st dose = 343000 µg*hr/mL
343000 / 12072 = **28** (exposure multiple)

102090 AUC after last dose = 268000 µg*hr/mL
268000 / 10752 = **25** (exposure multiple)

103981 AUC after 1st dose = 139000 µg*hr/mL
139000 / 12072 = **11** (exposure multiple)

103981 AUC after last dose = 171000 µg*hr/mL
171000 / 10752 = **16** (exposure multiple)

102842 AUC after 1st dose = 16700 µg*hr/mL
16700 / 12072 = **1.3** (exposure multiple)

102842 AUC after last dose = 41000 µg*hr/mL
41000 / 10752 = 4 (exposure multiple)

These approximations were considered invalid by the nonclinical reviewers and supervisors in both DBOP and DRUP for a number of reasons, which are outlined here. Following consultation with the clinical pharmacology group, the nonclinical discipline was informed that in order to compare the clinical and nonclinical AUC values following a single dose, the calculations must be based on $AUC_{0-\infty}$, not $AUC_{0-\tau}$. The sponsor was requested to provide the values for $AUC_{0-\infty}$ for each study but was unable to do so, and therefore comparison of the AUC values was not considered a valid approach for presentation of the data in labeling. Additionally, the data presented in the tables above show that the exposure measures (C_{max} and $AUC_{0-\tau}$) after the final dose in the pivotal, 12-month repeat-dose nonclinical study #102090 are decreased by 22% as compared to the values obtained following the first dose. Animals in this study also exhibited a high rate of anti-drug antibody, or immunogenicity development, with 28/30 monkeys positive for anti-denosumab antibody at the end of treatment or recovery period. With this high level of

reported immunogenicity, it is likely that the actual exposure to denosumab in the nonclinical studies is underrepresented by the calculated AUC values.

Monoclonal antibodies exhibit a limited volume of distribution at steady state, and most frequently are confined to the plasma space with very little extravascular distribution noted. Conventionally, nonclinical and clinical dose comparisons are made strictly on a mg/kg basis, since the plasma volume scales to body weight (i.e. approximately 40-55 ml/kg), and is relatively consistent between human and test animal species. In the absence of the appropriate $AUC_{0-\infty}$ values following a single dose of denosumab and considering the high degree of immunogenicity observed in the pivotal nonclinical repeat-dose toxicology study, and following a discussion with the nonclinical team and the clinical pharmacologists from DRUP, it was decided that the most consistent way to determine the exposure multiple between humans and cynomolgus monkeys would be to base the calculation on straight mg/kg basis. Based on a 50 mg/kg dose in cynomolgus monkeys and the fixed 60 mg (approximately 1 mg/kg) dose in humans, the exposure multiple in the test animals is 50-fold greater relative to humans exposures. For reference purposes, if the calculations are based on body surface area only, the 50 mg/kg monkey dose is 16 times the 60 mg clinical dose. Either of these calculations provides a sufficient multiple of the clinical dose, and is recommended for use in labeling for the purpose of comparison of the nonclinical and clinical exposure data.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

STN BLA NUMBER:	**125332 and 125333**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**12/19/2008**
PRODUCT:	Prolia™ **(Denosumab)**
INDICATION:	Treatment of bone loss associated with hormone ablation therapy with breast cancer or treatment of bone loss associated with hormone ablation therapy in patients with prostate cancer
SPONSOR:	**Amgen, Incorporated**
DOCUMENTS REVIEWED:	**E-BLA Submission**
REVIEW DIVISION:	**Division of Biologic Oncology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Michael S. Orr, Ph.D., D.A.B.T.**
PHARM/TOX SUPERVISOR:	**Anne M. Pilaro, Ph.D.**
DIVISION DIRECTOR:	**Patricia Keegan, M.D.**
PROJECT MANAGER:	**Melanie Pierce**
DATE OF REVIEW COMPLETION:	September 9, 2009

Reference ID: 3168397

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The Biologic Licensing Applications BLA #125332/0 and 125333/0 are approvable based on the data contained in the preclinical pharmacology and toxicology sections of the original submission.

B. Recommendation for nonclinical studies

There are no recommendations at the present time for the sponsor to conduct and submit any additional nonclinical studies with denosumab, in support of either safety or efficacy.

C. Recommendations on labeling

Modifications to the Carcinogenicity, Mutagenicity, and Impairment of Fertility sections are being requested. These include revisions to of the sponsor's language and modifying the exposure level multiple, as this reviewer does not agree with the Sponsor's approach for calculating the multiple used in comparing exposure levels between cynomolgus monkeys and humans in the clinical trials. The requested labeling revisions are included as Appendix 1 to this review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Denosumab was evaluated for pharmacologic activity in cynomolgus monkeys, ovariectomized cynomolgus monkeys and in C57/B6 human RANKL knock-in mice. The genetically engineered mice knock-in mouse model was developed to study the pharmacology of denosumab *in vivo*, since denosumab does not bind or neutralize rodent (rat and mouse) RANKL. However, denosumab is able to bind to cynomolgus monkey RANKL and inhibit osteoclast bone resorption in the ovariectomized cynomolgus monkey model, providing evidence that the cynomolgus monkey was a pharmacologically relevant species in which to perform the pivotal repeat dose toxicology studies. Tissue cross-reactivity of denosumab was limited to the lymph node in human tissues, and lymph node, spleen and GALT in cynomolgus monkey and rabbit tissues.

In cynomolgus monkeys, denosumab had a half-life of approximately 11-19 days at the higher doses. When administered intravenously (IV), denosumab pharmacokinetics were non-linear from 0.0016-1 mg/kg, and were dose linear for doses ≥ 1 **mg/kg. Based on the volume of** distribution, denosumab remained in the vascular space following IV dosing. Similar to IV dosing, subcutaneous administration of denosumab resulted in non-linear pharmacokinetics for the dose ranges from 0.0016- 1 mg/kg, and dose proportional PK from 1-3 mg/kg. Mean residence time increased with dose while clearance decreased. Anti-drug antibody formation occurred at a high rate in monkeys dosed with denosumab by either the IV or SC routes of administration. In mice, a comparison between the subcutaneous (SC) and intravenous route of administration of 1 mg/kg showed that the serum concentration, regardless of the route of administration was similar between the 1 mg/kg SC and 1 mg/kg IV dose groups. The

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bioavailability of denosumab in mice was 86.1% following SC administration, as compared to the 1 mg/kg IV dose group.

In the 1-month repeat dose toxicology study, calcium (Ca) levels were significantly lower in males of the 1.0 (SC) and 10 (SC and IV) mg/kg groups relative to the control. The reductions in blood Ca levels were not observed in the female monkeys. The transient reductions in calcium were observed in 12-month pharmacology study as well.

In the 6-/12-month study, there did not appear to be any overt treatment-related toxicological findings that were not pharmacodynamic (PD)-related. Effects of Denosumab AMG 162 on bone were evidenced by a reduced rate of bone remodeling, reduced serum levels of osteocalcin, C-telopeptide and urine N-telopeptide, and increased BMD and BMC in both cortical and trabecular bone of the radius, tibia and femur. In the HD (50 mg/kg; SC) group, there were treatment-related deleterious changes in the epiphyseal growth plates that were not closed prior to treatment. Two HD males died while on treatment, which was determined to be the likely result of infection. There were some indications from this study that AMG 162 may be immunosuppressive due to the unexplained HD male deaths (i.e. possible impairment of the ability to control infection), abscesses of the teeth/jaw, and additional supportive data found in the literature. However, further literature review indicated that a clear association could not be established between AMG 162 treatment and definitive immunosuppression, and further nonclinical studies were not deemed necessary. In addition, unscheduled deaths due to infection were not observed in the 1-month repeat dose toxicology study, 12-month ovariectomized cynomolgus monkey (OVX) pharmacology, and 16 month OVX monkey pharmacology studies.

B. Pharmacologic activity

Denosumab is a fully human IgG_2 monoclonal antibody that binds to the receptor activator of nuclear factor-κB (RANK) ligand (RANKL). RANKL binds to RANK on osteoclast precursors and mature osteoclasts, stimulates osteoclasts to resorb bone, and promotes differentiation of the precursor cells into osteoblasts. Binding of denosumab to RANKL inhibits interaction of the ligand with target receptors such as RANK, thereby neutralizing the effects of RANKL. Since RANKL binding to RANK is involved with the formation, function, and survival of cells that resorb bone such as osteoclasts, the inhibition of RANKL binding to RANK by denosumab leads to the suppression in osteoclast-mediated bone turnover.

The nonclinical data provides evidence that denosumab is able to prevent bone loss due to reductions of estrogen in the OVX monkeys, and supports the hypothesis that denosumab may prevent bone loss in human breast cancer patients that are undergoing hormone ablation therapy with subsequent bone loss. In the 12-month pharmacology study in ovariectomized (OVX) monkeys, denosumab alone, denosumab in combination with alendronate pretreatment, and alendronate alone were able to induce significant reductions in biochemical markers of bone formation. Bone biomarkers remained elevated in the vehicle control ovariectomized female cynomolgus monkeys, and these animals developed mild osteopenia with increased bone turnover and loss of bone mass, based on bone densitometry measurements. OVX monkeys treated with denosumab alone, alendronate alone, and combination of alendronate pretreatment and denosumab showed increased BMD in the whole body, lumbar spine, tibial diaphysis, and radial cortical diaphysis, and prevented the OVX-induced BMD changes in both cortical and cancellous bone. In addition, bone strength was increased in the three respective treatment groups; denosumab alone, alendronate alone, and the combination of alendronate and denosumab. At least for the denosumab alone group, similar changes in bone turnover markers, BMD changes in

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cortical and cancellous bone were observed in an additional, 16-month study (Study # 103981; reviewed by Dr. Hatfield, and cross-referenced to her review of STN BLAs #125320 and #125331). Taken together, the data from two independent OVX cynomolgus monkey studies show that denosumab was able to prevent OVX induced BMD changes in both cortical and cancellous bone.

The comparison of alendronate and denosumab effects on murine fracture healing in the huRANKL genetically engineered knock-in mice provided evidence that both alendronate and denosumab treatment delayed the removal of cartilage and remodeling of the fracture callus, and resulted in a distinct morphology relative to the control mice with fractured femurs. However, the mechanical strength was not negatively affected. Treatment with either denosumab or alendronate induced increases in strength and stiffness relative to the nonfractured control or vehicle control group. Overall, fractures took greater time to repair when the huRANKL mice were treated with denosumab or alendronate, as compared to the vehicle control.

C. Nonclinical safety issues relevant to clinical use

Delayed Fracture Healing:
Overall, fractures took greater time to repair when the huRANKL mice were treated with denosumab or alendronate, as compared to the vehicle control.

Approximation of the exposure multiple:
The sponsor calculated nonclinical exposure multiples compared to human as 150 fold greater than the human exposure while basing the exposure multiple on just the AUC is 25 fold greater than the human exposure. This reviewer believes that the exposure level should be based on the AUC values without the inclusion of the approximation factor. Alternatively, the sponsor could base the total exposure in humans ($AUC_{0-\infty}$) versus total exposure in monkeys ($AUC_{0-\infty}$) as a method for determining the exposure multiple.

Comment: Following a discussion with Division of Reproductive and Urologic Products (DRUP), it was decided that the most consistent way to determine the exposure multiple between humans and monkeys would be to base the calculation on mg/kg basis. Based on a 50 mg/kg dose in monkeys and the 1 mg/kg dose in humans, the exposure multiple is 50 fold greater dose in the monkeys relative to humans.

Carcinogenicity:
No carcinogenicity studies were performed in this submission. In the three long term studies (12-month toxicity, 12-month pharmacology and 16-month pharmacology) in cynomolgus monkeys, there were no incidences of tumor formation detected. The only finding was in the 12-month study, where one LD and one HD female each exhibited squamous metaplasia (benign) in the uterus. No general organ histopathology was conducted for the 16-month study.

Nonclinical safety issues being addressed in the label and at the clinical level:
Other potential nonclinical safety issues being addressed at the clinical level include the potential immune modulations and increased susceptibility to infections, transient calcium reductions following denosumab dosing, and exclusion of pediatric populations due to reproductive and development issues secondary to the pharmacologic action of denosumab. Furthermore, denosumab should not be used in pregnant women or women who are breast feeding due to the potential development issues. These include absence of lactation due to impaired mammary

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gland development, impaired B cell and osteoclast development, defective tooth eruption, absence of lymph nodes, and severe osteoporosis. These findings are of concern as they were either seen in knock-out mice, or are reported as pharmacologic effects of the inhibition of the RANK/RANKL signaling pathway.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

BLA number: 125332/0 and 125333/0
Review number: 1
Sequence number/date/type of submission: 000/12-19-2008/original licensing application
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Amgen Incorporated, One Amgen Center Drive, Thousand Oaks, CA, 91320-1799
Manufacturer for drug substance:

Site 1: Boehringer Ingelheim Pharma, GmbH & Co. Kg, Birkendorfer Strasse 65 88397 Biberach an der Riss, Germany
Site 2: Amgen Inc., 5550 Airport Boulevard, Boulder, CO 80301
Site 3: Amgen Inc., 4000 Nelson Rd, Longmont, CO 80503
Site 4: Amgen Manufacturing Limited, State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777

Reviewer name: Michael S. Orr, Ph.D., D.A.B.T.
Division name: Division of Biologic Oncology Products
HFD #: 107
Review completion date: August 10, 2009

Drug:

Trade name: Prolia™
Generic name: Denosumab
Code name: AMG-162
Chemical name: Immunoglobulin G2 Human Monoclonal Antibody to RANK Ligand
CAS registry number: 615258-40-7
Molecular formula/molecular weight: Molecular formula for denosumab light chain (b) (4) and heavy chain isoform without N-linked glycans is (b) (4) The most prevalent glycan moiety (b) (4) (b) (4) Denosumab has a molecular weight of 147,352 Da.

Structure: Denosumab is a full-length human monoclonal antibody of the IgG2 subclass, consisting of 2 heavy chains and two light chains of the kappa subclass, which are covalently linked through 18 disulfide bonds. Denosumab contains 36 total cysteine

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residues, which are involved with intrachain and interchain disulfide bonds. Each heavy chain contains an N-linked glycan at the consensus glycosylation site at asparagine 298. Each light chain contains 215 amino acids with 2 intramolecular disulfides. Each heavy chain contains 448 amino acids with 4 intramolecular disulfides.

Schematic of Denosumab Structure provided by Amgen:



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Table 1. Physical and Chemical Properties of Denosumab

(b) (4)

[redacted]

Relevant INDs/NDAs/DMFs:

BB-IND 9837 – initial IND – DRUP – treatment of postmenopausal osteoporosis
BB-IND 9838 – DBOP – treatment of bone disease associated with cancer
BB-IND 11709 – DBOP – treatment of sex hormone ablation bone loss associated with aromatase inhibitors in patients with breast or prostate cancer
BB-IND 11707 – DAARP – treatment of bony erosions, osteoporesis, and osteopenia associated rheumatoid arthritis

(b) (4)

[redacted]

Drug class: Prolia™ is a receptor activator of nuclear factor kappa B (RANK) Ligand inhibitor

Intended clinical population: Denosumab is indicated for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer.

Clinical formulation: 60 mg/ml denosumab, 10 mM sodium acetate, 5% (w/v) sorbitol, and 0.01% (w/v) polysorbate 20, at a pH of 5.2

Route and schedule of administration: subcutaneous injection of 60 mg denosumab once every 6 months

Disclaimer: Tabular and graphical information are provided by Amgen Inc., unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of BLA 125332/0 and 125333/0 are owned by Amgen Inc., are from studies published in the open literature, or are data for which Amgen Inc. has obtained a written right of reference

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Studies reviewed within this submission:

Studies reviewed by Michael Orr, Ph.D. (DBOP Toxicologist)

Pharmacology:

106564 – A 12-month osteoporosis prevention study of denosumab with and without 6-month alendronate pretreatment in the cynomolgus monkey

R2006458 – Comparison of two anti-resorptive therapies (alendronate versus AMG-162 monoclonal anti-RANKL antibody) on murine fracture healing

101606 – A single-dose subcutaneous administration of AMG-162 for cardiovascular and respiratory evaluation in cynomolgus monkeys

Pharmacokinetics:

101494 – Pharmacokinetic study of denosumab (AMG-162) in male mice following intravenous or subcutaneous administration

106893 – A single dose pharmacokinetics study of denosumab (AMG-162) following intravenous administration to male or female FcRn knockout and wild type mice

104105 – Quantitative whole body autoradiography of cynomolgus monkeys following a single subcutaneous administration of ^{125}I-AMG-162.

101758 – Cross-reactivity of AMG-162 with normal cynomolgus monkey and human tissues

101348 – Cross-reactivity of AMG-162 with normal human tissues

102700 – Cross-reactivity of AMG-162 with cynomolgus monkey, rat, and rabbit tissue ex vivo

Toxicology:

101447 – A 1-month study evaluating the effect on bone of AMG-162 administered subcutaneously or intravenously in cynomolgus monkeys with a 3-month recovery period

Studies reviewed by Ronald Wange, Ph.D. (DMEP Toxicologist)

Toxicology:

102090 – A 6/12-month subcutaneous toxicity study of AMG-162 in the cynomolgus monkey with an interim kill after 6 months and a 3-month recovery period

102842 – Subcutaneous embryo-fetal development study of AMG-162 in the cynomolgus monkey

Studies reviewed by Kimberly Hatfield, Ph.D. (DRUP Toxicologist)

Pharmacology:

R2004430 – Effects of denosumab (AMG-162) on bone mass and bone resorption in human RANKL knock-in mice

R2004321 – Effects of denosumab (AMG-162) on bone mass and bone resorption in aged human RANK ligand knock-in mice

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R2006351 – Denosumab, a fully human monoclonal antibody, has selective effects on human RANK ligand and human osteoclasts
103981 – AMG-162: A monthly subcutaneous injection osteoporosis prevention study for 16 months in the cynomolgus monkey
R20080340 – The effects of OPG-Fc, RANK-Fc, or alendronate on tooth eruption and on bone density, geometry, and strength in neonatal rats

Pharmacokinetics:

106892 – Pharmacokinetics report for "A single dose pharmacokinetics study of denosumab (AMG-162) following intravenous administration to male or female huRANKL knock-in and wild-type mice
101398 – A single-dose intravenous and subcutaneous pharmacokinetic and pharmacodynamic study of AMG-162 in cynomolgus monkeys
103948 – Pharmacokinetic and pharmacodynamic comparability study for two manufacturing processes of AMG-162 in female cynomolgus monkeys

Toxicology:

102843 – Subcutaneous fertility evaluation of AMG-162 in the female cynomolgus monkey

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Pharmacology studies evaluated the activity of denosumab (AMG-162) in ovariectomized female cynomolgus monkeys with and without alendronate pretreatment. A single dose safety pharmacology study evaluating the effects of denosumab on cardiovascular and respiratory parameters was also performed. A unique safety pharmacology study was conducted that utilized the huRANKL knock-in mice and WT mice to compare the effects of denosumab and alendronate on fracture healing, in order to determine if denosumab was capable of interfering with the normal fracture healing process. The development of the huRANKL knock-in mice model was necessary because *in vitro* binding and activity studies with denosumab indicated that AMG-162 did not bind to murine RANKL, and lacked pharmacologic activity in rodents. In the 12-month pharmacology study in ovariectomized (OVX) monkeys, denosumab alone, denosumab in combination with alendronate pretreatment, and alendronate alone were able to induce significant reductions in biochemical markers of bone formation (serum osteocalcin; sALP (bone specific alkaline phosphatase) and resorption (CTx, serum C-telopeptide). Bone biomarkers remained elevated in the OVX vehicle control female cynomolgus monkeys, and these animals developed mild osteopenia with increased bone turnover and loss of bone mass, based on bone densitometry measurements. Treatment with denosumab resulted in transient reductions in serum calcium following subcutaneous administration. OVX monkeys treated with denosumab alone, alendronate alone, and combination of alendronate pretreatment and denosumab showed increased BMD in the whole body, lumbar spine, tibial diaphysis, and radial cortical diaphysis. In OVX cynomolgus monkeys, treatment with denosumab alone, alendronate alone, or the

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combination prevented the OVX-induced BMD changes in both cortical and cancellous bone, and bone strength was increased by the three respective treatments. At least for the denosumab alone group, similar changes in bone turnover markers, BMD changes in coritical and cancellous bone were observed in an additional, 16-month study (Study # 103981; this study was reviewed by Dr. Hatfield, and is cross-referenced to her review of STN BLAs #125320 and #125331). Taken together, these data from two independent OVX cynomolgus monkey studies show that denosumab was able to prevent OVX induced BMD changes in both cortical and cancellous bone. The nonclinical data provides evidence that denosumab is able to prevent bone loss due to reductions of estrogen in the OVX monkeys, and supports the hypothesis that denosumab may prevent bone loss in human breast cancer patients that are undergoing hormone ablation therapy with subsequent bone loss.

The safety pharmacology study in male cynomolgus monkeys was performed to evaluate cardiovascular and respiratory parameters following a single subcutaneous administration of denosumab. In the mid-dose group (3 mg/kg), 1/3 monkeys had a run of four ventricular premature complexes, which returned to normal for rest of the 7 days following the single dose administration. The toxicological significance of this finding is unknown at this time, as it only occurred in 1/12 monkeys in the study and there were no dose dependent effects observed. Furthermore, this cardiovascular effect was not observed in the 1 month (Study # 101447) and 6/12 month (Study # 102090) subcutaneous repeat dose toxicology studies, in which denosumab plasma levels were able to reach steady state and potentially allow deep tissue exposure to the test article. The comparison of alendronate and denosumab effects on murine fracture healing in the huRANKL genetically engineered knock-in mice provided evidence that both alendronate and denosumab treatment delayed the removal of cartilage and remodeling of the fracture callus, and resulted in a distinct morphology relative to the control mice with fractured femurs. However, the mechanical strength was not negatively affected. Treatment with either denosumab or alendronate induced increases in strength and stiffness relative to the nonfractured control or vehicle control group. Overall, fractures took greater time to repair when the huRANKL mice were treated with denosumab or alendronate, as compared to the vehicle control. Patients with new and/or healing fractures should consider starting denosumab treatment once the fracture has healed, as denosumab delays fracture repair.

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

Denosumab is a fully human IgG_2 monoclonal antibody that binds to the receptor activator of nuclear factor-**κB (RANK) ligand (RANKL).** RANKL binds to RANK on osteoclast precursors and mature osteoclasts, stimulates osteoclasts to resorb bone, and promotes differentiation of the precursor cells into osteoblasts. The binding of denosumab to RANKL inhibits binding of the ligand to target receptors such as RANK, thereby neutralizing the effects of RANKL. Since RANKL binding to RANK is involved with the formation, function, and survival of cells that resorb bone such as osteoclasts,

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the inhibition of RANKL binding to RANK by denosumab leads to the suppression in osteoclast-mediated bone turnover.

Drug activity related to proposed indication:

Study title: A 12-Month Osteoporosis Prevention Study of Denosumab With and Without a 6-Month Alendronate Pretreatment in the Cynomolgus Monkey

Key findings:

- Denosumab exposure based on C_{max} and AUC was maintained during the duration of the study, but 25/32 (~78%) monkeys developed anti-drug antibodies (ADA). In the monkeys positive for ADA, 7/32 tested positive for neutralizing antibodies. The development of ADA corresponded with approximately 50% reduction in denosumab exposure based on AUC as compared to animals that were antibody negative.
- The estrogen depletion in monkeys following ovariectomy (OVX) resulted in mild osteopenia, based on loss of bone mass as measured by bone densitometry with DXA or pQCT. In addition, increases were observed in the biochemical markers of bone turnover during the 12 month duration of the study.
- Denosumab treatment increased bone mineral density (BMD) in the whole body by 4% following 6 months of dosing and 7% after 12 months of dosing relative to the OVX vehicle controls. Pretreatment with alendronate and subsequent treatment with denosumab resulted in whole body BMD increases of 3.6% at 6 months, and 1.5% at 12 months as compared to baseline.
- Denosumab treatment increased BMD and significantly increased bone strength at the lumbar spine, based on bone densitometry and biomechanical tests.
- Denosumab treatment increased BMD in trabecular and cortical bone mass at the lumbar spine (5% at 6 months and 8.5% at 12 months), femur (1.6% and 8.7%), proximal tibia and distal radius (1% and 4%), respectively, based on bone densitometry measurements by either DXA or pQCT evaluation.
- Alendronate (Fosamax, ALN) treatment, which is currently approved for osteoporosis treatment increased the BMD in the lumbar spine (5.8% at 6 months and 5.5% at 12 months), proximal femur (6.5% and 4.2%), and central tibia (1.6% and 1.3%).
- Pretreatment with alendronate followed by denosumab treatment induced similar increases in BMD as was observed in the denosumab-only treated group. Furthermore, the reductions in biochemical biomarkers of bone turnover in the combination of alendronate and denosumab treatment group were greater than alendronate treatment group alone.
- There were significant reductions in biochemical markers of bone turnover such as C-telopeptide, TRAP-5b, sALP, and osteocalcin (OC) relative to both baseline

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and the ovariectomized vehicle control monkeys, providing evidence to support the sponsor's hypothesis that denosumab treatment is inhibiting bone resorption. Alendronate induced a less robust reduction in the bone biomarkers as compared to the denosumab and denosumab in combination with alendronate pretreatment dose groups.

- Histomorphometry evaluation provided evidence that both alendronate and denosumab treatment were associated with significant decreases in tissue-level bone resorptions/formation parameters in cortical and trabecular sites. Specifically, denosumab prevented bone resorption, formation and turnover parameters in the ilia, L2, rib (6 and 12 months), tibial diaphysis and proximal tibia as compared to the OVX vehicle controls.
- Significant increases in PTH (Parathyroid Hormone) were noted following the first dose of denosumab in treatment-naïve monkeys, and the PTH remained elevated during the first 6 months of treatment. The PTH levels were reduced to control or baseline levels during the last 6-months of the 12-month treatment period.
- Treatment with denosumab induced a statistically significant decrease (4.5-15% reduction) in serum calcium for up to 14-28 days post dose relative to baseline or vehicle control levels.

Study #: (b) (4) Amgen Study # 106564

Volume # and Page #: EDR file
Conducting Laboratory and Location: (b) (4)

Date of Study Initiation: not specified (final report dated July 9, 2008)
GLP Compliance: yes
QAU statement: yes (X) no ( )
Drug Lot #: 049A053686 (denosumab), 124K4712 (alendronate), 049A022940 (denosumab vehicle)

Methods: The objectives of this study were to investigate the effects of a pretreatment of ovariectomized (OVX) cynomolgus monkeys (*Macaca fascicularis*; weight range 3.3 to 5.9 kg) with bi-weekly dosing with Alendronate for 6 months, followed by once monthly subcutaneous injections of denosumab on the bone mineral density (BMD), serum calcium, phosphorous levels, bone markers, pharmacokinetics, and immunogenicity of the test articles.

Dosing Procedure:
The vehicle and denosumab were administered by subcutaneous injection once every 28 days. For the group 1 animals (denosumab vehicle), a total of 12 does were subcutaneously administered once every 28 days and the animals also received 24 doses of PBS administered intravenously once every 14 days.

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For group 2 (vehicle + denosumab), for the first 6 months of the study, this group of animals were subcutaneously administered a total of 6 doses of vehicle (vehicle for denosumab) once every 28 days. A single dose level of denosumab at 25 mg/kg was used in this study, and the monkeys were dosed s/c every 28 days for an additional 6 months. The animals in group two also received 24 doses of PBS (vehicle for alendronate) administered intravenously once every 14 days during the study.

Group 3 animals received a total of 24 doses of alendronate, administered intravenously once every 14 days. The dose level of 50 mcg/kg alendronate was the effective dose used in previous primate studies.[1]

For group 4, the animals received a total of 12 doses of alendronate administered intravenously once every 14 days. Following 6 months of dosing with alendronate, group 4 monkeys then received 6 doses of denosumab administered subcutaneously once every 28 days, and received 12 doses of phosphate buffered saline intravenously once every 14 days, starting with the first dose of denosumab on Day 169.

The group 5 animals were subcutaneously administered 12 doses of denosumab once every 28 days for 1 year. The monkeys in group 5 also received 24 doses of phosphate buffered saline once every 14 days starting on Day 1. Animals were euthanized 14 days following last dose.

Comment: The dose level of denosumab tested in this study was 25 mg/kg, administered every 28 days for 6 months, while a dose of approximately 1 mg/kg denosumab administered every 6 months was used in the clinical study. The bi-weekly dose of alendronate provided an approximately 3.5-fold exposure margin compared to the weekly clinical dose (70 mg/week, PO; assuming 0.64% bioavailability as per Fosamax label, and a 60 kg patient).

The following parameters were evaluated in the study: clinical signs, menstrual regularity, body weight, appetence, hematology, clinical biochemistry, urinalysis, hormones, biochemical markers of bone turnover, bone densitometry (DXA, pQCT), radiographs, pharmacokinetics, immunogenicity, macroscopic observations at necropsy, organ weights, histopathology, histomorphometry, micro CT evaluation, and biomechanical testing.

Serum Bone Formation Markers: Osteocalcin, Bone specific alkaline phosphatase (sALP)

Serum Bone Resorption Marker: C-telopeptide (CTx), TRAP-5b

[1] Balena R, Toolan BC, Shea M. The effects of 2-year treatment with the aminobisphosphonate alendronate on bone metabolism, bone histomorphometry, and bone strength in ovariectomized nonhuman primates. *J.Clin. Invest.* 1993; 92:2577-2586

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Dose Group Number Reference:

Group Number	Phase I: (Dose 1 to 6)	Phase II: (Dose 7 to 12)
1	Vehicle	Vehicle
2	Vehicle	Denosumab
3	ALN	ALN
4	ALN	Denosumab
5	Denosumab	Denosumab

Blood Collection Time points:

Text Table 5 - Blood Collection Time Points

	Base-line 1	Base-Line 2	Dose 1					Dose 2	Dose 3	Dose 4	Dose 7					Dose 8	Dose 10	Term
			Pre	24	72	168	336	Pre	Pre	Pre	Pre	24	72	168	336	Post	Pre	
Urine	X																	
Hematology	X	X																
Clinical Chemistry	X	X																
Selected Clinical Chemistry			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hormones																		
PTH	X	X	X	X	X	X		X		X	X	X	X	X			X	X
1,25-VIT D	X	X	X							X								
25-OH VIT D	X	X	X							X								
Estradiol	X	X	X							X	X						X	X
Biomarkers																		
Osteocalcin	X	X	X							X	X						X	X
sALP	X	X	X							X	X						X	X
CTx	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
TRACP-5b	X	X	X							X	X						X	X

Pre - predose
1,25-VIT D - 1,25-dihydroxyvitamin D
25-OH VIT D - 25-hydroxyvitamin D

Dual Energy X-Ray Absorptiometry (DXA):

DXA is used to measure bone mineral density (BMD), BMC (Bone mineral content) and area using the Hologic Discovery A bone densitometer.

Scan site	Scan Type	Scan Mode	Analysis Method	Reporting
Whole Body	Infant Whole Body	Array	Infant Whole Body	Global BMD
AP Lumbar Spine	AP Spine	Array	Lumbar Spine (L1-L4)	Total BMD
Right Prox. Tibia	Left Forearm	Array	Left Forearm	Distal (1/3) BMD
Right Prox. Femur	Right Hip	Array	Subregion Array Hip	Global BMD, Neck (R1), BMD, Trochanter (R2) BMD
Right Dist. Radius	Right Forearm	Array	Right forearm	Total, Distal (1/3) BMD, ultra distal (UD) BMD

* Whole body area, BMC and BMD reported for acclimation/baseline occasion only.

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Peripheral Quantitative Computed Tomography (pQCT):

Peripheral QCT was performed on all animals. Scans were acquired once during the acclimation/baseline period and once following doses 3, 6, and 12 during treatment.

Radiographs:

Radiographs of both radii (caudo-cranial views), both femora (caudo-cranial views), both tibia (medio-lateral views) and the lumbar and thoracic spine (dorso-ventral and lateral views), were taken once during the acclimation/baseline period, and at the end of the treatment period.

Bone Tissues at Necropsy:

On completion of the necropsy of each animal examined during or at the end of the treatment period, the following bone samples were retained:

Bone	Histomorphometry	Biomechanics
Femur	-	Left whole
Tibia	Right proximal and middle	-
Lumbar vertebrae	L2	L3, L4, L5, L6
Ilium	Left	-
Rib	Left 7th	-
Back-up bones:		
Femur	Right, proximal and middle	-
Tibia	Left, proximal and middle	-
Thoracic vertebrae	T10	L1, T11, T12
Mandible (bisected)	Right half	Left half *
Humerus	Right	Left*
Radius	Right	Left*

* - Ultimate use to be documented and maintained in study file.

Histomorphometry:

Sections of right ilium and rib biopsy samples collected after Dose 6, as well as sections of the left ilium, left 7th rib, lumbar vertebra (L2), and right tibia from each euthanized animal at the end of the treatment period were prepared for all groups, without decalcification, for histomorphometric evaluation. The thoracic vertebra T10, left proximal and middle tibia, right proximal and middle femur, right half mandible, right humerus and right radius were retained and stored in fixative for possible future analyses. Shortly after bone biopsy or necropsy, the bones were trimmed using a diamond cutting saw to expose the bone marrow and placed immediately into 10 % neutral buffered formalin, then transferred to 70% alcohol. Specimens processed included medially and frontally cut tissue blocks through the L2 vertebral body and proximal tibia, respectively. For the ilium specimens, two parallel slices were cut at the vicinity of the cortical dorsal spine, starting approximately 1.0 cm caudal to the spine. For the rib specimens, transverse sections were taken from the middle of each specimen. At least one block from each bone was dehydrated then infiltrated and embedded in methyl-methacrylate (MMA). Unstained sections were cut and ground for evaluation of cortical bone. Sections stained

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with toluidine blue and Goldner's trichrome stain, as well as unstained sections were prepared to evaluate the cancellous bone.

Reference Terms Key for results section:

Evaluation of the cancellous bone region was done on the proximal tibia (1 section level), ilium (biopsies and terminally sampled specimens, 2 section levels) and lumbar vertebra (1 section level). The following static and dynamic parameters of bone were reported using a BIOQUANT/TCW image analyzer:

STRUCTURAL	DYNAMIC
Tissue area (T.Ar)	Mineralizing surface (MS/BS)
Bone volume (BV/TV)	Single label surface (sLS/BS)
Mineralized volume (Md.V/TV)	Double label surface (dLS/BS)
Osteoid volume (OV/BV)	Mineral apposition rate (MAR)
Osteoid thickness (O.Th)	Adjusted apposition rate (Aj.AR)
Trabecular thickness (Tb.Th)	Osteoid maturation rate (Omt)
Trabecular number (Tb.N)	Mineralization lag time (Mlt)
Trabecular separation (Tb.Sp)	BFR*, surface referent (BFR/BS)
Osteoblast surface (Ob.S/BS)	BFR*, volume referent (BFR/BV)
Osteoclast surface(Oc.S/BS)	Activation frequency (Ac.F)
Osteoclast number (N.Oc/BS)	Formation period (FP)
Eroded surface (ES/BS)	Resorption period (Rs.P)
Osteoid surface (OS/BS)	
Wall thickness (W.Th)	

*BFR: Bone Formation Rate

Evaluation of cortical bone was done on the right mid tibia and ribs (biopsies and terminally sampled specimens), using two section levels per bone (one section level for Haversian system of right mid tibia). The following static and dynamic parameters of bone were reported using a BIOQUANT/TCW image analyzer:

STRUCTURAL	DYNAMIC
Total tissue area (Tt.T.AR)	Periosteal single label surface (Ps.sL.Pm/Ps.Pm)
Cortical area (Ct.Ar)	Periosteal double label surface (Ps.dL.Pm/Ps.Pm)
Medullary area (Me. Ar)	Periosteal labelled surface (Ps.L.Pm/Ps.Pm)
Cortical area, relative (%Ct.Ar)	Periosteal MAR (Ps.MAR)
Medullary area, relative (%Me.Ar)	Periosteal BFR, surface referent (Ps.BFR/BS)
Cortical width (Ct.Wi)	Endocortical single label surface (Ec.sL.Pm/Ec.Pm)
Periosteal perimeter (Ps.Pm)	Endocortical double label surface (Ec.dL.Pm/Ec.Pm)
Endocortical perimeter (Ec.Pm)	Endocortical labelled surface (Ec.L.Pm/Ec.Pm)
Percent porosity area (%Po.Ar)	Endocortical mineral apposition rate (Ec.MAR)
Haversian wall thickness (H.W.Th)	Endocortical BFR, surface referent (Ec.BFR/BS)
	Haversian single label surface (H.sL.Pm/H.Pm)
	Haversian double label surface (H.dL.Pm/H.Pm)
	Haversian labelled surface (H.L.Pm/H.Pm)
	Haversian mineral apposition rate (H.MAR)
	Haversian BFR, surface referent (H.BFR/BS)
	Haversian BFR, volume referent (H.BFR/BV)

MicroCT Scanning and Evaluation:

The right femur from all animals was scanned using a Micro-CT system, and analyzed using the 3-D morphometry evaluation program by the Sponsor. The scans were done in the fixative (70% denatured alcohol).

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Biochemical Testing:

Testing was performed for each animal euthanized at the end of the treatment period, using an MTS Servohydraulic test system, model 242.03, using TestWorks™ version 3.8A for TestStar® software version 4.0C. The following bone samples were cleaned of excess tissue and muscle and retained frozen (ca -20°C) at necropsy for each animal euthanized as scheduled or prior to the end of the treatment period:

vertebrae (L3, L4, L5 and L6)
left whole femur
vertebra L1, T11, T12 - back-up

The bones that were evaluated and tests that were performed are listed below:

Bone Specimen	Test Type	Test Rate	Results Reported
Left femur (shaft)	3-point bending	1 mm/sec	Peak load, Ultimate Stress, Stiffness, Modulus, Energy to Break (area under the curve), Toughness
	pQCT		Cross Sectional Moment of Inertia (IX-CRT-A) Area Periosteal circumference (PERI) BMC (CRT-CNT), BMD (CRT-DEN) Cortical Area (CRT_A), Cortical Thickness (CRT_THICK), Endosteal circumference (ENDO_C)
	DXA		Area, BMC, BMD
Left proximal femur	Femoral neck shear	1 mm/sec	Peak load, Stiffness Energy to Break (area under the curve)
	DXA		Area, BMC, BMD
L3, L4 vertebrae	Compression	20 mm/min	Peak Load, Apparent strength, Yield Load, Yield Stress, Stiffness, Modulus, Energy to Break (area under the curve), Toughness
	Measurement by caliper		Height
	DXA		Area, BMC, BMD
	pQCT		Area (TOT_A), BMC (TOT_CNT), BMD (TOT_DEN), Area (TRAB_A), BMC (TRAB_CNT), BMD (TRAB_DEN)
L5, L6 vertebral core	Trabecular Core Compression	20 mm/min	Peak Load, Ultimate Stress, Yield Load, Yield Stress, Stiffness, Modulus, Energy to Break (area under the curve), Toughness
	Measurement by Caliper		Height
	DXA		Area, BMC, BMD
	pQCT		Area (TOT_A), BMC (TOT_CNT), BMD (TOT_DEN)

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Results for Study 106564:

Mortality: There were no unscheduled deaths during this study.

Clinical Observations: There were no clinical signs associated with the treatments during the course of this study. No compound related histological changes were identified at the injection sites of the monkeys.

Food consumption: Nothing noteworthy

Opthalmoscopy: Not investigated

EKG: Not investigated

Body weights: There were no treatment related changes in the body weights.

Hematology: Not investigated

Dose Group Numbers for Reference:

Group Number	Phase I: (Dose 1 to 6)	Phase II: (Dose 7 to 12)
1	Vehicle	Vehicle
2	Vehicle	Denosumab
3	ALN	ALN
4	ALN	Denosumab
5	Denosumab	Denosumab

Efficacy End-point Results:

Results from Study 106564- Serum Calcium Levels: There was a statistically significant, transient reduction in serum calcium relative to the vehicle controls observed following the first and second dose of denosumab (see Figure 6 below). The transient reduction in serum calcium was even more pronounced in the cohort previously treated with vehicle as the first dose. Alendronate displayed a trend for reductions in serum calcium levels; however, the reductions observed in the alendronate (dose 1) and alendronate (dose 2) cohorts were not statistically significant, except for the 7 day time point. The reduction in serum calcium by denosumab was diminished in animals previously exposed to denosumab, (i.e. first versus second dose of denosumab). The serum calcium levels returned to baseline levels approximately three to five weeks following the initial dose and the second (transition) dose of denosumab (see Figure 6 below, from the sponsor's final study report).

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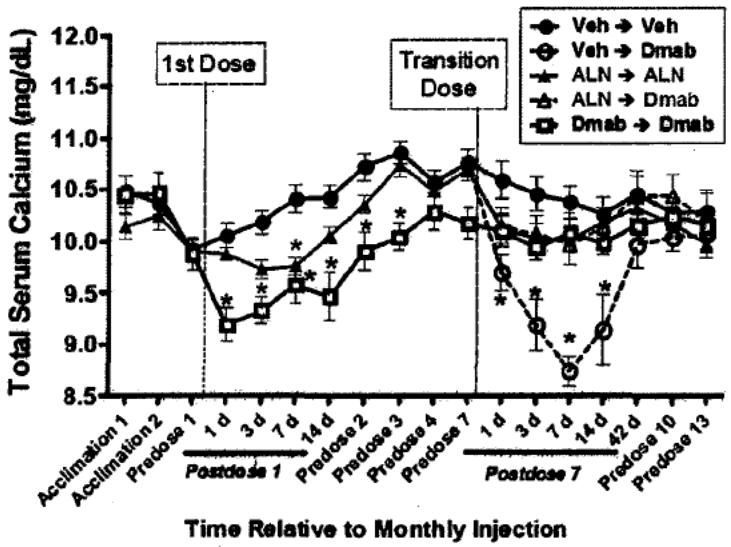
Figure 6. Total Serum Calcium in OVX Cynomolgus Monkeys Treated With Denosumab With and Without 6 Months of Alendronate Pretreatment



Serum calcium was assessed before and after therapeutic transition from vehicle (Veh) or alendronate (ALN) to denosumab (Dmab) at month 6. Time is expressed relative to the monthly injections such that Predose 1, 2, 3, 4, 7, 10, and 13 refer to samples drawn at baseline and after 1, 2, 3, 6, 9, and 12 months of treatment, respectively. Data are presented as the mean ± SE, n = 7 to 10/group. *$p \le 0.05$ vs Veh→Veh. Prior to the transition dose, group differences in baseline-adjusted serum calcium between the 3 treated groups (vehicle, alendronate, and denosumab) were assessed using an ANOVA followed by contrast pairwise post-tests. From the transition dose to termination, group differences in pre-transition-adjusted serum calcium were assessed across all 5 treatment groups and Tukey's pairwise comparisons were performed. No significant differences were found between continued alendronate treatment (ALN→ALN) and transition from ALN to denosumab (ALN→Dmab), significant differences between Veh→Dmab and ALN→Dmab or Dmab→Dmab were found but are not shown. Equal variance across groups was assessed using Levene's tests; rank-transformation was used to equalize variance if $p \le 0.05$. If variance remained unequal, an ANOVA model accounting for unequal variance was utilized.

Source: Study Report No. 106564

Results from Study 106564- Biomarkers of Bone Turnover: After ovariectomy of female cynomolgus monkeys, the serum biomarkers of bone formation and resorption were elevated from baseline for animals in the vehicle control group. Both alendronate and denosumab treatments significantly reduced the levels of these biomarkers (i.e. bone resorption and formation) during this 12-month pharmacology study, as shown in Figure 7. As shown in Table 6, the percent change was calculated relative to predose levels of the bone biomarkers; there was an 87% reduction in CTx, a 73% reduction in TRACP-5b, a 60% reduction in sALP, and a 57% reduction in OC at the end of phase I treatment with denosumab relative to the vehicle controls. Alendronate alone reduced the levels of CTx (39%), TRACP-5b (23%), sALP (37%), and OC (18%) relative to the vehicle controls, at the end of phase I treatment. Similar reductions in the bone biomarkers were observed at the end of phase II of the study in both the denosumab and alendronate treated monkeys (see Text Table 6).

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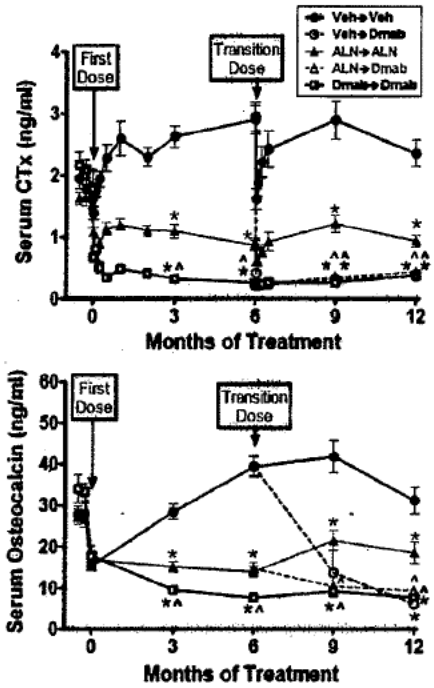
Figure 7. Biomarkers of Bone Turnover in OVX Cynomolgus Monkeys Treated With Denosumab With and Without 6 Months of Alendronate Pretreatment



Serum CTx (resorption marker, upper panel) and serum osteocalcin (formation marker, lower panel). Therapeutic transition occurred at month 6, Data are presented as the mean ± SE, n = 7 to 10/group. *p ≤ 0.05 vs Veh→Veh and ^p ≤ 0.05 vs ALN→ALN; for CTx, statistics are shown only for the month 3, 6, 9, and 12 timepoints. One way ANOVA was performed across all groups, with Tukey's post-tests for the changes from baseline in the Veh, ALN, and Dmab 12-month treatment groups. For the transition groups after 6 months, additional Tukey's post-test comparisons (Veh→Veh vs. Veh→Dmab and ALN→ALN vs ALN→Dmab) were performed to examine biomarker changes from the pre-transition timepoint. Equal variance across groups was assessed using Levene's tests; rank-transformation was used to equalize variance if p ≤ 0.05. If variance remained unequal, an ANOVA model accounting for unequal variance was utilized.

Source: Study Report No. 106564

Text Table 6 Percent (%) Change in Biochemical Markers of Bone Turnover

	% Change Relative to Predose 1						% Change Relative to End Phase I				
	End Phase I			End Phase II			End Phase II				
Rx Phase II				Veh (1)	ALN (3)	Denosumab (5)	Veh (1)	Denosumab (2)	ALN (3)	Denosumab (4)	Denosumab (5)
Rx Phase I	Veh (1)	ALN (3)	Denosumab (5)	Veh (1)	ALN (3)	Denosumab (5)	Veh (1)	Veh (2)	ALN (3)	ALN (4)	Denosumab (5)
CTx	+54	-39	-87	+47	-35	-78	-4	-90	+7	-51	+64*
TRACP-5b	+45	-23	-73	+12	-33	-60	-23	-77	-12	-54	+47*
sALP	+31	-37	-60	+39	-25	-63	+6	-75	+19	-26	-7
OC	+131	-18	-57	+74	+1.4	-56	-24	-83	+24	-35	+1.8

Rx (treatment) for Phase I and II, group number in parentheses.

% change calculated using group mean values.

* Note negligible change in very low absolute values becomes a large percent change.

Veh: Vehicle

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Results from Study 106564- In Vivo Densitometry: Denosumab treatment of OVX cynomolgus monkeys with and without 6 months of alendronate pretreatment induced statistically significant increases in the whole body bone mineral density (BMD), lumbar spine BMD, and radial diaphysis cortical BMD, proximal tibial metaphysis BMC, and radial diaphysis cortical BMD. Denosumab alone was unable to increase the tibial diapysis cortical BMD following 6 months of weekly subcutaneous injections. Overall, data from the female OVX cynomolgus monkeys shows that denosumab treatment prevents the reduction of BMD in the whole body, and in specific bone areas such as the lumbar spine, tibial diaphysis cortical, and radial diaphysis cortical bones, based on *in vivo* densitometry of female OVX cynomolgus monkeys treated with and without 6 months of alendronate pretreatment.

Specifically, statistically significant increases in cortical BMD of 1 and 4% at the distal radius and proximal tibia were observed, relative to the vehicle controls at the end of phase I of the nonclinical study.

Comment: According to the medical officer reviewing this application, a clinically significant increase in BMD is >/= 1.25% from baseline. Many of the increases in BMD shown above were greater than 1.25% following 12-months of treatment, so a clinical response was observed in the OVX cynomolgus monkeys treated with denosumab, with or without 6 months of alendronate pretreatment. Furthermore, alendronate (positive control comparator, currently marketed for the treatment of osteoporosis by inhibiting osteoclast-mediated bone-resorption) increased the BMD as well as the combination of alendronate and denosumab (see Figure 9 below, from the sponsor).

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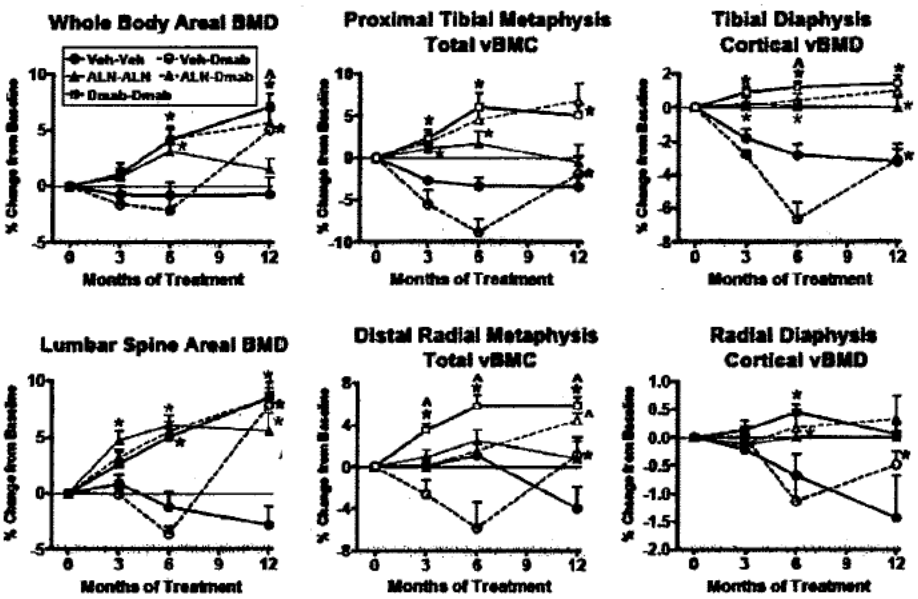
Figure 9. In Vivo Densitometry in OVX Cynomolgus Monkeys Treated With Denosumab With and Without 6 Months of Alendronate Pretreatment



Data are presented as mean + SE, n = 7 to 10/group. *p ≤ 0.05 vs. OVX + vehicle. ^p ≤ 0.05 vs. ALN. Statistics for months 3 and 6 are presented after combining the groups similarly treated before the transition to denosumab, although these groups are illustrated separately for clarity. Group differences in the percent change from baseline for the Veh-Veh, ALN-ALN, and Dmab-Dmab groups at 3, 6, and 12 months were assessed by one way ANOVA followed by Tukey's pairwise comparisons. For the transition groups at month 12, additional Tukey's post-test comparisons (Veh→Veh vs. Veh→Dmab and ALN→ALN vs ALN→Dmab) were performed to examine changes from the pre-transition timepoint.

Source: Study Report No. 106564

Whole Body (Text from Study No. 106564)

Denosumab vs. Vehicle: Vehicle control groups showed only minor decreases in whole body BMD in response to OVX relative to baseline. Treatment of OVX monkeys with denosumab resulted in increases in whole body BMD of approximately 4% following 6 monthly doses (Group 5), continuing to increase to 7% after 12 months of treatment relative to baseline. The increases in BMD in the denosumab treated animals were statistically significant compared to changes observed in vehicle controls. Treatment with denosumab for 6 months starting 6 months post-OVX (Group 2) resulted in a significant increase in whole body BMD of approximately 7% (relative to end of phase I), and an increase of approximately 5% relative to baseline (pre-OVX). Thus denosumab appeared to reverse the effects of OVX-induced bone loss following a 6 month treatment-free period. The overall effect of 6 months of treatment relative to baseline was similar (4 to 5%) for these two groups.

Alendronate vs. Vehicle: Compared to changes in vehicle controls, treatment of OVX monkeys with bimonthly doses of ALN for 6 months (Group 3) resulted in a significant increase in whole body BMD of approximately 3.6% relative to baseline, an effect which was not sustained after12 months of treatment. Whole body BMD decreased slightly (by 1.6%, relative to end of phase I) during the last 6 months of treatment, although values

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did remain slightly increased relative to baseline, and compared to changes observed in vehicle controls.

Denosumab vs. Alendronate: Although treatment with denosumab and ALN for 6 months resulted in similar increases in whole body BMD (4.1% and 3.6%, Groups 5 and 3, respectively), the increase following treatment with denosumab for 12 months was significantly greater than that observed after 12 months of ALN treatment (7.1% and 1.5%, respectively).

Pretreatment with Alendronate: OVX monkeys pretreated with ALN for 6 months, then dosed with denosumab for 6 months showed increases in whole body BMD of 1.4% compared to 2.9% (relative to end of phase I) for animals continuing on denosumab treatment for an additional 6 months. This schedule resulted in increases in BMD for ALN-denosumab-treated animals which were only slightly below animals treated continuously with denosumab for 12 months (5.7% and 7.1%, Groups 4 and 5, respectively, relative to baseline). Increases were greater following 6 months of denosumab treatment compared to continued ALN treatment (Group 4 vs. Group 3). Denosumab administered to treatment-naïve, OVX animals (Group 2) and OVX animals pretreated with ALN for 6 months (Group 4) increased whole body BMD to similar levels. The magnitude of the changes relative to predose levels were therefore significantly different for these two groups, since BMD was markedly increased following administration of denosumab to treatment-naive animals compared to the relatively smaller additional increases seen in animals pretreated with ALN (Group 2 vs. Group 4).

Lumbar Spine (Text from Study No. 106564)

Denosumab vs. Vehicle: Vehicle control groups showed slight decreases in lumbar spine BMD (≤ 3%) in response to OVX relative to baseline. Treatment of OVX monkeys with denosumab resulted in increases in lumbar spine BMD of approximately 5% following 6 monthly doses (Group 5), continuing to increase to 8.5% after 12 months of treatment relative to baseline. These findings were statistically significant compared to changes observed in vehicle controls. Treatment with denosumab for 6 months starting 6 months post-OVX (Group 2) resulted in a significant increase in lumbar spine BMD of approximately 12% (relative to end of phase I), and an increase of approximately 7.8% relative to baseline (pre-OVX). Thus denosumab reversed the effects of OVX-induced bone loss which occurred in this group during the 6 month treatment-free period. The overall effect of 6 months of denosumab treatment relative to baseline was slightly greater starting 6 months post-OVX in high turnover, osteopenic animals (i.e. BMD increased 7.8%) compared to the effects of treatment given immediately post-OVX in animals with normal rates of bone turnover (i.e. BMD increased 5%).

Alendronate vs. Vehicle: Compared to changes in vehicle controls, treatment of OVX monkeys with bimonthly doses of ALN for 6 months (Group 3) resulted in a significant increase in lumbar spine BMD of approximately 5.8% relative to baseline, an effect which was sustained during the last 6 months of treatment (5.5%).

Denosumab vs. Alendronate: Treatment with denosumab or ALN for 6 months resulted in similar increases in lumbar spine BMD (5.0% and 5.8%, Groups 5 and 3, respectively), with a slight although not significantly greater increase following treatment with denosumab compared to ALN for 12 months (8.5% and 5.5%, respectively).

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Pretreatment with Alendronate: OVX monkeys pretreated with ALN for 6 months then dosed with denosumab for 6 months showed increases in lumbar spine BMD similar to animals treated with denosumab for a total of 12 months, resulting in comparable increases in BMD for ALN-denosumab-treated animals and animals on denosumab for 12 months (8.5% for both Group 4 and 5, relative to baseline). Increases were greater in monkeys treated with ALN followed by 6 months of denosumab treatment, compared to the group receiving continued ALN treatment (Group 4 vs. Group 3). Denosumab administered for 6 months to treatment-naive animals (Group 2) and animals pretreated with ALN for 6 months (Group 4) increased lumbar spine BMD to similar levels. The magnitude of the changes relative to predose levels were therefore significantly different for these two groups, since BMD was markedly increased following administration of denosumab to treatment-naïve animals compared to the relatively smaller additional increases seen in animals pretreated with ALN (Group 2 vs. Group 4).

Proximal Femur

The effects on global proximal femur data will be discussed, with reference to the femoral neck and trochanteric subregions of interest made as appropriate. At the femoral neck and trochanteric region, vehicle control Group 1 showed slight increases in BMD while Group 2 showed decreases relative to baseline during the first 6 months of the study, confounding interpretation of the effects of OVX and treatment at these subregions of interest.

Denosumab vs. Vehicle: Vehicle control groups showed no consistent decreases in proximal femur BMD (≤ 2%) in response to OVX relative to baseline, with a slight increase noted during the last 6 months of the study (1.6%,relative to end of phase I). Relative to baseline, denosumab treatment of OVX monkeys resulted in a significant increase in proximal femur BMD of approximately 10% following 6 monthly doses (Group 5), with no further increases observed following dosing for an additional 6 months. Proximal femur BMD was increased 8.7% after 12 months of treatment relative to baseline. Treatment with denosumab for 6 months starting 6 months post-OVX (Group 2) resulted in a significant increase in proximal femur BMD of 8.4% (relative to end of phase I), representing an increase of approximately 6.2% relative to baseline (pre-OVX). At this site, the overall effect of 6 months of denosumab treatment starting 6 months post-OVX (i.e. BMD increased 8.4%) was essentially comparable to the effects seen when given immediately post-OVX (BMD increased 10.1%).

Alendronate vs. Vehicle: Compared to changes in vehicle controls, treatment of OVX monkeys with bimonthly doses of ALN for 6 months (Group 3) resulted in a significant increase in proximal femur BMD of approximately 6.5% relative to baseline. This effect was reduced slightly during the last 6 months of treatment (i.e. 4.2% increase overall).

Denosumab vs. Alendronate: Treatment with denosumab for up to 12 months resulted in slightly greater increases in proximal femur BMD compared to ALN, although differences relative to baseline did not attain statistical significance (6.5% and 10.1%, Group 5 and 3, respectively at 6 months and 4.2% and 8.7%, respectively, at 12 months).

Pretreatment with alendronate: OVX monkeys pretreated with ALN for 6 months then dosed with denosumab for 6 months showed minimal increases in proximal femur BMD of approximately 1% (relative to end of phase I), compared to no change observed in animals continuing on denosumab a further 6 months. Relative to baseline, increases in

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BMD for ALN-denosumab-treated animals were only slightly lower than for animals dosed with denosumab for 12 months (7.7% for Group 4 and 8.7% for Group 5). Increases were slightly greater following 6 months of denosumab treatment compared to continued ALN treatment (Group 4 vs. Group 3).

Distal Radius (Text from Study No. 106564)
No effects of either denosumab or alendronate on the distal radius.

Central Tibia (Text from Study No. 106564)
Denosumab vs. Vehicle: Vehicle control groups showed consistent decreases in tibial BMD (≤ 6%) in response to OVX during the study relative to baseline. Relative to baseline, treatment of OVX monkeys with denosumab resulted in a significant increase in tibial BMD of approximately 1.6% following 6 monthly doses (Group 5) compared to vehicle controls, with no further increases observed following dosing for an additional 6 months. Tibial BMD was significantly increased 1.3% after 12 months of treatment relative to baseline compared to vehicle controls. Treatment with denosumab for 6 months starting 6 months post-OVX (Group 2) resulted in a significant increase in tibial BMD of 3.2% (relative to end of phase I), although values were approximately -2.6% below baseline values (pre-OVX). At this site, the overall effect of 6 months of denosumab treatment starting 6 months post-OVX (i.e. BMD increased 3.2%) was slightly greater than the effects seen when given immediately post-OVX (i.e.BMD increased 1.6%).
Alendronate vs. Vehicle: Similar to the distal radius, the effects of treatment of OVX monkeys with bimonthly doses of ALN during the first 6 months of the study differed between Groups 3 and 4. The effect of combining data for these two groups for analysis (Group 3/4) resulted in a significant increase in tibial BMD of approximately 1.0% relative to baseline, compared to changes in vehicle controls. Continued treatment of animals in Group 3 with ALN resulted in a slight loss in BMD relative to baseline (i.e. 3.7% decreases) with values comparable to controls.
Denosumab vs. Alendronate: Treatment with denosumab for up to 12 months resulted in slight increases in tibial BMD relative to baseline compared to slight losses for the groups dosed with ALN, although differences between these two groups did not attain statistical significance.
Pretreatment with Alendronate: OVX monkeys pretreated with ALN for 6 months then dosed with denosumab for 6 months showed slight decreases in tibial BMD of approximately -2.2% (relative to end of phase I), compared to no change observed in animals continuing on denosumab a further 6 months. BMD for ALN-denosumab-treated animals was similar to animals dosed with denosumab for 12 months and both groups showed no meaningful changes relative to baseline.
There were no meaningful differences between ALN-treated groups treated for 6 months with denosumab compared to continued ALN treatment (Group 4 vs. Group 3). Denosumab administered for 6 months to treatment-naive animals (Group 2) significantly increased tibial BMD (3.2% relative to end of phase I) compared to changes in vehicle controls, while animals pretreated with ALN for 6 months (Group 4) showed slight decreases in tibial BMD (-2.2%, similar to losses seen in vehicle controls). The magnitude of the changes relative to predose levels was therefore significantly different

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for these two groups, since BMD was increased following administration of denosumab to treatment-naive animals compared to slight losses seen in animals pretreated with ALN (Group 2 vs. Group 4).

Histomorphometry (Text from Study No. 106564)

Cancellous Bone Evaluation at the End of Phase I
No qualitative histological changes in the iliac biopsies, other than those that were quantifiable with histomorphometry, were noted in any animals.

Effects of Denosumab upon Cancellous Bone at Post Dose 6
At post dose 6, treatment with denosumab markedly suppressed bone resorption, formation and turnover variables when compared to the OVX controls.
All measured resorption variables (eroded surface [ES/BS], Osteoclast surface (Oc.S/BS) and Osteoclast number (N.Oc/BS) were significantly decreased in the denosumab-treated group. The effect of the compound was striking upon osteoclasts, as these cells were not found at all in the iliac biopsy ROI of any of the treated monkeys. All bone formation variables (osteoid volume [OV/BV], O.Th, osteoid surface [OS/BS], osteoblast surface [Ob.S/BS], mineralizing surface (MS/BS), mineral apposition rate (MAR), adjusted apposition rate [Aj.Ar] and surface referent bone formation rate [BFR/BS]) were significantly decreased after six doses of denosumab. Even though a sham-operated group was not available to confirm prevention of the OVX-induced increases in bone turnover, levels reached for these bone resorption and formation variables in the denosumab-treated group were consistent with complete prevention of these effects in the model. Bone turnover was significantly decreased, as measured with the volume referent bone formation rate [BFR/BV] and activation frequency (Ac.f.) Other significant changes associated with denosumab treatment included an increase in FP along with a decrease in resorption period (Rs.P.). There was no significant effect upon the cancellous bone volume (BV/TV) in the denosumab-treated group when compared to the controls. Nevertheless, a slight increase (13%) was noted after Phase I in the denosumab-treated group.

Effects of Alendronate upon Cancellous Bone at the End of Phase I
At the end of phase I, significant reductions in all bone resorption variables (ES/BS, Oc.S/BS and N.Oc/BS) were found in the ALN-treated group when compared to the controls. Treatment with ALN markedly suppressed bone formation and turnover variables as shown by significant reductions of OV/BV, O.Th, OS/BS, Ob.S/BS, MS/BS, MAR, Aj.Ar, BFR/BS, BFR/BV and Ac.f. Significant increases in FP completed the response associated with this treatment. Despite these effects upon bone dynamics, there were no effects upon BV/TV in the ALN-treated group.

Comparisons Between Denosumab and Alendronate upon Cancellous Bone at the End of Phase I
At the end of phase I, significant differences between denosumab and ALN treatments were limited to decreased osteoclast-derived variables Oc.S/BS, N.Oc/BS and Rs.P in the denosumab-treated group.

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Cortical Bone Evaluation at the End of Phase I
No qualitative histological changes in the rib biopsies, other than those that were quantifiable with histomorphometry, were noted in any animals examined.

Effects of Denosumab upon Cortical Bone at Post Dose 6
Compared to controls, denosumab treatment caused marked effects at the haversian systems, which included significant decreases in percent porosity (%Po.Ar), harversian labeled surface (H.L.Pm/H.Pm), harversian mineral apposition rate (H.MAR), surface referent haversian bone formation rate (H.BFR/BS) and volume referent haversian bone formation rate (H.BFR/BV). The magnitude of these changes was regarded as indicating a complete prevention of the expected OVX-induced increases in bone turnover. The overall size of the bone compartments and cortical width (Ct.Wi) of the rib biopsies was unaffected by denosumab at post Dose 6. In addition when compared to the vehicle controls, no significant changes were noted at the periosteal and endocortical envelopes.

Effects of Alendronate upon Cortical Bone at the End of Phase I
Compared to controls, ALN treatment caused significant decreases in %Po.Ar, H.L.Pm/H.Pm, H.MAR, H.BFR/BS and H.BFR/BV at the haversian systems. The overall size of the bone compartments including Ct.Wi in the rib biopsies was unaffected by ALN at post dose 6. In addition, when compared to the vehicle controls, no significant changes were noted at the periosteal and endocortical envelopes.

Comparisons Between Denosumab and Alendronate Upon Cortical Bone at the End of Phase I
At post Dose 6, significant differences between denosumab and ALN treatments were limited to several haversian-derived variables. Decreases in %Po.Ar, H.L.Pm/H.Pm, H.MAR, H.BFR/BS and H.BFR/BV were found in the denosumab-treated group.

Cancellous Bone Evaluation at Study End
No qualitative histological changes in the ilia collected at necropsy, other than those that were quantifiable with histomorphometry, were noted in any animals examined at the end of Phase II. Treatments with denosumab, ALN or their combination were not associated with histological defects of bone mineralization or collagen arrangement at L2 and proximal tibia in any of the monkeys. In these sites, several other histological changes were noted. Based upon their nature and low incidence, either sporadic or scattered in most groups including the vehicle controls, they were regarded as incidental in origin and unrelated to the compounds tested. The most common findings were subchondral osteosclerosis in the proximal tibia and degeneration/loss of end plate(s) and/or focal/multifocal osteosclerosis in L2. Histopathological findings noted during qualitative evaluation did not justify exclusion from histomorphometric analyses with the exception of the right proximal tibia of one animal (Animal No. 557). This monkey had marked focal bone atrophy associated with medullary fibrosis in the region of interest (ROI), which correlated with severe degenerative joint disease detected radiologically at baseline. This finding was the justification to use the animal's contralateral proximal tibia for conducting histomorphometric measurements.

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Effects of Denosumab Upon Cancellous Bone at Study End
At post Dose 12, treatment with denosumab markedly suppressed bone resorption, formation and turnover variables in the ilia, L2 and proximal tibia when compared to the OVX controls. Most resorption variables measured (Oc.S/BS and N.Oc/BS) were significantly decreased in the denosumab-treated group at L2 and proximal tibia. This compound-related effect upon osteoclasts was so marked that these cells were absent in the measured ROI at both cancellous bone sites in most treated monkeys. All bone formation variables measured in L2 and tibia (OV/BV, O.Th [L2 only], OS/BS, Ob.S/BS [L2 only], MS/BS, MAR, Aj.Ar and BFR/BS were significantly decreased after 12 doses of denosumab. In the absence of a reliable determination of Ac.f in these bones, significant decreases in BFR/BV were regarded as indirect evidence that the bone turnover was depressed. Other significant changes associated with denosumab treatment were limited to the proximal tibia and included an increase in FP, osteoid maturation time (Omt) and mineralization lag time (mLt) along with a decrease in resorption period (Rs.P). The increased Omt and mLt were not regarded as indicative of a defective mineralization because the O.Th was reduced. Compared to controls, there were no significant differences in the ilium for the denosumab-treated group when using results adjusted to the end of Phase I. This reflects that the response to the compound had reached a plateau during the first half of the study. Even though no significant effects upon BV/TV were noted in the denosumab-treated group when compared to controls, all three cancellous bone sites showed mild increases in BV/TV, ranging from 13% to 20%, at post dose 12.

Effects of Alendronate Upon Cancellous Bone at Study End
Compared to Vehicle controls at study end, treatment with ALN resulted in paradoxical effects upon bone resorption variables. While the osteoclast-derived variables (Oc.S/BS and N.Oc/BS) were reduced (attaining significance only for N.Oc/BS in proximal tibia), the ES/BS were markedly increased (attaining significance in ilium and L2) in all three cancellous bone sites for the ALN-treated group, attaining significance for the ileum and L2 sites. Comparison with the biopsy data showed that this effect upon ES/BS became apparent in the second half of the study, with significant increase in the ilium for the ALN-treated group when using results adjusted to the end of Phase I. Marked and significant decreases in all bone formation markers (OV/BV, O.Th, OS/BS, Ob.S/BS, MS/BS, MAR, Aj.Ar and BFR/BS) were noted in L2 after ALN treatment. The reductions in bone formation and turnover variables were similar in the ilium compared to L2 but there were no significant differences in the latter bone for the ALN-treated group when using results adjusted to the end of Phase I. This finding reflects that the response to ALN had reached a plateau during the first half of the study. The effects of ALN upon bone formation were less conclusive in the proximal tibia, for which only the Aj.Ar was significantly decreased. Bone turnover variables (BFR/BV and Ac.f) measured in L2 and proximal tibia were significantly decreased in the ALN-treated group. Other significant effects included increases in mLt and FP at the proximal tibia and increased Rs.P at L2. The increased mLt was not indicative of defective mineralization because O.Th was concurrently reduced. No significant or consistent effects upon BV/TV were

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noted in various cancellous bone sites evaluated the ALN-treated group when compared to the controls.

Effects of a Treatment Switch to Denosumab in Phase II Upon Cancellous Bone at Study End

Compared to ALN treatment, cancellous bone changes in the group switched from ALN to denosumab (ALN + denosumab) were characterized by decreases of resorption variables, reaching significance for N.Oc/BS and ES/BS in L2 and N.Oc/BS and Oc.S/BS in tibia. Most bone formation and turnover variables were significantly decreased in the proximal tibia of the ALN + denosumab-treated group. In L2 and ilium, differences for bone formation and turnover variables were generally small for the compared groups. No significant or consistent effects upon BV/TV were noted in the ALN + denosumab-treated group when compared to the ALN group-treated group.

The cancellous bone response in the group switched from vehicle to denosumab (Vehicle + denosumab) included marked and significant decreases of all calculated bone resorption, formation and turnover variables in L2 and proximal tibia. Compared to the controls, affected variables included Oc.S/BS, N.Oc/BS, ES/BS, OV/BV, O.Th, OS/BS, Ob.S/BS, MS/BS, MAR, Aj.Ar, BFR/BS, BFR/BV and Ac.f, with the exception of tibial Ob.S/BS. The ilium responded similarly based upon marked decreases in variables of bone resorption, formation and turnover but these differences were less consistently significant. Even though no significant effects upon BV/TV were noted in the Vehicle + denosumab-treated group, all three cancellous bone sites showed mild increases in BV/TV, ranging from 13% to 18% increases, when compared to vehicle controls.

Effects of the Phase I Treatment Upon Denosumab Response in Phase II Upon Cancellous Bone at Study End

Compared to the vehicle + denosumab-treated group, there were no significant differences noted in any histomorphometric variables measured at L2, ilium and proximal tibia in the group treated continuously with denosumab for 12 months. In the ilium, significant differences were noted for all bone resorption and most bone formation and turnover variables when using adjusted results to the end of Phase I. These observations reflect differences present in Phase I because of the small intergroup variations noted for these variables at study end. No meaningful effects upon BV/TV were noted at any of the cancellous bone sites between the denosumab and Vehicle + denosumab-treated groups. Compared to the Vehicle + denosumab-treated group, there were no significant differences noted in any variables measured at L2 and proximal tibia in the ALN + denosumab treated group. In the ilium, significant differences were noted for most bone formation and turnover variables when using adjusted results. These observations reflect differences present in Phase I because of the small intergroup variations noted for these variables at study end. No significant or consistent effects upon BV/TV were noted at any of the cancellous bone sites between the Vehicle + denosumab and Alendronate + denosumab-treated groups. Compared to the ALN +denosumab-treated group, there were no significant differences in bone structure or dynamics for the denosumab-treated group at any of the three measured cancellous bone sites.

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Cortical Bone Evaluation at Study End
No qualitative histological changes in the rib and mid tibia, other than those that were quantifiable with histomorphometry, were noted in any animals examined at study completion.

Effects of Denosumab Upon Cortical Bone at Study End
At study end compared to controls, the denosumab treatment caused marked effects at the haversian systems marked effects which included decreases in %Po.Ar, H.L.Pm/H.Pm, H.MAR, H.BFR/BS and H.BFR/BV. These responses were very similar at the rib and tibia and were comparable to those measured in the rib biopsies at post Dose 6. At least for the rib, the effects of denosumab upon the haversian systems had attained by post Dose 6 had attained a plateau that was maintained through post Dose 12. Compared to controls, the denosumab treatment was associated with marked decreases the dynamic variables measured at the periosteal and endocortical envelopes. At the tibia, significant decreases in Ps.L.Pm/Ps.Pm, Ec.L.Pm/Ec.Pm, Ps.MAR, Ec.MAR and, consequently, bone formation rates (Ps.BFR/BS and Ec.BFR/BS) were noted. The rib at study end responded similarly for these variables when compared to the tibia. Unlike the haversian systems, the decreases in periosteal and endocortical turnover were less rapid and decrescent over the study course based on the rib data. Despite these effects upon bone dynamics, the overall size of the bone compartments including Ct.Wi in the rib and mid tibia remained unaffected by the treatment when compared to the controls.

Effects of Alendronate Upon Cortical Bone at Study End
Compared to controls at study end, the ALN treatment caused effects at the tibial haversian systems which included decreases of several dynamic variables including H.L.Pm/H.Pm, H.MAR, H.BFR/BS and H.BFR/BV. These variables were similarly decreased at post Dose 12 in the ribs but based on comparison with the biopsy data, it appeared that these effects had attained a plateau by post Dose 6 had attained that was maintained through post Dose 12. No significant decrease in %Po.Ar was evident at the tibia after 12 months of ALN treatment. A consistent response was noted at the rib cortex so comparison between both time points suggests that the %Po.Ar decrease noted at post Dose 6 was a transient effect of ALN. Compared to controls at post dose 12, ALN treatment was associated with marked and significant decreases of Ec.L.Pm/Ec.Pm, Ec.MAR and Ec.BFR/BS at the mid tibia. At the rib, the response for these variables in the ALN-treated group headed in the same direction but was less marked and non-significant. The overall size of the bone compartments including Ct.Wi in the rib and tibia remained unaffected by ALN at post Dose 12. In addition when compared to the controls, no consistent changes were noted at the periosteal envelope.

Effects of a Treatment Switch to Denosumab in Phase II Upon Cortical Bone at Study End
Compared to ALN treatment, cortical bone changes in the group switched from ALN to denosumab (ALN +denosumab) were mainly evident at the haversian systems with significant decreases of H.MAR at both tested sites and H.L.Pm/H.Pm, H.BFR/BS and

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H.BFR/BV at the tibia. A significant decrease of tibial Ps.BFR/BS was another significant difference noted between these two groups. Compared to the Vehicle controls, the cortical bone response in the group switched from vehicle to denosumab (Vehicle + denosumab) was characterized at the haversian systems by significant decreases of %Po.Ar (tibia only), H.L.Pm/H.Pm, H.MAR, H.BFR/BS and H.BFR/BV at both cortical bone sites. In addition, significant decreases in formation variables at the endocortical surface were limited to Ec.MAR in both cortical bone sites. Significant decreases of periosteal variables (Ec.L.Pm/Ec.Pm, Ec.MAR and Ps.BFR/BS) following the switch to denosumab appeared site-dependent, being limited to the tibia. The overall size of the bone compartments including Ct.Wi in the rib and tibia remained unaffected when comparing these data sets for differences during Phase II when treatments were changed to denosumab.

Effects of the Phase I Treatment upon Denosumab Response in Phase II Upon Cortical Bone at Study End

Compared to the Vehicle + denosumab-treated group, most tibial haversian-derived variables were significantly decreased in the denosumab-treated group, including H.L.Pm/H.Pm, H.BFR/BS and H.BFR/BV. At the rib, only the H.L.Pm/H.Pm was significantly reduced in the denosumab-treated group. No other significant differences were noted at other costal and mid-tibial bone envelopes for this comparison.

Compared to the Vehicle + denosumab-treated group, several of the haversian-derived variables at the tibia were significantly decreased in the alendronate + denosumab-treated group, including H.L.Pm/H.Pm, H.BFR/BS and H.BFR/BV. No other significant differences were noted at other costal and mid-tibial bone envelopes for this comparison. Compared to the ALN + denosumab-treated group, there were no significant differences for the denosumab-treated group at the mid-tibial and costal site. At the rib, a few haversian variables (H.MAR and H.BFR/BS) were significantly decreased in the denosumab-treated group. These differences reflected the smaller relative contribution of the ALN + denosumab treatment in Phase I despite that at study end the magnitude of these decreases were very similar. No other significant differences were noted at other costal and mid tibial bone envelopes for this comparison.

As shown in Figure 8 provided by the sponsor, the histomorphometry evaluation provides evidence that denosumab prevented bone resorption, formation and turnover parameters in the ilia, L2, rib and proximal tibia as compared to the OVX vehicle controls. A similar response was observed in the alendronate alone group and in the combination of alendronate and denosumab cohort except for the Eroded Surface/Bone Surface (%) parameter the alendronate alone group was initially reduced in the ilia at 6 months but was present at greater levels as compared to the vehicle control in the ilia, L2, and proximal tibia at 12 months.

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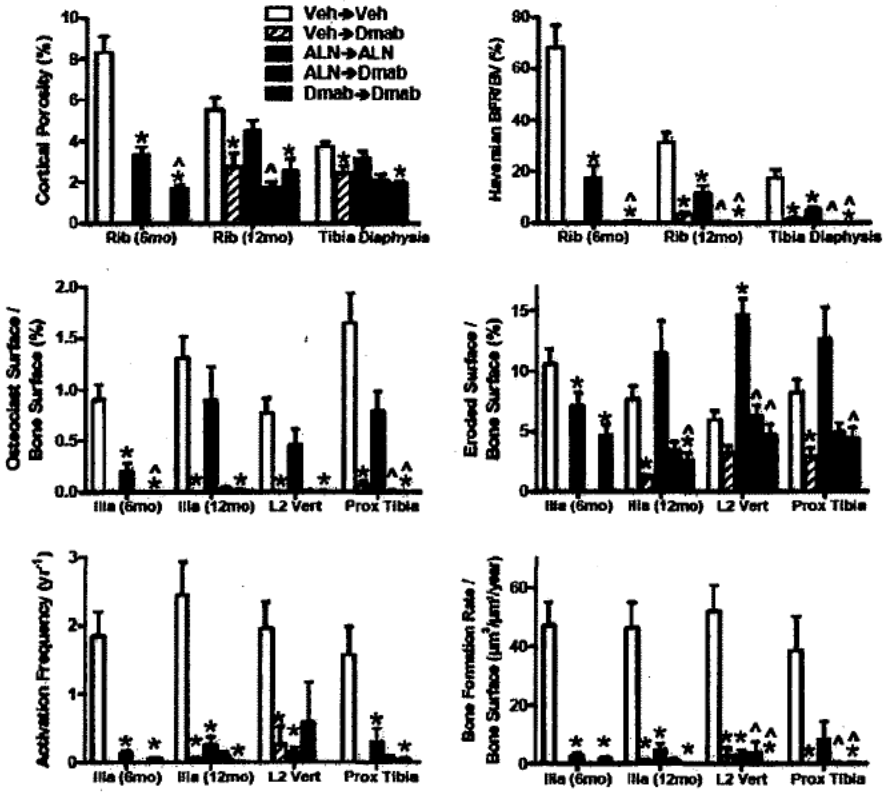
Summary of Histomorphometry (Figure 8 below, as provided by the sponsor:

Figure 8. Local Bone Turnover in OVX Cynomolgus Monkeys Treated With Denosumab With and Without 6 Months of Alendronate Pretreatment by Histomorphometry



Data are presented as the mean ± SE, n = 7 to 10/group. *p ≤ 0.05 vs. OVX + Vehicle, ^p ≤ 0.05 vs. ALN. Cortical regions analyzed within the month 6 and month 12 rib biopsies and tibia diaphysis. Cancellous regions analyzed within L2, proximal (prox) tibia metaphysis, and month 6 and month 12 iliac crest biopsies. Veh = vehicle; ALN = alendronate; Dmab = denosumab; transition from Veh and ALN to Dmab was made at month 6 in the Veh-Dmab and ALN-Dmab groups, respectively. One way ANOVAs were performed with Bonferroni correction for post-tests were performed, data was pooled for the pre-switch biopsy data at month 6. The Veh vs ALN-Dmab post-test was not included in the prescribed statistics. BFR/BV = bone formation rate per bone volume. For the 6 month biopsy data, group differences in baseline-adjusted serum calcium between the 3 treated groups (vehicle, alendronate, and denosumab) were assessed using an ANOVA followed by contrast pairwise post-tests. For the terminal data, group differences were assessed by ANOVA across all 5 treatment groups and Tukey's pairwise comparisons were performed; these did not include Veh→Veh vs. ALN→Dmab. Equal variance across groups was assessed using Levene's tests; rank-transformation was used to equalize variance if p ≤ 0.05. If variance remained unequal, an ANOVA model accounting for unequal variance was utilized.

Source: Study Report No. 106564

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Bone Strength (Text from Study No. 106564)

Femur 3-point Bending

Denosumab vs. Vehicle: Femur BMD (DXA and pQCT derived) was increased relative to vehicle controls. Peak load, ultimate stress and stiffness and modulus were increased up to 11% compared to vehicle controls for monkeys treated with denosumab for 12 months, although the AUC (Area Under the Curve) and toughness were similar to vehicle controls. Slight increases in mean ultimate stress (2%) and modulus (1%) were noted compared to vehicle controls. Peak load and stiffness were increased by 9% and 11%, respectively, compared to the vehicle controls. AUC and toughness increased slightly (7% and 4%, respectively) relative to controls.

Alendronate vs. Vehicle: Treatment with ALN for 12 months showed slight increases in all biomechanics parameters relative to vehicle controls (up to 13%) with the greatest increases in AUC and toughness of all treated groups.

Denosumab vs. Alendronate: Compared to treatment with ALN, treatment with denosumab for 12 months resulted in slightly greater increases in ultimate stress (2%) and modulus (6%) Peak load and stiffness were similar between the two dose groups while AUC and toughness were slightly lower (13%).

Pretreatment with alendronate: Overall, ultimate stress and modulus were increased slightly (2% and 9%, respectively) for OVX monkeys in the group pretreated with ALN for 6 months followed by dosing with denosumab for 6 months (Group 4) compared to OVX monkeys that did not receive prior treatment (i.e. received vehicle only before denosumab treatment for 6 months, Group 2). Peak load, stiffness, AUC and toughness were similar for these two groups. Samples form animals pretreated with ALN followed by denosumab compared to continuous denosumab treatment for 12 months showed a tendency for marginally greater biomechanics strength parameters with the exception of ultimate stress which was slightly lower (2%).

Overall, denosumab-treated bones were similar to controls with respect to the work required for failure (AUC) and toughness. Femurs also tended to be stiffer and less ductile form animals dosed with denosumab for 12 months relative to monkeys treated with ALN treatment for 12 months. The biomechanics strength parameters ultimate stress and modulus were increased for animals pretreated with ALN followed by denosumab relative to denosumab treatment for 6 months post-OVX. Pretreatment with ALN followed by denosumab showed slight increases in AUC and toughness relative to denosumab alone.

Correlation Analyses:

A statistically significant linear and positive association was found for all groups for peak load versus pQCT-derived cortical BMC (r=0.89). Femur bone mass (BMC) was correlated with bone strength.

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Femoral Neck Shear:

There were no statistically significant differences between Groups 1 through 5 for any biochemical strength parameters measured at the femoral neck.

Vertebral Compression L3/L4:

Data were analyzed for L3 and L4 separately and averaged. The results discussed below are for the averaged data.

Denosumab vs. Vehicle: Lumbar spine (L3/L4) BMC and BMD (DXA and pQCT-derived) were slightly increased relative to vehicle controls following 12 months of denosumab treatment and were the highest among the denosumab-treated groups (Group 2, 4 and 5). For animals treated with denosumab for 12 months, peak load, apparent strength, yield load, yield stress, stiffness and modulus were statistically significantly increased 31 to 47% compared to vehicle controls.

Alendronate vs. Vehicle: Treatment with ALN for 12 months showed slight increases in all biomechanics parameters compared to vehicle controls of 8 to 19%.

Denosumab vs. Alendronate: Compared to treatment with ALN, treatment with denosumab for 12 months resulted in greater increases in all biomechanical strength parameters (peak load, apparent strength, yield load, yield stress, stiffness, modulus, AUC and toughness) of 14 to 30%, and the findings were statistically significant for stiffness when compared to the ALN treated group.

Pretreatment with alendronate: Biomechanical parameters with the exception of stiffness and modulus were similar for OVX monkeys pretreated with ALN for 6 months followed by dosing with denosumab for 6 months (Group 4) compared to OVX monkeys that did not receive prior treatment (i.e. received vehicle only before denosumab treatment for 6 months, Group 2). Stiffness and modulus were slightly lower (13% and 15%, respectively) for Group 2 compared to Group 4. Biomechanical parameters were similar to or slightly lower (up to 8%) for the group pretreated with ALN followed by denosumab (Group 4) compared to the group given 12 months of denosumab treatment (Group 5). Compared to continued treatment with ALN for 12 months (Group 3), animals treated with ALN for 6 months followed by denosumab for 6 months (Group 4) showed increases in all biomechanical strength parameters (peak load, apparent strength, yield load, yield stress, stiffness, modulus, AUC and toughness) of 8 to 27%. At the lumbar spine, biomechanical strength parameters were increased relative to vehicle controls for all groups treated with denosumab, with the greatest effects noted following denosumab treatment for 12 months. Prior treatment with ALN did not meaningfully modify the response to denosumab. The effect of denosumab treatment for 12 months on lumbar spine strength was superior to 12 months ALN treatment.

Correlation Analyses:

For pQCT and biomechanics parameters (peak load vs. total BMC and apparent strength vs. total BMD) the slopes of the regression lines were significantly different between

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groups precluding an analysis of all groups combined. Statistically significant linear and positive associations were found for individual groups for peak load vs. lumbar spine total slice BMC ($r = 0.76$ to 0.96). Positive and significant associations were found for all groups combined for peak load vs. DXA BMC ($r = 0.88$). Significant but generally weaker associations were found for other associations for some but not all dose groups.

Vertebral Core Compression L5/L6:
Data were analyzed for L5 and L6 separately and averaged. The results discussed below are for the averaged data.

Denosumab vs. Vehicle: Lumbar spine vertebral core (L5/L6) BMC and BMD (DXA and pQCT-derived) were slightly increased relative to vehicle controls for all treated groups. DXA BMC and BMD were statistically significantly increased for animals in Group 5 that were treated for 12 months with denosumab. Specifically, peak load, apparent strength, yield load, yield stress, stiffness and modulus were statistically significantly increased 37 to 46% compared to vehicle controls.

Alendronate vs. Vehicle: Treatment with ALN for 12 months showed non-significant increases in all biomechanics parameters of 23 to 43%, which were the least changes of all treated groups relative to vehicle.

Denosumab vs. Alendronate: Compared to treatment with ALN, treatment with denosumab for 12 months resulted in slightly greater increases in all biomechanical strength parameters (peak load, apparent strength, yield load, yield stress, stiffness, modulus, AUC and toughness) of 8 to 18%.

Pretreatment with Alendronate: Biomechanical parameters with the exception of AUC and toughness were generally similar (within 5%) for OVX monkeys pretreated with ALN for 6 months then dosed with denosumab for 6 months (Group 4) compared to OVX monkeys that did not receive prior treatment (received vehicle only before denosumab treatment for 6 months, Group 2). AUC and toughness were slightly lower (16% and 10%, respectively) for Group 2 compared to Group 4. Biomechanical parameters were similar (within 3%) for the group pretreated with ALN followed by denosumab treatment (Group 4) compared to the group given 12 months of denosumab treatment alone (Group 5). Compared to treatment with ALN for 12 months (Group 3), animals treated with ALN for 6 months followed by denosumab treatment for 6 months (Group 4) showed increases in all biomechanical strength parameters (peak load, apparent strength, yield load, yield stress, stiffness, modulus, AUC and toughness) of 9 to 18%. Biomechanical strength of lumbar spine vertebral cores was increased relative to vehicle controls for all groups treated with denosumab, with the greatest effects noted following denosumab treatment for 12 months. Prior treatment with ALN did not meaningfully modify the response to denosumab. The effect of denosumab treatment for 12 months on lumbar spine vertebral core strength was superior to 12 months ALN treatment alone.

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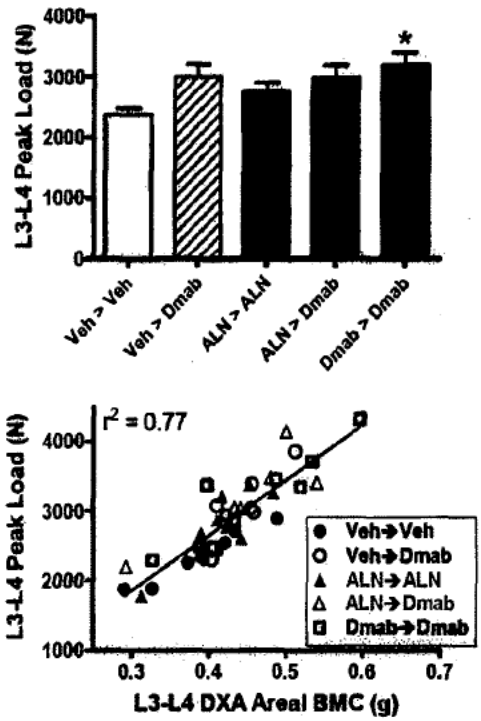
Correlation Analyses:
Lumbar vertebral core BMC and BMD were positively and significantly correlated with bone strength. Statistically significant linear and positive associations were found for peak load vs. DXA BMD/BMC (r =0.90 to 0.91). For pQCT and biomechanics parameters (peak load/apparent strength vs. total BMC) the slopes of the regression lines were significantly different between groups precluding an analysis of all groups combined.

Based on the L3-L4 Peak Load parameters displayed in Figure 10 below, bone strength in the OVX cynomolgus monkeys were similar whether the OVX cynomolgus monkeys were treated with the vehicle for 12 months, vehicle followed by denosumab, alendronate alone for 12 months, pretreatment with alendronate (6 months) followed by denosumab (6 months), or denosumab treatment for 12 months.

Figure 10. Bone Strength in OVX Cynomolgus Monkeys Treated With Denosumab With and Without 6 Months of Alendronate Pretreatment



Peak load data are presented as mean ± SE, n = 7 to 10/group. *p ≤ 0.05 vs OVX + vehicle. Group differences were assessed by ANOVA across all 5 treatment groups and Tukey's pairwise comparisons were performed, not including Veh→Veh vs. ALN→Dmab. Linear regression analysis of peak load vs. ex vivo areal BMC demonstrated similar and strong correlations for each group. Data for all treatment groups were therefore pooled; the line shown illustrates the regression across groups with an r^2 = 0.77.

Source: Study Report No. 106564

Reference ID: 3168397

Toxicokinetics:

[a] Immunoassay negative animals

Mean (SD) Denosumab PK Parameter Estimates Following Monthly SC Administration of 25 mg/kg to Ovariectomized Cynomolgus Monkeys

Group (Treatment)	Month	t_{max}[c] (day)	C_{max} (ug/mL)	AUC_{0-336} (mg*hr/mL)	AR	N
2 (Vehicle + denosumab)	7	7 (3-14)	145 (31)	41.6 (10.2)	N/A N/A	10
4 (ALN + denosumab)	7	3 (3-14)	172 (65)	43.7 (10.8)	N/A N/A	11
5 (denosumab)	1	7 (1-7)	152 (45)	40.3 (10.2)	N/A N/A	11
5 (denosumab)[a]	7	3 (1-7)	372 (132)	90.4 (25.8)	2.25 (0.46)	5
5 (denosumab)[b]	7	3 (3-14)	220 (142)	45.6 (24.9)	1.14 (0.53)	6

[a] Values calculated from immunoassay negative animal data.
[b] Values calculated from immunoassay positive animal data.
[c] t_{max} reported as a median (min-max) value
All values were rounded to 3 significant figures after calculations were performed, except t_{max}, which is presented as a whole number. SD is reported to the same precision as the mean value.
C_{max}: maximum observed concentration.
t_{max}: time at observed maximum concentration
AUC_{0-336}: area under the concentration-time curve from 0 to 336 hours postdose.
AR: $AUC_{0-336,\ month7}/AUC_{0-336,\ month1}$.
N/A: not applicable

Comment: The development of antibodies to denosumab in treated monkeys corresponded with an approximately 50% reduction in exposure, based on the AUC values in monkeys with (AUC_{0-t} ~ 45 mg*hr/mL) or monkeys without (~AUC_{0-t} 90 mg*hr/mL) anti- denosumab antibodies. Twenty-five of 32 (78%) monkeys in the SC denosumab treatment groups tested positive for the development of binding antibodies to denosumab. Seven of 32 (21%) monkeys in the SC treatment group tested positive for the neutralizing antibodies.

Based on mg/kg basis for determining the exposure multiple between animals and humans, denosumab (25 mg/kg) exposure was 25 fold greater in the monkeys relative to the human exposure of approximately 1 mg/kg of denosumab.

Study conclusion: This study was designed to evaluate the effects of biweekly intravenous dosing of alendronate for 6 months, followed by once monthly subcutaneous injection of denosumab for 6 months in ovariectomized monkeys. Parameters evaluated included bone mineral density (BMD), serum calcium and phosphorous levels, and bone

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biochemical turnover of markers. Statistically significant decreases in calcium levels relative to the control values in the study were observed following the first dose and second dose of denosumab but they were transient, and the levels of calcium returned close to control or baseline levels 3-5 weeks following dosing. Denosumab treatment induced statistically significant increases in PTH compared to vehicle controls, which remained elevated for approximately 28 days following the 3 and 6 monthly doses. The PTH levels declined gradually and returned to vehicle controls and baseline levels during the remaining 6 months of the monthly administration of denosumab.

Treatment of the ovariectomized monkeys with denosumab suppressed the biochemical markers of bone turnover below baseline levels. In addition, after 6 months of treatment with 25 mg/kg/dose of denosumab, animals displayed slightly increased bone mineral density and increased lumbar bone strength. Both alendronate and denosumab reversed the increases in biochemical markers of bone turnover such as C-telopeptide, TRACP-5b, sALP and OC relative to baseline and ovariectomized vehicle controls, providing evidence that both alendronate and denosumab treatment were able to induce reductions in bone turnover. In conjunction with the biochemical bone turnover markers, there were statistically significant increases in bone mineral density, and increased bone strength at the lumbar spine based on bone densitometry and biomechanical tests. Denosumab increased BMD in trabecular and cortical bone mass at the lumbar spine (5% at 6 months and 8.5% at 12 months), femur (1.6% and 8.7%), proximal tibia and distal radius (1% and 4%) respectively based on bone densitometry measurements by DXA and pQCT evaluation. Alendronate (Fosamax) treatment, which is currently approved for osteoporosis treatment, increased the BMD in the lumbar spine (5.8% at 6 months and 5.5% at 12 months), proximal femur (6.5% and 4.2% respectively), and central tibia (1.6% and 1.3% respectively). Histomorphometry evaluation provided evidence that denosumab prevented bone resorption, formation and turnover parameters in the ilia, L2, rib and proximal tibia, as compared to the OVX vehicle controls. A similar response was observed in the alendronate alone group and in the combination of alendronate and denosumab cohort except for the Eroded Surface/Bone Surface (%) parameter, which in the alendronate alone treated group was initially reduced in the ilia at 6 months, but was at greater levels as compared to the vehicle control in the ilia, L2, and proximal tibia at 12 months.

Overall, denosumab treatment was able to induce robust reductions in bone biomarkers of bone turnover as compared to dosing with alendronate, to induce similar modulations in histomorphometry parameters as alendronate treatment did, and bone strength was similar across the different treatment groups. Denosumab induced immunogenicity in 78% of the cynomolgus monkeys evaluated and reduced denosumab exposure by 50% in ADA positive animals; however, reasonable pharmacological activity was maintained for the duration of the study based on efficacy endpoints such as BMD, biochemical markers of bone turnover, histomorphometry parameters, and biomechanic endpoints. These data provide substantial evidence that denosumab treatment of OVX cynomolgus monkeys at 25 mg/kg/dose was able prevent the OVX-induced increases in markers of bone turnover, and based on histomorphometry parameters, maintain bone mass and bone strength. Pretreatment with alendronate did not change the activity of denosumab treatment, and

Reference ID: 3168397

dosing with alendronate alone at 50µg/kg was able to induce similar modulations in the bone biomarkers, bone mass and bone strength. However, the response at this dose was not as robust as what was observed for denosumab in some of the parameters, such as in the biochemical markers of bone turnover. This may be just a reflection that alendronate was used at a dose approximately 3 fold higher than the clinical dose, while densomab treatment was at a dose approximately 25 fold higher than the clinical dose based on a mg/kg basis (25 mg/kg for the cynomolgus monkeys versus 1 mg/kg for the human dose).

Title: Comparison of Two Anti-Resorptive Therapies (Alendronate Versus AMG-162 Monoclonal Anti-RANKL Antibody) on Murine Fracture Healing

Key Findings:

- Alendronate and AMG-162 treatment **delayed** the removal of cartilage, remodeling of the fracture callus, and induced changes in the morphology and time course of tissue remodeling of the fractured femur, as compared to the control mice with fractured femur.

- In addition, the fractured calluses for the AMG-162 treated knock-in mice 42 days post fracture had increased bone volume (BV), BV (%), bone mineral content (BMC), and BV/TV (%) relative to alendronate and vehicle control mice.

- The mechanical strength of healing/healed bone was not negatively affected in this study. At the 42 day time point, the AMG-162 and alendronate treated mice had increases in fractured bone strength and stiffness either relative to the contralateral (nonfractured) control, or to the vehicle control group.

Study #: R2006458
Volume # and Page #: EDR file
Conducting Laboratory and Location: (b) (4)
Date of Study Initiation: November 15, 2007 (final report dated March 14, 2008)
GLP Compliance: No
QAU statement: yes () no (X)
Drug Lot #: This reviewer could not find the lot # for either denosumab or alendronate in the report.

Methods:

The purpose of this study was to compare the effects of AMG-162 and alendronate on fracture healing to determine if denosumab was capable of interfering with normal fracture healing process.

AMG-162 (denosumab) neutralizes human RANKL, but based on the scientific data provided to date it does not appear to bind or neutralize mouse or rat RANKL. Thus,

Reference ID: 3168397

transgenic, knock-in mice were created by Amgen Inc. that were genetically engineered to express a chimeric form of RANKL by exchanging the 5th exon of the murine RANKL gene for the human 5th exon, which is thought to include the critical AMG-162 (denosumab) binding or neutralizing epitope. The chimeric RANKL expressed by the knock-in mice is bound and neutralized by AMG-162. This model was used to test the effects of denosumab (AMG-162) on bone mass and bone resorption in study R2004430, which provides data to support that the genetically engineered knock-in (KI) mouse was a useful model to study the pharmacology of denosumab *in vivo*. Furthermore, the genetically engineered mice were used to evaluate the bone mass and bone resorption in aged human RANKL KI mice, in study R2004321, which was review by Dr. Kim Hatfield in BLA # 125320 and #125331.

In this study, the C57/B6/ human RANKL knock in mice were shipped directly from a breeding colony at (b) (4) to (b) (4) (b) (4) Ninety male C57/B6/RANK Human RANKL knock-in mice received unilateral transverse femur fractures on the right femora. Mice (8 to 17 weeks of age) then received biweekly subcutaneous injections of alendronate at 0.1 mg/kg, AMG-162 at 10 mg/kg, or the vehicle (PBS, 0.1ml) until sacrifice at days 21 or 42 post-fracture. Each treatment group evaluated 15 mice per time point at terminal necropsy (day 21 or day 42). The right fractured and the normal contralateral femurs were then evaluated by microCT analysis and torsional testing. Subsets of fractured femora from day 21 were also examined by histological evaluation, which included special staining techniques for the marker TRAP-5b staining, to demonstrate the presence of osteoclasts.

Micro-computed Tomography (mCT)-generated images were used to evaluate the three dimensional structure of the bone. The following were quantified: total volume, bone volume, bone volume fraction (BV%), total callus bone mineral density (BMD), bone mineral content (BMC), and average cross-sectional area (Cs.Ar).

After the microCT scans were performed, the fractured and non fractured femora were subjected to torsion testing using an Instron 55MT1 MicroTorsion testing system. The torsional testing evaluated the maximum torque at failure, torsional stiffness, and toughness for each femur. Mechanical testing parameters were calculated using MATLAB.

Results:

The figures and tables below were copied from sponsor's submission:

Reference ID: 3168397

Results: For the alendronate (0.1 mg/kg) treated mice, a statistically significant reduction in TRAP-5b occurred as early as 1 week after initiation of the biweekly subcutaneous (SC) injections of denosumab at 10 mg/kg. However, biweekly SC injections of alendronate did not induce significant reductions in TRAP-5b within 6 weeks of treatment.

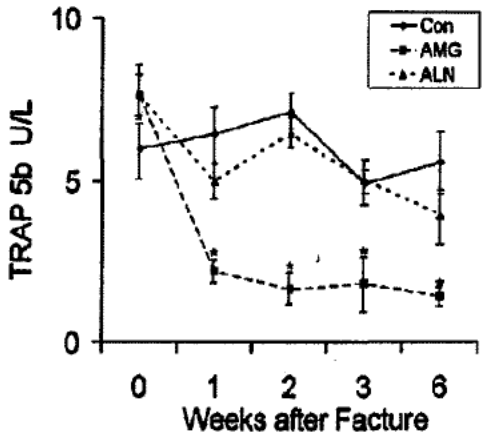

Figure 2. Averaged TRAP-5b for each drug group across the time of treatment. Error bars are depicted in the figure are for SD and levels of significance between individual drug groups to the control are denoted by asterisks.

Overall, a total of 157 bones (84 fracture bones and 73 contralateral bones were included in the data collected from torsion testing. Ten fracture bones were excluded due to physical damage to the bone during handling prior to testing, and ten contralateral bones were excluded due to technical reasons. Based on the summarized mechanical assessment data for the fractured bones in Table 1 and Figure 3, fractured bones from mice in all treatment groups (i.e. alendronate, denosumab and vehicle) required higher maximum torque to failure as compared to the contralateral bones, but the differences were not significantly different except on day 42 for both the alendronate and denonsumab treated groups (see Figure 3A). Alendronate treatment significantly increased the maximum torque required to failure on day 42 relative to day 21 post-fracture, while results from the denosumab-treated animals were similar to control values (see Figure 3B). Comparison of the contralateral bone (Figure 3C) indicated that the maximum torque to fracture was similar for the contralateral bone on day 21 and day 42 across all treatment groups. As shown in Table 1, denosumab treatment induced statistically significant increases in torsional rigidity on day 42 relative to the vehicle control fractured bones, while alendronate increased the maximum torque on day 42 relative to the vehicle control. Alendronate induced a transient but statistically significant reduction in maximum torque on day 21 that changed to a statistically significant increase in maximum torque on day 42 relative to the vehicle controls. Other than the changes described above, maximum torque and torsional rigidity values in

Reference ID: 3168397

samples from alendronate and denosumab treated mice were similar to those obtained for the vehicle control group.

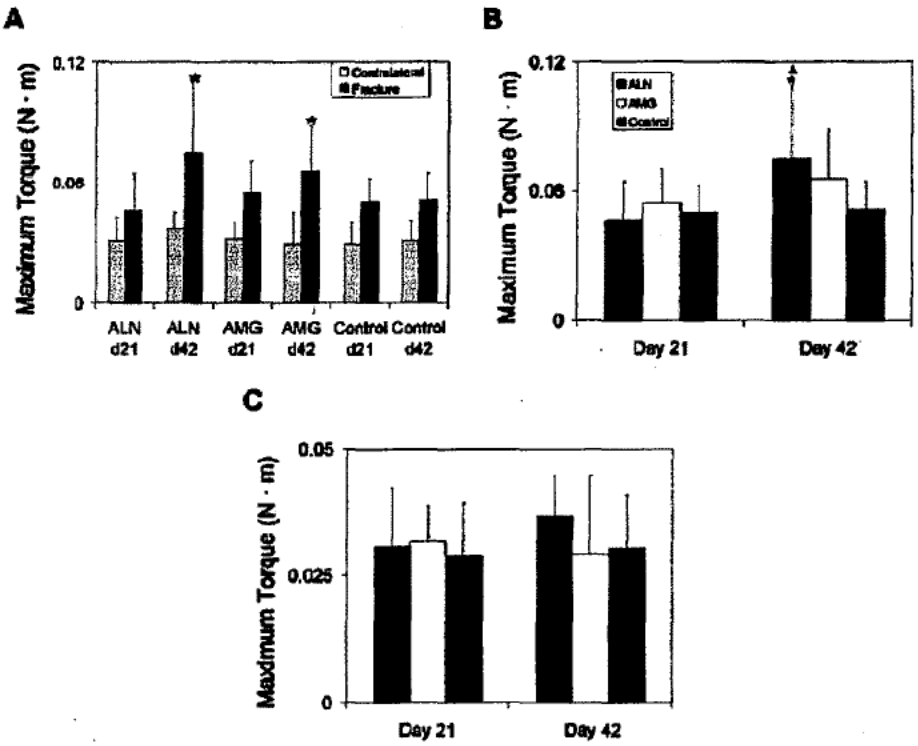

Figure 3. Graphical analysis of maximum torque to failure. (A) Comparison between fracture and intact bones. Stars indicate significance between fracture and contralateral bones, $p < 0.05$ (B) Comparison of fracture bones at both time points after fracture. Triangles indicate significance relative to the same treatment group at day 21. Asterisks indicate significance relative to the control at the same time point, $p < 0.05$. (C) Comparison of contralateral bone at both time points after fracture. For all graphs, error bars are ± SD.

As shown in Table 3, there were statistically significant differences in BV, BV/TV (%), callus Cs.AR (mm^2) and BMC for the AMG-162 treated mice, as compared to the alendronate treated mice at 42 days post fracture. Alendronate treatment increased BV, BV/TV (%), and BMC significantly relative to the vehicle control 42 days post-fracture. In addition, denosumab had an increase in cross sectional area as compared to the vehicle control mice, based on MicroCT analysis of the fractured bones.

Reference ID: 3168397

TABLE 3. MICROCT ANALYSIS OF FRACTURED BONES

	ALN	AMG	Control
Post-fracture - Day 21			
TV (mm^3)	49.79 ± 21.49	50.23 ± 15.88	41.12 ± 13.70
BV (mm^3)	23.74 ± 7.98	33.99 ± 8.44*D	17.31 ± 5.83
BV/TV (%)	50.28 ± 9.15	70.72 ± 16.17*D	42.38 ± 3.85
BMC (mg HA)	23.152 ± 7.83	30.47 ± 6.64*	18.26 ± 5.92
Callus Cs.Ar (mm^2)	7.53 ± 2.39	7.46 ± 1.59	6.35 ± 1.63
Post-fracture - Day 42			
TV (mm^3)	42.33 ± 16.60	43.13 ± 11.35	28.41 ± 15.11
BV (mm^3)	23.12 ± 9.08*	39.20 ± 11.83*D	11.91 ± 4.65
BV/TV (%)	56.36 ± 10.69*	90.15 ± 10.5*D	46.94 ± 11.91
BMC (mg HA)	26.70 ± 9.23*	41.07 ± 11.44*D	14.00 ± 5.29
Callus Cs.Ar (mm^2)	6.34 ± 1.96	6.77 ± 1.24*	4.51 ± 1.92

Data shown are mean values ± SD. Significant differences between ALN, AMG, and the control within the same time point are denoted with Significant differences between ALN or AMG, to control within the same time point are shown by*. D indicates significant difference between AMG and ALN. All values indicated as significant are at $p < 0.05$.

In Figure 4B below, the stiffness of the fractured bone between vehicle, denosumab, and alendronate treated, knock-in mice were similar on day 21, while both alendronate and denosumab treatment induced statistically significant increases in stiffness in the mice femurs. As shown in Figure 5, the twist to failure parameter was similar between all treatment groups, and at both the time points. Furthermore, in Figure 6, the toughness parameter was similar between all treatments and at both the time points.

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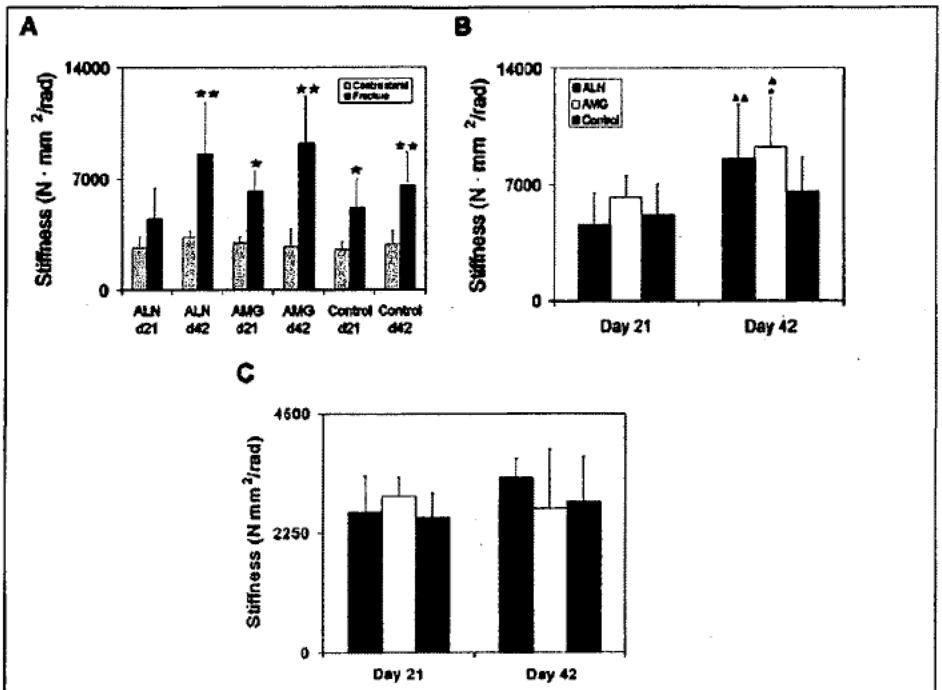

Figure 4. Graphical analysis of torsional stiffness. (A) Comparison between fracture and intact bones. Stars indicate significance between fracture and contralateral bones. (B) Comparison of fracture bones at both time points after fracture. Triangles indicate significance relative to the same treatment group at day 21. Asterisks indicate significance relative to the control at the same time point. (C) Comparison of contralateral bone at both time points after fracture. For all graphs, error bars are ± SD. Single notations indicate significance at $p < 0.05$; double notations indicate significance at $p < 0.01$.

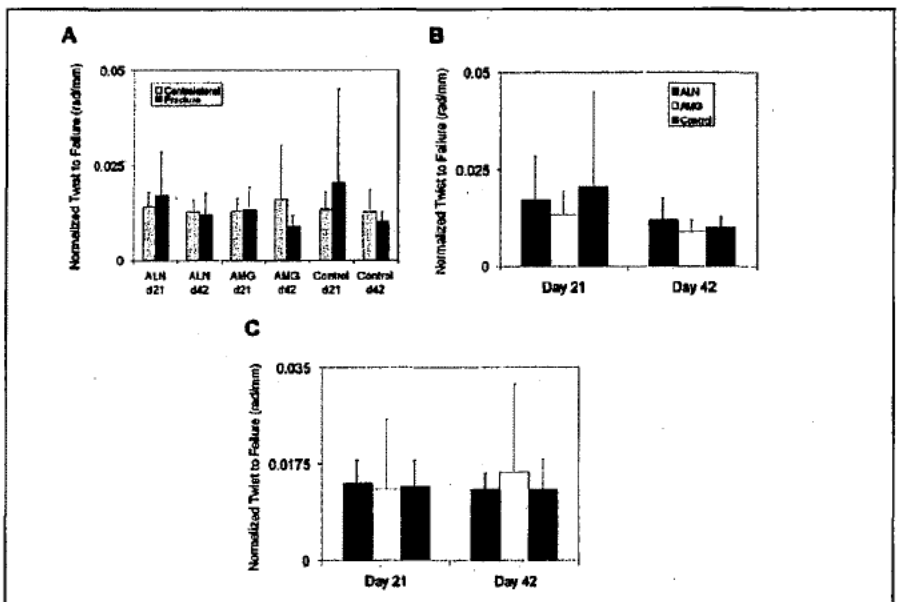

Figure 5. Graphical analysis of twist to failure normalized by gauge length. (A) Comparison between fracture and intact bones. (B) Comparison of fracture bones at both time points after fracture. (C) Comparison of contralateral bone at both time points after fracture. For all graphs, error bars are ± SD. No significant differences were observed.

Reference ID: 3168397

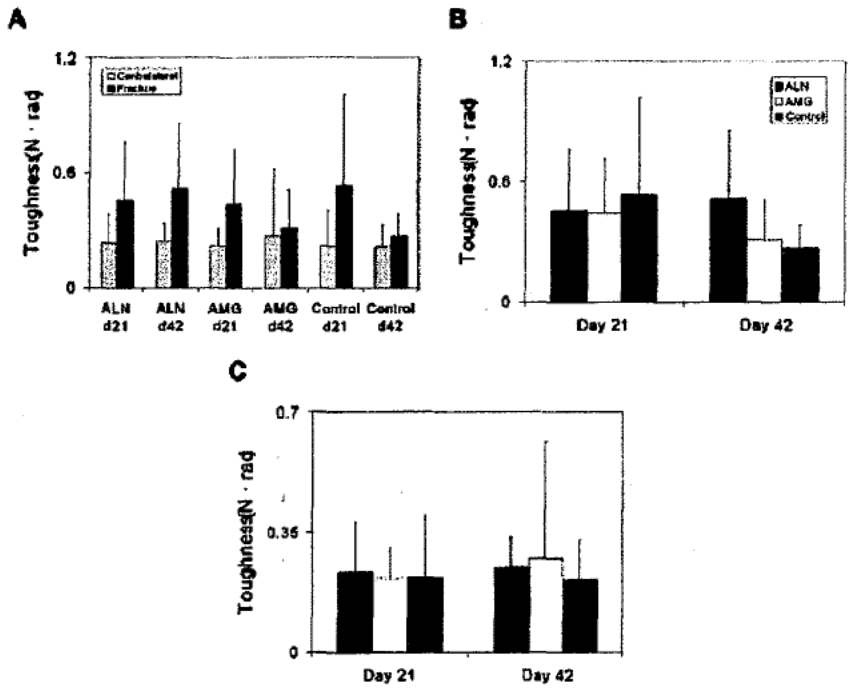

Figure 6. Graphical analysis of toughness (work to failure). (A) Comparison between fracture and intact bones. (B) Comparison of fracture bones at both time points after fracture. (C) Comparison of contralateral bone at both time points after fracture. For all graphs, error bars are ± SD. No significant differences were observed.

As displayed in Figure 8 below showing the representative microCT single slices of the fracture calluses 42 days after fracture, the morphometry of bone healing, i.e. fracture calluses from the AMG 162-treated mice were morphologically distinct as compared to the alendronate and vehicle-treated mice. In addition, the fracture calluses for the AMG-162 treated knock-in mice 42 days post fracture had increased bone volume (BV), BV (%), bone mineral content (BMC), trabecular thickness, and BV/TV (%) relative to alendronate and vehicle control mice (see Figure 9, below).

Reference ID: 3168397

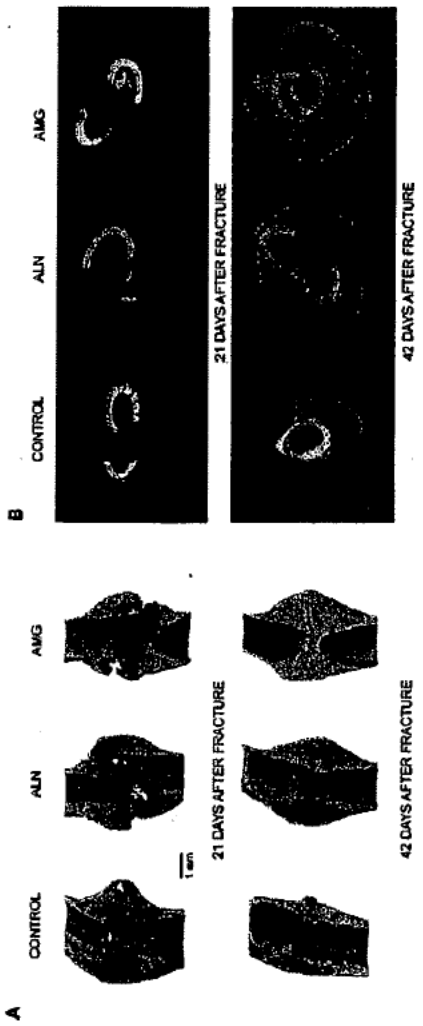

Figure 8. MicroCT images of fracture healing in control, ALN, and AMG mice showing delay in remodeling. (A) Representative 3-D reconstructions of fracture calluses at 21 and 42 days after fracture (coronal plane cutaway). (B) Representative microCT single slices of fracture calluses at 21 and 42 days after fracture (transverse section).

Reference ID: 3168397

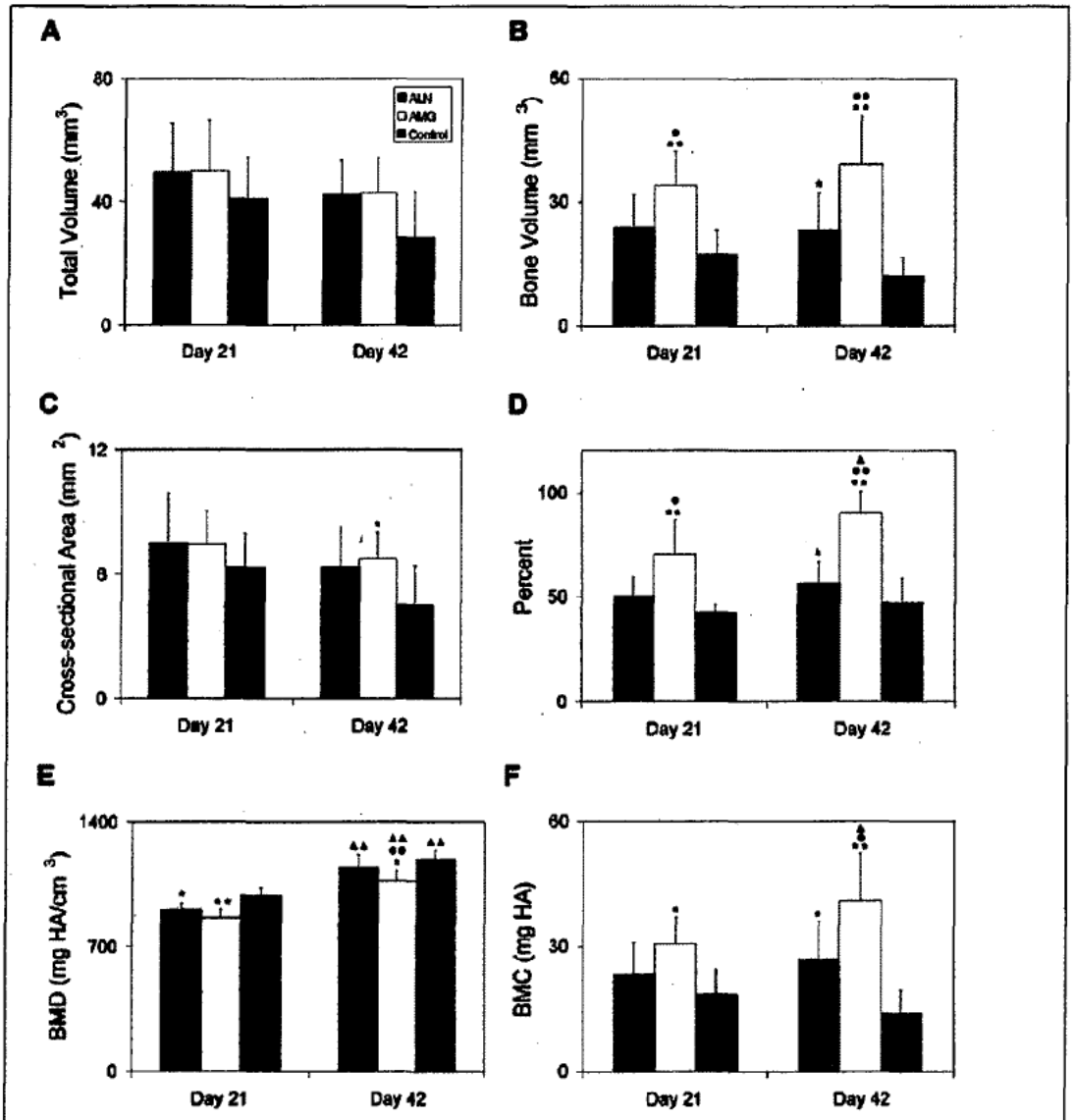

Figure 9. Graphical analysis of microCT measurements of fracture calluses. (A) TV. (B) BV. (C) Cs.Ar. (D) BV%. (E) BMD. (F) BMC. For all graphs, error bars are ± SD. Triangles indicate significance relative to the same treatment group at day 21. Dots indicate significance between ALN and AMG treatment groups at the same time point. Asterisks indicate significance relative to the control at the same time point. Single notations indicate significance at $p < 0.05$; double notations indicate significance at $p < 0.01$.

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Study Conclusions:

The results from this study provide evidence that both alendronate and AMG-162 induced morphological delays in fracture healing, based on the results from the 21 and 42 post-fracture time points. Furthermore, both alendronate and AMG-162 treatment delayed the removal of cartilage, remodeling of the fracture callus, and resulted in altered bone morphologies as compared to the control mice. Both alendronate and denosumab treated mice had greater areas of tissues with reduced amounts of mineral content in the 21 day post-fracture calluses, as compared to the control calluses. The areas of low mineral content correlated with areas of unresorbed cartilage based on the qualitative histological analysis at day 21. The data indicate that the time course of cartilage resorption and tissue remodeling was delayed in mice treated with either AMG-162 or alendronate fracture healing, as compared to fracture healing in the control mice.

The fracture calluses in the AMG-162-treated mice were morphologically distinct as compared to the vehicle control or alendronate-treated mice. In addition, the fracture calluses for the AMG-162 treated knock-in mice 42 days post fracture had increased bone volume (BV), BV (%), bone mineral content (BMC), trabecular thickness, and BV/TV (%), relative to alendronate and vehicle control mice (see Figure 9).

Even with the morphological differences observed on Day 42, and the increased BV, BV (%), BV/TV (%), BMC, and trabecular thickness, the mechanical strength of the bone was not negatively affected. Instead, at the 42 day time point both AMG-162 and alendronate treatment induced increases in the strength and stiffness (see Table 1; Figures 4 and 5 above for the supporting data). Alendronate and AMG-162 increased the torsional stiffness of the bone as compared to the contralateral (nonfractured) femur on days 21 and 42. In addition, alendronate and AMG-162 treatment increased the stiffness of the healing, fractured femur relative to the vehicle control mice at day 42 post-fracture.

There was a small (~ 8%) but significant reduction in maximum torque in the alendronate treated group femurs as compared to the control, and an increase in maximum torque relative to vehicle control on days 21 and 42 post-fracture. AMG-162 increased the torsional rigidity at day 42 post-fracture relative to the control. Overall, the maximum torque and torsional rigidity were approximately similar between the treatment groups (alendronate, AMG-162, and vehicle control) on day 21 and day 42 post-fracture.

2.6.2.2 **Secondary pharmacodynamics**

In addition to the RANK/RANKL pathway being a key regulator of osteoclast formation, survival, and function, RANKL is expressed on activated T and B cells, and RANK is expressed in mature dendritic cells. The RANKL-RANK pathway has been shown to modulate AIRE+ (autoimmune regulator) thymic medullary epithelial cells and RANKL mRNA is expressed in the adult thymus in mice[23]. It should be noted that Aire-

[2] White et al. Sequential phases in the development of Aire-expressing medullary thymic epithelial cells involve distinct cellular input. Eur. J. Immunol. 2008; 38: 942-947.

Reference ID: 3168397

expressing medullary thymic epithelial cells play a roll in preventing autoimmunity. Of importance, dendritic cells are specialized cells designed to capture and process antigens. Contact with an antigen induces the maturation of the dendritic cells in response to inflammatory stimuli. The mature dendritic cells then migrate to secondary lymphoid organs and interact with T and B cells that are involved with the adaptive immune responses. There is evidence in the literature indicating that RANKL expression is induced in the skin following inflammation of the skin by ultraviolet radiation exposure or infection[4]. Furthermore, mice engineered to overexpress RANKL, albeit high levels via the keratin-14 promoter, displayed decreases in cutaneous contact hypersensitivity responses[4]. There are data in the literature using animal models which indicate that the inhibition of the RANK/RANKL signal transduction pathway could potentially compromise immune functions necessary to avoid the development of infections, result in increases in contact hypersensitivity responses (contact dermatitis), or increase autoimmunity responses. It is currently unclear what threshold of suppression of the RANK/RANKL pathway is necessary to modulate the immune functions discussed above, as many of the studies were performed in animals completely devoid of RANKL or RANK expression, or in animal models that express exceedingly high levels of RANKL or RANK. Studies investigating osteoprotegerin (OPG) that inhibits RANKL in mice indicated that OPG did not affect cell-mediated reactions such as contact hypersensitivity to the hapten oxazolone, or liver damage, granuloma formation, and infectious load in response to mycobacterial infection. However, OPG increased humoral reactions such as production of IgM, IgG, and IgE against the T cell dependent keyhole limpet hemocyanin, and the production of IgM against the T cell independent antigen Pneumovax[5].

The absence of RANKL or RANK genes in knock-out mice leads to the complete failure of lymph node development and an absence of lactation via the inhibition of mammary gland maturation. High levels of protein expression have been observed in skeletal and lymphoid tissues. In addition, RANKL mRNA expression has been detected in keratinocytes of skin, mammary epithelial cells, heart, skeletal muscle, lung, stomach, placenta, thyroid gland and brain[6]

Inhibition of the RANK/RANKL in knock-out mice and in rats expressing osteoprotegerin (OPG) induced a failure of incisor tooth eruption. The 12-month toxicology study in cynomolgus monkeys (study number 102090; previously reviewed by Dr. Ron Wange) provides evidence that inhibition of the RANKL/RANK pathway with denosumab induced deleterious changes in the epiphyseal growth plates that were not closed prior to treatment. A copy of Dr. Wange's review is included as an appendix in

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[3] Rossie S. et al. RANK singals from CD4+3- inducer cells regulate development of Aire-expressing epithelial cells in the thymic medulla. J. Exp. Med. 2007; 204: 1267-72.
[4] Loser, K. et al. Epidermal RANKL controls regulatory T-cell numbers via activation of dendritic cells. Nat. Med. 2006; 12: 1372-1379.
[5] Stolina, M. et al. Regulatory effects of osteoprotegerin on cellular and humoral immune responses. Clin Immunol. 2003; 109: 347-54.
[6] Leibbrandt A. and Penninger J. RANK/RANKL: Regulators of Immune Responses and Bone Physiology. Ann. N.Y.Acad.Sci. 2008; 1143: 123-150.

Reference ID: 3168397

Dr. Kim Hatfield's review (cross-reference review STN BLAs #125320 and #125331 for more details).

Based on this study and data provided in the submission and reviewed by Dr. Kim Hatfield (please cross-reference review STN BLAs #125320 and #125331 for more details), the sponsor has indicated that denosumab should not be used in pediatric patients in the proposed product label.

2.6.2.4 Safety pharmacology

Study title: A Single-Dose Subcutaneous Administration of AMG-16 for Cardiovascular and Respiratory Evaluation in Cynomolgus Monkeys

Key findings:

- A single subcutaneous injection of AMG-162 (denosumab) at 0.3, 3, 30 mg/kg did not induce changes in clinical signs, body weight, blood pressure, heart rate, body temperature or respiration rate, relative to the vehicle control dose group.
- The ECG recordings were normal for animals in all dose groups evaluated throughout the seven day monitoring period, except for one male monkey in the 3 mg/kg dose group that had a run of four ventricular premature complexes approximately 45 minutes following administration of AMG-162. Following this run of four ventricular premature complexes, the ECG readings for this animal returned to normal for the rest of the 7 day duration of this study.

Comment: Female monkeys were not evaluated in this safety pharmacology study. As the indicated patient populations include women with breast cancer undergoing hormone ablation therapy and women with postmenopausal osteoporosis, it is unclear why female monkeys were not evaluated in this safety pharmacology study (b) (4)

Study #: (b) (4), Amgen study number 101606

Volume # and Page #: EDR file
Conducting Laboratory and Location: (b) (4)

Date of Study Initiation: not specified (final report dated July 27, 2001)
GLP Compliance: yes
QAU statement: yes (X) no ( )
Drug Lot #: 049A053686 (denosumab), 124K4712 (alendronate), 049A022940 (denosumab vehicle)

Reference ID: 3168397

Methods: (abstracted from the final study report)

The test article, AMG 162, and the vehicle control article, AMG 162 Placebo, were supplied by the Sponsor as preformulated aqueous solutions in 1- and 5-mL vials, respectively, and were maintained at –70° to –76° and 3° to 5°C, respectively, when not in use. The concentration of the active ingredient in the test article solution was 30 mg/mL. This solution was used as received for administration of the highest dose, and was diluted with AMG 162 Placebo for preparation of the middle- and low-dose solutions.

A total of 12 male cynomolgus monkeys were used in this study. The animals were experimentally naïve, and ranged from 2.3 to 7.3 years of age and 2.4 to 5.2 kg in weight at the outset of the study. At least 10 days prior to administration of the test or control article, a radiotelemetry transmitter was surgically implanted into each animal for monitoring and recording cardiovascular parameters.

The animals were assigned to treatment groups as shown in the table below.

Group No.	Day of Dosing	Dose Level (mg/kg)	Dose Volume (mL/kg)	Dose Solution Concentration (mg/mL)	Route of Administration	Number of Animals (Male)
1	Day 1	0 (control)	1.0	0	Subcutaneous	3
2	Day 1	0.3	1.0	0.3	Subcutaneous	3
3	Day 1	3	1.0	3	Subcutaneous	3
4	Day 1	30	1.0	30	Subcutaneous	3

Each animal received a single dose of test or vehicle-control article by subcutaneous injection on Day 1. Cardiovascular data (i.e., blood pressure, heart rate and electrocardiographic activity) and body temperature data were collected via telemetry prior to and following dose administration, beginning approximately one hour prior to dose administration and continuing until approximately 168 hours (7 days) postdose. In addition, the study animals were evaluated for changes in clinical signs by way of routine cageside observations, and respiration rate was measured by visual observation predose and 72 hours postdose. Blood samples were collected for test article concentration analysis prior to dosing, at approximately 48 and 96 hours (T_{max}) postdose, and on Day 8 (final day of the study). At the end of the study, the animals were returned to the (b) (4) animal colony.

Results:

A single subcutaneous injection of AMG-162 at 0.3, 3, 30 mg/kg did not induce changes in clinical signs, body weight, blood pressure, heart rate, body temperature or respiration rate based on the evaluation of three male monkeys per dose group relative to the vehicle control cohort. The ECG recordings were normal for animals in all dose groups evaluated throughout the seven day monitoring period, except for one monkey (F7481CQM) in the 3 mg/kg dose group, who had a run of four ventricular premature complexes (VPC) approximately 45 minutes following administration of AMG-162. This particular monkey did not display changes in blood pressure or heart rate near the time of the multiple VPC occurrences (see Table 4a and 5a below). Furthermore, the ECG readings returned to normal at the subsequent time points following this isolated event.

Reference ID: 3168397

Table 4a: Individual Animal and Group Mean Blood Pressure
Study Number: 1129-01

Animal Number	Sex	Mean Arterial Pressure mmHg Approximate Recording Intervals (minutes) -60	-50	-40	-30	-20	-10	10	20	30	40	50	60	70
Group 1: Control (0 mg/kg)														
F20-122M	M	124	126	128	128	139	142	141	142	141	130	120	120	122
FN14930M	M	123	123	119	119	120	130	131	120	120	116	109	108	103
FN15538M	M	134	133	123	110	111	129	139	113	106	98	97	97	96
Mean		127	127	123	119	123	134	134	125	122	116	109	108	107
S.D.		6	5	5	9	14	7	6	15	18	16	12	12	13
Group 2: AMG 162 (0.3 mg/kg)														
FN14001M	M	119	130	124	121	119	111	115	114	111	110	104	98	98
FN14560M	M	138	123	125	134	139	134	129	118	114	109	105	109	106
F15633M	M	94	90	87	89	87	91	88	79	76	78	82	78	70
Mean		117	114	112	115	115	112	111	104	100	99	97	95	92
S.D.		22	21	22	23	26	22	21	21	21	16	13	15	20
Group 3: AMG 162 (3 mg/kg)														
F15544M	M	104	101	92	88	89	105	89	82	84	83	79	86	95
F15676M	M	96	101	102	99	95	94	98	94	89	87	88	86	86
F7481CGM	M	123	122	118	117	114	115	112	102	103	109	105	103	99
Mean		108	108	104	101	99	105	100	93	92	93	91	92	93
S.D.		14	12	13	15	13	11	12	10	10	14	13	10	7
Group 4: AMG 162 (30 mg/kg)														
F7958CGM	M	105	102	99	105	108	106	101	100	97	91	90	90	90
FN14928M	M	150	146	142	145	157	159	154	148	133	131	126	127	127
FN15411M	M	131	131	126	128	124	136	132	127	112	110	110	109	106
Mean		129	126	122	126	130	134	129	124	114	111	109	108	108
S.D.		23	22	22	20	25	27	27	23	18	20	18	19	19

Reference ID: 3168397

Table 5a: Individual Animal and Group Mean Heart Rate
Study Number: 1129-01

Animal Number	Sex	Heart Rate (beats per minute) Approximate Recording Interval (minutes) -60	-50	-40	-30	-20	-10	10	20	30	40	50	60	70
Group 1: Control (0 mg/kg)														
F20-122M	M	243	234	238	233	238	241	242	246	240	219	196	201	204
FN14910M	M	230	230	229	227	219	230	238	235	229	218	205	193	180
FN16038M	M	229	236	228	204	219	249	246	222	202	183	172	170	166
Mean		267	233	232	221	225	240	242	234	224	207	191	188	183
S.D.		7	3	6	15	11	10	4	12	20	21	17	16	19
Group 2: AMG 162 (0.3 mg/kg)														
FN14001M	M	194	228	218	210	215	223	206	184	180	171	149	139	134
FN14960M	M	250	226	221	231	240	250	238	216	204	183	167	164	177
F15629M	M	232	231	209	192	187	203	195	169	150	142	144	131	114
Mean		225	228	216	211	214	225	213	190	178	166	153	161	142
S.D.		29	3	11	20	27	24	22	24	27	21	12	29	32
Group 3: AMG 162 (3 mg/kg)														
F15544M	M	214	219	204	185	176	204	192	183	170	140	130	146	158
F15675M	M	179	204	213	202	189	187	196	206	197	169	164	148	144
F7481CQM	M	255	238	226	231	231	236	216	197	170	162	160	150	154
Mean		216	220	214	206	199	209	201	192	179	157	151	151	152
S.D.		38	17	11	23	29	25	13	12	16	15	19	6	7
Group 4: AMG 162 (30 mg/kg)														
F7958CQM	M	242	242	230	233	241	246	242	232	226	202	199	199	196
FN14028M	M	220	208	190	190	202	209	215	201	169	187	154	152	148
FN15411M	M	258	251	250	247	251	258	254	244	223	206	201	202	193
Mean		240	267	228	228	231	238	237	226	206	192	185	184	179
S.D.		19	27	31	30	26	26	20	22	32	21	27	28	27

Comment: The toxicological significance of the ECG findings for the one monkey (F7481CQM) in the 3 mg/kg dose cohort is unknown at this time. The isolated ventricular premature complexes were not evident at later time points in this particular monkey. No other abnormalities in the electrocardiograms were observed in animals in the vehicle control, 0.3 or 30 mg/kg dose groups, which comprised the evaluation of 11 other monkeys. This reviewer does not believe that the ECG abnormality documented for this one monkey was due to the administration of AMG-162, based on the collective information provided in this study.

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Toxicokinetics: (as provided in the final study report)

Title: Toxicokinetics from "A Single Dose Subcutaneous Administration of AMG 162 for Cardiovascular and Respiratory Evaluation in Cynomolgus Monkeys"

Responsible Scientist: (b) (6) **Final Report: June 18, 2001**

Objectives: To examine the effects of subcutaneous administration of AMG 162 on cardiovascular parameters and respiratory rate in conscious, unrestrained cynomolgus monkeys.

Study Design:

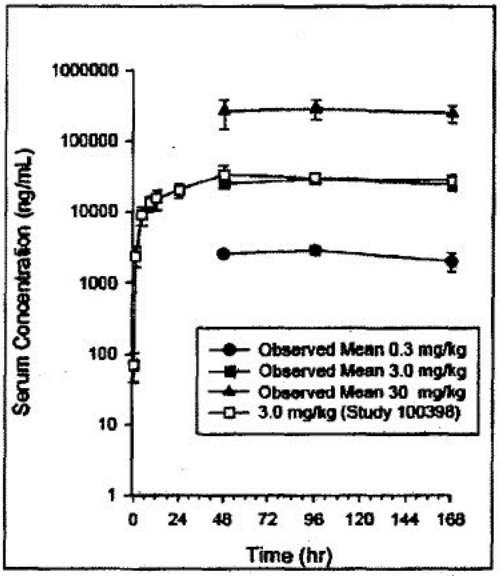
Test Compound: AMG 162
Dosing Scheme: Single Dose Subcutaneous
Lot Number(s): AMG 162 #A0010170015
AMG 162 Placebo #A0010260000
Formulation: liquid, Solution of 5% sorbitol and 10mM sodium acetate

Assay Type: ELISA, GLP
LOQ: 0.960 ng/mL
Compliance: GLP

Mean ± SD AMG 162 Serum Concentrations[a] (ng/mL)

Time (hr)	Placebo (n=3)		0.3 mg/kg (n=3)		3.0 mg/kg (n=3)		30 mg/kg (n=3)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Predose	0[b]	0	0	0	0	0	0	0
48	0	0	2570	231	25100	2710	269000	119000
96	0	0	2890	350	29200	1190	291000	94100
168	0	0	2000	576	24100	3850	249000	63500

[a]Values are reported to 3 significant figures. [b]All values below the quantification limit are reported as zero



Summary:

No animals that were to be dosed with placebo had measurable levels of AMG 162, while all animals that were to receive AMG 162 via subcutaneous injection had measurable post-dose levels. Maximum mean concentrations of test article were observed on day 5 for all dose groups. Serum levels at the 3 mg/kg dose were consistent with serum levels from a previous study, which included the same dose of the test article. The mean concentrations at each time point increased in a dose proportional manner in the dose range of 0.3 to 30 mg/kg. There is no evidence to contradict the assumption that all animals received the correct dose of test article.

Comments: AMG-162 exposure levels were maintained for the duration of this study. A dose-dependent increase in the concentrations of AMG-162 from 0.3, 3, and 30 mg/kg were observed in the monkeys following subcutaneous administration.

Study conclusions: A single subcutaneous dose of AMG-162 from 0.3, 3, and 30 mg/kg did not induce blood pressure, heart rate, body temperature, or respiration rate changes over a seven day follow-up evaluation period. This reviewer believes that the lack of time and dose dependence for the development of the ventricular premature complexes in one out of the 12 male monkeys suggest that this ECG abnormality was not due to a

Reference ID: 3168397

treatment effect of the 3 mg/kg dose of AMG-162. Currently, there is no clear scientific explanation for why the four ventricular premature complexes were observed in the single male monkey from this dose cohort.

Comment: The ability to identify cardiac or pulmonary safety pharmacology issues based on single dose of denosumab is limited. Furthermore, this study utilized a single dose of AMG-162, which would not enable concentrations of denosumab to reach steady state and subsequent penetration of deep tissue compartments in the animals.

Abuse liability: Not applicable

2.6.2.5 Pharmacodynamic drug interactions

No studies of this type were included in the present submission.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Table 1. Pharmacology Overview – Safety Pharmacology
Test Article: AMG 162

Type of Study	Species/ Strain	Method of Administration	Doses (mg/kg)	Sex and No. per Group	Evaluation	Noteworthy Findings	GLP Compliance	Study Number
	Cynomolgus Monkeys	SC (single dose)	0 (vehicle), 0.3, 3.0, 30	3M	Cardiovascular	No treatment-related effects on evaluated cardiovascular parameters (heart rate, systolic pressure, diastolic pressure, mean arterial pressure, body temperature, or ECG recordings). NOAEL: 30 mg/kg	Yes	101606 (1129-01)
					Respiratory	No treatment-related effects on evaluated respiratory parameter (respiratory rate) NOAEL: 30 mg/kg		
					Toxicokinetics	Concentration (ng/mL)[a]		
						Dose (mg/kg) / Mean / SD		
						0 (Vehicle) / 0 / (0)		
						0.3 / 2890 / (350)		
						3.0 / 29200 / (1190)		
						30 / 29100 / (94100)		

[a] Serum concentration measured at 96 hours postdose; n = 3/group. ECG = electrocardiogram; GLP = Good Laboratory Practice; SC = subcutaneous; M = male; NOAEL = no observed adverse effect level; SD = standard deviation.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The single dose and multiple dose pharmacokinetics (PK) of subcutaneous (SC) or intravenous (IV) administration of denosumab were evaluated in mice and cynomolgus monkeys. A comparison between the SC and IV route of administration of a 1 mg/kg

Reference ID: 3168397

dose in mice indicated that regardless of the route of administration, the serum concentration was similar between the 1 mg/kg SC and 1 mg/kg IV dose groups. The bioavailability in mice was 86.1% following SC administration as compared to the 1 mg/kg IV dose group. Following IV administration of denosumab to mice, the V_{ss} values observed indicated that denosumab was residing in the vascular space, and was not distributing to other extravascular compartments.

Based on the studies conducted in male and female FcRn knockout and wild type mice, the presence of FcRn decreases the clearance and tissue distribution of denosumab. The half-life in the WT mice was ~ 26 fold longer as compared to the FcRn knock-out (KO) mice, and there was ~ 15 fold increase in the clearance rate for the FcRn KO mice as compared to the WT mice administered denosumab. There was a reduction in the V_{ss} in the FcRn KO animals (V_{ss} = 52.3 mL/Kg at 0.1 mg/kg and 58.6 ml/kg at 1 mg/kg) as compared to the WT animals (V_{ss} = 97.6 at 0.1 mg/kg and 100 at 1 mg/kg). The WT mice displayed ~ 15 fold greater exposure based on the $AUC_{0\text{-}inf}$ as compared to FcRn KO mice.

Radiolabeled ^{125}I-AMG-162 was widely distributed in animals administered 0.1 and 1 mg/kg doses. In the 0.1 mg/kg dose group, radioactivity was identified in all tissues except bone marrow, brain and muscle at 672 hours postdose. The highest concentrations were observed at the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, serum, axillary lymph nodes, inguinal lymph nodes, blood, spleen, and ovaries. In the 1 mg/kg dose group, radioactivity was quantified in all tissue types examined at 672 hours and in approximately half of the tissues at the 1344 hours postdose. The highest concentrations of radioactivity were observed at the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, axillary lymph nodes, serum, blood, ovaries, and lungs. As expected, high concentrations of ^{125}I-AMG-162 were present in the various lymph nodes. An unexpected finding was that ^{125}I-AMG-162 accumulated in the cornea of the eye in both the male and female cynomolgus monkeys.

The distribution of denosumab was evaluated *ex vivo* in a series of tissue cross-reactivity studies using samples from adult, fetal human, cynomolgus monkey, rabbit, and rat tissue sections. In tissue cross-reactivity studies in the rabbit and monkey, AMG-162 bound to cells in the periphery of the cortex of lymph nodes and lymphoid nodules of the spleen, and the periphery of lymphoid nodules in the gut-associated lymphoid tissue of the small and large intestines. In human tissues, denosumab cross reacted to cells in the lymph node of 1/3 human donors, and displaying weak to moderate (1-2^{+}) membrane staining of lymphocytes lining the periphery of the paracortex in the lymph node. In the rat, AMG-162 bound to chondrocytes and the margins of their surrounding lacunae in the articular cartilage.

In cynomolgus monkeys, the major route of elimination of ^{125}I-AMG-162 and or radioactively labeled protein fragments was in the urine, with 80-95% of the administered activity was present in the urine 672 hours postdose. Fecal elimination represented 1.8 to 3% of the administered radioactivity.

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2.6.4.2 Methods of Analysis

[see under individual study reviews]

2.6.4.3 Absorption

^{125}I-AMG-162 was widely distributed in animals administered the 0.1 and 1 mg/kg doses. In the 0.1 mg/kg dose group, radioactivity was identified in all tissues except bone marrow, brain and muscle at 672 hours postdose. The highest concentrations were observed at the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, serum, axillary lymph nodes, inguinal lymph nodes, blood, spleen, and ovaries.

In the 1 mg/kg dose group, radioactively was quantified in all tissue types examined at 672 hours and in approximately half of the tissues at the 1344 hours postdose. The highest concentrations of radioactivity were observed at the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, axillary lymph nodes, serum, blood, ovaries, and lungs.

Study title: Absorption, Distribution, and Excretion in Cynomolgus Monkeys Following a Single Subcutaneous Administration of ^{125}I-AMG-162

Key findings:

- The highest concentrations of radioactivity were observed in the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, axillary lymph nodes, inguinal lymph nodes, serum blood, lungs, spleen and ovaries following administration of 0.1 or 1 mg/kg of ^{125}I-AMG-162.

- The major route of elimination of ^{125}I-AMG-162 and or radioactively labeled protein fragments was in the urine, as 80-95% of the administered activity was present in the urine 672 hours postdose. Fecal elimination represented 1.8 to 3% of the administered radioactivity.

Study Number: Amgen Study No. 104192 and (b) (4)
Volume # and Page #: EDR file
Conducting Laboratory and Location: (b) (4)

Date of Study Initiation: September 2, 2004 (final report dated December 20, 2007)
GLP Compliance: Yes
QAU statement: yes () no (X)
Drug Lot #: ^{125}I-Denosumab # 52318-18; Denosumab # A0206120000, Vehicle # A0108030000

Reference ID: 3168397

Methods: The goal of this study was to determine the extent of absorption, distribution, and excretion of radioactivity following a single subcutaneous administration of ^{125}I-AMG-162 given to female monkeys. The study took serum samples to determine if anti-AMG-12 antibodies were present or absent, determined C-Telopeptide concentrations, and AMG-162 concentrations. Fourteen female drug naïve Cynomolgus monkeys from [redacted] (b) (4) were used, but these animals were originally of Chinese origin. The animals were fasted overnight prior to the subcutaneous dose administered via syringe and needle in the dorsal scapular region. The animals were observed twice daily and weighed on the day of dose administration, and every two weeks during the test period. Blood collections were taken predose 1 (3 days prior to dose administration), predose 2 (on the day of dose administration), and at 0.5, 4, 12, 24, 120, 168, 336, 408, 504, 672, 1008, 1176, and 1344 hours postdose.

Study Design below:

Study Design

Monkeys were assigned to two groups for this study. At designated times following dosing, blood, urine, feces, and selected tissues were collected. The group designations, number of animals, target dose levels, and target dose volumes were as follows:

Group	Number of Female Animals	Target Dose Level (mg/kg)	Dose Route	Target Dose Volume (mL/kg)	Samples Collected
1	6	0.1	Subcutaneous	1	Blood, Urine, Feces, and Tissues
2	8	1	Subcutaneous	1	Blood, Urine, Feces, and Tissues

Note: Animals in Group 1 received approximately 64 µCi/kg. Animals in Group 2 received approximately 77 µCi/kg.

Tissue distribution was evaluated in the tissues listed below for 2 monkeys per/time point at 12, 120 and 672 hours, following blood collections and necropsy:

Adrenal glands	Lungs
Bladder (urinary)	Lymph nodes (axillary)
Blood	Lymph nodes (inguinal)
Bone (femur)	Muscle (thigh)
Bone (lumbar vertebrae L3 and L4), see protocol deviations	Ovaries
Bone (thoracic vertebrae T3 and T4), see protocol deviations	Salivary glands
Bone marrow (from femur)	Serum
Brain	Skin (abdominal)
Dose site (skin)	Small intestine
Dose site (subcutaneous tissue)	Spleen
Eyes (both)	Stomach
Fat (reproductive)	Synovial fluid (knee)[a]
Heart	Thymus
Kidneys	Thyroid/parathyroid
Large intestine	Uterus
Liver	

a Collection was attempted. In some instances, no synovial fluid was obtained.

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Radioanalysis:

The radioactivity in the serum samples was analyzed for radioactivity in a Packard COBRA II 5003 solid scintillation counter for at least 5 minutes or until 1,000,000 counts. The results were calculated as ^{125}I dpm/g sample. All samples were analyzed in duplicate as long as the sample size was of sufficient size to process in duplicate.

Results:

The ^{125}I-AMG-162 was widely distributed in animals administered the 0.1 and 1 mg/kg doses. In the 0.1 mg/kg dose group, radioactivity was identified in all tissues except bone marrow, brain and muscle at 672 hours postdose. The highest concentrations were observed at the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, serum, axillary lymph nodes, inguinal lymph nodes, blood, spleen, and ovaries.

In the 1 mg/kg dose group, radioactively was quantified in all tissue types examined at 672 hours and in approximately half of the tissues at the 1344 hours postdose. The highest concentrations of radioactivity were observed at the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, axillary lymph nodes, serum, blood, ovaries, and lungs.

Anti-AMG-162 antibodies were present in all animals that were on-study through 672 and 1344 hours postdose.

The percent of radioactive dose in urine following a single subcutaneous dose of ^{125}I-AMG-162 at 0.1 mg/kg was approximately 80 to 95% of the administered radioactivity and fecal elimination represented approximately 1.8 to 3.1% of the administered amount at 672 hours postdose. Overall recoveries of radioactivity at the 672 hour postdose time were approximately 92-106% of the dosed radioactivity.

For the animals administered 1 mg/kg of ^{125}I-AMG-162, approximately 76-79% of the radioactive dose was recovered in the urine, and 1.1 to 2.8% administered radioactivity was recovered in the feces at the 1344 hours postdose. At the 1344 hour time-point, approximately 81 to 88% of the dosed radioactivity was recovered in the study. Approximately 12-19% of the ^{125}I-AMG-162 and or radioactively labeled fragments of ^{125}I-AMG-162 were not accounted for at the 1344 hour time-point.

Study conclusion:

The major route of elimination for AMG-162 is in the urine with approximately 80-95% of the administered radiolabel detected in urine by 1344 hours post-dose. The minor route of elimination was in the feces, with approximately 1-3% being recovered through this route of elimination.

The highest concentrations of radioactivity were observed at the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, axillary lymph nodes, serum, blood, and ovaries

Reference ID: 3168397

for both the 0.1 mg/kg and 1 mg/kg dose groups of ^{125}I-AMG-162. For monkeys treated with the 0.1 mg/kg dose of ^{125}I-AMG-162, there were higher concentrations of radioactivity in the inguinal lymph nodes and spleen that were not observed in the 1 mg/kg dose group. The 1 mg/kg dose group had higher concentrations of radioactivity in the lungs; this finding was not observed in the lower dose group.

Comment:
The data provides evidence that denosumab concentrates in the lung. However, based on the 1 month and 6/12 month toxicology studies that utilized doses that were 10 and 50 fold higher (10 mg/kg and 50 mg/kg respectively), no lung toxicity was observed in these repeat dose toxicology studies.

Study title: Pharmacokinetic Study of Denosumab (AMG-162) in Male Mice Following Intravenous or Subcutaneous Administration

Key Findings:

- Following subcutaneous (SC) administration of 1 mg/kg, the C_{max} was reached 72 hours post-dose and the half-life was 18.5 hours, which was similar to the half-life observed following IV administration. The clearance was similar between the 1 mg/kg SC and 1 mg/kg IV dose groups.

- Bioavailability was 86.1% following SC administration

Study Number: Amgen Study No. 101494
Volume # and Page #: EDR file
Conducting Laboratory and Location: Amgen Inc., One Amgen Center Drive, Thousan Oaks, CA 91320-1799
Date of Study Initiation: Not specified when study was initiated (final report dated February 1, 2007)
GLP Compliance: No
QAU statement: yes () no (X)
Drug Lot #: Denosumab # A0010170015; Denosumab formulation buffer A0010260000

Methods: Two hundred male C57BL/6J mice between 7 and 11 weeks old and weighing between 15 and 30 grams were dosed with a single SC or IV injection of denosumab (Lot Number A0010170015) or vehicle (denosumab formulation buffer, lot number A0010260000), as shown in Table 6-1. Approximately 0.5 ml of whole blood was collected via cardiac puncture from 2 animals from each group at sampling times (pre-dose, 15 and 30 minutes post dose, 1, 4, 8, 12, 24, 48, 72, 120, 168, 216, 336, 408, 504, 576, 672, 744, 912, 1080, 1248, 1416, 1584, and 1752 hours post-dose). Whole blood samples were collected into Microtainer Brand Serum Separator Tubes, and kept at room temperature for approximately 20 minutes to clot. The samples were then centrifuged at approximately 11,500 rpm for 10 minutes at 26°C, and the collected serum stored at approximately -70°C. Concentrations of denosumab in serum were determined using a sandwich ELISA assay with a limit of detection (LOD) of 0.781 ng/ml. The ELISA used

Reference ID: 3168397

utilized osteoprotegerin (OPG) for capture and detection of the analyte (denosumab). Noncompartmental analysis was performed using WinNonlin Professional (version 4.1e, Pharsight Corporation, Mountain View, CA). This was a non-GLP study.

Study Design (from the sponsor's study report):

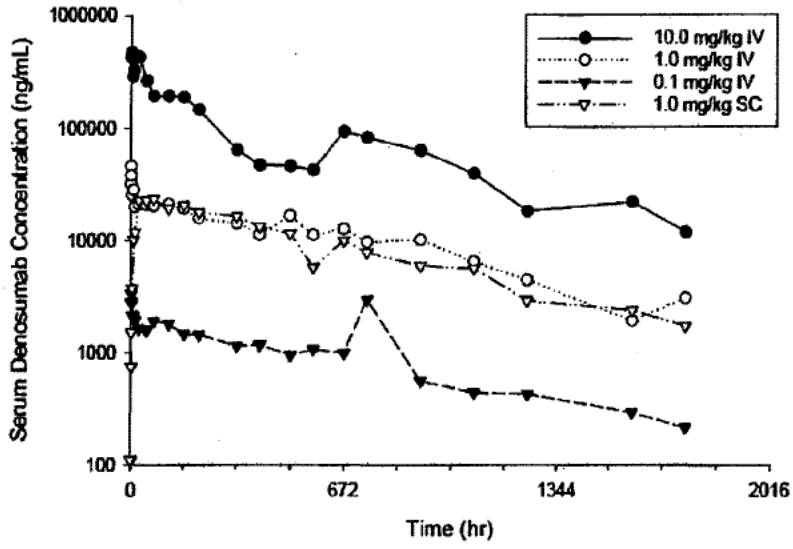
Table 6-1. Experimental Design

Group	Animal Numbers	Route	Dose (mg/kg)	Dose Rate (mL/kg)	Approximate Dose Volume[a] (mL)
1	1-50	SC	1.0	1	0.025
2	51-100	IV	0.1	1	0.025
3	101-150	IV	1.0	1	0.025
4	151-200	IV	10.0	1	0.025

[a]Approximate dose volumes assumes a body weight of approximately 0.025 kg per mouse.

Results: The V_{ss} was approximately 40.1 mL/kg following IV administration of 1 mg/kg denosumab in mice, which indicates that denosumab is staying in the vascular space and is not widely distributed in the body. Following SC administration of denosumab at 1 mg/kg, the half-life was similar as compared to 1 mg/kg administered via IV, the C_{max} was reached 72 hours post-dose, and the bioavailability was approximately 86% in mice. Furthermore, as displayed in Figure 8-1, the serum concentrations of denosumab in mice over time were similar regardless whether the route of administration was 1 mg/kg IV or 1 mg/kg SC.

Figure 8-1. Composite Mean Serum Denosumab Concentration-Time Profiles Following SC or IV Administration to Male Mice (N=2/timepoint/group)



Reference ID: 3168397

Table 8-1. Denosumab Pharmacokinetic Parameters Following SC or IV Administration of Denosumab to Male Mice
(based on composite sampling, N=2 mice/timepoint/group)

Parameter	Units	Route (Dose, mg/kg)			
		SC (1.0)	IV (0.1)	IV (1.0)	IV (10.0)
T_{max}	hr	72	NA	NA	NA
C_0[a]	µg/mL	23.1	3.91	31.9	511
$t_{1/2,z}$	days	18.5	17.5	19.3	19.2
$AUC_{0\text{-}inf}$	µg*hr/mL	15600	1680	18100	128000
CL[b]	mL/hr/kg	0.0642	0.0594	0.0553	0.0778
V_{ss}	mL/kg	NA	43.5	40.2	48.6
F	%	86.1	NA	NA	NA

[a] C_{max} for SC dose group
[b] CL/F for SC dose group
NA = Not applicable
C_0 = initial serum concentration
C_{max} = maximum observed concentration
T_{max} = time of C_{max}
$t_{1/2,z}$ = half-life
$AUC_{0\text{-}inf}$ = Area under the concentration time curve from time 0 to infinity
CL = Clearance
CL/F = Apparent clearance
V_0 = Initial volume of distribution
V_{ss} = Volume of distribution at steady state
F = Bioavailability
Values are reported to 3 significant figures, except for T_{max} which is reported to 2 significant figures.

Study Conclusion: The serum concentrations of denosumab in mice over time were similar regardless of whether the route of administration was 1 mg/kg subcutaneous or 1 mg/kg intravenous. Furthermore, the bioavailability was approximately 86% in mice administered denosumab through the subcutaneous route of administration.

Study title: A Single Dose Pharmacokinetics Study of Denosumab (AMG-162) Following Intravenous Administration to Male and Female FcRn Knockout and Wild Type Mice

Key Findings:

- The presence of the FcRn decreases the clearance and tissue distribution of denosumab in mice.
- The half-life in the WT mice was ~ 26 fold longer as compared to the FcRn KO mice, and there was ~ 15 fold increase in the clearance rate for the FcRn KO mice as compared to the WT mice administered denosumab.

Reference ID: 3168397

- There was a reduction in the V_{ss} in the FcRn KO animals (V_{ss} = 52.3 mL/Kg at 0.1 mg/kg and 58.6 ml/kg at 1 mg/kg) as compared to the WT animals (V_{ss} = 97.6 at 0.1 mg/kg and 100 at 1 mg/kg). The WT mice displayed ~ 15 fold greater exposure based on the $AUC_{0\text{-}inf}$.

Study Number: Amgen Study No. 106892
Volume # and Page #: EDR file
Conducting Laboratory and Location: Amgen Inc., One Amgen Center Drive, Thousan Oaks, CA 91320-1799
Date of Study Initiation: Not specified when study was initiated (final report dated February 1, 2007)
GLP Compliance: No
QAU statement: yes () no (X)
Drug Lot #: Denosumab # 049A041380; Denosumab formulation buffer 049A037350

Methods: The purpose of the study was to characterize the single dose pharmacokinetics of denosumab following intravenous administration to male or female FcRn knockout (KO) and wild type (WT) mice, with a weight range of 15-27 grams. One hundred and eighty male and female FcRn KO or WT mice were administered 0.1 mg/kg or 1 mg/kg denosumab via a single bolus IV injection. Whole blood was collected via cardiac puncture from three mice per time point specified below, under section 6.3 (from the sponsor's final study report). The concentration of denosumab in serum was determined using an ELISA assay with a Lower Limit of Quantitation (LLOQ) of 10 ng/ml. Noncompartmental analysis was performed using WinNonlin Professional (version 4.1e, Pharsight Corporation, Mountain View, CA).

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Study Design:

6.2 Control and Test Articles

Test Article:	Denosumab (AMG 162) (60 mg/mL)
Lot Number:	049A041380
Dose Vehicle:	Denosumab (AMG 162) Placebo
Lot Number:	049A037350
Formulation:	10mM Sodium Acetate, 5% Sorbitol, pH 5.2

6.3 Study Design

One hundred eighty male or female B6.129P2-*B2m*^{tm1Unc}/J (FcRn Knockout) and C57BL/6J (Wild Type) mice between 5 and 15 weeks of age and weighing between 15 and 27 grams, were administered a 0.1 or 1.0 mg/kg single bolus IV dose of denosumab as described in Table 6-1. Whole blood was collected via cardiac puncture from three mice per time point per group at pre-dose, 1, 8, 24, 48, 72, 96, 120, 168, 240, 336, 504, 672, 1008, and 1344 hours post-dose. Whole blood samples were collected in Microtainer Brand Serum Separator Tubes and stored at room temperature for approximately 20 minutes or until fully clotted. Serum was extracted by centrifugation at approximately 11,500 rpm for 10 minutes.

Table 6-1. Study Design

Group	Test System Number	Strain	Dose (mg/kg)
1	1-45	Wild Type	0.1
2	46-90	FcRn KO	0.1
3	91-135	Wild Type	1.0
4	136-180	FcRn KO	1.0

Results: Following a single intravenous dose of 0.1 or 1 mg/kg denosumab, pharmacokinetic parameters were similar for the FcRn KO and WT mice (see Table 8-1 above). There was a dose-proportional increase based on the serum concentration and $AUC_{0\text{-}inf}$ from 0.1 and 1 mg/kg denosumab in both the FcRn KO and WT mice, and the initial volume of distribution was similar as well.

However, the half-life in the WT mice was ~ 26 fold longer as compared to the FcRn KO mice, and there was ~ 15 fold increase in the clearance rate for the FcRn KO mice as compared to the WT mice administered denosumab. There was a reduction in the V_{ss} in the FcRn KO animals (V_{ss} = 52.3 mL/Kg at 0.1 mg/kg and 58.6 ml/kg at 1 mg/kg) as compared to the WT animals (V_{ss} = 97.6 at 0.1 mg/kg and 100 at 1 mg/kg). The WT mice displayed ~ 15 fold greater exposure based on the $AUC_{0\text{-}inf}$.

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Figure 8-1. Composite Mean (±SD) Serum Denosumab Concentration-Time Profiles Following IV Administration of Denosumab to FcRn Knockout or Wild Type Mice (N = 3 mice/timepoint/group)

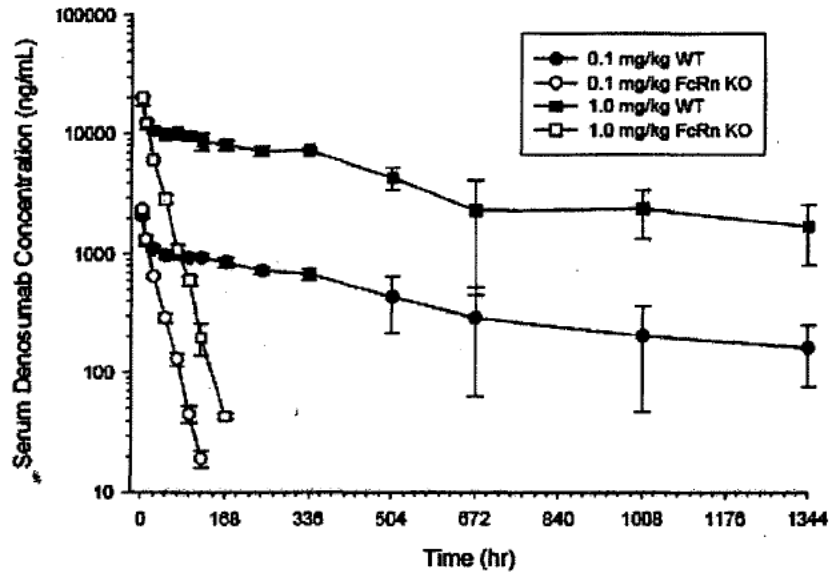

Table 8-1. Pharmacokinetic Parameter Estimates Following a Single IV Administration of 0.1 mg/kg or 1.0 mg/kg Denosumab to FcRn Knockout or Wild Type Mice

Parameter	0.1 mg/kg IV		1.0 mg/kg IV	
	Group 1 (WT)	Group 2 (FcRn KO)	Group 3 (WT)	Group 4 (FcRn KO)
C_0 (µg/mL)	2.21	2.55	20.8	21.7
$AUC_{0\text{-}inf}$ (µg•hr/mL)	685	48.5	6910	455
$t_{1/2,z}$ (hr)	489	18.1	506	20.2
CL (mL/hr/kg)	0.146	2.06	0.145	2.20
V_0 (mL/kg)	45.2	39.3	48.0	46.0
V_{ss} (mL/kg)	97.6	52.3	100	58.6

Values are reported to 3 significant figures

Study Conclusion:

Overall, the presence of the FcRn in mice leads to an increase in the clearance of denosumab, and a reduction in the steady-state tissue distribution, based on the calculated V_{ss} values.

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2.6.4.4 Distribution

The three studies below were designed to determine the potential for denosumab cross-reactivity with human and animal tissues. Densoumab bound to the lymph nodes of human and cynomolgus monkey tissues. Specific binding of denosumab (AMG-162) in the monkey and rabbit occurred in a periphery of the cortex of the lymph nodes, the periarteriolar lymphoid sheaths, and lymphoid nodules of the spleen and at the periphery of lymphoid nodules in the gut-associated lymphoid tissue (GALT) of the small and large intestine, at concentrations of 5 and 25 mcg/mL. In the rat, denosumab at 5 and 25 mcg/mL stained chondrocytes and the margins surrounding lacunae in the articular cartilage.

The fourth study reviewed in this section was titled "Quantitative Whole Body Autoradiography of Cynomolgus Monkeys Following a Single Subcutaneous Administration of ^{125}I-AMG-162" that determined in which areas of the body that ^{125}I-AMG-162 distributed following a single subcutaneous dose.

Study title: Cross-Reactivity of AMG-162 with Normal Human Tissues

Key findings:

- AMG-162 cross-reacted to the lymph node of one human donor. AMG-162 displayed weak to moderate (1-2^{+}) membrane staining of lymphocytes lining the periphery of the paracortex in the lymph node.

Study Number: Amgen Study No. 101348 and (b) (4)
Volume # and Page #: EDR file
Conducting Laboratory and Location: (b) (4)
Date of Study Initiation: ~ initiation on January 8, 2001 (final report dated May 15, 2001)
GLP Compliance: Yes
QAU statement: yes (X) no ()

Methods: Fresh unfixed tissue samples were stored in OCT embedding medium and maintained at -70°C until sectioning. Tissue sections were cut to approximately 5 µm thickness and fixed in acetone for 10 minutes, desiccated and stored below -70°C. Sections were then fixed in 10% neutral buffered formalin (NBF) for 10 seconds just prior to staining. AMG-162 conjugated with FITC was applied to human tissues (three donors per tissue) at 1 and 10 µg/mL. The negative control antibody was a Human IgG2 conjugated with FITC. The (b) (4) cell line capable of overexpressing osteoprotegerin ligand was used as the positive control and the cell line (b) (4) that did not express osteoprotegerin was used as the negative control.

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Results: AMG-162 cross-reacted to the lymph node tissue sample from one human donor, with weak to moderate (1-2$^+$) membrane staining of lymphocytes lining the periphery of the paracortex in the lymph node at 1 and 10 mcg/mL of denosumab.

Study conclusion: AMG-162 had very limited binding to normal human tissues based on this cross-reactivity study. Only lymphocytes in the paracortex in the lymph node provided a positive signal in this study.

Study title: Cross-Reactivity of AMG-162 with Normal Cynomolgus Monkey and Human Tissues

Key findings:

- AMG-162 cross-reacted in the lymph node in 3/3 cynomolgus monkey donors.
- AMG-162 cross-reacted to the lymph node tissue from one human donor.

Study Number: Amgen Study No. 101758 and (b) (4)
Volume # and Page #: EDR file
Conducting Laboratory and Location: (b) (4)

Date of Study Initiation: Initiation date was identified in the report (final report dated July 2, 2001)
GLP Compliance: No
QAU statement: yes () no (X)

Methods: Fresh unfixed tissue samples were stored in OCT embedding medium and maintained at -70°C until sectioning. Tissue sections were cut to approximately 5 µm thickness and fixed in acetone for 10 minutes, desiccated and stored below -70°C. Sections were then fixed in 10% neutral buffered formalin (NBF) for 10 seconds just prior to staining. AMG-162 conjugated with FITC was applied to human tissues (three donors per tissue) at 1 and 10 µg/mL. The negative control antibody was a Human IgG2 conjugated with FITC. The (b) (4) cell line capable of overexpressing osteoprotegerin ligand was used as the positive control, and the cell line (b) (4) that did not express osteoprotegerin was used as the negative control.

Results: AMG-162 cross-reacted to the lymph node tissue from one human donor. AMG-162 displayed weak to moderate (1-2$^+$) membrane staining of lymphocytes lining the periphery of the paracortex of lymph nodes in normal cynomolgus monkey tissues. Nonspecific staining based on binding of both denosumab and negative control antibodies to multiple tissue structures was observed for bone marrow cells, lymphoid organs, gastrointestinal lamina propria and whole blood neutrophils and eosinophils.

Study conclusion: AMG-162 had very limited binding to normal human tissues based on this cross-reactivity study. Only lymphocytes in the paracortex of the lymph node provided a positive signal in the monkey.

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Study title: Cross-Reactivity of AMG-162 with Cynomolgus Monkey, Rat and Rabbit Tissue *Ex Vivo*.

Key findings:

- In the rabbit and monkey, AMG-162 bound to the periphery of the cortex of lymph nodes and lymphoid nodules of the spleen, and at the periphery of lymphoid nodules in the gut-associated lymphoid tissue of the small and large intestines.

- In the rat, AMG-162 bound to chondrocytes and the margins of their surrounding lacunae in the articular cartilage.

Study Number: Amgen Study No. 102700 and [redacted]
Volume # and Page #: EDR file
Conducting Laboratory and Location: [redacted]
Date of Study Initiation: August 30, 2002 (final report May 8, 2003)
GLP Compliance: Yes
QAU statement: yes (X) no ()

Methods: Cynomolgus monkey, rat and rabbit tissues were from the [redacted] tissues bank collected by [redacted]. Tissues used in this study were from naive animals. Fresh unfixed cynomolgus monkey, rat and rabbit tissue samples were collected as necropsy specimens, frozen in Tissue-Tek OCT compound and maintained at approximately -65 to -80°C **until use.** The positive control was [redacted] cells that expressed human OPG ligand, and the negative control was [redacted] cells that lacked expression of human OPG. Tissue sectioning and fixation process consisted of placing fresh unfixed tissue samples into molds filled with Tissue-Tek OCT compound and frozen on dry ice. **Sections of approximately 7 µm in thickness were cut and** mounted onto slides. The slides with the tissues were fixed in acetone for 10 minutes at room temperature and then air dried overnight. Slides were used immediately or stored at approximately 65 to -86°C **until they were stained.** The staining procedure consisted of incubating dilutions of AMG-162 or human IgG2 kappa with biotinylated goat anti-human IgG and adding this mixture to the slides. Avidin/biotin incubations were performed and the labeling reagent utilized was [redacted] After immunohistochemical staining with AMG-162 (denosumab), sections were visualized under light microscopy for determination of AMG-162 binding.

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Slide Evaluation Procedure:

Test and Measurements

All slides were evaluated by the Pathologist and/or Study Director to ensure that the quality of stain was sufficient for interpretation. Each slide was examined for the presence and strength of labeling, as well as the distribution and relative density of positive cells for each antibody.

The relative density of positive cells was graded on the following scale:

0 or – or Blank	No labeled cells
1+ or +	Light stain and/or occasional cells
2+ or ++	Light-medium stain and/or small numbers of cells/types of cells
3+ or +++	Moderate stain and/or medium numbers of cells/types of cells
4+ or ++++	Dark stain and/or large numbers of cells/types of cells
N/A	Not applicable or Not available

The distribution and intensity of each of the markers studied was summarized in a Microsoft Excel (Version Excel 2000) spreadsheet detailing the finding for individual slides. There were no statistical analyses performed on these data.

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The following tissues from three separate individuals per species were evaluated in this study.

Cynomolgus Monkey Tissue from 3 Separate Individuals

- Adrenal
- Bladder
- Blood
- Bone
- Bone Marrow
- Breast
- Cerebellum
- Cerebral Cortex
- Colon
- Endothelium*
- Eye
- Fallopian Tube
- Gastrointestinal Tract
- Heart
- Kidney (glomerulus)
- Kidney (tubule)
- Liver
- Lung
- Lymph Node
- Ovary
- Pancreas
- Parathyroid
- Pituitary
- Prostate
- Skin
- Spinal Cord
- Spleen
- Striated Muscle
- Testes
- Thymus
- Thyroid
- Tonsils
- Ureter
- Uterus (cervix)
- Uterus (endometrium)

*Cynomolgus monkey endothelium was evaluated from multiple tissue types.

Rat Tissue from 3 Separate Individuals

- Adrenal
- Bladder
- Blood
- Bone
- Bone Marrow
- Breast
- Cerebellum
- Cerebral Cortex
- Colon
- Endothelium (Aorta)
- Eye
- Fallopian Tube
- Gastrointestinal Tract
- Heart
- Kidney (glomerulus)
- Kidney (tubule)
- Liver
- Lung
- Lymph Node
- Ovary
- Pancreas
- Parathyroid
- Pituitary
- Prostate
- Skin
- Spinal Cord
- Spleen
- Striated Muscle
- Testes
- Thymus
- Thyroid
- Uterus (cervix)
- Uterus (endometrium)

Rabbit Tissue from 3 Separate Individuals

- Adrenal
- Bladder
- Blood
- Bone
- Bone Marrow
- Breast
- Cerebellum
- Cerebral Cortex
- Colon
- Endothelium
- Eye
- Fallopian Tube
- Gastrointestinal Tract
- Heart
- Kidney (glomerulus)
- Kidney (tubule)
- Liver
- Lung
- Lymph Node
- Ovary
- Pancreas
- Parathyroid
- Pituitary
- Prostate
- Skin
- Spinal Cord
- Spleen
- Striated Muscle
- Testes
- Thymus
- Thyroid
- Uterus (cervix)
- Uterus (endometrium)

Results: In the rabbit and monkey, AMG-162 bound to the periphery of the cortex of lymph nodes and lymphoid nodules of the spleen, and at the periphery of lymphoid

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nodules in the gut-associated lymphoid tissue of the small and large intestines. In the rat, AMG-162 bound to chondrocytes and the margins of their surrounding lacunae in the articular cartilage, based on evaluating tissue from 3 separate rats.

Study conclusion: In both cynomolgus monkey and rabbit, AMG-162 bound to lymph nodes, lymphoid nodules in the spleen, and gut-associated lymphoid tissue (GALT) of the small and large intestine.

Study Title: Quantitative Whole Body Autoradiography of Cynomolgus Monkeys Following a Single Subcutaneous Administration of ^{125}I-AMG-162.

Key Findings:

- As expected, high concentrations of ^{125}I-AMG-162 were present in the various lymph nodes.
- An unexpected finding was that ^{125}I-AMG-162 accumulated in the cornea of the eye in both the male and female cynomolgus monkeys.

Comments: Based on the toxicology studies, there was no evidence that the eye was a target organ for toxicity following monthly subcutaneous administration of 1, 10, or 50 mg/kg doses of AMG-162 to cynomolgus monkeys for 12 months. In addition, there was no evidence of an increased incidence of cataracts in the monkey toxicology studies. It should be noted that a higher incidence of cataract formation was only observed in the clinical study of prostate cancer patients treated with denosumab.

Study Number: Amgen Study No. 104105
Volume # and Page #: EDR file
Conducting Laboratory and Location: (b) (4) (b) (4)
Date of Study Initiation: August 30, 2002 (final report May 8, 2003)
GLP Compliance: No
QAU statement: yes () no (X)
Drug Lot #: ^{125}I-Denosumab # 52318-35; Denosumab # A0206120000, Vehicle # A0108030000

Methods:

^{125}I-AMG-162 was administered subcutaneously in the back to non-fasted cynomolgus monkeys at 0.1 (3 males and 3 females) and 1 mg/kg doses (4 males and 4 females). The animals were observed twice daily for any signs of pain or distress. Once daily observations of general health and appearance were performed, and the monkeys were weighed every 2 weeks during the study. Blood was collected at two predose time points and at time intervals from 0.5, 4, 12, 24, 120, 336, 408, 504, 672, 840, 1008, 1176, and

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1344 hours post dose. Furthermore, whole-body autoradiography was performed at 12, 120 and 672 hours following the 12, 120 and 672 hour blood collections (1 animal/sex/time) in 0.1 mg/kg dose group. In the 1 mg/kg dose group, blood collections and whole body autoradiography were performed on 1 animal/sex/time at 12, 120, 672, and 1344 hour time points.

Group	Number of Animals		Target Dose Level (mg/kg)	Dose Route	Target Dose Volume (mL/kg)	Samples Collected
	Males	Females				
1	3	3	0.1	Subcutaneous	1	Blood and Carcasses for WBA
2	4	4	1	Subcutaneous	1	Blood and Carcasses for WBA

WBA Whole-body autoradiography.

Results: Highest concentrations of radioactivity were observed following administration of 0.1 mg/kg dose of ^{125}I-AMG-162 at the dose site, thyroid, axillary lymph nodes, inguinal lymph nodes, cervical lymph nodes, gastric mucosa, esophageal contents, stomach contents, and areas in the spleen for both males and females. For the 1 mg/kg ^{125}I-AMG-162 dosed animals, the highest concentrations of ^{125}I-AMG-162 was observed in the dose site, thyroid, gastric mucosa, blood, lung, liver and cervical lymph nodes in both males and females. Males had high levels of ^{125}I-AMG-162 in the stomach contents, mesenteric lymph nodes, prostate, and stomach. Females had high levels of radiolabel present in the axillary lymph nodes, ovary, and nasal turbinates.

Comment: No basis was identified for the differences in the distribution patterns for either gender or different doses of denosumab.

All animals in the 0.1 and 1 mg/kg groups of ^{125}I-AMG-162 displayed anti-AMG-162 antibodies. Male monkeys in the 0.1 mg/kg dose group gave positive ADA results at the 672 hour time point, and female monkeys in this same dose group were positive for ADA at the 336 and 672 hour time points. For the 1 mg/kg ^{125}I-AMG-162 group, both male and female monkeys tested positive for anti-AMG 126 antibodies at the 336 hour, 672 hour, and Day 56 time points.

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Figures 33 and 43 below were copied from the submission. The figures indicated that ^{125}I-AMG-162 is accumulating in the cornea in both male and female monkeys 672 hours postdose.

Figure 33
Whole-body autoradiograph of radioactivity at 672 hours postdose for Animal I02715 (Group 2 male Cynomolgus monkey) after administration of a single subcutaneous dose of ^{125}I-AMG 162 (1 mg/kg, Levels 3 and 4)

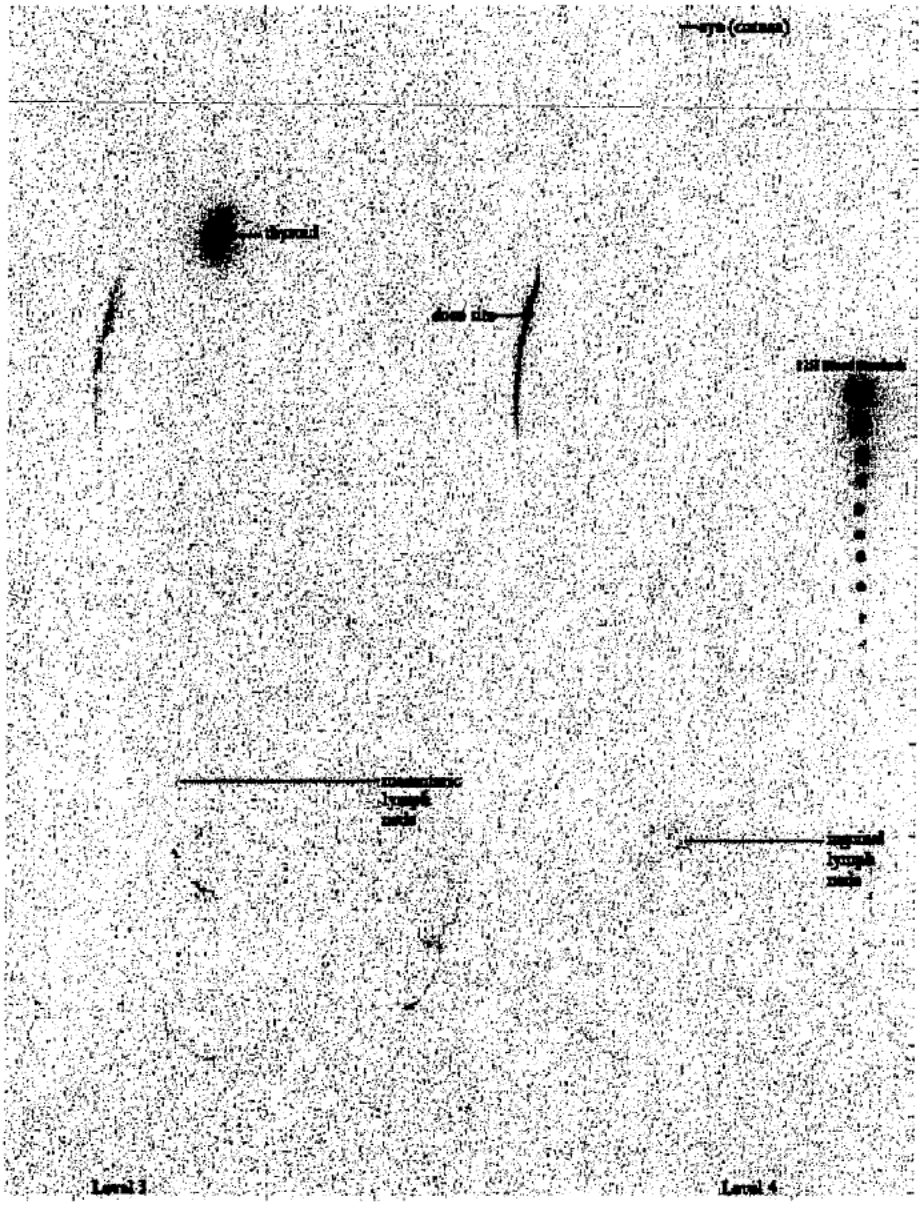

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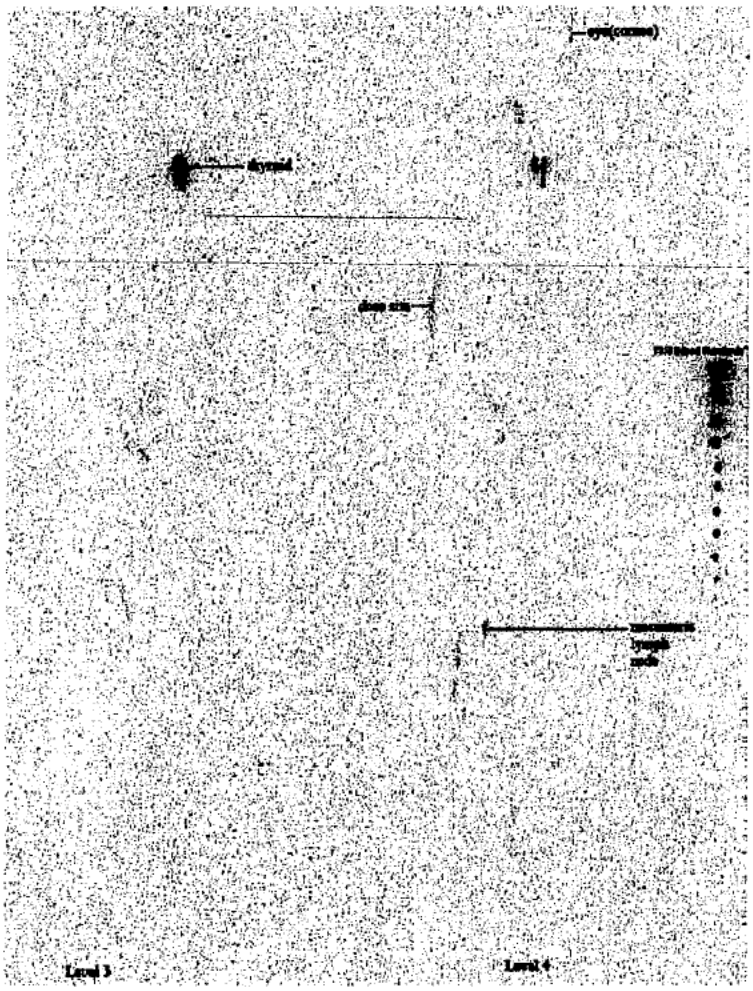
Figure 43
Whole-body autoradiograph of radioactivity at 672 hours postdose for Animal I02723 (Group 2 female Cynomolgus monkey) after administration of a single subcutaneous dose of ^{125}I-AMG 162 (1 mg/kg, Levels 3 and 4)



Except for the 0.5 hours postdose, at which time TCA-precipitable radioactivity was 51.5% for males and 42.9% for females, the mean serum TCA-precipitable radioactivity values in males and females were greater than 83% for all collection time points.

Comments:

It is unknown what the effects of anti-AMG-162 antibodies have on the distribution of ^{125}I-AMG-162 in the cynomolgus monkey at this time. It is clear that AMG-162 induces a robust immunogenicity response in monkeys.

Based on the previous experience in the monkey, naked AMG-162 has maintained pharmacological activity between monthly dosing intervals. During the study, C-telopeptide levels were monitored, and there were reductions in C-telopeptide (serum

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bone resorption biomarker) from 38-70% depending on the time point and dose group evaluated. This provides supporting data that the ^{125}I-AMG-162 was pharmacologically active during the duration of the study. It is unclear, however, how much intact ^{125}I-AMG-162 versus ^{125}I-AMG-162 antibody fragments were present in the tissues that the ^{125}I-AMG-162 is accumulating in, such as the cornea. Based on the tissue-cross reactivity study, AMG-162 did not bind to the monkey or human eye tissue (see Studies #101348 [human] and #101750 [monkey]). However, ^{125}I-AMG-162 accumulated in the lymph nodes in both female and male monkeys (see Figures 33 and 43), which was an expected finding, i.e. based on the tissue cross-reactivity studies (Studies # 101348 and #101750, above), AMG-162 bound to the lymph nodes in both monkey and human tissues.

It is currently unclear what the physiological significance of potentially intact ^{125}I-AMG and/or ^{125}I-AMG-162 antibody fragment(s) accumulation in the cornea of the monkey is. Based on the toxicology studies provided in this submission, ocular toxicity was not detected in the cynomolgus monkeys at the doses and time points examined in the 1 and 6-12 month repeat dose toxicology studies (Study #101447 and Study #102090; Study #102090 was initially reviewed by Dr. Ron Wange and is included in Dr. Hatfield's review, and is hereby cross-referenced to her review of STN BLAs #125320 and #125331).

2.6.4.5 Metabolism

No studies of this type were included in the present submission.

2.6.4.6 Excretion

After a single SC administration of ^{125}I-denosumab, approximately 80-95% of the administered radioactivity was recovered in the urine, while 1.8 to 3% of the administered radioactivity was recovered in the feces. The overall recovery of administered radioactivity was 83-100%.

2.6.4.7 Pharmacokinetic drug interactions

No studies of this type were included in the submission.

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

In cynomolgus monkeys, denosumab had a half-life of approximately 11-19 days at the higher doses. When administered intravenously (IV), denosumab pharmacokinetics were non-linear from 0.0016-1 mg/kg, and were dose linear for doses $\geq$ 1 mg/kg. Based on the volume of distribution, denosumab remained in the vascular space following IV dosing. Similar to IV dosing, non-linear pharmacokinetics occurred following subcutaneous administration of denosumab at dose ranges from 0.0016 to 1 mg/kg and, and PK were dose proportional after dosing with 1-3 mg/kg. Mean residence time increased with

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increasing dose, while clearance decreased. Anti-drug antibody formation occurred at a high rate in monkeys dosed with denosumab by either the IV or SC routes of administration.

A comparison between the PK following subcutaneous (SC) and intravenous route of administration of 1 mg/kg in mice showed that the serum concentration, regardless of the route of administration was similar between the 1 mg/kg SC and 1 mg/kg IV dose groups. The bioavailability in mice was 86.1% following SC administration, as compared to the 1 mg/kg IV dose group. The volume of distribution after IV administration of denosumab to mice provided evidence that denosumab was residing in the vascular space.

Based on the studies conducted in male and female FcRn knockout and wild type (WT) mice, the presence of FcRn decreases the clearance and tissue distribution of denosumab. The half-life in the WT mice was ~ 26 fold longer as compared to the FcRn knock-out (KO) mice, and there was ~ 15 fold increase in the clearance rate for denosumab in the FcRn KO mice as compared to the WT mice. There was a reduction in the V_{ss} in the FcRn KO animals (V_{ss} = 52.3 mL/Kg at 0.1 mg/kg and 58.6 ml/kg at 1 mg/kg) as compared to the WT animals (V_{ss} = 97.6 at 0.1 mg/kg and 100 at 1 mg/kg). The WT mice displayed ~ 15 fold greater exposure based on the $AUC_{0\text{-inf}}$, as compared to FcRn KO mice. In huRANKL knock-in (KI) and WT mice, single dose i.v. administration of AMG 162 resulted in faster elimination in KI mice versus WT mice, as no ligand exists for AMG 162 to bind in WT mice.

The ^{125}I-AMG-162 was widely distributed in cynomolgus monkeys administered subcutaneously at 0.1 and 1 mg/kg doses. In the 0.1 mg/kg dose group, radioactivity was identified in all tissues except bone marrow, brain and muscle at 672 hours postdose. The highest concentrations were observed at the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, serum, axillary lymph nodes, inguinal lymph nodes, blood, spleen, and ovaries. In the 1 mg/kg dose group, radioactively was quantified in all tissue types examined at 672 hours, and in approximately half of the tissues at the 1344 hours postdose. The highest concentrations of radioactivity were observed at the dose site skin, dose site subcutaneous tissue, thyroid/parathyroid, axillary lymph nodes, serum, blood, ovaries, and lungs. As expected, high concentrations of ^{125}I-AMG-162 were present in the various lymph nodes. An unexpected finding was that ^{125}I-AMG-162 accumulated in the cornea of the eye in both the male and female cynomolgus monkeys.

The distribution of denosumab was evaluated in a series of *ex vivo* tissue binding studies using samples from adult, fetal human, cynomolgus monkey, rabbit, and rat tissue sections. In tissue cross-reactivity studies with rabbit and monkey samples, AMG-162 bound to cells in the periphery of the cortex of lymph nodes and lymphoid nodules of the spleen, and the periphery of lymphoid nodules in the gut-associated lymphoid tissue of the small and large intestines. In human tissues, denosumab cross reacted to the lymph node cells from 1/3 human donors, showing weak to moderate (1-2^{+}) membrane staining of lymphocytes lining the periphery of the paracortex in the lymph node. In the rat, AMG-162 bound to chondrocytes and the margins of their surrounding lacunae in the articular cartilage.

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In cynomolgus monkeys, the major route of elimination of ^{125}I-AMG-162 and or radioactively labeled protein fragments were in the urine, with 80-95% of the administered radioactivity present in the urine 672 hours postdose. Fecal elimination represented 1.8 to 3% of the administered radioactivity.

2.6.4.10 Tables and figures to include comparative TK summary

Tables and figures as provided by the sponsor are incorporated into the relevant sections of the review.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Table 1. Pharmacokinetics Tabular Summary: Absorption After a Single Dose Test Article: Denosumab

Type of Study / Title	Status	Test System	Objective	Methods	Summary of Results
101494- Pharmacokinetic Study of Denosumab (AMG 162) in Male Mice Following Intravenous or Subcutaneous Administration	Single Dose/ Non-GLP	Mouse	To determine the pharmacokinetics of denosumab in mice following intravenous or subcutaneous administration.	IV, SC bolus dosing 0.1, 1.0, 10.0 mg/kg IV, 1.0 mg/kg SC; Serum samples were collected to determine denosumab concentrations; serum denosumab concentration-time data were analyzed by non-compartmental methods.	Following IV dosing of 0.1 to 10.0 mg/kg, denosumab PK was approximately linear with dose. Exposure based on C_0 and $AUC_{0\text{-}\infty}$ values increased approximately dose-proportionally (76- to 130-fold for the 100-fold increase in dose). Across the IV dose range, CL values were similar (<41% different, mean value 0.0642 mL/hr/kg), as were V_{ss} (<21% different, mean value 44.1 mL/kg) and $t_{1/2,z}$ (<11% different, mean value 18.7 days) values. Following SC administration of 1.0 mg/kg, C_{max} was reached 72 hours post-dose, $t_{1/2,z}$ was similar to those observed following IV dosing, and bioavailability was approximately 86%.
101002 – Pilot Pharmacokinetic Study of AMG 162 Administered Subcutaneously or Intravenously in Male and Female Sprague Dawley Rats	Single Dose/ Non-GLP	Rat	To determine the pharmacokinetic profiles of a human IgG_2 monoclonal antibody (Hu-Mab) to osteoprotegrin ligand (OPGL), AMG 162 in rats following intravenous or subcutaneous administration.	IV, SC bolus dosing 0.0628, 1.0, 10 mg/kg IV, 1.0 mg/kg SC; Serum samples were collected to determine denosumab concentrations and the presence of anti-denosumab antibodies; serum denosumab concentration-time data were analyzed by non-compartmental methods.	Denosumab displayed dose-linear IV pharmacokinetics in the dose range of 0.0628 to 10 mg/kg, with a steady state volume of distribution of approximately 101 mL/kg. The mean terminal-phase half-life was 270 ± 19.4 hrs. Following SC administration of 1.0 mg/kg, peak levels of 6,870 ng/mL occurred 72 hr post-dose and mean bioavailability was 58%.

Reference ID: 3168397

Table 1. Pharmacokinetics Tabular Summary: Absorption After a Single Dose Test Article: Denosumab

Type of Study / Title	Status	Test System	Objective	Methods	Summary of Results
101398 – A Single Dose Intravenous and Subcutaneous Pharmacokinetic and Pharmacodynamic Study of AMG 162 in Cynomolgus Monkeys	Single Dose/ GLP	Cynomolgus Monkey	To evaluate the pharmacokinetics and pharmacodynamics of AMG 162 when administered, as a single subcutaneous or intravenous injection to cynomolgus monkeys.	IV, SC bolus 0.0016, 0.00532, 0.0848, 1.0, 3.0 mg/kg (IV or SC); Serum samples were collected to determine denosumab concentrations and the presence of anti-denosumab antibodies; serum denosumab concentration-time data were analyzed by non-compartmental methods.	Denosumab displayed non-linear pharmacokinetics in cynomolgus monkeys following IV and SC administration. CL increased 16-fold (0.277 to 4.40 mL/hr/kg) following IV administration and CL/F increased 30-fold (0.353 to 10.6 mL/hr/kg) following SC administration as dose decreased from 3.0 mg/kg to 0.0016 mg/kg. However, denosumab PK was approximately dose-linear from 1 to 3 mg/kg for both IV and SC administration. Mean V_{ss} was similar to that of plasma volume (~ 40 mL/kg). Denosumab IV PK was well described by a two-compartmental model with parallel linear and nonlinear Michaelis-Menten elimination. Following SC administration, bioavailability showed a trend of increasing from 28% to 100% with increasing dose (based on compartmental analysis). SC dosing of denosumab caused a rapid (within 24 hours) reduction in bone resorption based on N-telopeptide in serum (sNTx), at doses above 0.00532 mg/kg. The duration of sNTx reduction increased with dose up to 6 weeks over the dose range investigated. A serum denosumab concentration corresponding to half-maximal inhibition of bone resorption (EC_{50}) of 464 ng/mL was estimated based on PK/PD modeling using an indirect effect model. The development of antibodies to denosumab was not route dependent and was associated with more rapid elimination of denosumab for doses above 0.0848 mg/kg.

Table 1. Pharmacokinetics Tabular Summary: Absorption After a Single Dose Test Article: Denosumab

Type of Study / Title	Status	Test System	Objective	Methods	Summary of Results
101606 - A Single Dose Subcutaneous Administration of AMG 162 for Cardiovascular and Respiratory Evaluation in Cynomolgus Monkeys	Single Dose/ GLP	Cynomolgus Monkey	To examine the effects of subcutaneous administration of AMG 162 on cardiovascular parameters and respiratory rate in conscious, unrestrained cynomolgus monkeys.	SC bolus 0.3, 3.0, 30 mg/kg; A limited number of serum samples were collected to determine denosumab concentrations; due to limited data, summary statistics were generated by timepoint, but no PK analysis was performed.	No animals that were to be dosed with placebo displayed quantifiable serum denosumab concentrations, while all animals that were to receive denosumab displayed quantifiable levels. Based on limited TK sampling, maximum mean serum denosumab concentrations were observed on day 5 for all dose groups and increased in an approximately dose-proportional manner.

Reference ID: 3168397

Table 2. Pharmacokinetics Tabular Summary: Absorption After Repeated Doses Test Article: Denosumab

Study Title	Type of Study / Status	Species	Objective	Methods	Summary of Results
102090 – Toxicokinetics Report for a 6/12-Month Subcutaneous Toxicity Study of AMG 162 in the Cynomolgus Monkey with an Interim Kill after 6 Months and a 3-Month Recovery Period	Multiple Dose/ GLP	Cynomolgus Monkey	To evaluate the toxicity of the test article, AMG 162, following subcutaneous administration to the Cynomolgus monkey for 6 or 12 months and to assess the reversibility of effects observed – if any – during a 3-month treatment free-period.	SC bolus 1.0, 10, 50 mg/kg SC once-monthly for 6 or 12 months; Serum samples were collected to determine denosumab concentrations and the presence of anti-denosumab antibodies; serum denosumab concentration-time data were analyzed by non-compartmental methods.	There was no evidence of serum denosumab exposure in control animals. Sex had no apparent impact on denosumab toxicokinetics. Following the first dose, exposure based on mean C_{max} and AUC_{0-t} values increased approximately dose-proportionally from 1 to 50 mg/kg. Following the last dose, exposure increased approximately dose-proportionally from 10 to 50 mg/kg and no accumulation was observed.. Anti-denosumab antibodies were detected in 55.3 % of denosumab-treated animals, which was associated with decreased serum denosumab exposure. However, importantly, only 2 of 16 animals treated with 50 mg/kg monthly (the No-Observed-Adverse-Effect-Level or NOAEL) for 12 months were antibody positive. In the remaining (antibody-negative) animals, the mean AUC_{0-t} value after the last dose was 268 mg*hr/mL, corresponding to an estimated cumulative AUC over a 6-month period of 1608 mg*hr/mL.

Table 2. Pharmacokinetics Tabular Summary: Absorption After Repeated Doses Test Article: Denosumab

Study Title	Type of Study / Status	Species	Objective	Methods	Summary of Results
103981 - A Monthly Subcutaneous Injection Osteoporosis Prevention Study of AMG 162 for 16 Months in the Cynomolgus Monkey	Multiple Dose/ GLP	Cynomolgus Monkey	The purposes of this study were 1) to determine the efficacy of two dose levels of monthly subcutaneous injections of AMG 162 after 16 months of treatment on the preservation of cortical and cancellous bone mass as determined by bone mineral density (BMD) and on strength as determined by biomechanical testing. 2) to evaluate mechanisms by which AMG 162 affects bone by evaluation of biomarkers of bone function and histomorphometric indices of bone function in surgically postmenopausal (ovariectomized or OVX) monkeys.	SC bolus 25, 50 mg/kg once-monthly for 16 months; Serum samples were collected to determine denosumab concentrations and the presence of anti-denosumab antibodies; serum denosumab concentration-time data were analyzed by non-compartmental methods.	There was no evidence of serum denosumab exposure in sham(-operated) or OVX control animals treated with vehicle. In denosumab-treated animals, exposure based on mean C_{max} and AUC_{0-t} values increased approximately dose-proportionally from 25 to 50 mg/kg following the first and last doses, and no accumulation was observed. Anti-denosumab antibodies developed in 25 and 15% of animals receiving 25 and 50 mg/kg, respectively, and were associated with decreased serum denosumab exposure.

Reference ID: 3168397

Table 3. Pharmacokinetics Tabular Summary: Organ Distribution Test Article: Denosumab

Study Title	Type of Study / Status	Species	Objective	Methods	Summary of Results
104105 – Quantitative Whole Body Autoradiography of Cynomolgus Monkeys Following a Single Subcutaneous Administration of ^{125}I-AMG 162 [see also Study 104192, Table 10]	Single Dose/ Non-GLP	Cynomolgus Monkey	To assess the extent of absorption and distribution of radioactivity following a single subcutaneous administration of ^{125}I-AMG 162 given to male and female monkeys.	Single SC bolus dose 0.1 or 1.0 mg/kg At 12, 120, 672, and 1344 (1 mg/kg only) hours post-dose, 1 animal/sex/time-point was sacrificed to examine the tissue distribution by QWBA. Serum samples collected up to 672 or 1344 hours were analyzed for total radioactivity, trichloroacetic acid (TCA)-precipitable radioactivity, and the development of antibodies to denosumab. In addition, serum denosumab and C-telopeptide (CTx) concentrations were determined. Serum denosumab concentration-time data were analyzed by non-compartmental methods.	For both the 0.1 and 1 mg/kg doses, radioactivity was widely distributed in both males and females, with radioactivity quantifiable in nearly all analyzed tissues at 12 and 120 hours post-dose, but at levels generally markedly less than those in serum. In the 0.1 mg/kg group, concentrations of radioactivity declined in all tissues to non-quantifiable levels by 672 hours post-dose except the injection site, eye (cornea), large intestinal contents (males), lymph nodes, spleen, stomach content (males), and thyroid. For the 1 mg/kg dose, concentrations of radioactivity declined in all tissues to non-quantifiable levels by 1344 hours post-dose, with the exception of the injection site, lymph nodes, ovary, spleen, and thyroid. Thus, radioactivity was generally measurable in the lymph nodes and spleen at 672 or 1344 hours post-dose for the 0.1 and 1 mg/kg doses, respectively. Overall, the results for male and female animals were similar, indicating a lack of sex difference in the distribution of ^{125}I-denosumab-derived radioactivity. Serum denosumab exposure based on AUC_{0-t} values increased greater than dose-proportionally (approximately 25-fold, respectively, for the 10-fold increase in dose) from 0.1 to 1 mg/kg. The percent change from baseline serum CTx ranged from approximately -38 to -54% from 12 to 336 hours post-dose for the 0.1 mg/kg dose group, while it ranged from approximately -49 to -70% over that time period for the 1 mg/kg dose group.

Table 5. Pharmacokinetics Tabular Summary: Study in Pregnant or Nursing Animals Test Article: Denosumab

Study Title	Type of Study / Status	Species	Objective	Methods	Summary of Results
102843 – Subcutaneous Fertility Evaluation of AMG 162 in the Female Cynomolgus Monkey	Multiple Dose/ GLP	Cynomolgus Monkey	To evaluate the potential effect on fertility of the test article AMG 162, when administered subcutaneously to the female cynomolgus monkey over two consecutive menstrual cycles until Day 20 post-mating.	Multiple SC bolus doses; 2.5, 5, 12.5 mg/kg weekly; Serum samples were collected to determine denosumab concentrations; serum denosumab concentration-time data were analyzed by non-compartmental methods.	Because the development of antibodies to denosumab was not assessed in this study, results for exposure dose-proportionality or accumulation may be confounded by the effects of anti-drug antibodies. Mean C_{max} and AUC_{0-t} values in all animals at the highest dose level (12.5 mg/kg weekly) were 476 µg/mL and 67,800 µg*hr/mL, respectively, prior to the first mating.
102842 – Subcutaneous Embryo-Fetal Development Study of AMG 162 in the Cynomolgus Monkey	Multiple Dose/ GLP	Cynomolgus Monkey	To investigate the embryonic and teratogenic effects of the test article AMG 162, when administered subcutaneously to the pregnant cynomolgus monkey during the period of organogenesis.	Multiple SC bolus doses; 2.5, 5, 12.5 mg/kg weekly; Serum samples were collected to determine denosumab concentrations and the presence of anti-denosumab antibodies; serum denosumab concentration-time data were analyzed by non-compartmental methods.	One animal in the control (vehicle-treated) group displayed quantifiable serum denosumab concentrations. Neutralizing antibodies were detected in 34% of denosumab-treated animals and were associated with decreased serum denosumab exposure. In antibody-negative animals, exposure based on mean C_{max} and AUC_{0-t} values increased approximately dose-proportionally from 2.5 to 12.5 mg/kgand moderate accumulation (>2 fold) was observed by the 5th weekly dose. Mean C_{max} and AUC_{0-t} values in antibody-negative animals at the highest dose level (12.5 mg/kg weekly) were 282 µg/mL and 41,000 µg*hr/mL, respectively, following the 5th dose. Quantifiable denosumab concentrations were observed in 70% of fetal serum samples, indicating that denosumab crosses the placental barrier.

Reference ID: 3168397

Table 7. Pharmacokinetics Tabular Summary: Metabolism In Vivo Test Article: Denosumab

Study Title	Type of Study / Status	Species	Objective	Methods	Summary of Results
108892 – A Single Dose Pharmacokinetics Study of Denosumab (AMG 162) Following Intravenous Administration to Male or Female huRANKL Knock-In and Wild-Type Mice	Single Dose/ Non-GLP	Mouse	To characterize the single dose pharmacokinetics (PK) of denosumab (AMG 162) following intravenous administration to male or female huRANKL knock-in and wild-type mice.	Single IV bolus dose of 0.1 mg/kg; Serum denosumab concentrations were determined up to 1344 hr post-dose and composite mean serum denosumab concentration-time data were analyzed by non-compartmental methods.	Exposure based on AUC_{0-inf} was 6.6-fold greater and the terminal half-life was 11-fold longer in wild-type relative to huRANKL knock-in mice. The difference in exposure reflects 6.6-fold higher clearance in the huRANKL knock-in animals. These results suggest that, in mice expressing a form of RANKL to which denosumab binds (huRANKL), binding of denosumab to its target antigen leads to an accelerated rate of elimination (relative to elimination in wild-type animals). Thus, binding of denosumab to huRANKL appears to play a significant role in the elimination of the antibody.

Table 14. Summary of Denosumab PK or TK Parameters from Preclinical Pharmacokinetics Studies

Single Dose Pharmacokinetics

Study	Species	Sex	Route	Dose (mg/kg)	n/ timepoint	T_{max} (hr)	C_{max} or C_0 (µg /mL)	$t_{1/2}$ (hr)	AUC_{0-t} (µg*hr/mL)	AUC_{0-inf} (µg*hr/mL)	CL or CL/F (ml/hr/kg)	V_{ss} (mL/kg)	MRT_{0-t} (hr)
101494	Mouse	M	SC	1	2	72	23.1	444	NA	15600	0.0642	NA	NA
		M	IV	0.1	2	NA	3.91	420	NA	1680	0.0594	43.5	NA
		M	IV	1	2	NA	31.9	463	NA	18100	0.0553	40.2	NA
		M	IV	10	2	NA	511	461	NA	128000	0.0778	48.6	NA
101002	Rat	F	SC	1	1	72	6.87	106	1760	1970	0.507	NA	NA
		M/F	IV	0.0628	2	NA	1.97	240	148	201	0.318	98.6	NA
		M/F	IV	1	2	NA	22.9	270	3090	3580	0.287	107	NA
		M/F	IV	10	2	NA	318	290	34700	41800	0.242	97.2	NA
101398	Cynomolgus Monkey	F	SC	0.0016	3	10.7 (11.5)	0.00433 (0.00166)	41.9 (0.134)	0.143 (0.0339)	0.301 (NA)	10.6 (3.56)	NA	17.0 (9.00)
		F	SC	0.0053	3	18.7 (9.24)	0.0229 (0.000500)	35.8 (6.30)	1.54 (0.119)	1.64 (0.203)	6.15 (0.720)	NA	40.4 (3.17)
		F	SC	0.0848	3	56.0 (36.7)	0.728 (0.0911)	24.1 (7.00)	126 (21.2)	126 (21.2)	0.808 (0.125)	NA	111 (4.29)
		F	SC	1.0	3	96.0 (0.00)	16.5 (5.83)	28.9 (18.8)	3940 (1820)	3940 (1820)	0.298 (0.147)	NA	182 (55.5)
		F	SC	3.0	3	64.0 (27.7)	35.8 (9.02)	29.5 (16.8)	8790 (2080)	8790 (2080)	0.353 (0.0737)	NA	192 (90.3)
		F	IV	0.0016	3	NA	0.0625 (0.0120)	8.37 (1.15)	0.779 (0.310)	0.753 (0.302)	4.40 (1.80)	51.4 (15.3)	12.1 (1.50)
		F	IV	0.0053	3	NA	0.243 (0.0199)	14.3 (1.80)	4.80 (0.320)	4.77 (0.310)	2.10 (0.133)	45.1 (1.88)	21.5 (2.31)
		F	IV	0.0848	3	NA	3.72 (0.245)	36.9 (17.5)	187 (34.1)	189 (37.0)	0.542 (0.106)	38.4 (1.38)	72.5 (13.6)
		F	IV	1.0	3	NA	35.9 (5.11)	19.3 (4.18)	3590 (1540)	3590 (1540)	0.310 (0.110)	38.7 (5.21)	108 (33.9)
		F	IV	3.0	3	NA	105 (40.5)	27.5 (11.7)	12400 (4850)	12400 (4850)	0.277 (0.134)	31.2 (7.96)	131 (63.6)

Median (range) for T_{max} not applicable for Studies 101494 and 101002 and not reported for Study 101398.

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Reference ID: 3168397

Table 14. Summary of Denosumab PK or TK Parameters from Preclinical Pharmacokinetics Studies

Multiple Dose Toxicokinetics

Study	Species	Dosing Schedule	Study Week	Sex	Route	Dose (mg/kg)	n/timepoint	T_{max} (hr)	C_{max} (ug/mL)	AUC_{0-t} (µg*hr/mL)
101447	Cynomolgus Monkey	Weekly	1	M/F	SC	0.1	12	72.0 (20.5)	1.51 (0.486)	195 (65.7)
				M/F	SC	1	12	92.0 (32.1)	14.0 (3.14)	1800 (430)
				M/F	SC	10	12	108 (36.2)	165 (27.6)	20200 (3640)
				M/F	IV	10	12	6.83 (8.56)	615 (183)	48700 (14400)
			4	M/F	SC	0.1	12	26.9 (47.7)	11.3 (31.2)	349 (869)
				M/F	SC	1	12	30.7 (33.1)	27.5 (14.0)	3410 (2080)
				M/F	SC	10	12	35.0 (38.6)	302 (151)	42000 (22700)
				M/F	IV	10	12	4.00 (6.66)	663 (133)	68600 (23000)
102090	Cynomolgus Monkey	Monthly	1[a]	M/F	SC	1	16	96 (48-96)	15.8 (1.81)	4100 (1150)
				M/F	SC	10	16	96 (48-336)	162 (25.4)	61500 (16000)
				M/F	SC	50	16	96 (48-96)	853 (79.3)	343000 (52200)
			13[a]	M/F	SC	10	4	24 (12-96)	115 (37.1)	48200 (21100)
				M/F	SC	50	7	48 (24-96)	666 (156)	268000 (90300)

a Dose number

Median (range) for Tmax not reported for Study 101447

Table 14. Summary of Denosumab PK or TK Parameters from Preclinical Pharmacokinetics Studies

Multiple Dose Toxicokinetics

Study	Species	Dosing Schedule	Study Week	Sex	Route	Dose (mg/kg)	n/timepoint	T_{max} (hr)	C_{max} (ug/mL)	AUC_{0-t} (µg*hr/mL)
103981	Cynomolgus Monkey	Monthly	First Dose	F	SC	25	15	96 (24-168)	143 (58.7)	59600 (22900)
			12th Dose	F	SC	25	14	96 (24-168)	234 (34.1)	113000 (21000)
			15th Dose	F	SC	25	14	96 (48-168)	222 (49.9)	101000 (26100)
			First Dose	F	SC	50	17	48 (48-96)	336 (67.6)	139000 (34600)
			12th Dose	F	SC	50	17	48 (24-168)	511 (132)	212000 (71900)
			15th Dose	F	SC	50	17	48 (24-96)	413 (160)	171000 (72400)

a Dose number

Median (range) for Tmax not reported for Study 101447

Table 14. Summary of Denosumab PK or TK Parameters from Preclinical Pharmacokinetics Studies

Drug-Drug Interactions

Study	Species	Dosing Schedule	Study Week	Sex	Route	Dose (mg/kg)	n/timepoint	T_{max} (hr)	C_{max} (ug/mL)	AUC_{0-t} (µg*hr/mL)
106564	Cynomolgus Monkey	Monthly	Month 7	F	SC	Vehicle + 25	10	168 (72-336)	145 (31)	41600 (10200)
			Month 7	F	SC	ALN + 25	11	72 (72-336)	172 (65)	43700 (10800)
			Month 1	F	SC	25	11	168 (24-168)	152 (45)	40300 (10200)
			Month 7	F	SC	25	5	72 (24-168)	372 (132)	90400 (25800)
			Month 7	F	SC	25	6	72 (72-336)	220 (142)	45600 (24900)

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Table 14. Summary of Denosumab PK or TK Parameters from Preclinical Pharmacokinetics Studies

Toxicokinetics in Pregnant or Nursing Animals

Study	Species	Dosing Schedule	Dose #	Sex	Route	Dose (mg/kg)	n	T_{max} (hr)	C_{max} (ug/mL)	AUC_{0-t} (mg*hr/mL)	AR
102842	Cynomolgus Monkey	Weekly doses	5	F	SC	2.5	7	24 (8-120)	58.8 (19.6)	8.80 (3.05)	2.46 (0.428)
			5	F	SC	5	10	16 (8-72)	114 (52.3)	15.5 (6.35)	2.59 (0.926)
			5	F	SC	12.5	14[a]	24 (8-72)	282 (89.6)	41.0 (10.6)	2.79 (0.696)
102843	Cynomolgus Monkey	Weekly doses	NA	F	SC	2.5	6	72 (24-120)	48.8 (11.9)	6.77 (1.50)	NA
			NA	F	SC	5	6	72 (72-120)	79.0 (16.4)	11.7 (2.53)	NA
			NA	F	SC	12.5	6	72 (72-168)	186 (24.4)	26.9 (2.70)	NA
			11	F	SC	2.5	4	24 (8-72)	26.5 (36.7)	4.22 (5.94)	0.787 (1.09)
			9	F	SC	5	4	24 (8-24)	115 (81.7)	16.4 (11.4)	1.54 (1.06)
			10	F	SC	12.5	5	24 (8-72)	476 (279)	67.8 (39.6)	2.59 (1.57)
			18	F	SC	2.5	2	64 (8-120)	121 (84.0)	17.6 (14.8)	3.27 (2.64)
			17	F	SC	5	3	24 (8-72)	163 (27.2)	16.9 (2.32)	1.61 (0.300)
			20	F	SC	12.5	4	8 (8-24)	727 (148)	85.5 (20.7)	3.31 (1.25)

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[a] n = 13 for AR

Table 14. Summary of Denosumab PK or TK Parameters from Preclinical Pharmacokinetics Studies

In Vivo Metabolism Studies

Study	Species	Route	Dose (mg/kg)	Sex	n/timepoint	C_0 (ug/mL)	AUC_{0-inf} (ug*hr/mL)	$t_{1/2,z}$ (hr)	CL (mL/hr/kg)	V_0 (mL/kg)	V_{ss} (mL/kg)
106892	WT mouse	IV	0.1	M/F	3	2.60	881	426	0.114	38.5	74.0
	KI mouse	IV	0.1	M/F	3	2.19	150	78.6	0.667	45.7	72.7
106893	WT mouse	IV	0.1	M/F	3	2.21	685	489	0.146	45.2	97.6
	FcRn KO mouse	IV	0.1	M/F	3	2.55	48.5	18.1	2.06	39.3	52.3
	WT mouse	IV	1	M/F	3	20.8	6910	506	0.145	48.0	100
	FcRn KO mouse	IV	1	M/F	3	21.7	455	20.2	2.2	46.0	58.6

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Table 14. Summary of Denosumab PK or TK Parameters from Preclinical Pharmacokinetics Studies

Other Pharmacokinetic Studies

Study	Species	Route	Dose (mg/kg)	Sex	N[a]	Process	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0-336\ hr}$ (ug*hr/mL)
103948	Cynomolgus Monkey	SC	0.1	F	5	CP1	72 (24-168)	958 (479)	188 (46.4)
		SC	0.1	F	3	CP2	78 (48-72)	785 (163)	163 (40.4)

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[a] Anti-denosumab antibody-negative on Day 14

Table 14. Summary of Denosumab PK or TK Parameters from Preclinical Pharmacokinetics Studies

Tissue Distribution / Excretion Studies

Study	Species	Route	Dose (mg/kg)	Sex	n/timepoint	T_{max} (hr)	C_{max} (ng/mL)	$t_{1/2,z}$ (hr)	AUC_{0-t} (µg•hr/mL)	AUC_{0-inf} (µg•hr/mL)	CL/F (mL/hr/kg)	MRT (hr)
104105	Cynomolgus Monkey	SC	0.1	M/F	7	120	564	ND	107	ND	ND	ND
		SC	1	M/F	7	120	9750	36.6	2760	2770	0.361	204
104192	Cynomolgus Monkey	SC	0.1	M/F	7	120	612	34.6	NR	126	0.795	139
		SC	1	M/F	7	120	8870	37.9	NR	2930	0.341	274

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2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Two repeat dose toxicology studies in cynomolgus monkeys were conducted to support the general toxicity of AMG 162 – a 1-month and a 12-month study. Toxicity was evaluated, as well as effects on bone parameters and potential immunogenicity. The results from the 12-month study are discussed in the integrated review section.

In the 1-month repeat dose toxicology study, there is evidence to support the pharmacological activity of denosumab was maintained during the duration of the study, as reductions in serum osteocalcin, N-telopeptide, and alkaline phosphatase were observed in all treatment groups in both males of the 10 mg/kg IV and SC groups and in all denosumab treated groups for females at week 4 of dosing. There were statistically significant increases in total and cortical bone mineral density in males in the 1 mg/kg AMG-162 SC group at week 4 of dosing. AMG-162 did not induce changes in BMD in the female monkeys in any dose group following 4 weeks of dosing. Also, there were increases in the bone mineral density of the proximal tibia in male monkeys of the 1 mg/kg SC and 10 mg/kg (IV and SC) dose groups during the recovery period. Similar to the 4 week time-point, AMG-162 did not change the bone mineral density in the female monkeys in this study.

There were no toxicologically significant findings in the clinical signs, food consumption, body weight change, and ophthalmology for the 1-month repeat dose toxicology study. Moderate occult blood in urine samples was observed at week 4 of dosing in one male in the 10 mg/kg IV group, and severe urinary occult blood was noted at week 4 of dosing in one female each in the 0.1 mg/kg SC group and the 10 mg/kg IV group. Calcium (Ca) levels were significantly lower in males of the 1.0 (SC) and 10 (SC and IV) mg/kg groups relative to the control. The reductions in blood Ca levels were not observed in the female monkeys. In the recovery group at week 13, there were no significant differences in Ca levels for the denosumab treated groups relative to the control group. There is approximately 4 fold greater exposure in the cynomolgus monkeys for the subcutaneous route of administration for the 10 mg/kg dose (AUC_{0-t} 42,000) mcg*hr/mL and 6 fold greater exposure via the intravenous route of administration (AUC_{0-t} 68,600 mcg*hr/mL) as compared to the human clinical exposure based on the AUC_{0-t} (human clinical study # 20010223; AUC_{0-t} 10,752 mcg*hr/mL). However, the high incidence of immunogenicity confounds the determination of the true exposure levels in this study. At least based on the pharmacology endpoints of increasing bone mineral density (male only) and reductions in biomarkers of bone turnover during the duration of the study, there is evidence to support that denosumab was pharmacologically active during the study. There was a high incidence of immunogenicity in this study with 28 out of the 30 animals testing positive for anti-drug-antibodies. In the animals testing positive for ADA, there was approximately 30% reduction in exposure in these animals as

Reference ID: 3168397

compared to ADA negative monkeys. There was an approximate two-fold increase in accumulation observed between the first and last dose of AMG-162 administered subcutaneously.

Reviewed by: Ronald Wange, Ph.D. August 31, 2006

In the 12-month study, major nonclinical findings included a high incidence of infection (protozoa: *Giardia lambia* and/or cryptosporidium) in the majority of animals (control and treated) which led to diarrhea and poor health, the development of abscesses of the teeth/jaws in MD and HD females, and immunogenicity that was inversely related to dose (100% LD, 50% MD, 13% HD) and subsequent formation of neutralizing antibodies. Two HD males died while on treatment, which was determined to be the likely result of infection. Effects of AMG 162 on bone were evidenced by a reduced rate of bone remodeling, reduced serum levels of osteocalcin, C-telopeptide and urine N-telopeptide, and increased BMD and BMC in both cortical and trabecular bone of the radius, tibia and femur. There were some indications from this study that AMG 162 may be immunosuppressive due to the unexplained HD male deaths (possible impairment of the ability to control infection), abscesses of the teeth/jaw, and from additional information found in the literature. More detailed information on this data can be found in the toxicology discussion/conclusions in section 2.6.6.9, but the overall assessment was that a clear association between AMG 162 treatment and definitive immunosuppression could not be established, and further nonclinical studies were not necessary. In addition, clinical trials had appropriate risk management plans in place to detect any clinical findings. Therefore, since the primary effects of AMG 162 were pharmacodynamic (PD)-related, the NOAEL for this study was 50 mg/kg. This results in an exposure multiple of 25X when AUC after Q1M treatment over 13 months in the monkey is compared to AUC after two Q6M doses of 60 mg in human. However, PD-related abscesses of the teeth/jaws did occur at doses ≥10 **mg/kg, which is only 4X higher than the proposed clinical dose** based on the same AUC assessments.

Genetic toxicology: No genotoxicity testing was performed for denosumab (biologic) in this submission.

Carcinogenicity: No evidence for the development of tumors was noted in the pharmacology and toxicology studies provided in the submission. However, a standard carcinogenicity study was not performed in rodents since they were not a pharmacologically relevant species for testing denosumab. Based on the combination of results from the 12- (Study #106564) and 16- month (Study # 103981) pharmacology studies in monkeys and the 6/12 month monkey toxicology study (Study number #102090), there was no evidence of tumor development in these chronic repeat dose studies.

Reproductive toxicology: These studies were reviewed by Dr. Hatfield, and are cross-referenced to her review of STN BLAs # 125320 and # 125331.

Special toxicology: No special toxicology studies were included in the submission.

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2.6.6.2 Single-dose toxicity

No single-dose toxicology studies were included in the submission.

2.6.6.3 Repeat-dose toxicity

Comment: Please note the that the 1-month toxicology study number 101447 was reviewed by Dr. Michael Orr, Ph.D. D.A.B.T. and the 6/12 month repeat dose study number 102090 was reviewed by Ronald Wange, Ph.D. on August 31, 2006. A complete review for study number 102090 is contained in Kimberly Hatfield's, Ph.D. review and is cross-referenced to her review of STN BLAs# 125320 and # 125331.

Study title: A 1-Month Study Evaluating the Effect on Bone of AMG-162 Administered Subcutaneously or Intravenously in Cynomolgus Monkeys, with a 3-Month Recovery Period

Key study findings:

- No denosumab-induced changes were observed in the clinical signs, food consumption, body weight change, and ophthalmology.

- Calcium levels were significantly lower in males of the 1.0 (SC) and 10 (SC and IV) mg/kg groups relative to the control. The reductions in blood Ca levels were not observed in the female monkeys. In the recovery group at week 13, there were no significant differences in Ca levels for the denosumab treated groups relative to the control group.

- There is evidence to support that the pharmacological activity of denosumab was maintained during the duration of the study, as reductions in serum osteocalcin, N-telopeptide, and alkaline phosphatase were observed in all treatment groups in both males of the 10 mg/kg IV and SC groups, and in all denosumab treated groups for females at week 4 of dosing.

- There were statistically significant increases in total and cortical bone mineral density in males in the 1 mg/kg AMG-162 SC group at week 4 of dosing. AMG-162 did not induce changes in BMD in the female monkeys in any dose group following 4 weeks of dosing. Also, there were increases in the bone mineral density of the proximal tibia in male monkeys of the 1 mg/kg SC and 10 mg/kg (IV and SC) dose groups during the recovery period. Similar to the 4 week time-point, AMG-162 did not change the bone mineral density in the female monkeys in this study.

- Moderate occult blood in urine samples was observed at week 4 of dosing in one male in the 10 mg/kg IV group, and severe urinary occult blood was noted at

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week 4 of dosing in one female each in the 0.1 mg/kg SC and the 10 mg/kg IV dose groups.

- There was a high incidence of immunogenicity in this study with 28 out of the 30 animals testing positive for anti-drug-antibodies. In the animals testing positive for ADA, there was approximately 30% reduction in exposure in these animals as compared to ADA negative monkeys.

- There was an approximate two-fold increase in accumulation observed between the first and last dose of AMG-162 administered subcutaneously.

- There is approximately 4 fold greater exposure in the cynomolgus monkeys for the subcutaneous route of administration for the 10 mg/kg dose group (AUC_{0-t} 42,000) mcg*hr/mL and 6 fold greater exposure via the intravenous route of administration in the 10 mg/kg dose group (AUC_{0-t} 68,600 mcg*hr/mL) as compared to the human clinical exposure based on the AUC_{0-t} (human clinical study # 20010223; AUC_{0-t} 10,752 mcg*hr/mL).

Study no.: (b) (4); Amgen Study Number 101447
Volume #, and page #: eCTD, 1-559
Conducting laboratory and location: (b) (4)
Date of study initiation: December 22, 2000
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: AMG162, Lot No. A0010170015, 99.4% purity

Methods:

Doses: Subcutaneous (SC) 0.1, 1, 10 mg/kg; IV 10 mg/kg; 4 doses on Days 0, 7, 14, and 21
Species/strain: cynomolgus monkeys (*Macaca fascicularis*)
Number/sex/group or time point (main study): 3 /males per group; 3 /female/per group; males and females necropsied on Day 28
Route, formulation, volume, and infusion rate:

Test Article: AMG-162
Lot Number S01344
Formulation: 30 mg/ml AMG-162, 10 mM Na Acetate, 5% Sorbitol, pH 5.2
Route of Administration:
SC, Dose Volume 0.1 to 1 ml/kg/day
IV, Dose Volume 1 ml/kg/day with an infusion rate of 5 ml/min

Control Article:
Lot Number A0010260000, SC
Formulation: 0 mg/ml AMG-162, 10 mM Na Acetate, 5% Sorbitol, pH 5.2

Reference ID: 3168397

Route of Administration:
SC, Dose Volume 1 ml/kg/day

Satellite groups used for toxicokinetics or recovery: 3/males/per group; 3/females/per group; necropsied on week 13 of recovery
Age: 3-5 years of age

Dose Groups and Observations Made (from the sponsor's final study report):

(b) (4)
Amgen study number : 101447
Final Report

SUMMARY

The purpose of this study was to evaluate the effect of AMG 162 on bone when administered subcutaneously or intravenously to cynomolgus monkeys once weekly for 4 weeks, and to assess the reversibility of any effects following a 13-week recovery period. The study design was as follows:

Group	Test Article	Dose Level (mg/kg/day)	Dose Route	Number of Animals (Animal No.)*	
				Male	Female
1	Placebo	0	SC	3+3*	3+3*
2	AMG 162	0.1	SC	3+3*	3+3*
3	AMG 162	1.0	SC	3+3*	3+3*
4	AMG 162	10.0	SC	3+3*	3+3*
5	AMG 162	10.0	IV	3+3*	3+3*

*: 3 animals/group were necropsied on Day 28 and 3 animals/group following a 13-week recovery period.

The test article was administered on Days 0, 7, 14 and 21 of dosing (total 4 times). All animals were observed for clinical signs of toxicity and mortality once daily during the acclimation period and twice daily during the dosing and recovery periods (except on the day of necropsy when animals were observed once). Food consumption was measured once daily from 7 days before dosing until the end of the experiment. The animals were weighed twice during the acclimation period and weekly during the dosing and recovery period. Ophthalmological examinations, urinalysis, hematological, serum biochemistry, and blood Ca^{++} examinations, and bone mineral density examinations, by peripheral quantitative computed tomography (pQCT), were performed once during the acclimation period and at Week 4 of dosing and at Week 4 or 13 of recovery. Urine and serum for bone metabolic marker analysis and serum for antibody measurement and toxicokinetics were collected periodically throughout the experimental period. At the scheduled necropsies on Day 28 of dosing and at the end of the recovery period, a gross pathological examination was conducted, organ weights were measured and a full light microscopy examination was also conducted.

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Weight: Males 3.6 to 4.58 kg; Females 2.87 to 4.04 kg on day of initiation of dosing
Sampling times: Scheduled necropsies were performed on week 4 following dosing and week 13 of the recovery phase of the study.

Results
Mortality: No remarkable findings
Clinical signs: No remarkable findings
Body weights: No remarkable findings
Food consumption: No remarkable findings
Ophthalmoscopy: No remarkable findings
EKG: Not evaluated in this study
Hematology: A statistically significant decrease in mean platelet volume was observed in females of the 10 mg/kg IV group. This was not observed in the male group.

Comment: It is not clear what the toxicological significance of the decrease in mean platelet volume in females is, as this finding was not observed in the male cynomolgus monkeys.

Clinical chemistry: As expected based on the pharmacological action of denosumab, statistically significant reductions in ALP were observed in the male monkeys following IV administration of AMG-162 at 10 mg/kg. In females, AMG-162 induced an approximately 47% reduction in ALP at the 1 mg/kg (SC) dose, 42% reduction in ALP at the 10 mg/kg dose (SC), and 49% reduction in ALP at the 10 mg/kg dose (IV). A decrease in Ca^{+2} levels was observed in males of the 1 mg/kg (SC) and 10 mg/kg (SC and IV) mg/kg groups.

Bone Biomarkers: Serum osteocalcin and N-Telopeptide were reduced in a dose-dependent manner in all treatment groups. The 0.1 mg/kg SC cohort had initial reductions of serum osteocalcin of 23% at the 24 hr time point but the levels increased to approximately 10% below baseline at later points. More robust reductions were observed in the 1 mg/kg and 10 mg/kg dose groups with approximately 40% reductions in serum osteocalcin being observed (data not shown).

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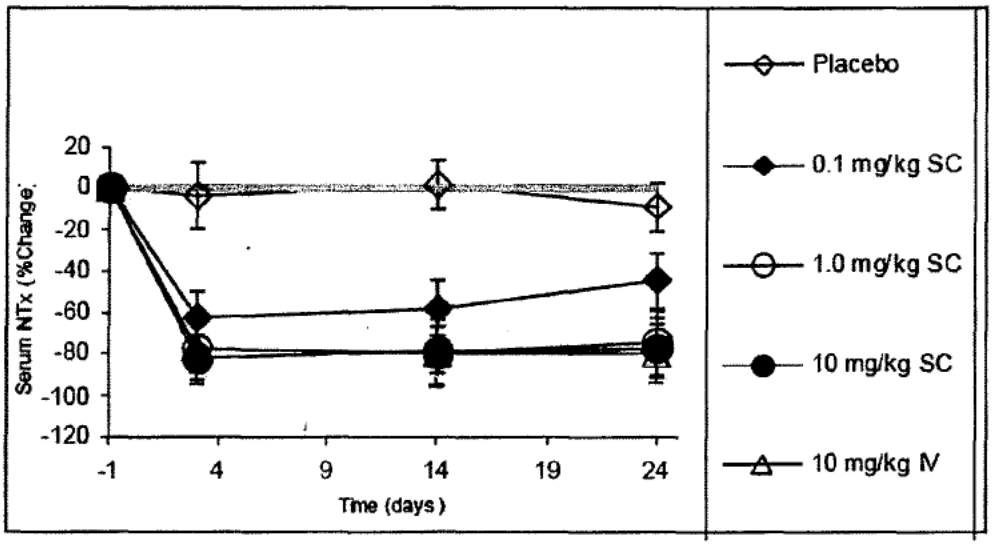
Figure 2. Serum NTx in Cynomolgus Monkeys Treated Weekly With Denosumab (% Change From Baseline +/- SD [n = 12])



NTx = cross-linked N-telopeptides; SC = subcutaneous, IV = intravenous.
Source: *Data from Study 101447, Appendix 2.*

As shown in Figure 2 above, the serum cross-linked N-Telopeptide (NTx; biomarker of bone resorption) was decreased by 60 to 80 % at all dose levels.

Urinalysis: Moderate occult blood in urine samples was observed at week 4 of dosing in one male in the 10 mg/kg IV group, and severe urinary occult blood was noted at week 4 of dosing in one female each in the 0.1 mg/kg SC group and the 10 mg/kg IV group.

Bone Mineral Density:

There were statistically significant increases in total and cortical bone mineral density in males in the 1 mg/kg AMG-162 SC group at week 4 of dosing. AMG-162 did not induce changes in BMD in the female monkeys in any dose group following 4 weeks of dosing.

Also, there were increases in the bone mineral density of the proximal tibia in male monkeys of the 1 mg/kg SC and 10 mg/kg (IV and SC) dose groups during the recovery period. Similar to the 4 week time-point, AMG-162 did not change the bone mineral density in the female monkeys in this study.

Gross pathology: Cysts in the ovaries (bilateral) were observed in 1/3 females. No changes were observed at the end of the recovery period.

Organ weights (specify organs weighed if not in the histopathology table): There was an elevation in thyroid weights in females in the 10 mg/kg IV group following denosumab dosing. There was no evidence of increased thyroid weights following the recovery period in either male or female monkeys. At the end of the recovery phase of the study,

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there were statistically significant increases in liver weights relative to the control group observed in female monkeys in the 0.1 mg/kg and 1 mg/kg AMG-162 groups. It is not clear what the toxicological significance of this finding is, as the 10 mg/kg IV and SC dose groups lacked the increase in liver response observed in the lower dose cohorts.

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes ( ), no (x)

No test article related changes were identified.

Comment: The Sponsor's SOP requires a pathology peer review for this study. However **no peer review** was performed, as no findings were identified following the initial histopathological examination.

Toxicokinetics: As shown in Figure 9-1 and Tables 7-1 to 7-4 from the submission, dose-dependent increases in exposure levels were evident over the duration of the study even with a high incidence of immunogenicity (28/30 treated monkeys were anti-drug-antibody positive).

Comments: There were decreases in the pharmacodynamic markers alkaline phosphatase, serum osteocalcin, and N-telopeptide at all doses evaluated in this study, which provides evidence that AMG-162 was pharmacologically active in this study (data not shown). Furthermore, there were increases in the bone mineral density of the proximal tibia in male monkeys of the 1 SC and 10 (IV and SC) mg/kg groups. It is not clear why no significant changes in bone mineral density were observed in the female monkeys in any of the dosing groups or at any time-points evaluated (i.e. end of 4 week dosing phase or end of 13 week recovery phase).

There was approximately a two-fold increase in accumulation observed between the first and last dose of AMG-162 administered subcutaneously (Tables 7-1 to 7-4, below).

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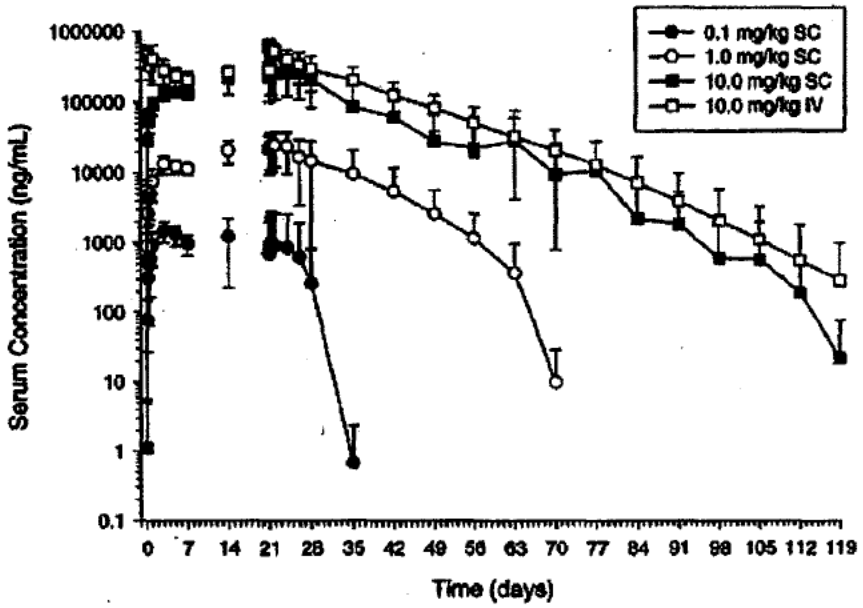

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Table 7-1. Combined Comparison of Mean (±SD) PK Parameters Following First and Last SC Dose of 0.1 mg/kg AMG 162 to Cynomolgus Monkeys

Parameter	Units	First		Last		AR
		Mean	SD	Mean	SD	
T_{max}	hr	72	20.6	26.9	47.7	N/A
C_{max}	µg/mL	1.51	0.486	11.3	31.2	7.48
$AUC_{(0-168)}$	hr*µg/mL	195	65.7	349	869	1.79
$AUC_{(0-\infty)}$/Dose	(µg*hr/mL)/(µg/kg)	1950	657	3490	8690	

Table 7-2. Combined Comparison of Mean (±SD) PK Parameters Following First and Last SC Dose of 1.0 mg/kg AMG 162 to Cynomolgus Monkeys

Parameter	Units	First		Last		AR
		Mean	SD	Mean	SD	
T_{max}	hr	92	32.1	30.7	33.1	N/A
C_{max}	µg/mL	14.0	3.14	27.5	14.0	1.96
$AUC_{(0-168)}$	hr*µg/mL	1900	430	3410	2080	1.69
$AUC_{(0-\infty)}$/Dose	(µg*hr/mL)/(µg/kg)	1800	430	3410	2080	

Table 7-3. Combined Comparison of Mean (±SD) PK Parameters Following First and Last SC Dose of 10.0 mg/kg AMG 162 to Cynomolgus Monkeys

Parameter	Units	First		Last		AR
		Mean	SD	Mean	SD	
T_{max}	hr	109	38.2	35	38.6	N/A
C_{max}	µg/mL	155	27.6	302	151	1.95
$AUC_{(0-168)}$	hr*µg/mL	20200	3640	42000	22700	2.08
$AUC_{(0-\infty)}$/Dose	(µg*hr/mL)/(µg/kg)	2020	364	4200	2270	

Table 7-4. Combined Comparison of Mean (±SD) PK Parameters Following First and Last IV Dose of 10 mg/kg AMG 162 to Cynomolgus Monkeys

Parameter	Units	First		Last		AR
		Mean	SD	Mean	SD	
T_{max}	hr	6.83	8.56	4	6.66	N/A
C_{max}	µg/mL	615	183	663	133	1.08
$AUC_{(0-168)}$	hr*µg/mL	46700	14400	66500	23000	1.41
$AUC_{(0-\infty)}$/Dose	(µg*hr/mL)/(µg/kg)	4670	1440	6660	2300	

Immunogenicity:

Overall, AMG-162 administered to cynomolgus monkeys was highly immunogenic in both male and female monkeys. The incidence of anti-drug-antibody increased during the 13-week recovery group relative to the study day 28 (for references see Tables 2A, 2B, and 2C below).

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Table 2A
Anti-AMG 162 Positive Incidence - Through Day 28 for Male Monkeys per Dosing Group

		No. of Positive Monkeys			% Incidence of Positives				
Group	Total No. of Monkeys	Pre Dose (day -9)	Post dose (Day 14)	Post dose (Day 28)	Pre Dose (day -9)	Post dose (Day 14)	Post dose (Day 28)	Total No. of Positive Monkeys	% Incidence of Positives
2 (0.1mg/kg SC)	6	0	5	6	0	100	100	6	100
3 (1.0mg/kg SC)	6	0	1	4	0	17	67	4	67
4 (10.0mg/kg SC)	6	0	0	1	0	0	17	1	17
5 (10.0mg/kg IV)	6	0	0	3	0	0	50	3	50

Table 2B
Anti-AMG 162 Positive Incidence Through Day 28 for Female Monkeys per Dosing Group

		No. of Positive Monkeys			% Incidence of Positives				
Group	Total No. of Monkeys	Pre Dose (day -2)	Post dose (Day 14)	Post dose (Day 28)	Pre Dose (day -2)	Post dose (Day 14)	Post dose (Day 28)	Total No. of Positive Monkeys	% Incidence of Positives
2 (0.1mg/kg SC)	6	0	1	6	0	17	100	6	100
3 (1.0mg/kg SC)	6	1	0	4	17	0	67	4	67
4 (10.0mg/kg SC)	6	0	1	3	0	17	50	3	50
5 (10.0mg/kg IV)	6	0	0	0	0	0	0	0	0

Table 2C
Anti-AMG 162 Positive Incidence in the Recovery Period for Male Monkeys per Dosing Group

		No. of Positive Monkeys				% Incidence of Positives				
Group	Total No. of Recovery Monkeys	Through Day 28 of Dosing	WEEK 4 of Recovery	WEEK 8 of Recovery	WEEK 13 of Recovery	WEEK 4 of Recovery	WEEK 8 of Recovery	WEEK 13 of Recovery	Total No. of Positive Monkeys	% Incidence of Positives
2 (0.1mg/kg SC)	3	3	3	3	3	100	100	100	3	100
3 (1.0mg/kg SC)	3	1	1	3	3	33	100	100	3	100
4 (10.0mg/kg SC)	3	1	1	1	3	33	33	100	3	100
5 (10.0mg/kg IV)	3	1	1	2	2	33	67	67	2	67

Comments: A high incidence of anti-drug –antibodies (ADA) was detected in this study (28 of 30 treated monkeys). In the animals testing positive for ADA, there was approximately 30% reduction in exposure as compared to ADA negative monkeys.

Histopathology inventory (optional)

Study	SBL 39-50			
Species	Cyno			
Adrenals	X			
Aorta	X			
Bone Marrow smear	X			
Bone (femur)	X			

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Brain	X			
Cecum	X			
Cervix	X			
Colon	X			
Duodenum	X			
Epididymis	X			
Esophagus	X			
Eye	X			
Fallopian tube				
Gall bladder	X			
Gross lesions				
Harderian gland				
Heart	X			
Ileum	X			
Injection site	X			
Jejunum	X			
Kidneys	X			
Lachrymal gland				
Larynx				
Liver	X			
Lungs	X			
Lymph nodes, cervical				
Lymph nodes mandibular	X			
Lymph nodes, mesenteric	X			
Mammary Gland	X			
Nasal cavity				
Optic nerves	X			
Ovaries	X			
Pancreas	X			
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary	X			
Prostate	X			
Rectum	X			
Salivary gland	X			
Sciatic nerve	X			
Seminal vesicles	X			
Skeletal muscle	X			
Skin	X			
Spinal cord	X			
Spleen	X			
Sternum	X			
Stomach	X			
Testes	X			
Thymus	X			
Thyroid	X			
Tongue	X			

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Trachea	X			
Urinary bladder	X			
Uterus	X			
Vagina	X			
Zymbal gland				

X, histopathology performed
*, organ weight obtained

2.6.6.4 Genetic toxicology

None included in the submission

2.6.6.5 Carcinogenicity

None included in the submission

2.6.6.6 Reproductive and developmental toxicology
These studies were reviewed by Dr. Hatfield, and are cross-referenced to her review of STN BLAs #125320 and #125331.

2.6.6.7 Local tolerance

Formal studies evaluating the local tolerance were not conducted. The injection sites were evaluated in the repeated-dose studies. The subcutaneous administration of denosumab was relatively well tolerated in monkeys and transgenic mouse models tested.

2.6.6.8 Special toxicology studies
No special toxicology studies were included in the submission.

2.6.6.9 Discussion and Conclusions

General Toxicology:

Two repeat dose toxicology studies in cynomolgus monkeys were conducted to support the general toxicity of AMG 162; a 1-month and a 12-month study. Toxicity was evaluated as well as effects on bone parameters and potential immunogenicity. The results from the 12-month study are discussed in the integrated review section.

In the 1-month repeat dose toxicology study, there is evidence to support that the pharmacological activity of denosumab was maintained during the duration of the study. Reductions in serum osteocalcin, N-telopeptide, and alkaline phosphatase were observed in all treatment groups for both males of the 10 mg/kg IV and SC groups, and in denosumab treated females in all dose groups at week 4 of dosing. There were statistically significant increases in total and cortical bone mineral density in males in the 1 mg/kg AMG-162 SC group at week 4 of dosing. AMG-162 did not induce changes in BMD in the female monkeys in any dose group following 4 weeks of dosing. Also,

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increases in the bone mineral density of the proximal tibia were observed in male monkeys from the 1 mg/kg SC and 10 mg/kg (IV and SC) dose groups during the recovery period. Similar to the 4 week time-point, AMG-162 did not change the bone mineral density in the female monkeys at this time point.

There were no toxicologically significant findings in the clinical signs, food consumption, body weight change, and ophthalmology for the 1-month repeat dose toxicology study. Moderate occult blood in urine samples was observed at week 4 of dosing in one male in the 10 mg/kg IV group, and severe urinary occult blood was noted at week 4 of dosing in one female each from the 0.1 mg/kg SC and 10 mg/kg IV dose groups. Calcium (Ca) levels were significantly lower in males in the 1.0 (SC) and 10 (SC and IV) mg/kg groups, relative to the control. The reductions in blood Ca levels were not observed in the female monkeys. In the recovery group at week 13, there were no significant differences in Ca levels for the denosumab treated groups, relative to the control group. There was approximately 4 fold greater exposure in the cynomolgus monkeys after subcutaneous administration of 10 mg/kg/dose (AUC_{0-t} 42,000 mcg*hr/mL) and 6 fold greater exposure via the intravenous route of administration for the 10 mg/kg dose cohort (AUC_{0-t} 68,600 mcg*hr/mL), as compared to the human clinical exposure based on the AUC_{0-t} (human clinical study # 20010223; AUC_{0-t} 10,752 mcg*hr/mL). Based on mg/kg dosing between species, the cynomolgus monkeys received a 10 fold higher dose relative to humans (10 mg/kg dose in monkeys relative to the approximately 1 mg/kg dose in humans). However, the high incidence of immunogenicity in the animals confounds the determination of the true exposure levels in this study. At least based on the pharmacology endpoints of increasing bone mineral density (male only) and reductions in biomarkers of bone turnover during the duration of the study, there is evidence to support that denosumab was pharmacologically active during the study. There was a high incidence of immunogenicity in this study with 28 out of the 30 animals testing positive for anti-drug-antibodies (ADA). In the animals testing positive for ADA, there was an approximate 30% reduction in exposure, as compared to ADA negative monkeys. There was an approximate two-fold increase in accumulation observed between the first and last dose of AMG-162 administered subcutaneously.

Reviewed by: Ronald Wange, Ph.D. August 31, 2006

In the 12-month study, major nonclinical findings included a high incidence of infection (protozoa: *Giardia lambia* and/or *Cryptosporidium sp.*) in the majority of animals (both control and treated), which led to diarrhea and poor health, and the development of abscesses of the teeth/jaws in MD and HD females. Two HD males died while on treatment, which was determined to be the likely result of infection. Effects of AMG 162 on bone were evidenced by a reduced rate of bone remodeling, reduced serum levels of osteocalcin, C-telopeptide and urine N-telopeptide, and increased BMD and BMC in both cortical and trabecular bone of the radius, tibia and femur. There were some indications from this study that AMG 162 may be immunosuppressive due to the unexplained HD male deaths (possible impairment of the ability to control infection), abscesses of the teeth/jaw, and from additional information found in the literature. A high incidence of immunogenicity that was inversely related to dose (100% LD, 50% MD, 13% HD), and

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subsequent formation of neutralizing antibodies were also observed. More detailed information on this data can be found in the toxicology discussion/conclusions in section 2.6.6.9, but the overall assessment was that a clear association between AMG 162 treatment and definitive immunosuppression could not be established, and further nonclinical studies were not considered necessary. Furthermore, unscheduled deaths due to infection were not observed in the 1-month repeat dose toxicology study, 12-month ovariectomized cynomolgus monkey (OVX) pharmacology, and 16 month OVX monkey pharmacology studies. In addition, clinical trials had appropriate risk management plans in place to detect any clinical findings.

Reproductive toxicology: (Reproductive studies reviewed by Dr. Kim Hatfield, please cross-reference review STN BLAs #125320 and #125331 for more details)

The fertility study in female monkeys showed no effect of AMG-162 on cycle length, mating performance, hormone analysis, or confirmed pregnancies. The embryofetal study showed no effect on prenatal loss or maternal clinical signs or weight, and there were no teratogenic effects of AMG-162. Although no significant trends in delayed ossification were noted, increased incidences of shortened, isolated, rudimentary and/or vestigial ribs were observed, along with slight decreases in adrenal, heart and fetal body weight, and a slight increase in ovary weight were observed in the offspring. A limited tissue panel was examined by histopathology, so gross findings could not be confirmed or correlated with histopathology. In the embryofetal study, histopathology evaluation of the fetal lymph nodes was not performed. This information would have been beneficial since signaling via RANK has been shown to be required for lymph node development in mice. Overall, the two reproductive toxicology studies indicate a minimal effect of AMG-162 on fertility and reproduction. However, while both studies were adequately designed and dosing during the embryofetal study covered the period of primate organogenesis, antibodies do not typically cross the placenta until later in fetal primate development.

2.6.6.10 Tables and Figures

Tables and figures as provided by the sponsor are incorporated into the relevant sections of the review.

Reference ID: 3168397

2.6.7 TOXICOLOGY TABULATED SUMMARY

Table 1. Toxicology Overview
Test Article: AMG 162

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [a]	GLP Compliance	Testing Facility	Amgen Study No. (CRO Study No.)
Repeated-dose Toxicity	Cynomolgus monkey	Subcutaneous or Intravenous	1 month	Once weekly: 0 (SC), 0.1 (SC), 1.0 (SC), 10.0 (SC), 10.0 (IV)	Yes	(b) (4)	101447 (b) (4)
	Cynomolgus monkey	Subcutaneous	6 and 12 months	Once monthly: 0, 1, 10, 50	Yes		102090 (b) (4)
Female Fertility	Cynomolgus monkey	Subcutaneous	Over 2 menstrual cycles before mating and for 4 weeks after mating	Once weekly: 0, 2.5, 5, 12.5	Yes		102843 (b) (4)
Embryo-fetal Development	Cynomolgus monkey	Subcutaneous	Gestation days 20-50	Once weekly: 0, 2.5, 5, 12.5	Yes		102842 (b) (4))

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[a] Unless otherwise specified. The no observed adverse effect level is underlined, as applicable. GLP = Good Laboratory Practices; IV = intravenous; NA = not applicable; SC = subcutaneous.

Table 1. Toxicology Overview
Test Article: AMG 162

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg) [a]	GLP Compliance	Testing Facility	Amgen Study No. (CRO Study No.)
Safety Pharmacology	Cynomolgus monkey	Subcutaneous	Single dose	0, 0.3, 3, 30	Yes	(b) (4)	101606 (b) (4))
Other Studies – Tissue Cross-reactivity	Cynomolgus monkey, rat, rabbit	In vitro	NA	5 or 25 µg/mL	Yes		102700 (b) (4)
	Cynomolgus monkey, human	In vitro	NA	1 or 10 µg/mL	Yes		101758 (b) (4)
	Human	In vitro	NA	1 or 10 µg/mL	Yes		101348 (b) (4)

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[a] Unless otherwise specified. The no observed adverse effect level is underlined, as applicable. GLP = Good Laboratory Practices; IV = intravenous; NA = not applicable; SC = subcutaneous.

Table 2. Overview of Toxicokinetics Studies
Test Article: AMG 162

Type of Study	Test System	Method of Administration	Doses (mg/kg)	GLP Compliance	CRO Study Number
Repeated-dose Toxicity	Cynomolgus monkey	Subcutaneous or Intravenous	Once weekly: 0 (SC), 0.1 (SC), 1.0 (SC), 10.0 (SC), 10.0 (IV)	Yes	(b) (4)
Repeated-dose Toxicity	Cynomolgus monkey	Subcutaneous	Once monthly: 0, 1, 10, 50	Yes	
Female Fertility	Cynomolgus monkey	Subcutaneous	Once weekly: 0, 2.5, 5, 12.5	Yes	
Embryo-fetal Development	Cynomolgus monkey	Subcutaneous	Once weekly: 0, 2.5, 5, 12.5	Yes	
Safety Pharmacology	Cynomolgus monkey	Subcutaneous	0, 0.3, 3, 30	Yes	

GLP = Good Laboratory Practices; IV = intravenous; SC = subcutaneous

Reference ID: 3168397

Table 3. Overview of Toxicokinetics Data
Test Article: AMG 162

Dose [c] (mg/kg)	Dose Frequency	Mean (SD) Steady-State [a] Exposure in Cynomolgus Monkeys			Exposure Margin [b] Based on:	
		C_{max} (µg/mL)	$AUC_{0\text{-}tau}$ (µg·hr/mL)	Corresponding [d] $AUC_{0\text{-}6\ month}$ (µg·hr/mL)	C_{max}	$AUC_{0\text{-}6\ month}$
0.1	weekly [e]	11.3 (31.2)	349 (869)	9074	1.6	0.8
1	weekly [e]	27.5 (14.0)	3410 (2080)	88660	4.0	8.2
2.5	weekly [f]	58.8 (19.8)	8800 (3050)	228800	8.5	21
5	weekly [f]	114 (52.3)	15500 (6350)	403000	16	37
10	weekly [e]	302 (151)	42000 (22700)	1092000	44	100
10 (IV)	weekly [e]	663 (133)	68600 (23000)	1783600	96	170
10	monthly [g]	115 (37.1)	48200 (21100)	289200	17	27
12.5	weekly [f]	282 (89.6)	41000 (10600)	1066000	41	99
50	monthly [g]	666 (156)	268000 (90300)	1608000	96	150

[a] At end of dosing. [b] Relative to mean C_{max} and $AUC_{0\text{-}6\ month}$ values [6.94 µg/mL and 448 µg·day/mL (10752 µg·hr/mL)], respectively; 2nd 60-mg dose for post-menopausal women in study 20010223 (rounded to 2 significant figures). [c] SC dosing except where indicated and compared to clinical exposure of 60 mg Q6M SC. [d] Calculated by multiplying $AUC_{0\text{-}tau}$ values for weekly and monthly dosing by 26 and 6, respectively. [e] Study 101447 (dosed for 4 weeks, combined male and female data). [f] Study 102842 (dosed for 5 weeks, gestation days 20 through 50, females only). [g] Study 102090 (dosed for 12 months, combined male and female data).
SD = standard deviation; C_{max} = maximum observed serum denosumab concentration; $AUC_{0\text{-}tau}$ = area under the concentration-time curve during the dosing interval; $AUC_{0\text{-}6\ month}$ = area under the concentration-time curve over a 6-month period; IV = intravenous; SC = subcutaneous; Q6M = once every 6 months.

Table 4. Toxicology: Drug Substance
Test Article: AMG 162

Lot #	Purity (%)	Placebo Lot No.	CRO Study Number	Type of Study
A0010170015	99.4 (SE-HPLC)	A0010260000	(b) (4)	1-Month toxicity in cynomolgus monkeys Safety pharmacology in cynomolgus monkeys
A0106290000	99.6 (SE-HPLC)	A0108030000		6/12-Month toxicity in cynomolgus monkeys
A0106290000		NA		Tissue cross-reactivity
A0111300000	99.3 (SE-HPLC)	A0108030000		6/12-Month toxicity in cynomolgus monkeys Female fertility in cynomolgus monkeys Embryo-fetal development in cynomolgus monkeys
092900 [a]		NA		Tissue cross-reactivity Tissue cross-reactivity

[a] Purity data not available. NA = not applicable.

Table 7A. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity	Report Title: A 1-Month Study Evaluating the Effect on Bone of AMG 162 Administered Subcutaneously or Intravenously in Cynomolgus Monkeys With a 3-Month Recovery Period	Test Article: AMG 162
Species/Strain: Monkey/Cynomolgus	Duration of Dosing: Once weekly for 1 month	Amgen Study No. 101447
Initial Age: 3 to 5 years	Duration of Postdose: 3 months	(b) (4)
Date of First Dose: 12 January 2001 (males) 19 January 2001 (females)	Method of Administration: Subcutaneous or Intravenous	
	Vehicle/Formulation: 10 mM Na acetate, 5% sorbitol, pH 5.2	GLP Compliance: Yes
Special Features: Antibody Analysis, Bone Biomarkers, Bone Mineral Density		
No Observed Adverse Effect Level: 10 mg/kg		

Dose (mg/kg/dose)	0 (SC)		0.1 (SC)		1.0 (SC)		10.0 (SC)		10.0 (IV)	
Number of Animals	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6	M:6	F:6
Toxicokinetics: $AUC_{0\text{-}168}$ (µg·hr/mL)										
Day 1	NA		195		1800		20200		48700	
Day 21	NA		349		3410		42000		68600	
Binding Antibodies % (incidence)										
End of Dosing	0 (0/12)		100 (12/12)		67 (8/12)		33 (4/12)		25 (3/12)	
End of Recovery	0 (0/12)		100 (6/6)		100 (6/6)		100 (5/6)		67 (4/6)	
Noteworthy Findings										
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0	0	0
Body Weight	-	-	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-	-	-

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[a] Percent change from baseline. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; F = females; IV = intravenous; M = males; NA = not applicable; SC = subcutaneous. * $p < 0.05$, ** $p < 0.01$ compared with control using Dunnett's t-test.

Reference ID: 3168397

Table 7A. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity										Amgen Study No. 101447
Dose (mg/kg/dose)	0 (SC)		0.1 (SC)		1.0 (SC)		10.0 (SC)		10.0 (IV)	
Number of Animals	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-	-	-
Coagulation	-	-	-	-	-	-	-	-	-	-
Serum Chemistry										
Alkaline Phosphatase (IU/L)	539.2	262.8	363.0	138.5**	374.2	151.7**	300.7*	133.3**	297.5*	177.7*
Ca^{++} (mg/dL)	10.73	9.85	10.45	9.80	9.27**	10.00	9.05**	9.97	9.50**	9.70
Blood Ca^{++} (mmol/L)	-	-	-	-	-	-	-	-	-	-
Urinalysis	-	-	-	-	-	-	-	-	-	-
Bone Metabolic Markers (Day 24)										
N-telopeptide (nM BCE)	55.6		41.8		18.3		10.6		8.6	
Osteocalcin (ng/ml)	42.2		30.9		26.5		24.8		22.4	
Bone Mineral Density (mg/cm^3, % change)[a]										
Tibia										
Total	9.0	2.7	5.5	7.3	25.8*	5.7	22.3	5.0	18.3	3.5
Cortical	8.8	3.0	4.8	5.8	25.3*	2.8	19.5	6.3	16.5	4.3

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[a] Percent change from baseline. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collegen equivalents; F = females; IV = intravenous; M = males; NA = not applicable; SC = subcutaneous. * $p < 0.05$, ** $p < 0.01$ compared with control using Dunnett's t-test.

Table 7A. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity										Amgen Study No. 101447
Dose (mg/kg/dose)	0 (SC)		0.1 (SC)		1.0 (SC)		10.0 (SC)		10.0 (IV)	
Number of Animals	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
Organ Weights	-	-	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-	-	-
Histopathology	-	-	-	-	-	-	-	-	-	-
Postdose Evaluation (Recovery)										
Number Evaluated	3	3	3	3	3	3	3	3	3	3
Bone Metabolic Markers (Day 119)										
N-telopeptide (nM BCE)	45.7		55.9		57.4		59.5		40.3	
Osteocalcin (ng/ml)	46.8		32.4		40.9		36.6		25.7	
Bone Mineral Density (mg/cm^3, % change)[a]										
Tibia										
Total (Recovery Week 13)	7.0	-1.0	1.0	-1.0	22.0	-2.7	23.0	8.3	14.0	2.7
Cortical (Recovery Week 13)	4.0	2.0	2.7	1.0	18.0	-0.7	19.3	6.3	12.7	-0.3
Radius										
Total (Recovery Week 4)	-0.3	-1.3	3.0	-2.0	16.0*	1.3	13.7	5.7	17.0	4.0
Cortical (Recovery Week 4)	-1.3	-1.0	2.3	0.7	13.7	0.7	12.0	4.0	15.0*	2.7

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[a] Percent change from baseline. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collegen equivalents; F = females; IV = intravenous; M = males; NA = not applicable; SC = subcutaneous. * $p < 0.05$, ** $p < 0.01$ compared with control using Dunnett's t-test.

Reference ID: 3168397

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity	Report Title: A 6/12-Month Subcutaneous Toxicity Study of AMG 162 in the Cynomolgus Monkey With an Interim Kill After 6 Months and a 3-Month Recovery Period	Test Article: AMG 162
Species/Strain: Monkey/Cynomolgus	Duration of Dosing: Monthly for 6 or 12 months	Amgen Study No. 102090
Initial Age: 2.5 to 4 years	Duration of Postdose: 3 months	CRO Study No. (b) (4)
Date of First Dose: 23 January 2003	Method of Administration: Subcutaneous	
	Vehicle/Formulation: 10 mM sodium acetate, 5% sorbitol, pH 5.2	GLP Compliance: Yes

Special Features: Immunophenotyping, Antibody Analysis, Immunoglobulin Levels, Bone Biomarkers, Testicular Tissue Evaluation of Sperm Motility, Bone Mineral Density, and Biomechanics

No Observed Adverse Effect Level: 50 mg/kg

Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Toxicokinetics: AUC (µg·hr/mL)								
Day 1[a]	NA		4100		61500		343000	
Day 337[a]	NA		BQL		48200		268000	
Antibody Analysis % (incidence)								
Binding Antibodies								
6 Month (Week 24)	0 (0/16)		100 (16/16)		50 (8/16)		7 (1/15)	
12 Month (Week 52)	0 (0/10)		100 (10/10)		60 (6/10)		22 (2/9)	
Recovery (Week 66)	0 (0/4)		100 (4/4)		75 (3/4)		67 (2/3)	

[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Antibody Analysis % (incidence)								
Neutralizing Antibodies[b]								
6 Month (Week 24)	0 (0/16)		75 (12/16)		38 (6/16)		13 (2/15)	
12 Month (Week 52)	0 (0/10)		70 (7/10)		60 (6/10)		22 (2/9)	
Recovery (Week 66)	0 (0/4)		75 (3/4)		75 (3/4)		67 (2/3)	
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	2	0
Body Weight	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-
Blood Pressure	-	-	-	-	-	-	-	-
Bone Mineral Density (mg/cm³, % change)[c]								
Tibia (total)	-11.4	-1.9	-6.4	-4.2	-2.1	7.3	30.1	14.6
Radius (total)	-7.6	-3.7	3.7	-2.3	-0.5	18.9	11.8	21.8
Bone Mineral Content (mg, % change)[c]								
Tibia (total)	-4.1	2.6	-3.8	-7.6	2.0	21.0	66.0	30.3
Radius (total)	-1.0	-4.6	7.0	-3.0	7.1	17.5	48.6	39.6

[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Reference ID: 3168397

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Bone Turnover Biomarkers								
Osteocalcin (ng/mL)								
Week 13	45.6	24.9	31.6	20.1	20.9*	7.9**	7.9**	5.9**
Week 25	37.3	26.0	38.4	25.4	30.3	13.5*	7.6*	6.6**
Week 37	60.0	21.8	46.0	27.3	31.1	14.3	9.6*	7.3
Week 53	58.0	27.9	47.4	25.2	36.8	16.4	17.4	6.8
Serum Crosslaps (pM)								
Week 13	14211.8	13742.7	13832.5	14857.5	8965.5	6693.0*	4675.9**	5160.7**
Week 25	20105.1	17494.6	25185.8	19203.2	17550.9	8582.6	9625.0	4411.1*
Week 37	24618.1	15570.0	27180.3	18020.4	23738.0	9429.9	12681.5	3908.2
Week 53	22123.9	12375.5	22283.2	13989.7	19244.5	8145.4	3688.9*	3685.9
Urine N-Telopeptide (nM BCE NTx/mM UCRT)								
Week 13	439.6	278.5	496.4	246.9	189.6	52.3*	22.7*	38.6**
Week 25	359.2	228.9	370.5	334.9	192.8	113.9	83.7	37.2*
Week 37	515.8	505.8	484.6	551.2	322.4	206.7	51.3*	99.3
Week 53	433.3	265.5	440.6	308.6	248.7	149.5	35.2	63.5

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[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Hematology	-	-	-	-	-	-	-	-
Coagulation	-	-	-	-	-	-	-	-
Serum Chemistry	-	-	-	-	-	-	-	-
Urinalysis	-	-	-	-	-	-	-	-
Immunoglobin Values	-	-	-	-	-	-	-	-
Immunophenotyping	-	-	-	-	-	-	-	-
Sperm Motility Evaluation	-	-	-	-	-	-	-	-
Testicular Tissue Composition	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-	-	-
Biomechanics	-	-	-	-	-	-	-	-

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[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Reference ID: 3168397

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Histopathology (Interim, number evaluated)[a]	3	3	3	3	3	3	2	3
Femur								
Epiphyseal growth plate, enlarged								
Minimal	0	0	0	0	1	1	0	0
Moderate	0	0	0	0	2	0	0	0
Marked	0	0	0	0	0	0	1	0
Decreased chrondroclasis								
Minimal	0	0	0	0	1	1	0	0
Moderate	0	0	0	0	2	0	0	0
Marked	0	0	0	0	0	0	1	0
Decrease of osteoclast/ostesoblast	0/0	0/0	0/0	0/0	2/2	2/2	2/2	2/2

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[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Histopathology (Interim, continued, number evaluated)[a]	3	3	3	3	3	3	2	3
Left Tibia								
Epiphyseal growth plate, enlarged								
Slight	0	0	0	0	0	1	0	0
Minimal	0	0	0	0	1	0	0	0
Moderate	0	0	0	0	2	1	1	3
Marked	0	0	0	0	0	0	1	0
Decreased chrondroclasis								
Slight	0	0	0	0	0	1	0	0
Minimal	0	0	0	0	1	0	0	0
Moderate	0	0	0	0	2	1	1	3
Marked	0	0	0	0	0	0	1	0
Decrease of osteoclast/ostesoblast	0/0	0/0	0/0	0/0	2/1	2/2	2/2	3/3

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[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Reference ID: 3168397

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Histopathology (Interim, continued, number evaluated)[a]	3	3	3	3	3	3	2	3
Sternum								
Decreased chrondroclasis, minimal	0	0	0	0	0	0	1	0
Decrease of osteoclast/ostesoblast	0/0	0/0	0/0	0/0	1/1	1/1	2/2	2/2
Histopathology (Terminal, number evaluated)[a]	3	3	3	3	3	3	3	3
Femur								
Epiphyseal growth plate, enlarged								
Slight	0	0	0	0	0	0	1	1
Moderate	0	0	0	0	0	0	1	0
Marked	0	0	0	0	1	0	1	0

[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Histopathology (Terminal, continued, number evaluated)[a]	3	3	3	3	3	3	3	3
Femur								
Decreased chrondroclasis								
Slight	0	0	0	0	0	0	1	1
Moderate	0	0	0	0	0	0	1	0
Marked	0	0	0	0	1	0	1	0
Decrease of osteoclast/ostesoblast	0/0	0/0	0/0	0/0	1/1	2/2	2/2	3/3
Left Tibia								
Epiphyseal growth plate, enlarged								
Slight	0	0	0	0	0	2	0	1
Moderate	0	0	0	0	0	0	1	1
Marked	0	0	0	0	1	0	1	1
Severe	0	0	0	0	0	0	1	0

[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Reference ID: 3168397

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Histopathology (Terminal, continued, number evaluated)[d]	3	3	3	3	3	3	3	3
Left Tibia								
Decreased chrondroclasis								
Slight	0	0	0	0	0	2	0	1
Moderate	0	0	0	0	0	0	1	1
Marked	0	0	0	0	1	0	1	1
Severe	0	0	0	0	0	0	1	0
Decrease of osteoclast/ostesoblast	0/0	0/0	0/0	0/0	1/1	2/2	3/3	3/3
Sternum								
Enlarged symphysis sternalis								
Slight	0	0	0	0	0	1	1	3
Minimal	0	0	0	0	1	0	1	0
Moderate	0	0	0	0	1	0	1	0

[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Histopathology (Terminal, continued, number evaluated)[d]	3	3	3	3	3	3	3	3
Sternum								
Decreased chrondroclasis								
Slight	0	0	0	0	0	1	1	3
Minimal	0	0	0	0	1	0	1	0
Moderate	0	0	0	0	1	0	1	0
Decrease of osteoclast/ostesoblast	0/0	0/0	0/0	0/0	1/1	2/2	2/2	3/3
Postdose Evaluation (Recovery)								
Histopathology (Number evaluated)[d]	2	2	2	2	2	2	1	2
Left Tibia								
Growth plate, enlarged, slight	0	0	0	0	0	0	1	0
Increase of trabeculae, marked	0	0	0	0	0	1	0	0
Femur								
Increase of trabeculae, moderate	0	0	0	0	0	1	0	0

[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Reference ID: 3168397

Table 7B. Repeated-dose Toxicity: Pivotal Studies
Test Article: AMG 162

Repeated-dose Toxicity								Amgen Study No. 102090
Monthly Dose (mg/kg/dose)	0 (Control)		1		10		50	
Number of Animals	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8	M: 8	F: 8
Early deaths								
Histopathology (number evaluated)[a]	0	0	0	0	0	0	2	0
Femur								
Epiphyseal growth plate, enlarged, moderate							2	
Decreased chrondroclasis, moderate							2	
Decrease of osteoclast/ostesoblast							2/2	
Left Tibia								
Epiphyseal growth plate, enlarged, moderate							2	
Decreased chrondroclasis, moderate							2	
Decrease of osteoclast/ostesoblast							2/2	
Sternum								
Decreased chrondroclasis, slight							1	
Decrease of osteoclast/ostesoblast							2/2	

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[a] Results based on animals negative for binding antibodies. [b] Data presented are for animals that were positive for binding antibodies. In addition, 1 animal dosed at 10 mg/kg and 5 animals dosed at 50 mg/kg were negative for binding antibodies but positive for neutralizing antibodies. [c] Group mean percent change from baseline to week 52. [d] Incidence is presented. *p < 0.05, **p < 0.01 compared with control using Dunnett's t-test. - No noteworthy findings; AUC = area under the plasma drug concentration-time curve; BCE = bone collagen equivalents; BQL = below quantification limit; NA = not applicable. NTx = urine N-telopeptide; UCRT = urine creatinine.

Table 12. Reproductive and Developmental Toxicity: Female Fertility (Pivotal)
Test Article: AMG 162

Reproductive and Developmental Toxicity – Female Fertility	Report Title: Subcutaneous Fertility Evaluation of AMG 162 in the Female Cynomolgus Monkey	Test Article: AMG 162
	Duration of Dosing: Once weekly over at least 2 consecutive menstrual cycles until day 20 post mating	Amgen Study No. 102843
Species/Strain: Cynomolgus Monkey	Method of Administration: Subcutaneous	CRO Study No: [redacted]
Initial Age: Sexually mature, at least 3 years of age	Vehicle/Formulation: 10 mM sodium acetate, 5% sorbitol, pH 5.2	GLP Compliance: Yes
Date of First Dose: 08 September 2003		
Special Features: None		
No Observed Effect Level: Maternal: 12.5 mg/kg/day Fertility: 12.5 mg/kg/day		

Dose (mg/kg/dose)	0 (Control)	2.5	5	12.5
Toxicokinetics: $AUC_{(0-t)}$ (mg· hr/mL)				
Premating cycle (n)	NA	6.77 (6)	11.7 (6)	26.9 (6)
Before first mating (n)	NA	4.22 (4)	16.4 (4)	67.8 (5)
Before second mating (n)	NA	17.6 (2)	16.9 (3)	85.5 (4)
Number Evaluated	6	6	6	6
Noteworthy Findings				
No. Died or Sacrificed Moribund	0	1[a]	0	0
Body Weight	-	-	-	-
Food Consumption	-	-	-	-
Clinical Observations	-	-	-	-

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[a] Animal was euthanized because of severe bite wounds sustained during mating. n = number of animals evaluated. - No noteworthy findings; $AUC_{(0-t)}$ = area under the plasma drug concentration-time curve over the dosing interval; NA = not applicable.

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Table 12. Reproductive and Developmental Toxicity: Female Fertility (Pivotal)
Test Article: AMG 162

Reproductive and Developmental Toxicity				Amgen Study No. 102843
Dose (mg/kg/dose)	0 (Control)	2.5	5	12.5
Fertility Parameters				
Hormone Analysis	-	-	-	-
Menstrual Cycle	-	-	-	-
Mating Performance				
Total Number Pregnant/Number Mated	2/6	2/6	2/6	5/6

[a] Animal was euthanized because of severe bite wounds sustained during mating. n = number of animals evaluated. - No noteworthy findings; $AUC_{(0-t)}$ = area under the plasma drug concentration-time curve over the dosing interval; NA = not applicable.

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Table 13. Reproductive and Developmental Toxicity: Effects on Embryo-fetal Development (Pivotal)
Test Article: AMG 162

Reproductive and Developmental Toxicity – Effects on Embryo-fetal Development	Report Title: Subcutaneous Embryo-fetal Development Study of AMG 162 in the Cynomolgus Monkey		Test Article: AMG 162
	Duration of Dosing: 5 weeks (once per week, from gestation days 20 through 50)		Amgen Study No. 102842
Species/Strain: Cynomolgus Monkey	Day of Mating: Gestation day 0		(b) (4)
Initial Age: Sexually mature, at least 3 years of age	Day of C-Section: Gestation day 100 ± 1		
Date of First Dose: 27 November 2003	Method of Administration: Subcutaneous		
Special Features: Antibody analysis	Vehicle/Formulation: 10 mM sodium acetate, 5% sorbitol, pH 5.2		GLP Compliance: Yes
No Observed Effect Level: F_0 Females: 12.5 mg/kg/day F_1 Fetuses: 12.5 mg/kg/day			

Dose (mg/kg/dose)		0 (Control)	2.5	5	12.5
Dams:	Toxicokinetics: $AUC_{(0-t)}$ (mg·hr/mL)				
	GD 21 (first dose)	NA	3.59	7.46	16.7
	GD 49 (final dose)[a]	NA	8.80	15.5	41.0
	Antibody Analysis: % (incidence)[b]				
	Binding Antibodies				
	GD49 (final dose)	7 (1/15)	33 (5/15)	19 (3/16)	0 (0/16)
	GD94 – GD101	8 (1/13)	80 (12/15)	69 (11/16)	50 (8/16)
	Neutralizing Antibodies				
	GD49 (final dose)	0 (0/15)	7 (1/15)	6 (1/16)	0 (0/16)
	GD94 – GD101	0 (0/13)	53 (8/15)	38 (6/16)	13 (2/16)

Page 1 of 3

[a] Results based on antibody negative animals. [b] One dam each in the control and low dose groups had only pre-dose analysis because of fetal deaths before gestation day 49. $AUC_{(0-t)}$ = area under the plasma drug concentration-time curve over the dosing interval; GD = gestation day; - No noteworthy findings; NA = not applicable.

Table 13. Reproductive and Developmental Toxicity: Effects on Embryofetal Development (Pivotal)
Test Article: AMG 162

Reproductive and Developmental Toxicity					Amgen Study No. 102842
Dose (mg/kg/dose)		0 (Control)	2.5	5	12.5
Dams:	No. Mated	16	16	16	16
	No. Pregnant	16	16	16	16
	No. Died or Sacrificed Moribund	0	0	0	0
	Clinical Observations	-	-	-	-
	Body Weight	-	-	-	-
	Food Consumption	-	-	-	-
Fetuses:	No. Fetuses Evaluated	13	15	15	16
	Antibody Positive Fetuses % (incidence)				
	Binding Antibodies	62 (8/13)	53 (8/15)	40 (6/15)	6 (1/13)
	Neutralizing Antibodies	0 (0/13)	20 (3/15)	27(4/15)	0 (0/13)
	Live Fetuses	13	15	15	16
	No. Aborted or Died in Uterus	3	1	1	0
	No. of Dead Fetuses at Cesarean-section	0	0	0	0
	Mean Fetal Body Weight (g)	-	-	-	-
	Gross Pathology	-	-	-	-
	Organ Weights	-	-	-	-
	Histopathology	-	-	-	-
	Fetal Sex Ratios (M/F)	7/6	8/7	10/5	8/8

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[a] Results based on antibody negative animals. [b] One dam each in the control and low dose groups had only pre-dose analysis because of fetal deaths before gestation day 49. $AUC_{(0-t)}$ = area under the plasma drug concentration-time curve over the dosing interval; GD = gestation day; - No noteworthy findings; NA = not applicable.

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Table 13. Reproductive and Developmental Toxicity: Effects on Embryofetal Development (Pivotal)
Test Article: AMG 162

Reproductive and Developmental Toxicity				Amgen Study No. 102842
Dose (mg/kg/dose)	0 (Control)	2.5	5	12.5
Fetuses: Fetal Anomalies (incidence)				
Gross External	-	-	-	-
Visceral Anomalies	-	-	-	-
Skeletal Anomalies	-	-	-	-

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[a] Results based on antibody negative animals. [b] One dam each in the control and low dose groups had only pre-dose analysis because of fetal deaths before gestation day 49. $AUC_{(0-t)}$ = area under the plasma drug concentration-time curve over the dosing interval; GD = gestation day; - No noteworthy findings; NA = not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The nonclinical pharmacology, pharmacokinetics, and toxicology data for Prolia™ support the safety and biologic activity of this product for use in the treatment of bone loss associated with hormone ablation therapy with breast cancer, or treatment of bone loss associated with hormone ablation therapy in patients with prostate cancer.

Unresolved toxicology issues (if any): None.

Recommendations: The nonclinical discipline recommends approval of denosumab (Prolia™) for the treatment of bone loss associated with hormone ablation therapy with breast cancer, or treatment of bone loss associated with hormone ablation therapy in patients with prostate cancer.

Suggested labeling: The nonclinical modifications to the label are provided as Appendix 1 to this review.

Signatures (optional):

Reviewer Signature Michael S Orr 09/09/09

Supervisor Signature 9/9/09 Concurrence Yes X No ___

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APPENDIX 1 DRAFT NONCLINICAL LABELING CHANGES

In Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility section

Reviewer Modified:

[redacted] (b) (4)

Sponsor submitted labeling in the Carcinogenicity section:

The carcinogenic potential of denosumab has not been evaluated in long-term animal studies. [redacted] (b) (4)

Sponsor submitted labeling in the Mutagenicity section:

The genotoxic potential of denosumab has not been evaluated. [redacted] (b) (4)

Reviewer Modified Impairment of Fertility Section:

Denosumab had no effect on female fertility or male reproductive organs in monkeys at [redacted] (b) (4) that were [redacted] (b) (4) higher than the recommended human dose [redacted] (b) (4)

Sponsor submitted labeling in the Fertility section:

Denosumab had no effect on female fertility or male reproductive organs in monkeys at [redacted] (b) (4) that were [redacted] (b) (4) higher than the human [redacted] (b) (4) administered once every 6 months.

In Section 13.2 Animal Toxicology and/or Pharmacology:

Reviewer Modified Section:

[redacted] (b) (4)

Sponsor submitted labeling:

[redacted] (b) (4)

Reference ID: 3168397

(b) (4)

Reviewer Modified Section:

Adolescent primates (b) (4) with denosumab (b) (4) the recommended human dose (b) (4) consistent with the pharmacological activity of denosumab *[see Use in Specific Populations (8.4)]*.

Sponsor submitted labeling:

Adolescent primates (b) (4) with denosumab at (b) (4) (b) (4) 60 (b) (4) had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab *[see Use in Specific Populations (8.4)]*.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA OR SUPPLEMENT

NDA/BLA Number: 125-332 & 125-333 **Applicant:** Amgen **Stamp Date:** 12-19-2008

Drug Name: Prolia (denosumab) **NDA/BLA Type:** NME

On **initial** overview of the BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	Y		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Y		
3	Is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	Y		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	Y		Tissue cross reactivity studies are provided with human and animal tissues; pivotal studies are in appropriate species (monkey); transgenic models used for pharmacodynamics; antibody formation addressed in studies 101447, 102090, 103948, 103981; CV and respiratory safety pharmacology with single dose study incorporated; PK and PD studies; repeat dose studies over appropriate duration; local tolerance incorporated into repeat dose studies. No carcinogenicity or genotoxicity studies are required since this is a biologic product.
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	Clinical and nonclinical studies have used the same formulation of drug product (5% sorbitol, 10mM sodium acetate, pH 5.2), but the proposed labeling gives a slightly different formulation content (4.7% sorbitol, 17mM acetate, pH 5.2). The formulation found in the labeling is also different than that noted on page 12 of the Quality overview (which is the same as that noted in clinical and nonclinical studies). Needs further investigation
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	Y		The subcutaneous route for clinical trials was used in all pivotal nonclinical studies.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	Y		Located on page 5 of the nonclinical overview.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Y		See comments below for information requested via meetings and submission comments.

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PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA OR SUPPLEMENT

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	Y		(b) (4), and Carcinogenicity and Mutagenicity sections should be added with a statement that they have not been evaluated. The Sponsor uses the terminology "x-fold higher than (b) (4) (b) (4) – this is appropriate. -At this time, the accuracy of dose multiples has not been evaluated.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	Y		Toxicity studies have not been performed on any impurities. Impurities are listed as product- (b) (4)) and process- related impurities, and are addressed in the Quality section.
11	Has the applicant addressed any abuse potential issues in the submission?	Y		No indication that drug interacts with receptors associated with drug dependence or neurotropic activity (p 29 of nonclinical overview). Label indicates "no experience with overdosage" and (b) (4) (b) (4)
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

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

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

Additional notes:

Nonclinical studies submitted to the BLA:

Pharmacology (PMO and HALT indications in the Bone Loss BLA on 19 December 2008)	
Study #	**Title**
R2004430	Effects of denosumab (AMG 162) on bone mass and bone resorption in human RANK ligand knock-in mice
R2004321	Effects of denosumab (AMG 162) on bone mass and bone resorption in aged human RANK ligand knock-in mice
106564	A 12-mo osteoporosis prevention study of denosumab with and without 6-month alendronate pretreatment in the cynomolgus monkey
R2006351	Denosumab, a fully human monoclonal antibody, has selective effects on human RANK ligand and human osteoclasts
R2006458	Comparison of two anti-resorptive therapies (alendronate vs AMG 162) on murine fracture healing
103981	AMG 162 - a monthly s.c. injection osteoporosis prevention study for 16-months in the cynomolgus monkey

Safety Pharmacology

Reference ID: 3168397

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA OR SUPPLEMENT

Study #	Title
R20080340	The effects of OPG-Fc, RANK-Fc, or alendronate on tooth eruption, bone density, geometry, and strength in neonatal rats
101606	Final report - A single dose s.c. admin of AMG 162 for cardiovascular and respiratory evaluation in cynomolgus monkeys

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Pharmacokinetics	
Study #	**Title**
101494	PK study of denosumab (AMG 162) in male mice following i.v. or s.c. administration
104192	Absorption, distribution and excretion in cynomolgus monkeys following a single s.c. administration of ^{125}I-AMG 162
106893	A single dose PK study of denosumab (AMG 162) following i.v. administration to male or female FcRn knockout and wild-type mice
106892	PK report for a single dose PK study of denosumab (AMG 162) following i.v. administration to male or female huRANKL knock-in and wild-type mice
101398	A single dose i.v. and s.c. PK and PD study of AMG 162 in cynomolgus monkeys
101002	Pilot PK study of AMG 162 administered s.c. or i.v. in male and female Sprague-Dawley rats
104105	Quantitative whole body autoradiography of cynomolgus monkeys following a single s.c. administration of ^{125}I-AMG 162
103948	PK and PD comparability study for two manufacturing processes of AMG 162 in female cynomolgus monkeys

Toxicology	
Study #	**Title**
101447	A 1-month study evaluating the effect on bone of AMG 162 administered s.c. or i.v. in cynomolgus monkeys with a 3-month recovery period
102090	A 6-12-month s.c. toxicity study of AMG 162 in the cynomolgus monkey with an interim kill after 6-months and a 3-month recovery period
102843	Subcutaneous fertility evaluation of AMG 162 in the female cynomolgus monkey
102842	Subcutaneous embryo-fetal development study of AMG 162 in the cynomolgus monkey
101758	Cross-reactivity of AMG 162 with normal cynomolgus monkey and human tissues
101348	Cross-reactivity of AMG 162 with normal human tissues
102700	Cross-reactivity of AMG 162 with cynomolgus monkey, rat and rabbit tissue ex vivo

Additional comments:

Information below provided by Dr. Kim Hatfield in DRUP:

Notes concerning the formulation of drug product:

During development, denosumab has been manufactured by two versions of the intended commercial process, CP1 and CP2 (b) (4)

Material from CP1 was used in the pivotal toxicology studies to support clinical development. It appears from meeting minutes that the discussions on this issue were handled by the CMC review team. At an April 20, 2004 meeting, FDA requested additional information to determine if CP1 was comparable to CP2, and stated that if CP2 was used in clinical studies prior to a comparability agreement, a bridging study might be required. Then at a September 21, 2004 meeting (after Amgen had submitted comparability data), FDA stated that open questions remained regarding consistency of amidation and the potential for difference in immunogenicity between CP1 and CP2. In addition, although the modification may not have an effect on toxicity, it may impact exposure levels, and the Agency would consult with colleagues and continue to collaborate to further examine comparability. The Sponsor did conduct a PK-PD study in female cynomolgus monkeys with CP2 material to determine if modifications had an influence on biological activity. To date, this study has not been reviewed, and no further information on whether this study was acceptable or if CP1 and CP2 were considered to be comparable has been located.

- The Sponsor stated in the nonclinical overview that the collective data indicated that changes introduced in CP2 denosumab did not have a meaningful effect on PK or PD in the monkey, and that the drug substance and product planned for commercial use are comparable to the test materials

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used previously in the pivotal nonclinical studies. Additional information is located in Module 2.5, Section 2 and Module 2.7.1, which are clinical overviews and summaries).

Reviewing Toxicologist – Michael S. Orr, Ph.D., DABT — Date 1/29/09

Team Leader/Supervisor – Anne M. Pilaro, Ph.D. — Date 1/29/2009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

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

Team Leader Review Memo

BLA/Serial Number:	BL STN 125332/0
Drug Name:	PROLIA (denosumab)
Indication(s):	Treatment of Bone Loss in Subjects Undergoing Aromatase Inhibitor Therapy for Nonmetastatic Breast Cancer
Applicant:	Amgen, Incorporated
Date(s):	Received Date: December 19, 2008 Application Review Due Date: October 19, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Mark Rothmann, Ph.D., Lead Mathematical Statistician
Concurring Reviewers:	Aloka Chakravarty, Ph.D., Division Director
Medical Division:	Division of Biologic Oncology Products
Clinical Team:	Dr. Suzanne Demko, Clinical Reviewer Dr. Jeffrey Summers, Acting Team Leader
Project Manager:	Melanie Pierce
Keywords:	

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1. EXECUTIVE SUMMARY

This original Biologic License Application (BLA) for Prolia (denosumab) primarily consists of the results of study 20040135. Study 20040135 is a randomized, multicenter, study of denosumab in subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. Two hundred fifty-two subjects were randomized (127 to denosumab and 125 to placebo) at sites in the United States and Canada. The primary endpoint of the percent change in lumbar spine bone mineral density (BMD) from baseline to month 12 demonstrated a statistically significant improvement for the denosumab arm compared to the placebo arm ($p < 0.0001$). The least squares means for the percent change since baseline at month 12 was a 4.8% increase in the denosumab arm and a 0.7% decrease in the placebo arm. The difference in the mean percent change was 5.5% (95% CI: 4.8, 6.3) at month 12. BMD is regarded as a potential surrogate endpoint for the likelihood of experiencing a fracture.

In oncology the bone-related clinical benefit endpoints of interest are the incidence of a skeletal-related event, and the time to the first skeletal-related event or death (i.e., skeletal-related event-free survival). Skeletal-related events consist of the need for bone radiotherapy, the need for bone surgery, a fracture, and spinal cord suppression.

This BLA submission of denosumab was one of four BLAs simultaneously submitted for denosumab. The sponsor also submitted BLA 125333 based on Study 20040138 submissions in subjects with hormone-ablative therapies for prostate cancer, and BLAs 125320 (based on Study 20030216) and BLA 125331 (based on Study 20040132) for the treatment and prevention of osteoporosis. BLAs 125332 and 125333 are under review by the Division of Biologic Oncology Products while BLAs 125320 and 125331 are under review by the Division of Reproductive and Urologic Products (DRUP). All four BLAs were presented at the August 13, 2009 meeting of the Reproductive Health Drugs advisory committee.

1.1 Conclusions and Recommendations

Study 20040135 met its primary endpoint. The data are not adequate on whether denosumab affects the recurrence of breast cancer or impacts overall survival. The study was not designed to adequately compare disease free survival (DFS) and overall survival (OS) between study arms. There was very little follow-up for overall survival with only four total deaths reported.

1.2 Brief Overview of Study 20040135

Study 20040135 is a multicenter, randomized, double-blind, placebo-controlled study in subjects receiving adjuvant aromatase inhibitor therapy for nonmetastatic breast cancer with BMD T-scores between -1.0 and -2.5 (which excludes women with osteoporosis and those with normal BMD). Two hundred fifty-two (252) subjects were randomized to receive either 60 mg denosumab (127 subjects) or placebo (125 subjects) subcutaneously once every 6 months for 24 months with a total of 4 injections. The randomization was stratified by the duration of aromatase inhibitor therapy ($\leq$ 6 months versus > 6 months) at study entry. Subjects were to be followed for 24 months after the last dose of investigational product. The sponsor's results for the mean percent change in lumbar spine BMD from baseline to month 12 are summarized

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below in Table 1. The results were statistically significant with a difference in the mean percent change from baseline of 5.5% (95% CI: 4.8, 6.3) at month 12.

Table 1. Sponsor's Primary Efficacy Results

	Placebo		Denosumab 60 mg Q6M		Difference		
	n/N	Estimate	n/N	Estimate	Estimate	95% CI	p-value
Lumbar Spine Bone Mineral Density Percentage change From Baseline at Month 12[a]							
	122/122	-0.7	123/123	4.8	5.5	(4.8, 6.3)	<0.0001

a: Based on ANCOVA model adjusting for stratification variable, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction.

Table 2 provides Kaplan-Meier estimates based on analyses performed by Dr. Lee of time to first new non-vertebral fracture. Estimates of the probability of a first new non-vertebral fracture by one and two years are provided, along with the difference between arms in the estimated probabilities and the estimated number needed to treat (NNT) with denosumab to prevent one subject from a first new non-vertebral fracture. No vertebral fractures were reported in this study.

Table 2. Kaplan-Meier estimates of the probability of any non-vertebral fracture by 1 and 2 years

	One year	Two years
Placebo	0.0346	0.0725
Denosumab	0.0330	0.0722
Difference	0.0016	0.0003
NNT with denosumab to prevent one subject from any new non-vertebral fracture	625	3333

From Table 2 an estimated 3333 subjects are needed to treat to prevent one subject from experiencing a first new non-vertebral fracture by two years.

1.3 Major Statistical Issues and Findings

The following questions (and the voting results) related to this BLA were asked by FDA to the Reproductive Health Drugs advisory committee:

Question 3.a: Is a favorable risk/benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors? (AC members vote: 2- yes, 13-No.)

Question 3.b: Is a favorable risk/benefit ratio demonstrated for denosumab for the prevention of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors? (AC members vote: 0- yes, 14-No, 1-abstain.)

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I have no major disagreements with the statistical review of Dr. Kyung Yul Lee. The major issues as I view them are discussed below. For additional statistical issues see the review of Dr. Kyung Yul Lee.

- Eight subjects (6%) in the denosumab group and 8 subjects (6%) in the placebo group had non-veterbral fracture events. Kaplan-Meier estimates of the risk of non-vertebral fracture were 3.3% for the denosumab group and 3.5% for the placebo group at month 12 and 7.2% for both treatment groups at month 24. No vertebral fractures were reported in this study. There is no indication from this study that denosumab reduces the likelihood of a fracture. The estimated number of subjects to treat to prevent one new non veterbral by two years is quite high (i.e. 3333 subjects).

  Due to the small sample size and the short followup, the number of subjects needed to treat to prevent one new fracture can not be reliably estimated. In study 20040138 of 1468 subjects, similar results were seen on BMD. Besides being larger study 20040138 had longer follow-up to semi-adequately assess the likelihood of experiencing a fracture within three years. For study 20040138, 37 subjects would need to be treated to prevent one subject from experiencing a first new fracture (a first new vertebral fracture) within three years. In order for denosumab to have a positive risk-benefit assessment the potential risks and toxicities of exposing 37 subjects to denosumab cannot outweigh the benefit of exactly one of those 37 subjects avoiding any new fracture (any new vertebral fracture). This is a high standard on the safety of denosumab. Differences in the severity of the fractures between arms (if known) and any benefits from improve bone mineral density would also need to be considered.

- The data are not adequate to examine for any potential detrimental effects on disease free survival (DFS) and/or overall survival. The follow-up for overall survival had only four deaths reported.

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SIGNATURES/DISTRIBUTION LIST

Statistical Team Leader and author of this review: Dr. Mark Rothmann, Ph. D.
Date: September 8, 2009

Concurring Reviewer(s): Aloka Chakravarty 9/8/09
Biometrics Division Director: Dr. Aloka Chakravarty, Ph. D.

cc:
HFD-107/Ms. Pierce
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HFD-711/Dr. Chakravarty
HFD-700/Ms. Patrician
C:\A_DB5\Review\BLAs\125332 0 TL memo

Reference ID: 3168397

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 125332 & 125333 **Applicant:** Amgen **Stamp Date:** 12/19/2008

Drug Name: PRORIA **NDA/BLA Type:** BLA

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.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓			20030216 → Women 20049132 20040138 → Men 20040131
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _____

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.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	✓			20030216
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.	✓			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

Reference ID: 3168397

Reference ID: 3168397

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Kyung Yul Lee — 1/29/2009

Reviewing Statistician — Date

Mark Rothmann — 1/29/2009

Supervisor/Team Leader — Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	BL STN 125333/0
Drug Name:	PROLIA (denosumab)
Indication(s):	Treatment of bone loss associated with hormone ablation therapy in subjects with prostate cancer
Applicant:	Amgen Incorporated
Date(s):	Received Date: December 19, 2008 Application Review Due Date: October 19, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Kyung Yul Lee, Ph.D., Statistical Reviewer
Concurring Reviewers:	Mark Rothmann, Ph.D., Lead Mathematical Statistician Aloka Chakravarty, Ph.D., Division Director
Medical Division:	Division of Biologic Oncology Products
Clinical Team:	Dr. Suzanne Demko, Clinical reviewer
Project Manager:	Melanie Pierce

Keywords: prostate cancer, hormone ablation, bone mineral density

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1. EXECUTIVE SUMMARY

BLA 125333 (Study 20040138) was designed to evaluate the safety and efficacy of denosumab compared with placebo on bone loss in men with nonmetastatic prostate cancer undergoing androgen deprivation therapy (ADT). Results of the Phase III study 20040138 are included in this submission.

The sponsor submitted four BLAs 125320, 125331, 125332, and 125333 for denosumab simultaneously. BLA 125332 consists of the results of Study 2004135 in subjects undergoing aromatase inhibitor therapies for nonmetastatic breast cancer. BLAs 125332 and 125333 are under review by the Division of Biologic Oncology Products (DBOP). BLA 125320 consists of the results of Study 20030216 in subjects with postmenopausal osteoporosis and BLA 125331 consists of the results of Study 20040132 in subjects with postmenopausal low bone mineral density. BLAs 125320 and 125331 are under review by the Division of Reproductive and Urologic Products (DRUP). Study 20030216 is the pivotal study for the treatment of postmenopausal osteoporosis (PMO) as the primary indication examining fracture risk reduction and increases in bone mineral density (BMD). This trial is to demonstrate the evidence of clinically relevant increases in BMD and reductions in fracture. Studies 20040132, 20040135 and 20040138 are pivotal trials supporting the treatment and prevention of PMO and bone loss associated with hormone ablation therapy for breast and prostate cancer, respectively, examining increases in BMD. The Advisory committee for the Reproductive Health Drugs met on August 13, 2009 for BLA submissions, 125320, 125331, 125332 and 125333.

BMD and fracture endpoints are clinically relevant. BMD is a major determinant of fracture risk and increases in BMD have been associated with a reduction in fracture risk in patients. Although the fracture incidence rate among patients with low bone mass is known to be relatively low, the total number of fractures among patients with low bone mass is known to be greater than that among patients with osteoporosis. BMD decrease over time is indicative of bone loss, microarchitecture deterioration and potential fractures. Low BMD is used as a surrogate endpoint for the risk of developing fractures.

1.1 Conclusions and Recommendations

The primary endpoint of the percentage change in lumbar spine bone mineral density (BMD) from baseline to month 24 demonstrated a statistically significant percentage change for the denosumab group as compared to the placebo group ($p < 0.0001$). The least squares mean estimate was 5.6% increase in denosumab and 1.0% decrease in placebo from baseline, the percentage difference between denosumab and placebo was 6.7% (95% CI: 6.2, 7.1) at month 24. The sensitivity analyses performed by the sponsor and by this reviewer confirmed the results of primary analysis.

The secondary endpoints for the percentage changes in femoral neck BMD and total hip BMD from baseline to month 24 and the percentage changes in lumbar spine, femoral neck and total hips BMDs from baseline to month 36 demonstrated statistically significant BMD percentage

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increases in the denosumab group as compared to the placebo group (all p <0.0001). The sensitivity analyses results by the sponsor and by this reviewer were consistent.

Secondary endpoints for the subject incidence of any fracture at month 36 endpoint did not reach statistical significance, but new vertebral fracture at month 36 was statistically significant (p=0.0063, adjusted p=0.0125). Further testing for the other fracture endpoints for steps 4 and 5 should be stopped at this point because of hierarchical testing procedures.

The data are not adequate whether denosumab affects prostate cancer. In particular, the study was not designed to adequately compare progression free survival (PFS) and overall survival (OS) between arms. There were no meaningful safety information about the primary disease progression-free survival and overall survival and no routine neoplastic disease assessment.

There is evidence that this study supports that denosumab 60 mg subcutaneously (SC) once every 6 months with a total of 6 doses over the 36-month treatment period as compared to placebo increases the percentage change in lumbar spine BMD from baseline to month 24 for subjects with nonmetastatic prostate cancer who were undergoing ADT. However, safe use of denosumab has not been evaluated for these prostate cancer patients based on tumor related outcomes.

1.2 Brief Overview of Clinical Studies

There are four pivotal trials for denosumab. These four pivotal trials are as follow;

Study 20040138 is a pivotal trial supporting the treatment and prevention of bone loss associated hormone ablation therapy for prostate cancer. This study is an international, multicenter, randomized, double-blind, placebo-controlled study in subjects with nonmetastatic prostate cancer who were undergoing ADT. Subjects were randomized (1:1) to receive either placebo or denosumab 60 mg subcutaneously (SC) once every 6 months with a total of 6 doses over the 36-month treatment period.

A total of 1468 subjects were randomized to receive denosumab or placebo, 734 subjects per group. Randomization stratification factors were age group (< 70 years vs. ≥ 70 years) and duration of ADT with gonadotropin-releasing hormone (GnRH) agonists or orchiectomy at study entry (≤ 6 months vs. > 6 months).

The total study duration was 60 months including a 36-month treatment period (with last dose administered at month 30) and a 24-month safety follow-up period. After completing the 36-month treatment period, subjects were continued on study for 24 months without administering investigational product, or offered enrollment in a 2-year extension study (20080537). Results from the 36-month treatment period are included in this submission.

The primary endpoint was the percentage change in lumbar spine BMD from baseline to month 24. Secondary efficacy endpoints were the percentage change in lumbar spine BMD from baseline to month 36, the percentage changes in femoral neck BMD and total hip BMD from

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baseline to month 24 and month 36, the incidence of any fracture (ie, osteoporotic fracture at any skeletal site, including vertebral, but excluding skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges), and the incidence of new vertebral fracture over the 36-month treatment period, time to first clinical fracture over the 36-month treatment period and the incidence of any fracture over the 24-month treatment period. The secondary efficacy endpoints analyses were contingent on rejection of the primary null hypothesis at a level of 0.05 and used the Hochberg procedure to adjust for multiplicity at level of 0.05.

Study 20040135 is a pivotal trial supporting the treatment and prevention of bone loss associated hormone ablation therapy for breast cancer. This study is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy of denosumab in subjects receiving adjuvant aromatase inhibitor therapy for nonmetastatic breast cancer. A total of 252 subjects with BMD T-scores between -1.0 and -2.5, excluding women with osteoporosis and those with normal BMD were randomized in a 1:1 ratio to receive either 60 mg denosumab or placebo subcutaneously once every 6 months for 24 months with a total of 4 injections. The stratification factor was duration of aromatase inhibitor therapy ($\leq$ 6 months versus > 6 months) at study entry.

The primary endpoint was the percentage change in lumbar spine BMD from baseline to month 12. The secondary endpoints were the percentage change in lumbar spine BMD from baseline to month 6 and percentage changes in total hip and femoral neck BMDs from baseline to months 6 and 12. The secondary efficacy endpoints analyses were contingent on rejection of the primary null hypothesis at a level of 0.05 and Hochberg procedure was used to adjust multiplicity at a level of 0.05. Denosumab demonstrated significant increases in percentage change in lumbar spine, total hip and femoral neck BMDs from baseline to month 24.

Study 20030216 is a pivotal study for the primary indication of the treatment of PMO. This study is an international, multicenter, randomized, double-blind, placebo-controlled study tested the clinical hypotheses that denosumab, as compared with placebo, is effective in reducing the risks of new vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis (BMD T-score < -2.5 at either the lumbar spine or the total hip, or at both locations, but ≥ -4.0 at both locations).

A total of 7808 subjects were randomized to receive either denosumab 60 mg (3902 subjects) or placebo (3906 subjects) every 6 months (Q6M) subcutaneously for 3 years (last dose at month 30; follow-up to month 36). Randomization was stratified by age at entry: 60 to 64 years, 65 to 69 years, 70 to 74 years; and $\geq$ 75 years.

The primary efficacy endpoint is the subject incidence of new vertebral fractures during the entire 36-month treatment period. Secondary efficacy endpoints are time to first nonvertebral fracture and time to first hip fracture. A fixed sequence testing procedure among these 3 endpoints was used for multiplicity adjustment to maintain the overall significance level at 0.05. Denosumab demonstrated significant reductions of risks in new vertebral, nonvertebral, and hip fractures at month 36. Denosumab demonstrated significant increases in percentage change in lumbar spine, total hip, and femoral neck BMDs from baseline to 36 months.

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Study 20040132 is a pivotal study for the prevention of PMO indication. This study is a multicenter, randomized, double-blind, 2-period, parallel group study to evaluate denosumab in the prevention of postmenopausal osteoporosis. This study enrolled postmenopausal women with lumbar spine BMD T-score between -1.0 and -2.5. A total of 332 subjects were randomized (1:1) to receive either denosumab 60 mg (166 subjects) or placebo (166 subjects) every 6 months (Q6M) subcutaneously for 2 years. Duration of study is approximately 50 months (2 months screening period, 24 months treatment period and 24 month follow-up period.) Randomization was stratified by time since onset of menopause ($\leq$ 5 years or > 5 years).

The primary efficacy endpoint is the percent change from baseline in the lumbar spine BMD (by DXA) at 24 months of treatment. Secondary efficacy endpoints are percent change from baseline in BMD (by DXA) of the total hip, femoral neck, trochanter, distal 1/3 radius, and total body (without head) at 24 months and percent change from baseline in trabecular, cortical, and total volumetric BMD of the distal radius as measured by QCT at 24 months Multiplicity adjustments of both hierarchical testing strategy and Hochberg procedure were applied to one primary and secondary efficacy endpoints to maintain the overall type I error at $\leq$ 0.025 within each strata. Denosumab demonstrated significant increases in percentage change in lumbar spine, total hip, and femoral neck BMDs from baseline to month 24.

1.3 Statistical Issues and Findings

1.3.1 Efficacy Analyses Results

The primary efficacy endpoint, the percentage change in lumbar spine bone mineral density, the least squares mean was 5.6% increase in the denosumab group and was 1.0% decrease in the placebo group from the baseline to month 24, the percentage difference between the denosumab group and the placebo group was 6.7% (95% CI: 6.2, 7.1) at 2 years and this percentage difference was statistically significant ($p<0.0001$).

For secondary endpoints, a hierarchical testing procedure was followed.
First set of secondary endpoints, femoral neck and total hip BMDs were increased by 2.4% and 2.7%, respectively, in the denosumab group and were decreased by 1.5% and 2.0%, respectively, in the placebo group at 2 years, the percentage differences between denosumab and placebo were 3.9% (95% CI: 3.5, 4.4) and 4.8% (95% CI: 4.4, 5.1), respectively, and these percentage differences were statistically significant (all $p<0.0001$).

Second set of secondary endpoints, lumbar spine, femoral neck and total hip BMDs were increased by 6.8%, 3.0% and 3.2%, respectively, at 3 years in the denosumab group and were decreased by 1.2%, 1.8%, and 2.6%, respectively, in the placebo group at 3 years, the percentage differences between denosumab and placebo were 7.9% (95% CI: 7.4, 8.4), 4.9% (95% CI: 4.4, 5.4) and 5.7% (95% CI: 5.4, 6.1), respectively, and all these percentage differences were statistically significant (all $p<0.0001$).

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Third set of secondary endpoints, 53 subjects (7.2%) among 734 placebo subjects and 38 (5.2%) subjects among 734 denosumab subjects observed any fracture events at 3 years. The odd ratio was 0.70 (95% CI: 0.46, 1.08) (p=0.1048). Denosumab failed to demonstrate a reduction in the incidence of any fractures at 3 years. Further formal testing of secondary endpoints for steps 4 and 5 should be stopped at this point. Denosumab demonstrated a reduction in incidence of new vertebral fractures of 1.5% as compared to 3.5% of placebo at 3 years (OR: 0.37, 95% CI: 0.18, 0.78: p=0.0063, adjusted p=0.0125).

Subjects in the denosumab group demonstrated significantly increased BMD percentage changes as compared to subjects in the placebo group in lumbar spine, femoral neck and total hip BMDs from baseline to months 24 and 36. Subjects in the denosumab group did not show the statistical significant results in any fracture endpoint, but denosumab demonstrated a significant reduction in incidence of new vertebral fractures at month 36.

1.3.2 Statistical Issues

- There was no adequate data to identify any potential for detrimental effects on progression free survival (PFS) or overall survival on how denosumab affects the primary disease of prostate cancer. There were no meaningful safety information about the primary disease progression or overall survival and no routine neoplastic disease assessment.

- The percent of subjects with missing lumbar spine BMD scores for the denosumab group and the placebo group were 21% and 24%, respectively, at month 24 and 38% and 40%, respectively, at month 36. Last observation carried forward imputation method was used for the efficacy analyses.

- Sponsor performed sensitivity analyses including repeated measures model, ANCOVA model using the per protocol analysis set, ANCOVA model using subjects categorized by their actual stratum and univariate and multivariate covariate analyses to demonstrate the robustness of the primary results.

- There was no demonstrated reduction in the incidence of any fractures endpoint during 3-year treatment periods, but there was a demonstrated reduction in incidence of new vertebral fractures at month 36. Most of new vertebral fractures (70%) in denosumab were reported at year 3. Absolute rate difference (placebo-denosumab) for any fractures between the two treatments were 0 %, 1.9 %, and 0.9 % for year 1, 2, and 3, respectively. Absolute rate difference (placebo-denosumab) for new vertebral fractures between the two treatments were 0.7%, 1.5%, and 0.4% for year 1, 2, and 3, respectively. Absolute risk reduction (placebo-denosumab) for any fractures during 2 years (cumulatively) and 3 years (cumulatively) were 1.8% and 2%, respectively. Absolute risk reduction (placebo-denosumab) for new vertebral fractures during 2 years (cumulatively) and 3 years (cumulatively) were 2.2%, and 2.4%, respectively.

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- There is no estimated difference in overall survival (HR=0.97 (95% CI: 0.64- 1.49); p-value = 0.89) after 86 deaths. In addition, this study was not designed to adequately compare overall survival and progression free survival (PFS).

- There was heterogeneity in the treatment effects on the percentage change form baseline in lumbar spine BMD between Europe and North America region. The difference of the lumbar spine percentage change from the baseline to month 24 between the two treatment groups for Europe and North America were 7.6% (95% CI: 6.7, 8.5) and 6.3% (95% CI: 5.8, 6.9), respectively.

- Subgroup analysis for age younger than 65 years group demonstrated a greater percentage change difference in lumbar spine BMD from baseline to month 24 as compared to age 65 years or older group, the percentage differences were 8.5% (95% CI: 6.6, 10.4) and 6.5% (95% CI:6.1, 7.0), respectively.

- Subgroup analyses for weight less than 75 kg and body mass index (BMI) less than 26 kg/m^2 subjects had a greater percentage change differences in lumbar spine BMD from baseline to month 24 as compared to weight greater than or equal to 75 kg and BMI greater or equal to 26 kg/m^2 subjects. The percentage differences for weight <75 kg vs. $\geq$ 75 kg and BMI <26 kg/m^2 vs. $\geq$ 26 kg/m^2 were 8.1% (95% CI 7.3, 9.00) vs. 6.2% (95% CI: 5.6, 6.7), and 7.7 % (95% CI: 6.9, 8.5) vs. 6.1% (95% CI: 5.6, 6.7), respectively.

- Subgroup analysis for subjects with higher baseline CTX1 values had a greater percentage change difference in lumbar spine BMD from baseline to month 24 than subjects with lower baseline CTX1 values. Subjects with baseline T-scores less than or equal to -1.0 had a greater percentage change difference in lumbar spine BMD than subjects with baseline T-scores greater than -1.0.

- Subgroup analysis for subjects' baseline vitamin D levels showed no association between the baseline vitamin D levels and the percentage change in lumbar spine BMD from baseline to month 24.

1.3.3 Advisory Committee Vote and Summary on Selected Questions

Questions and voting results of advisory committee meeting for reproductive health drugs held on August 13, 2009 are summarized below. The advisory committee meeting is for BLA submissions, 125320, 125331, 125332 and 125333.

Question 1.a: Is there a population of postmenopausal women with osteoporosis in which the benefit of treatment with denosumab is likely to outweigh the risks? AC members vote: 15- yes, 0-No.

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Question 2.a: Is there a population of postmenopausal women with low bone mineral density who do not meet the criteria for of osteoporosis in which the benefit of prevention of osteoporosis with denosumab is likely to outweigh the risks? AC members vote: 3- yes, 12-No.

Question 3.a: Is a favorable risk/benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors? AC members vote: 2- yes, 13-No.

Question 3.b: Is a favorable risk/benefit ratio demonstrated for denosumab for the prevention of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors? AC members vote: 0- yes, 14-No, 1-abstain.

Question 4.a: Is a favorable risk/benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy? AC members vote: 9- yes, 4-No (all 3 oncologists voted No).

Question 4.b: Is a favorable risk/benefit ratio demonstrated for denosumab for the prevention of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy? AC members vote: 3- yes, 11-No.

Question 6a: If approved, do you recommend that denosumab have a Risk Evaluation and Mitigation Strategy or REMS? AC members vote: 12- yes, 1-No.

Summary of Committee Recommendation:

- Denosumab should be limited to PMO high risk patients (second-line).
- Denosumab should not be approved for PMO prevention.
- Denosumab hould not be approved for treatment or prevention of bone loss in breast cancer population receiving aromatase inhibitors.
- Denosumab should be approved for treatment of bone loss in men with prostate cancer receiving androgen deprivation therapy.
- Denosumab should not be approved for prevention of bone loss in men with prostate cancer receiving androgen deprivation therapy.
- Denosumab should have a Risk Evaluation and Mitigation Strategy or REMS.

2. INTRODUCTION

2.1 Overview

Study 20040138 is an international, multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of denosumab in men undergoing ADT for nonmetastatic prostate cancer.

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The objective of the study was to determine whether treatment with denosumab preserves lumbar spine BMD and reduces fractures in subjects with nonmetastatic prostate cancer undergoing ADT. Men with prostate cancer undergoing ADT are at significantly higher risk of developing osteoporotic fractures in the spine and nonvertebral locations including hip, pelvis, extremities, skull and ribs.

Subjects were randomized in a 1:1 ratio to receive 6 doses of either 60 mg denosumab or placebo subcutaneously injection once every 6 months for 30 months (ie, the 36-month treatment period). All subjects received supplemental calcium (1 gram/day) and vitamin D (≥ 400 IU/day) during the treatment period of the study. After completing the 36-month treatment period, subjects continued the study in a 24–month safety follow-up period which no investigational product was administered or were offered enrollment in a 2-year extension study (20080537). Results of the 36-month treatment period are included in this submission.

Randomization stratification factors were age group (< 70 years vs. ≥ 70 years) and duration of ADT with GnRH agonist or orchiectomy at study entry (≤ 6 months vs. > 6 months).

There were 156 study centers worldwide (121 centers in North America [United States, Canada, and Mexico] and 35 centers in Europe). Most of the subjects (66%) were enrolled at sites in North America and only 34% were enrolled at sites in Europe. Among 1468 subjects, 578 subjects (39%) were enrolled in the USA. The 24-month safety follow-up period is ongoing.

Eligible subjects were men with histologically confirmed prostate cancer and were ≥ 70 years, or were < 70 years of age with either low baseline BMD (T-score at the lumbar spine, total hip, or femoral neck < -1.0) or history of an osteoporotic fracture.

The primary endpoint was the percentage change from baseline to month 24 in lumbar spine BMD. Secondary endpoints were the percentage changes in lumbar spine BMD from baseline to month 36, the percentage changes in total hip, femoral neck BMDs from baseline to month 24 and month 36, the incidence of any fractures, new vertebral fractures, osteoporotic fracture at any site (any fracture), and the time to first clinical fracture.

2.2 Data Sources

The sponsor provided electronic datasets for this phase III Study 20040138. The data utilized for the review are as follows:

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3. STATISTICAL EVALUATION

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3.1 Evaluation of Efficacy

3.1.1 Study Design

The study design is an international, multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of denosumab in men undergoing ADT for nonmetastatic prostate cancer.

Subjects were randomized 1:1 to receive either 60 mg denosumab or placebo subcutaneously once every 6 months for 30 months (a total of 6 injections). Randomization was stratified based on age group (< 70 vs. ≥ 70 years of age) and duration of ADT with GnRH agonist or orchiectomy (≤ 6 months vs. > 6 months) at study entry. During the study, all subjects received daily supplemental calcium (≥ 1 g) and were instructed to take vitamin D (≥ 400 IU). The primary analyses were conducted when all subjects had completed the 36-month treatment period. When subjects completed their month 60 follow-up visit the safety follow-up period will be summarized. The first subject's enrolled date was August 2, 2004 and the data cutoff date and last subject's completed 36 months treatment date was May 16, 2008.

3.1.2 Study Endpoints

The primary endpoint was the percentage change in lumbar spine BMD from baseline to month 24. BMD was assessed by dual X-ray absorptiometry (DXA). DXA spine, DXA femoral neck and total hip, DXA distal radius and total body were measured at the screening, months, 1, 3, 6 12, 34 and 36. The central imaging vendor monitored BMD over the course of the treatment period. Two DXA machine types (Hologic and GE Lunar) were used to measure BMDs.

Secondary efficacy endpoints were the following:

- percentage change in femoral neck BMD and total hip BMD from baseline to month 24
- percentage change in lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36
- subject incidence of any fracture and subject incidence of new vertebral fracture over the 36-month treatment period
- time to first clinical fracture over the 36-month treatment period
- subject incidence of any fracture over the 24-month treatment period

Any fracture was defined as osteoporotic fracture at any skeletal site, including vertebral fractures, but excluding skull, facial, mandible, metacarpus, finger phalanges and toe phalanges.

Recorded new vertebral fracture was confirmed by copies of radiographs and radiography records that were submitted to the central imaging vendor.

A clinical facture was defined as any nonvertebral fracture or clinically evident fracture at the cervical vertebrae, thoracic vertebrae, and lumbar vertebrae that are associated with signs and/or

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symptoms indicative of a fracture excluding fractures with high trauma severity and pathologic fractures.

Nonvertebral fractures included all fractures except those at the skull, facial, mandible, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, metacarpus, finger phalanges, and toe phalanges excluding fractures with high trauma severity and pathologic fractures.

3.1.3 Statistical Methodologies

Sample Size Determination

The planned sample size of 1226 subjects (613 per group) provides at least 95% power at a 2% difference percentage change in lumbar spine BMD from baseline after 24 months of treatment at an alpha of 0.05 using a 2-sided t-test and provides 80% power at a 45% reduction in incidence of any fracture and vertebral fracture at an alpha of 0.05 at 24 months using Cochran-Mantel-Haenszel test (CMH) by taking into account 10% expected loss to follow-up DXA assessment rate per year.

Statistical Methods

The primary analysis of the primary endpoint, the percentage change from baseline to month 24 in lumbar spine BMD, was analyzed using an analysis of covariance (ANCOVA) approach adjusting for baseline BMD value, machine type (GE lunar versus Hologic), the interaction of baseline BMD value and machine type, age group (< 70 years vs. ≥ 70 years), and duration of ADT (≤ 6 months vs. > 6 months) as covariates. Missing 24-month BMD data were imputed using the last-observation carried-forward (LOCF) method. The primary analysis of BMD endpoints were analyzed with BMD analysis subset which included all randomized subjects who had a non-missing baseline and ≥ 1 non-missing post-baseline evaluation at or prior to the time point under consideration.

The sponsor analyzed the sensitivity analyses to demonstrate the robustness of the results from the primary analysis as follows;

- Repeated measures model
- ANCOVA model using the per protocol analysis set
- ANCOVA model using subjects categorized by their actual stratum, instead of their "as randomized" stratum (only performed if the error rate for the randomization stratification was > 5%)
- Univariate and multivariate covariate analysis

The statistical inferences on secondary efficacy endpoints were only made when the treatment effect on the primary efficacy endpoint was statistically significant in favor of denosumab over placebo in a stepwise fashion over 5 steps at a significance level of 0.05. There would be no further testing if any 1 of the hypotheses was not rejected at a previous step. If there were

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multiple null hypotheses within a single step, the Hochberg procedure was used for multiplicity adjustment within that step.

The secondary endpoints at each step are as follows:
Step 1:
- percent change in femoral neck BMD from baseline to month 24
- percent change in total hip BMD from baseline to month 24

Step 2:
- percent change in lumbar spine BMD from baseline to month 36,
- percent change in femoral neck BMD from baseline to month 36,
- percent change in total hip BMD from baseline to month 36

Step 3:
- subject incidence of any fracture during the 36-month treatment period
- subject incidence of new vertebral fracture during the 36-month treatment period

Step 4:
- time to first clinical fracture during the 36-month treatment period

Step 5:
- subject incidence of any fracture during the 24-month treatment period

Secondary BMD Endpoints
The secondary BMD endpoints at the lumbar spine, total hip, and femoral neck were analyzed in a manner similar to the primary endpoint.

Subject Incidence of Any Fracture and New Vertebral Fracture
For the endpoints of subject incidence of any fracture over the 24-month and 36-month, the primary analysis was analyzed with a logistic regression model adjusting for age group (< 70 years vs. ≥ 70 years) and duration of ADT at study entry (≤ 6 months vs. > 6 months) as covariates. The treatment effect was measured using the odds ratio of denosumab compared with placebo. The estimate of the odds ratio and its corresponding 95% 2-sided CI and p-values using a score test were provided. If the logistic regression model did not converge due to sparse data or separation, a conditional logistic regression stratified by age group and duration of ADT at study entry was used. In addition, the point estimates of absolute risk difference (difference in proportion, placebo – denosumab) and risk ratio (ratio of proportions, denosumab/placebo) as well as their corresponding 95% CI were calculated using the Mantel-Haenszel method adjusting for age group (< 70 years vs. ≥ 70 years) and duration of ADT at study entry (≤ 6 months vs. > 6 months).

If a large difference in the dropout rate between the treatment groups was observed, (≥ 3%), analysis using a Cox proportional hazards model based on the time to the first any fracture would be employed as the primary analysis.

Time to First Clinical Fracture at 36-Month Evaluation Period
The time to first clinical fracture was summarized by the number of subjects at risk, the percentage of censored subjects, and the Kaplan-Meier event rates at months 12, 24, and 36. The difference of the event rates between denosumab and the placebo group at month 36 with

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corresponding 95% CI was provided using the inverse variance-weighted method to adjust for the stratification variables. Subjects who did not experience a clinical fracture during the 36-month treatment period were censored at their last observation time on study. Time to first clinical fracture analysis during the 36-month evaluation period was conducted using a stratified Cox proportional hazards model adjusting for age group (< 70 years vs. ≥ 70 years) and duration of androgen deprivation therapy at study entry (≤ 6 months vs. > 6 months) as covariates.

Sensitivity analyses were conducted to demonstrate the robustness of the results obtained from the analysis, as follows:

- Cox proportional hazards model based on the time to first any fracture (subjects who did not experience a fracture were censored at their last observation time on study during the evaluation period)
- Logistic regression model using the per protocol analysis set
- Logistic regression model using subjects categorized by their actual stratum, instead of their "as randomized" stratum (only performed if the error rate for the randomization stratification was > 5%).
- Univariate and multivariate covariate analysis

The incidence of any fracture and the time to first clinical fracture endpoints were analyzed with full analysis subset which included all randomized subjects. The vertebral fracture analysis set included all randomized subjects who had a non-missing baseline and ≥ 1 post-baseline Genant semi-quantitative grades in ≥ 1 of the vertebrae (T4 to L4) during at or prior to the time point under consideration.

The per-protocol analysis set was used to analyze the primary efficacy endpoint and the secondary efficacy endpoints of subject incidence of any fracture and subject incidence of new vertebral fracture through the 36-month evaluation period in the sensitivity analyses.

The primary efficacy endpoint and the secondary efficacy endpoints of incidence of any fracture and new vertebral fracture over the 36-month treatment period were each analyzed adjusting for each of the following covariates separately and all covariates simultaneously as exploratory analyses:

- Baseline BMD T-score in lumbar spine (continuous)
- Prevalent vertebral fracture (Yes, No)
- Age (continuous)
- Race (Caucasian, non-Caucasian)
- Baseline BMI (kg/m2, continuous) (for the primary endpoint only)
- Baseline weight (kg, continuous) (for the primary endpoint only)

Changes in Statistical Methods

Version 2.0 (March 11, 2008)

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- Due to many early dropouts, mean-of-the-other-group imputation (MOTH) would severely bias the treatment effect and was removed. An imputation of missing on-study vertebral fracture as a fracture was considered inappropriate and removed due to small fracture rate and large dropouts.
- Updated BMD endpoint analysis methods:
  - Primary analysis method was changed to an analysis of covariance model with last observation carried forward (LOCF)
  - Repeated measures model became a sensitivity analysis.
  - Added a sensitivity analysis based on actual strata.
- Updated analysis of new vertebral fracture:
  - Analysis was changed to using a logistic regression model with a score test from the CMH test
  - Added sensitivity analyses using actual strata, and based on time to first new vertebral fracture
  - Removed a sensitivity analysis based on a missing Genant score imputation method

Version 3.0 (June 10, 2008)

- Stratified logistic regression would be used in case that the logistic regression did not converge

Patient Disposition, Demographic and Baseline Characteristic

Total of 2033 subjects were screened, only 1468 subjects were randomized for the study. Among 1468 enrolled subjects, 1456 subjects (726/denosumab, 730/placebo) received at least 1 dose of investigational product.

Table 1 Subject Disposition and Exposure to Investigational Product (IP)

	Placebo N=734 n (%)	Denosumab 60 mg Q6M N=734 n (%)	All N=1468 n (%)
Completed 36 months	445 (60.6)	467 (63.6)	912 (62.1)
Completed IP	442 (60.2)	462 (62.9)	904 (61.6)
Discontinued IP	3 (0.4)	5 (0.7)	8 (0.5)
Discontinued prior to 36 months	289 (39.4)	267 (36.4)	556 (37.9)
Completed IP	17 (2.3)	26 (3.5)	43 (2.9)
Discontinued IP	268 (36.5)	233 (31.7)	501 (34.1)
Never received IP	4 (0.5)	8 (1.1)	12 (0.8)

Four hundred sixty seven subjects (64%) in the denosumab group and 445 subjects (61%) of subjects in the placebo group completed the 36-month treatment period. Reasons for study discontinuation were summarized in Table 2 below.

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Table 2 Reasons for Study Discontinuation (36 months)

	Placebo N=734 n (%)	Denosumab 60 mg Q6M N=734 n (%)	All N=1468 n (%)
Completed study	445 (60.6)	467 (63.6)	912 (62.1)
Discontinued study	289 (39.4)	267 (36.4)	556 (37.9)
Consent withdrawn	143 (19.5)	127 (17.3)	270 (18.4)
Death	43 (5.9)	43 (5.9)	86 (5.9)
Adverse event	23 (3.1)	29 (4.0)	52 (3.5)
Disease progression	21 (2.9)	23 (3.1)	44 (3.0)
Lost to follow-up	21 (2.9)	17 (2.3)	38 (2.6)
Ineligibility determined	8 (1.1)	10 (1.4)	18 (1.2)
Other	5 (0.7)	9 (1.2)	14 (1.0)
Requirement for alternative therapya	14 (1.9)	4 (0.5)	18 (1.2)
Noncompliance	7 (1.0)	3 (0.4)	10 (0.7)
Administrative decision	4 (0.5)	2 (0.3)	6 (0.4)

Consent withdrawn was the most common reason for discontinuation from study. A number of subjects withdrew consent at month 24 because they were unwilling to reconsent to an additional 12 months of blinded treatment.

Among subjects who received at least 1 dose of investigational product, 490 (67%) of denosumab subjects and 450 (62%) of placebo subjects received all 6 planned doses of investigational product.

On-study important protocol deviation was summarized in Table 3 below.

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Table 3 Important On-study Protocol Deviations (All Randomized Subjects)

	Placebo (N = 734) n (%)	Denosumab 60 mg Q6M (N = 734) n (%)	All (N = 1468) n (%)
Number of subjects with ≥ 1 important protocol deviation other than eligibility criteria deviation	125 (17.0)	141 (19.2)	266 (18.1)
Missing data	48 (6.5)	66 (9.0)	114 (7.8)
Missing per protocol baseline, M24, or M36 X-ray	30 (4.1)	45 (6.1)	75 (5.1)
Missing per protocol baseline, M24, or M36 DXA	29 (4.0)	39 (5.3)	68 (4.6)
Investigational product administration	59 (8.0)	49 (6.7)	108 (7.4)
Subject received IP that had not been stored at the correct temperature AND was not supported post-hoc after consideration by Amgen-Stability	45 (6.1)	35 (4.8)	80 (5.4)
Subject missed 2 or more doses before early termination or completion of study	7 (1.0)	7 (1.0)	14 (1.0)
Subject received incorrect box ID compared to IVRS randomization assignment	7 (1.0)	7 (1.0)	14 (1.0)
Off-schedule study procedures (Day 1 X-ray spine)	20 (2.7)	30 (4.1)	50 (3.4)
Non Withdrawal (bone metastases, but no removed)	3 (0.4)	7 (1.0)	10 (0.7)
Exclusionary medication taken on study	13 (1.8)	6 (0.8)	19 (1.3)
Any use of IV bisphosphonates, parathyroid hormone (or derivative)	6 (0.8)	3 (0.4)	9 (0.6)
Cumulative use of oral bisphosphonates and calcitonin > 30 days	7 (1.0)	2 (0.3)	9 (0.6)
Any use of Testosterone	0 (0.0)	1 (0.1)	1 (<0.1)

On-study important protocol deviations were reported for 266 subjects (18%) of overall (141 subjects (19%) from denosumab, 125 subjects (17%) from placebo). The most common reason of on-study deviations were missing data, 114 missing subjects (8%) (66 subjects (9%) from denosumab, 48 subjects (7%) from placebo), and 108 subject errors (7%) in investigational product administration (49 subjects (7%) from denosumab, 59 subjects (8%) from placebo).

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Baseline demographics are summarized in Table 4 and cancer disease history are summarized in Table 5 and Table 6 below.

Table 4 Baseline Demographics (All Randomized Subjects)

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	Placebo (N = 734)	Denosumab 60 mg Q6M (N = 734)	All (N = 1468)
Ethnic group / race - n (%)			
White or Caucasian	609 (83.0)	615 (83.8)	1224 (83.4)
Black or African American	32 (4.4)	36 (4.9)	68 (4.6)
Hispanic or Latino	81 (11.0)	77 (10.5)	158 (10.8)
Asian	7 (0.9)	6 (0.8)	13 (0.8)
American Indian or Alaska Native	2 (0.3)	0 (0.0)	2 (0.1)
Other	3 (0.4)	0 (0.0)	3 (0.2)
Age (years)			
Mean (SD)	75.5 (7.1)	75.3 (7.0)	75.4 (7.1)
Median (Q1, Q3)	76.0 (71.0, 80.0)	76.0 (71.0, 80.0)	76.0 (71.0, 80.0)
Min, Max	50, 97	48, 92	48, 97
Age group – n (%)			
< 50 years	0 (0.0)	1 (0.1)	1 (<0.1)
50 - 59 years	20 (2.7)	23 (3.1)	43 (2.9)
60 - 69 years	103 (14.0)	100 (13.6)	203 (13.8)
70 - 79 years	396 (54.0)	405 (55.2)	801 (54.6)
80 - 89 years	205 (27.9)	197 (26.8)	402 (27.4)
≥ 90 years	10 (1.4)	8 (1.1)	18 (1.2)
Geriatric age group - n (%)			
≥ 65 years	679 (92.5)	685 (93.3)	1364 (92.9)
≥ 75 years	424 (57.8)	415 (56.5)	839 (57.2)
Randomization: Age; ADT Duration			
< 70 years; ≤ 6 months	25 (3.4)	26 (3.5)	51 (3.5)
	24 (3.3)	19 (2.6)	43 (2.9)
≥ 70 years; ≤ 6 months	150 (20.4)	149 (20.3)	299 (20.4)
	134 (16.3)	134 (16.3)	268 (18.3)
< 70 years; > 6 months	99 (13.5)	99 (13.5)	198 (13.5)
	99 (13.5)	105 (14.3)	204 (13.9)
≥ 70 years; > 6 months	460 (62.7)	460 (62.7)	920 (62.7)
	477 (65.0)	476 (54.9)	953 (64.9)
ADT duration (months)			
Mean (SD)	30.62 (33.26)	31.70 (33.80)	31.16 (33.53)
Median	20.40	20.80	20.50
Q1, Q3	7.30,43.60	8.20, 42.50	7.50, 42.85
Min, Max	0.0, 354.6	0.0, 195.3	0.0, 354.6
ECOG at study entry - n (%)			
0	538 (73.3)	552 (75.2)	1090 (74.3)
1	174 (23.7)	154 (21.0)	328 (22.3)
2	21 (2.9)	28 (3.8)	49 (3.3)
Unknown	1 (0.1)	0 (0.0)	1 (<0.1)

The number of subjects in the actual stratification.

Baseline demographics were balanced across treatment groups. Most subjects (83%) were white, the mean (SD) age was 75.4 (7.1) years, and 93% of enrolled subjects were ≥ 65 years of age. Mean (SD) weight and BMI were 83.58 (13.46) kg and 28.2 (4.0) kg/m^2, respectively.

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The majority of subjects (63%) (460 denosumab, 460 placebo) were in the stratum of subjects ≥ 70 years of age who had received > 6 months of ADT among 4 groups stratification strata; the other 3 strata had fewer subjects, but were balanced. A total of 139 subjects (10%) (65 denosumab, 74 placebo) were assigned to the incorrect stratum, largely due to inconsistent definitions for the duration of ADT. Actual stratifications are also summarized in blue.

Table 5 Cancer Disease History (All Randomized Subjects)

	Placebo (N = 734)	Denosumab 60 mg Q6M (N = 734)	All (N = 1468)
Time from initial diagnosis - n (%)			
< 2 years	242 (33.0)	234 (31.9)	476 (32.4)
2 - < 5 years	193 (26.3)	203 (27.7)	396 (27.0)
5 - < 10 years	189 (25.7)	184 (25.1)	373 (25.4)
≥ 10 years	110 (15.0)	113 (15.4)	223 (15.2)
Mean Years (SD)	4.91 (4.20)	4.97 (4.20)	4.94 (4.20)
Median Years	3.75	3.75	3.75
Q1, Q3	1.30, 7.80	1.40, 7.80	1.40, 7.80
Min, Max	0.1, 21.3	0.1, 19.0	0.1, 21.3
Primary tumor at diagnosis (NCCN)-n (%)			
T0 or T1-T2a	269 (36.6)	263 (35.8)	532 (36.2)
T2 or T2b-T2c	221 (30.1)	241 (32.8)	462 (31.5)
T3 or T3a	133 (18.1)	111 (15.1)	244 (16.6)
T3b-T4	53 (7.2)	62 (8.4)	115 (7.8)
Tx	58 (7.9)	57 (7.8)	115 (7.8)
Primary tumor at diagnosis (per TNM) - n (%)			
T0 or T1 or T1a-T1c	190 (25.9)	183 (24.9)	373 (25.4)
T2 or T2a-T2c	300 (40.9)	321 (43.7)	621 (42.3)
T3 or T3a-T3b	169 (23.0)	151 (20.6)	320 (21.8)
T4	17 (2.3)	22 (3.0)	39 (2.7)
Tx	58 (7.9)	57 (7.8)	115 (7.8)
Regional lymph node at diagnosis - n (%)			
N0	393 (53.5)	391 (53.3)	784 (53.4)
N1	29 (4.0)	36 (4.9)	65 (4.4)
Nx	312 (42.5)	307 (41.8)	619 (42.2)

Table 6 Cancer Disease History (All Randomized Subjects)

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	Placebo (N = 734)	Denosumab 60 mg Q6M (N = 734)	All (N = 1468)
Distant metastasis at diagnosis - n (%)			
M0	659 (89.8)	655 (89.2)	1314 (89.5)
M1	1 (0.1)	0 (0.0)	1 (<0.1)
Mx	74 (10.1)	79 (10.8)	153 (10.4)
Gleason score at diagnosis - n (%)			
2-6	319 (43.5)	286 (39.0)	605 (41.2)
7	219 (29.8)	213 (29.0)	432 (29.4)
8-10	142 (19.3)	163 (22.2)	305 (20.8)
Unknown	54 (7.4)	72 (9.8)	126 (8.6)
Prostate cancer recurrence risk at diagnosis (NCCN-adapted) - n (%)			
Low	201 (27.4)	176 (24.0)	377 (25.7)
Intermediate	242 (33.0)	263 (35.8)	505 (34.4)
High	218 (29.7)	209 (28.5)	427 (29.1)
Very high	73 (9.9)	86 (11.7)	159 (10.8)
Primary tumor stage at initial diagnosis - n (%)			
II	533 (72.6)	543 (74.0)	1076 (73.3)
III	158 (21.5)	139 (18.9)	297 (20.2)
IV	43 (5.9)	52 (7.1)	95 (6.5)
Type of primary therapy - n (%)			
Radiation	185 (25.2)	191 (26.0)	376 (25.6)
Surgery	143 (19.5)	139 (18.9)	282 (19.2)
Surgery and radiation	21 (2.9)	23 (3.1)	44 (3.0)
No primary therapy	385 (52.5)	381 (51.9)	766 (52.2)
Prior chemotherapy -n (%)			
Yes	3 (0.4)	1 (0.1)	4 (0.3)
No	731 (99.6)	733 (99.9)	1464 (99.7)
Chemical castration - n (%)			
Yes	685 (93.3)	678 (92.4)	1363 (92.8)
No	49 (6.7)	56 (7.6)	105 (7.2)
Surgical castration - n (%)			
Yes	61 (8.3)	77 (10.5)	138 (9.4)
No	673 (91.7)	657 (89.5)	1330 (90.6)
Bisphosphonate (oral) - n (%)			
Yes	8 (1.1)	9 (1.2)	17 (1.2)
No	726 (98.9)	725 (98.8)	1451 (98.8)
Bisphosphonate (IV) -n (%)			
Yes	2 (0.3)	1 (0.1)	3 (0.2)
No	732 (99.7)	733 (99.9)	1465 (99.8)

Cancer disease history was balanced across treatment groups. Most subjects had stage II (74% denosumab, 73% placebo) or stage III disease (19% denosumab, 22% placebo). Gleason scores

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for most subjects were ≤ 7 (68% denosumab, 73% placebo) and most subjects' risk of prostate cancer recurrence was low or intermediate (60% in both groups).

Most subjects (52%) had received no primary therapy. Radiation had been received by 26% of subjects, and surgery had been received by 19% of subjects. Most of the enrolled subjects (93%) were receiving therapy for androgen deprivation (chemical castration); 9% of subjects were surgically castrated.

Baseline BMD T-scores are summarized in Table 7 below.

Table 7 Baseline Bone Mineral Density T-scores

	n	Mean	SD	Min	Q1	Median	Q3	Max
Lumbar spine (N = 1468)	1456	-0.36	1.79	-6.8	-1.60	-0.50	0.70	7.6
Placebo (N = 734)	729	-0.41	1.80	-4.8	-1.60	-0.60	0.60	7.6
Denosumab 60 mg Q6M (N = 734)	727	-0.31	1.78	-6.8	-1.50	-0.50	0.70	7.3
Total hip (N = 1468)	1430	-0.87	1.01	-3.6	-1.60	-0.90	-0.30	3.3
Placebo (N = 734)	718	-0.88	1.03	-3.6	-1.60	-0.95	-0.20	3.1
Denosumab 60 mg Q6M (N = 734)	712	-0.87	1.00	-3.6	-1.50	-0.90	-0.30	3.3
Femoral neck (N = 1468)	1430	-1.42	0.89	-3.8	-2.00	-1.50	-0.90	3.0
Placebo (N = 734)	718	-1.42	0.91	-3.5	-2.00	-1.50	-0.90	1.9
Denosumab 60 mg Q6M (N = 734)	712	-1.41	0.86	-3.8	-2.00	-1.50	-0.90	3.0
Trochanter (N = 1468)	1430	-0.63	1.26	-4.7	-1.40	-0.70	0.10	4.3
Placebo (N = 734)	718	-0.64	1.27	-4.7	-1.50	-0.70	0.10	4.3
Denosumab 60 mg Q6M (N = 734)	712	-0.62	1.25	-4.5	-1.40	-0.70	0.10	3.5

Median baseline BMD T-scores were similar between treatment groups.

Pre-existent fractures are summarized in Table 8 below.

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Table 8 Prevalent Vertebral Fractures Based on Baseline Spine Radiographs (Randomized Subjects)

	Placebo (N = 734)	Denosumab 60 mg Q6M (N = 734)	All (N = 1468)
	n (%)	n (%)	n (%)
Prevalent vertebral fracture			
Yes	174 (23.7)	155 (21.1)	329 (22.4)
No	504 (68.7)	531 (72.3)	1035 (70.5)
Not readable	43 (5.9)	35 (4.8)	78 (5.3)
Missing	13 (1.8)	13 (1.8)	26 (1.8)
Number of prevalent vertebral fractures[a]			
0	504 (68.7)	531 (72.3)	1035 (70.5)
1	123 (16.8)	104 (14.2)	227 (15.5)
≥ 2	51 (6.9)	51 (6.9)	102 (6.9)
Not readable / missing	56 (7.6)	48 (6.5)	104 (7.1)
Most severe Genant semi-quantitative grade			
Normal	504 (68.7)	531 (72.3)	1035 (70.5)
Mild	138 (18.8)	124 (16.9)	262 (17.8)
Moderate	26 (3.5)	24 (3.3)	50 (3.4)
Severe	10 (1.4)	7 (1.0)	17 (1.2)
Not readable / missing	56 (7.6)	48 (6.5)	104 (7.1)

There were prevalent vertebral fractures (T4 to L4) in 155 subjects (21%) in the denosumab group and 174 subjects (24%) in the placebo group. The incidence and severity of prevalent vertebral fractures were well balanced between the treatment groups. Baseline spine radiographs were evaluated by the central imaging vendor.

3.1.4 Results and Conclusions

Sponsor's Efficacy Results

The primary endpoint of the percentage change in lumbar spine BMD from the baseline at month 24 is summarized below Table 9.

Table 9 Primary Efficacy Endpoint Results

Placebo		Denosumab 60 mg Q6M		Difference from placebo		
n/N	Estimate	n/N	Estimate	Estimate	95% CI	p-value
Percent change in Lumbar Spine from baseline at Month 24a						
716/716	-1.0	714/714	5.6	6.7	(6.2, 7.1)	<0.0001

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Lumbar spine bone mineral density increased by 5.6% in denosumab and decreased by 1.0% in placebo, the percentage change difference between denosumab and placebo was 6.7% (95% CI: 6.2, 7.1) at 2 years (p<0.0001).

Secondary efficacy endpoints of 5 steps are summarized in Table 10 below.

Table 10 Secondary Efficacy Endpoints Results

	Placebo		Denosumab 60 mg Q6M		Difference from placebo		
	n/N	Estimate	n/N	Estimate	Estimate	95% CI	p-value*
Step 1							
Percent change in femoral neck BMD from baseline to month 24[a]							
	706/716	-1.5	701/714	2.4	3.9	(3.5, 4.4)	<0.0001
Percent change in total hip BMD from baseline to month 24[a]							
	706/716	-2.0	701/714	2.7	4.8	(4.4, 5.1)	<0.0001
Step 2							
Percent change in lumbar spine BMD from baseline to month 36[a]							
	716/716	-1.2	714/714	6.8	7.9	(7.4, 8.4)	<0.0001
Percent change in femoral neck BMD from baseline to month 36[a]							
	706 /716	-1.8	701/714	3.0	4.9	(4.4, 5.4)	<0.0001
Percent change in total hip BMD from baseline to month 36[a]							
	706/716	-2.6	701/714	3.2	5.7	(5.4, 6.1)	<0.0001
Step 3							
Subject incidence of any fracture during the 36-month treatment period[b]							
	53/734 (7.2%)		38/734 (5.2%)		OR: 0.70	(0.46, 1.08)	0.1048
Subject incidence of new vertebral fracture during the 36-month treatment period[a,b]							
	26/673 (3.9%)		10/679 (1.5%)		OR: 0.37	(0.18, 0.78)	0.0125
Step 4							
Time to first clinical fracture during the 36-month treatment period[c]							
	31/734 (4.2%)		30/734 (4.1%)		HR: 0.94	(0.57, 1.55)	0.7961
Step 5							
Subject incidence of any fracture during the 24-month treatment period[b]							
	45/734 (6.1%)		32/734 (4.4%)		OR: 0.70	(0.44, 1.11)	0.1282

*: P-values for all endpoints are adjusted for multiplicity according to the prespecified sequential testing strategy
a: Difference from placebo based on ANCOVA model adjusting for age group, ADT duration at study entry, baseline value, machine type, and baseline value-by -machine type interaction
b: Odds ratio relative to placebo based on logistic regression model adjusting for the stratification variables of age group and ADT duration at study entry.
c: Hazard ratio relative to placebo based on Cox proportional hazards model stratified by the stratification variables of age group and ADT duration at study entry.
d: P-values for all endpoints are adjusted for multiplicity according to the prespecified sequential testing strategy.

For step 1 of secondary endpoints, femoral neck and total hip BMDs increased by 2.4% and 2.7%, respectively in denosumab and decreased by 1.5 % and 2.0%, respectively in placebo at 2

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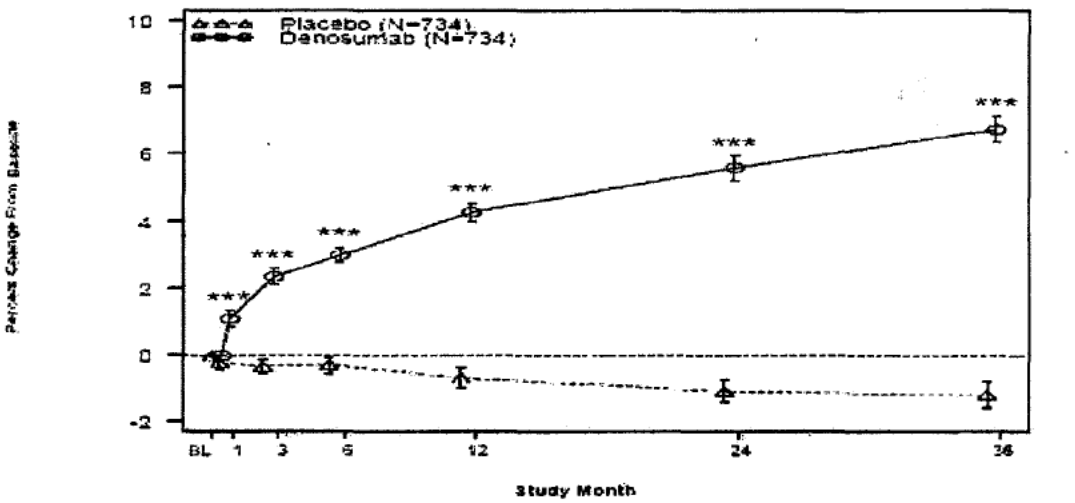
years, the percentage change differences between denosumab and placebo were 3.9% (95% CI: 3.5, 4.4) and 4.8% (95% CI: 4.4, 5.1), respectively (all p <0.0001).

For step 2 of secondary endpoints, lumbar spine, femoral neck and total hip BMDs increased by 6.8%, 3.0% and 3.2%, respectively at 3 years and decreased by 1.2%, 1.8%, and 2.6%, respectively at 3 years, the percentage change differences between denosumab and placebo were 7.9% (95% CI: 7.4, 8.4), 4.9% (95% CI: 4.4, 5.4) and 5.7% (95% CI: 5.4, 6.1), respectively (all p<0.0001).

For step 3 of secondary endpoints, 53 subjects among 734 placebo subjects (7.2%) and 38 subjects among 734 denosumab (5.2%) subjects observed any fracture events at 3 years. The odd ratio was 0.70 (95% CI: 0.46, 1.08) (p=0.1048). Denosumab did not reduce the incidence of any fractures at 3 years. Absolute risk reduction (placebo-denosumab) for any fractures during 2 years (cumulatively) and 3 years (cumulatively) were 1.8% and 2%, respectively. Denosumab demonstrated the reduction in incidence of new vertebral fractures of 1.5% as compared to placebo of 3.5% at 3 years (OR: 0.37, 95% CI: 0.18, 0.78) (p=0.0063, adjusted p=0.0125). Absolute risk reduction (placebo-denosumab) for new vertebral fractures during 2 years (cumulatively) and 3 years (cumulatively) were 2.2%, and 2.4%, respectively. Further formal testing of secondary endpoints for steps 4 and 5 should be stopped at this point.

In summary, denosumab significantly increased lumbar spine, femoral neck and total hip BMDs as compared to placebo from baseline to months 24 and 36. Denosumab did not demonstrate the statistically significant reduction in the subject incidence of any fracture endpoints at month 36, but denosumab demonstrated the statistically significant reduction in the subject incidence of new vertebral fractures at month 36.

Figure 1 Lumbar Spine BMD Percentage Change from Baseline by Visit – Least Squares Means and Confidence Intervals (ANCOVA (LOCF), BMD Analysis Set)



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Sponsor's sensitivity analyses for the primary endpoint were performed as follows.

1. Repeated measures model
2. ANCOVA model using per protocol analysis set
3. ANCOVA model using actual stratum
4. Univariate and multivariate covariate analysis using planned covariates such as baseline BMD T-score in lumbar spine, prevalence vertebral fracture, age, race, baseline BMI and baseline weight.

Table 11 Sensitivity Analyses for the Primary Endpoint for Percentage Change in Lumbar Spine from Baseline at Month 24

		% Change from baseline		Difference from Placebo		
	n	LS mean	95% CI	LS mean	95% CI	p-value
1. Repeated Measures						
Placebo	537	-1.2	(-1.6, -0.9)			
Denosumab 60 mg Q6M	560	6.2	(5.8, 6.5)	7.4	(6.9, 7.9)	<.0001
2. Per protocol Analysis						
Placebo	580	-1.2	(-1.6, -0.8)			
Denosumab 60 mg Q6M	605	6.0	(5.6, 6.4)	7.2	(6.7, 7.7)	<.0001
3. ANCOVA using Actual Stratum						
Placebo	716	-1.0	(-1.4, -0.7)			
Denosumab 60 mg Q6M	714	5.6	(5.3, 5.9)	6.6	(6.2, 7.1)	<.0001

Sensitivity analyses for lumbar spine BMD percentage change from baseline to month 24 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Table 12 Sensitivity Analyses for the Primary Endpoint for Percent Change in Lumbar Spine from Baseline at Month 24 (Covariate analysis)

		Covariate Effect			Treatment Effect (Difference)		
	n	LS Mean	95% CI	p-value	LS mean	95% CI	P-value
4. Covariate Analysis							
Age (years)	1430	-0.01	(-0.06, 0.04)	0.6491	6.7	(6.2, 7.1)	<0.0001
Race					6.6	(6.2, 7.1)	<0.0001
Caucasian	1198	0.69	(0.07, 1.31)	0.0290			
Non Caucasian	234	0					
Baseline BMI (kg/m^2)	1429	0.02	(-0.04, 0.08)	0.4949	6.6	(6.2, 7.1)	<0.0001
Baseline weight (kg)	1429	0.01	(0.00, 0.03)	0.1313	6.6	(6.2, 7.1)	<0.0001
Baseline lumbar spine BMD T-score	1430	0.86	(-5.00, 6.71)	0.7739	6.7	(6.2, 7.1)	<0.0001
Prevalent vertical fracture					6.6	(6.1, 7.0)	<0.0001
No	1018	-0.10	(-0.65, 0.44)	0.7093			
Yes	321	0					
All Covariates	1338				6.6	(6.1, 7.0)	<0.0001

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Sensitivity analysis results using a covariate analysis were consistent to the primary analysis.

Table 13 Sensitivity Analyses for the Secondary Endpoints: Step 1. Percent Change in Femoral Neck BMD Score from Baseline at Month 24

		% Change from baseline		Difference from Placebo		
	n	LS mean	95% CI	LS mean	95% CI	p-value
1. Repeated Measures						
Placebo	523	-1.8	(-2.2, -1.4)			
Denosumab 60 mg Q6M	543	2.7	(2.3, 3.1)	4.5	(3.9, 5.0)	<.0001
2. Per protocol Analysis						
Placebo	572	-1.6	(-2.0, -1.2)			
Denosumab 60 mg Q6M	593	2.7	(2.3, 3.1)	4.3	(3.8, 4.8)	<.0001
3. ANCOVA using Actual Stratum						
Placebo	706	-1.5	(-1.8, -1.1)			
Denosumab 60 mg Q6M	701	2.4	(2.1, 2.8)	3.9	(3.4, 4.4)	<.0001

Sensitivity analyses for femoral neck BMD percentage change from baseline to month 24 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Table 14 Sensitivity Analyses for the Secondary Endpoints: Step 1. Percent Change in Total Hip BMD Score from Baseline at Month 24

		% Change from baseline		Difference from Placebo		
	n	LS mean	95% CI	LS mean	95% CI	p-value
1. Repeated Measures						
Placebo	523	-2.4	(-2.7, -2.1)			
Denosumab 60 mg Q6M	543	3.0	(2.7, 3.3)	5.4	(5.0, 5.8)	<.0001
2. Per protocol Analysis						
Placebo	572	-2.2	(-2.5, -1.9)			
Denosumab 60 mg Q6M	593	3.0	(2.7, 3.3)	5.2	(4.8, 5.6)	<.0001
3. ANCOVA using Actual Stratum						
Placebo	706	-2.0	(-2.3, -1.8)			
Denosumab 60 mg Q6M	701	2.7	(2.5, 3.0)	4.8	(4.4, 5.1)	<.0001

Sensitivity analyses for total hip BMD percentage change from baseline to month 24 demonstrated a significant increase in the denosumab group as compared to the placebo group.

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Table 15 Sensitivity Analyses for the Secondary Endpoints: Step 2 Percent Change in Lumbar Spine BMD from Baseline to Month 36

		% Change from baseline		Difference from Placebo		
	n	LS mean	95% CI	LS mean	95% CI	p-value
1. Repeated Measures						
Placebo	422	-1.4	(-1.9, -1.0)			
Denosumab 60 mg Q6M	435	8.0	(7.6, 8.5)	9.4	(8.8, 10.1)	<.0001
2. Per protocol Analysis						
Placebo	580	-1.4	(-1.8, -0.9)			
Denosumab 60 mg Q6M	605	7.4	(7.0, 7.8)	8.7	(8.2, 9.3)	<.0001
3. ANCOVA using Actual Stratum						
Placebo	716	-1.2	(-1.5, -0.8)			
Denosumab 60 mg Q6M	714	6.7	(6.4, 7.1)	7.9	(7.4, 8.4)	<.0001

Sensitivity analyses for lumbar spine BMD percentage change from baseline to month 36 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Table 16 Sensitivity Analyses for the Secondary Endpoints: Step 2. Percent Change in Femoral Neck BMD Score from Baseline at Month 36

		% Change from baseline		Difference from Placebo		
	n	LS mean	95% CI	LS mean	95% CI	p-value
1. Repeated Measures						
Placebo	406	-2.5	(-2.9, -2.0)			
Denosumab 60 mg Q6M	424	3.5	(3.1, 4.0)	6.0	(5.4, 6.6)	<.0001
2. Per protocol Analysis						
Placebo	572	-2.1	(-2.5, -1.7)			
Denosumab 60 mg Q6M	593	3.4	(3.0, 3.8)	5.5	(4.9, 6.1)	<.0001
3. ANCOVA using Actual Stratum						
Placebo	706	-1.8	(-2.2, -1.5)			
Denosumab 60 mg Q6M	701	3.0	(2.6, 3.4)	4.9	(4.4, 5.4)	<.0001

Sensitivity analyses for femoral neck BMD percentage change from baseline to month 36 demonstrated a significant increase in the denosumab group as compared to the placebo group.

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Table 17 Sensitivity Analyses for the Secondary Endpoints: Step 2. Percent Change in Total Hip BMD Score from Baseline at Month 36

		% Change from baseline		Difference from Placebo		
	n	LS mean	95% CI	LS mean	95% CI	p-value
1. Repeated Measures						
Placebo	406	-3.3	(-3.7, -3.0)			
Denosumab 60 mg Q6M	424	3.7	(3.4, 4.0)	7.0	(6.6, 7.5)	<.0001
2. Per protocol Analysis						
Placebo	572	-2.9	(-3.2, -2.6)			
Denosumab 60 mg Q6M	593	3.5	(3.2, 3.8)	6.4	(5.9, 6.8)	<.0001
3. ANCOVA using Actual Stratum						
Placebo	706	-2.6	(-2.8, -2.3)			
Denosumab 60 mg Q6M	701	3.2	(2.9, 3.4)	5.7	(5.3, 6.1)	<.0001

Sensitivity analyses for total hip BMD percentage change from baseline to month 36 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Conclusions for Efficacy Endpoints:

All BMD endpoints of lumbar spine, total hip, and femoral neck demonstrated significant percentage increases in the denosumab group as compared to the placebo group from baseline to months 24 and 36 and the differences in % change were 6.7% (95% CI: 6.2, 7.1), 3.9% (95% CI: 3.5, 4.4) and 4.8% (95% CI: 4.4, 5.1), respectively, at month 24 and 7.9% (95% CI: 7.4, 8.4), 4.9% (95% CI: 4.4, 5.4) and 5.7% (95% CI: 5.4, 6.1), respectively at month 36.

Any fractures endpoint did not show the statistical significant results. Denosumab demonstrated a reduction in the incidence of new vertebral fractures as compared to placebo at month 36. Because the incidence of any fractures in Step3 did not show the statistical significance, no further testing for steps 4 and 5 should be done.

For the breast cancer study 20040135, all BMD endpoints of lumbar spine, total hip, and femoral neck showed significant percentage increases in the denosumab group as compared to the placebo group from baseline to month 24 and the differences in percentage change were 7.5% (95% CI: 6.5, 8.6), 4.7% (95% CI: 4.9, 5.4), and 3.6% (95% CI: 2.6, 4.6) at month 24, respectively.

All sensitivity analyses results for BMD endpoints were consistent with the results of the respective primary analysis.

Two key clinical studies of denosumab for post menopausal osteoporosis (PMO) indication are summarized Table 18 below.

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Table 18 Key Clinical Studies of Denosumab for Post-menopausal Osteoporosis (PMO) Indication

Study	Design	Population	Objectives	Region	N	Duration(trt)
Pivotal Efficacy Studies						
20030216	Phase 3 randomized, double-blind, placebo-controlled	Women with PMO (-4.0≤ T<-2.5 at the lumbar spine or total hip or both) Age: 60-90	Efficacy (incidence and time to new vertebral fracture)	Global	7868 (3096/P) (3092/D)	3 yrs
20040132	Phase 3 randomized, double-blind, placebo-controlled	Postmenopausal women with low BMD (-2.5 ≤T≤-1.0 at the lumbar spine)	Efficacy (BMD)	Us and Canada	332 (166/P) **(166/D)**	2 yrs (trt) 2 yrs off

The efficacy results for study 20030216 were summarized in Table 19 below.

Table 19 Study 20030216 Efficacy Results

Incidence (%;n/N) or KM % through Month 36					
Placebo	Denosumab	Absolute Risk reduction	Relative Risk reduction[a]	95% CI	p
Primary Endpoint: Incidence of New Vertebral Fractures at Month 36[b]					
7.2% (264/3691)	2.3% (86/3702)	4.8%	68% HR:0.32	50%,74% (0.26, 0.41),	.0001
Secondary Endpoints					
Time to first Nonvertebral Fracture[c]					
8.0% Crude (293/3906)	6.5% (238/3902)	1.5%	20% HR=0.80	5%, 33% (0.67, 0.95)	.0106
Time to first Hip Fracture[c]					
1.2% Crude (43/3906)	0.7% (26/3902)	0.3%	40% HR=0.60	3%, 63% (0.37, 0.97)	.0362

a: calculated from risk or hazard ratio compared with placebo at month 36; risk reduction > 0% (ratio < 1) favors denosumab
b: Risk ratio based on the Mantel-Haenszel method stratified by age stratification variable; p-value based on a logistic regression model adjusting for age stratification variable
c Hazard ratio and p-value based on the Cox proportional hazards model stratified by age stratification variable

For Study 20030216 efficacy results;

- *Denosumab significantly reduced the risk of new vertebral, nonvertebral, and hip fractures during 36 months treatment period compared to placebo*

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- *Denosumab demonstrated significant increases in % change in lumbar spine, total hip, and femoral neck BMDs from baseline to month 36 as compared to placebo (difference in % changes were 9.2 (8.2, 10.1); 6.0 (5.2, 6.7) and 6.0 (5.2, 6.7); respectively).*

For study 20040132 efficacy results;

- *Denosumab demonstrated significant increases in % change from baseline in lumbar spine, total hip, and Femoral Neck BMDs to month 24 compared to placebo (difference in % changes were 6.5% (5.8, 7.1); 3.4 % (3.0, 3.8) and 2.8% (2.3, 3.4); respectively).*

Reviewer's Results:

One drawback was the missing bone mineral density scores because of dropouts. The number of subjects missed lumbar spine BMDs are summarized by visit in Table 20 below.

Table 20 Number of Missing Lumbar Spine BMD Measurement by Visit Month

	Month 1	Month 3	Month 6	Month 12	Month24	Month 36	Total
Denosumab	40 (5.4)	28 (3.8)	37 (5.0)	68 (9.3)	154 (21.0)	279 (38.0)	734
Placebo	38 (5.2)	37 (5.0)	50 (6.8)	83 (11.3)	179 (24.4)	294 (40.1)	734
Total	78 (5.3)	65 (4.4)	87 (5.9)	151 (10.3)	333 (22.7)	573 (39.0)	1468

There were missing lumbar spine BMDs, 10%, 23% and 39 % at months 12, 24, and 36. The placebo group had 2% to 3% more missing lumbar spine BMDs than that of the denosumab group.

Thirty two subjects (12 from denosumab and 20 from placebo) missed lumbar spine BMD from month 12 to month 36, 145 subjects (64 from denosumab and 81 from placebo) missed lumbar spine BMD from month 24 to month 36 and 327 subjects (152 from the denosumab and 175 from the placebo) missed lumbar spine BMD only month 36.

Mean lumbar spine BMD T-scores and percentage changes from baseline are summarized in Table 21 by visit.

Table 21 Mean Lumbar Spine BMD Scores and Percentage Change from Baseline BMD Scores

	Placebo (N=734)			Denosumab (N=734)		
	Mean (SD)	n	%Change(SD)	Mean (SD)	n	%Change (SD)
Baseline	1.126 (0.122)	729		1.137 (0.225)	727	
Month 1	1.125 (0.219)	678	-0.163 (2.641)	1.152 (0.225)	674	1.027 (2.713)
Month 3	1.123 (0.223)	680	-0.235 (2.869)	1.164 (0.227)	686	2.405 (3.033)
Month 6	1.119 (0.220)	667	-0.235 (3.049)	1.167 (0.224)	677	2.977 (3.147)
Month12	1.117 (0.226)	635	-0.623 (3.797)	1.181 (0.230)	646	4.249 (3.630)
Month 24	1.111 (0.228)	538	-0.989 (4.559)	1.195 (0.230)	560	5.617 (4.273)
Month 36	1.104 (0.229)	423	-1.121 (4.985)	1.205 (0.235)	435	6.768 (4.981)

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Mean changes of lumbar spine BMD T-scores from baseline to months 24 and 36 were -0.015 and -0.022 in the placebo group and 0.058 and 0.068 in the denosumab group. The mean percentage changes from baseline to months 24 and 36 were -0.989% and -1.121% in the placebo group and 5.617% and 6.768% in the denosumab group.

Baseline lumbar spine BMD values were imputed for missing lumbar spine BMDs both placebo and denosumab for a sensitivity analysis by this reviewer. The results are summarized Table 22 below.

Table 22 Least Squares Means for Percent Change from Baseline for Lumbar BMD with Baseline Observation Carried Forward Imputation: Sensitivity Analysis

		Placebo	Denosumab	Difference	95% CI	p-value
Month 1	1430	-0.209	0.991	1.200	(0.92, 1.48)	<.0001
Month 3	1430	-0.317	2.298	2.615	(2.31, 2.92)	<.0001
Month 6	1430	-0.349	2.805	3.154	(2.84, 3.47)	<.0001
Month 12	1430	-0.863	3.750	4.614	(4.24, 4.99)	<.0001
Month 24	1430	-1.312	4.458	5.770	(5.33, 6.21)	<.0001
Month 36	1430	-0.959	4.778	5.737	(5.24, 6.23)	<.0001

Sensitivity analysis results using baseline observation carried forward imputation were consistent to the primary analysis results.

For a worst case sensitivity analysis, this reviewer performed a sensitivity analysis by imputing baseline values for missing lumbar spine BMD values if subjects' last lumbar spine BMD values were decreased, otherwise imputing last observation carried forward lumbar spine BMD values in the placebo group and by imputing baseline values if subjects' last lumbar spine values were increased from the baseline values, otherwise imputing the last observation carried forward values in the denosumab group. The worst case sensitivity analysis results are summarized in Table 23 below.

Table 23 Least Squares Means for Percent Change from Baseline for Lumbar Spine BMD with a Worst Case Sensitivity Analysis

		Placebo	Denosumab	Difference	95% CI	p-value
Month 1	1430	-0.209	0.991	1.200	(0.92, 1.48)	<.0001
Month 3	1430	-0.275	2.258	2.533	(2.23, 2.84)	<.0001
Month 6	1430	-0.294	2.759	3.054	(2.74, 3.37)	<.0001
Month 12	1430	-0.783	3.676	4.458	(4.07, 4.84)	<.0001
Month 24	1430	-1.062	4.333	5.395	(4.94, 5.85)	<.0001
Month 36	1430	-0.530	4.587	5.117	(4.60, 5.64)	<.0001

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Sensitivity analysis results with a worst case imputation method were consistent to the primary analysis results.

The number of subjects whose BMD scores increase, remain the same, or decrease compared to that of baseline by visit months are summarized Table 24 below.

Table 24 Number of Subjects' Lumbar Spine BMD values Increase, Same or Decrease from Baseline Lumbar Spine Value by Visit

From Baseline	Month1	Month3	Month 6	Month 12	Month24	Month 36
Denosumab						
N	674	707	684	654	564	435
Increase	454 (67.4)	584 (82.6)	588 (86.0)	597 (91.3)	538 (95.4)	413 (94.9)
Same	11 (1.6)	4 (0.6)	3 (0.4)	5 (0.8)	1(0.2)	0
Decrease	209 (31.0)	119 (16.8)	93 (13.6)	52 (8.0)	25(4.4)	22 (5.1)
Placebo						
N	679	703	671	644	543	423
Increase	317 (44.2)	321 (45.7)	303 (45.2)	261 (40.5)	212 (39.0)	162 (38.3)
Same	7 (1.0)	16 (2.3)	14 (2.1)	9 (1.4)	6 (1.1)	2 (0.5)
Decrease	355 (54.8)	366 (52.1)	354 (52.8)	374 (58.1)	325 (59.9)	259 (61.2)

The number of subjects whose BMD scores decreased since baseline was greater in the placebo group than in the denosumab group at 3 years.

Actual total hip BMD mean scores and percentage changes from baseline BMD are summarized in Table 25 by visit.

Table 25 Mean Total Hip BMD and Percentage Change from Baseline BMD

	Placebo (N=734)				Denosumab (N=734)			
	Mean (SD)	n	% Change(SD)	n	Mean (SD)	n	% Change (SD)	n
Baseline	0.956 (0.151)	718			0.956 (0.144)	712		
Month 1	0.955 (0.149)	671	-0.118 (2.029)	671	0.963 (0.143)	655	0.421 (1.870)	655
Month 3	0.953 (0.147)	670	-0.182 (2.237)	666	0.965 (0.144)	673	1.041 (2.116)	669
Month 6	0.953 (0.149)	658	-0.349 (2.398)	654	0.969 (0.144)	661	1.614 (2.173)	657
Month12	0.947 (0.151)	622	-1.128 (2.970)	619	0.975 (0.144)	632	2.149 (2.407)	628
Month 24	0.937 (0.153)	527	-2.288 (3.921)	523	0.981 (0.144)	548	3.118 (2.749)	543
Month 36	0.926 (0.153)	409	-3.144 (4.367)	406	0.992 (0.142)	429	3.805 (3.209)	424

Mean changes of total hip BMDs from baseline to months 24 and 36 were -0.019 and -0.030 in the placebo group and 0.025 and 0.036 in the denosumab group. The mean percentage changes from baseline to months 24 and 36 were -2.288% and -3.144% in the placebo group and 3.118% and 3.805% in the denosumab group. Baseline total hip BMD values were imputed for missing

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total hip BMDs both placebo and denosumab for a sensitivity analysis by this reviewer. The results are summarized Table 26 below.

Table 26 Least Squares Means of Percentage Change in Total Hip BMD from Baseline with Baseline Observation Carried Forward Imputation: Sensitivity Analysis

		Placebo	Denosumab	Difference	95% CI	p-value
Month 1	1407	-0.129	0.380	0.510	(0.31, 0.71)	<.0001
Month 3	1407	-0.146	1.026	1.172	(0.95, 1.39)	<.0001
Month 6	1407	-0.232	1.615	1.847	(1.62, 2.08)	<.0001
Month 12	1407	-0.988	1.963	2.951	(2.68, 3.22)	<.0001
Month 24	1407	-1.807	2.326	4.133	(3.81, 4.46)	<.0001
Month 36	1407	-1.671	2.441	4.112	(3.76, 4.46)	<.0001

Sensitivity analysis results using the baseline observations carried forward imputation were consistent to the primary analysis results.

Sensitivity analysis results using a worst case imputation are summarized in Table 27 below.

Table 27 Least Squares Means of Percentage Change in Total Hip BMD from Baseline with Worst Case Imputation Method

		Placebo	Denosumab	Difference	95% CI	p-value
Month 1	1407	-0.129	0.380	0.509	(0.31, 0.71)	<.0001
Month 3	1407	-0.090	1.016	1.106	(0.88, 1.33)	<.0001
Month 6	1407	-0.193	1.572	1.765	(1.53, 2.00)	<.0001
Month 12	1407	-0.839	1.967	2.807	(2.53, 3.08)	<.0001
Month 24	1407	-1.642	2.280	3.922	(3.59, 4.26)	<.0001
Month 36	1407	-1.400	2.362	3.763	(3.39, 4.14)	<.0001

Sensitivity analysis results using a worst case imputation method were consistent to the primary analysis results.

Table 28 Mean Femoral Neck BMD and Percentage Change in Femoral Neck BMD from baseline BMD

	Placebo (N=734)				Denosumab (N=734)			
	Mean (SD)	n	% Change(SD)	n	Mean (SD)	n	% Change (SD)	n
Baseline	0.837 (0.143)	718			0.837 (0.139)	712		
Month 1	0.836 (0.141)	671	-0.129 (2.915)	671	0.842 (0.139)	655	0.402 (2.928)	655
Month 3	0.835 (0.140)	670	-0.145 (3.150)	666	0.844 (0.139)	673	0.858 (3.048)	669
Month 6	0.833 (0.138)	658	-0.396 (3.206)	654	0.847 (0.138)	661	1.288 (3.297)	657
Month12	0.830 (0.142)	622	-0.983 (3.663)	619	0.852 (0.139)	632	1.894 (3.473)	628
Month 24	0.823 (0.144)	527	-1.661 (5.677)	523	0.855 (0.138)	548	2.772 (3.846)	543
Month 36	0.816 (0.142)	409	-2.381 (5.071)	406	0.859 (0.138)	429	3.696 (4.189)	424

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Mean changes of femoral neck BMD from baseline to months 24 and 36 were -0.014 and -0.021 in the placebo group and 0.018 and 0.022 in the denosumab group. The mean percentage changes from baseline to months 24 and 36 were -1.661% and -2.381% in the placebo group and 2.772% and 3.696% in the denosumab group.

Sensitivity analysis results for imputing baseline BMD values for the missing femoral neck BMD values are summarized in Table 29 below.

Table 29 Least Squares Means of Percentage Change from Baseline in Femoral Neck BMD with Baseline Observation Carried Forward Imputation

	n	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	1408	0.005	0.493	0.489	(0.19, 0.78)	0.0012
Month 3	1444	0.224	1.172	0.948	(0.64, 1.26)	<.0001
Month 6	1414	-0.122	1.443	1.566	(1.24, 1.89)	<.0001
Month 12	1423	-0.586	1.988	2.574	(2.22, 2.93)	<.0001
Month 24	1416	-1.165	2.240	3.405	(2.96, 3.85)	<.0001
Month 36	1407	-1.057	2.554	3.612	(3.21, 4.01)	<.0001

Sensitivity analysis results using the baseline observations carried forward imputation were consistent to the primary analysis results.

Sensitivity analysis results for a worst case using a worst case imputation method are summarized in Table 30 below.

Table 30 Least Squares Means of Percentage Change from Baseline in Femoral Neck BMD with a Worst Case Imputation

	n	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	1407	0.003	0.494	0.492	(0.20, 0.79)	0.0011
Month 3	1407	0.303	1.168	0.866	(0.55, 1.18)	<.0001
Month 6	1407	-0.040	1.408	1.448	(1.12, 1.78)	<.0001
Month 12	1407	-0.385	1.954	2.339	(1.98, 2.70)	<.0001
Month 24	1407	-0.867	2.113	2.980	(2.52, 3.44)	<.0001
Month 36	1407	-0.549	2.330	3.386	(2.40, 3.35)	<.0001

Sensitivity analysis results using a worst case imputation method were consistent to the primary analysis results.

Conclusion:

Reviewer's sensitivity analyses using a baseline observation carried forward imputation and a worst case imputation methods showed the robustness of the results.

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In addition, Study 20030216 and Study 20040132 which are designed to demonstrate the efficacy for the treatment and prevention of postmenopausal osteoporosis (PMO) and Study 20040135 which is designed for bone loss in subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer showed the similar results for BMD endpoints. The BMD efficacy results are summarized below.

Table 31 Change in BMD from baseline to Month 24 for Study 20030216, Study 20040132, Study 20040135, and Study 20040138

	Study 20030216	Study 20040132	Study 20040135	Study 20040138
Percent Change (least squares mean (95% CI))				
Lumbar Spine	7.5 (6.6, 8.3)	6.5 (5.8, 7.1)	7.6 (6.6, 8.6)	6.7 (6.2, 7.1)
Total Hip	4.8 (4.2, 5.4)	3.4 (3.0, 3.8)	4.7 (4.0, 5.5)	4.8 (4.4, 5.1)
Femoral Neck	4.5 (3.7, 5.2)	2.8 (2.3, 3.4)	3.6 (2.7, 4.6)	3.9 (3.5, 4.4)

Denosumab demonstrated significant percentage increases in lumbar spine, total hip and femoral neck BMDs from baseline to month 24 across all 4 studies.

Kaplan-Meier curves for time to first any fractures and time to new vertebral fractures were plotted for the proportion of not experiencing the event by study months.

Figure 2 Kaplan-Meier Curves for Time to First Any Factures

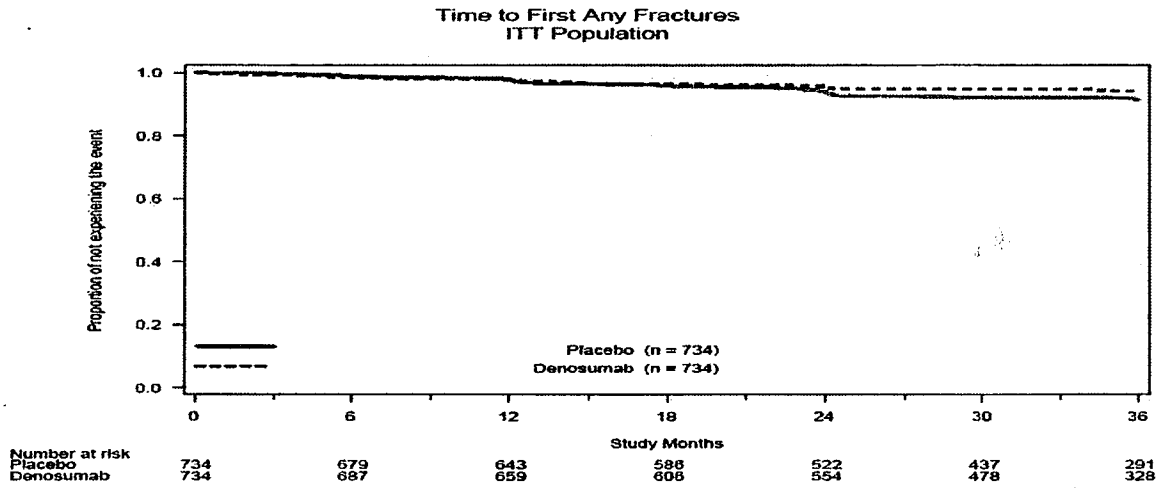

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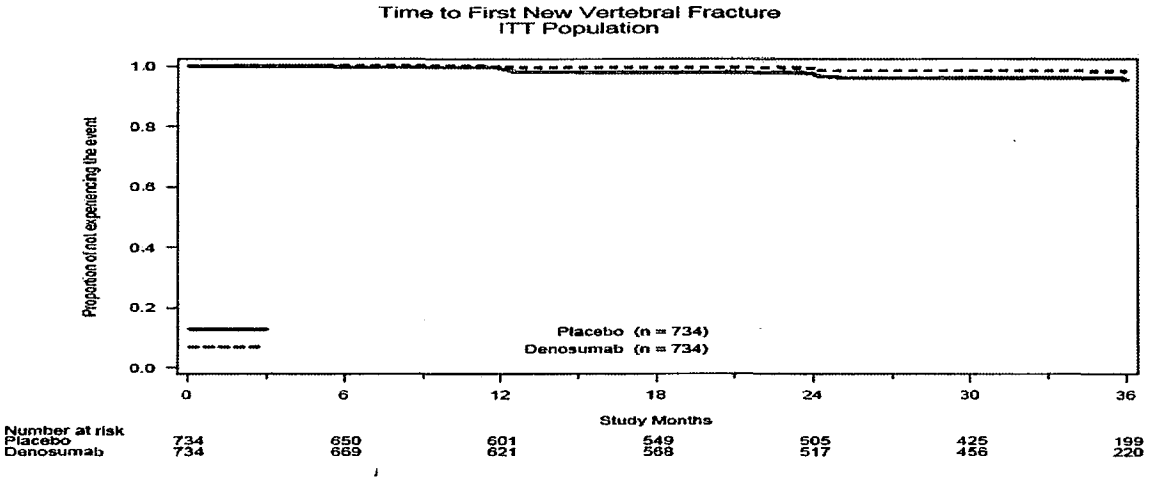
Figure 3 Kaplan-Meier Curves for Time to First New Vertebral Fractures



For exploratory analyses, number and percentage of any osteoporotic fractures, hip, nonvertebral, and new vertebral fractures are summarized yearly to examine whether there is an evidence of suppression of bone resorption.

Table 32 Number and Percentage of Any Fractures within Each 1-Year Time Interval

	Year 1		Year 2		Year 3	
	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)
Denosumab	734	15 (2.04)	659	14 (2.12)	545	9 (1.65)
Placebo	734	15 (2.04)	618	25 (4.05)	509	13 (2.55)

Any osteoporotic fractures absolute rate (placebo-denosumab) difference between the two treatment groups were, 0%, 1.9%, and 0.9%, at year 1, 2, and 3 respectively.

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Table 33 Number and Percentage of New Vertebral Fractures within Each 1-Year Time Interval

	Year 1		Year 2		Year 3	
	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)
Denosumab	734	1 (0.14)	621	2 (0.32)	517	7 (1.35)
Placebo	734	6 (0.82)	601	11 (1.83)	505	9 (1.78)

Source: Figure 14-2.5 on page 1523 of Study 20040138 report and Statistical Reviewer's calculations.

New vertebral fractures absolute difference rate (placebo-denosumab) between the two treatment groups were 0.7%, 1.5%, and 0.4% for year 1, 2, and 3, respectively.

Table 34 Number and Percentage of Hip Fractures within Each 1-Year Time Interval

	Year 1		Year 2		Year 3	
	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)
Denosumab	734	3 (0.41)	669	3 (0.45)	571	0 (0.0)
Placebo	734	1 (0.14)	654	3 (0.46)	553	1 (0.18)

Source: Statistical Reviewer's Kaplan-Meier Curves and calculation using ASLEFF dataset

Hip fractures absolute rate (placebo-denosumab) difference between the two treatment groups were, -0.3%, 0 %, and 0.2%, at year 1, 2, and 3 respectively.

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Table 35 Number and Percentage of Non-Vertebral Fractures within Each 1-Year Time Interval

	Year 1		Year 2		Year 3	
	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)	Number of subjects at beginning of interval	Number of fractures in interval (%)
Denosumab	734	14 (1.91)	660	12 (1.82)	556	2 (0.36)
Placebo	734	9 (1.23)	647	14 (2.16)	536	6 (1.12)

Source: Figure 14-2.3 on page 1521 of Study 20040138 report and Statistical Reviewer's calculations

Non-vertebral fractures absolute difference rate (placebo-denosumab) between the two treatment groups were -0.7%, 0.3%, and 0.7% for year 1, 2 and 3, respectively.

New vertebral fractures were observed 0.14 % and 0.32% at year 1 and 2, respectively, but the number of fractures at year 3 increased to 1.35 % in the denosumab group. Most of new vertebral fracture events (70%) were observed at year 3 in the denosumab group.

Overall Survival

There were a total of 86 deaths, 43 deaths per arm. The overall survival analysis results are summarized in Table 36 below.

Table 36 Results of Overall Survival Analysis

Overall Survival	Denosumab N = 734	Placebo N = 734
Number of Patients With OS Event	43 (5.9%)	43 (5.9%)
Number of Patients Without OS Event	691 (94.1%)	691 (94.1%)
Median Duration of OS months (95% CI)	NA	NA
Hazard Ratio (95% CI)		0.97 (0.64- 1.49)
P-Value (Stratified Log-Rank Test)		0.89

*Stratification factors were age group (< 70 years vs. ≥ 70 years) and duration of ADT at study entry (≤ 6 months vs. > 6 months).

There was no demonstrated difference in overall survival between the two groups. Kaplan-Meier plots for overall survival are presented in Figure 2..

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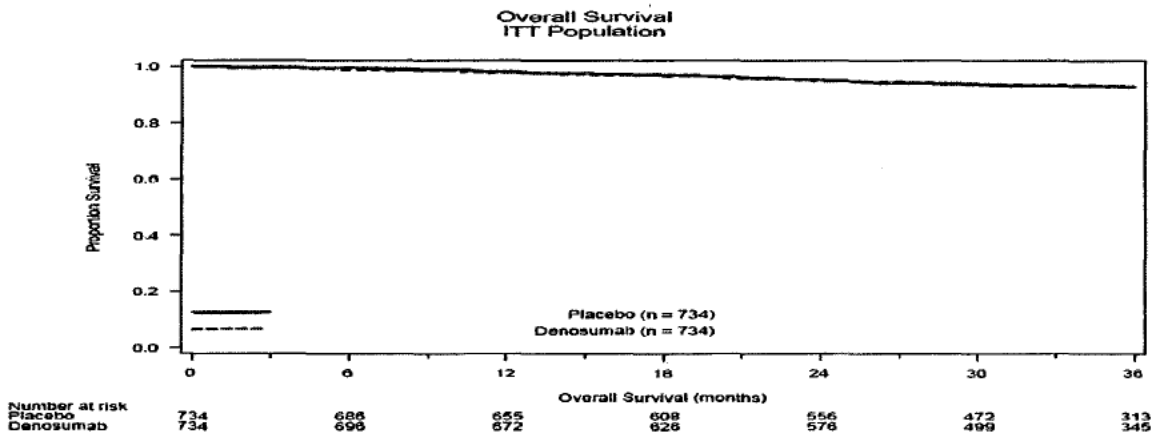
Figure 4 Kaplan-Meier Curves for Overall Survival

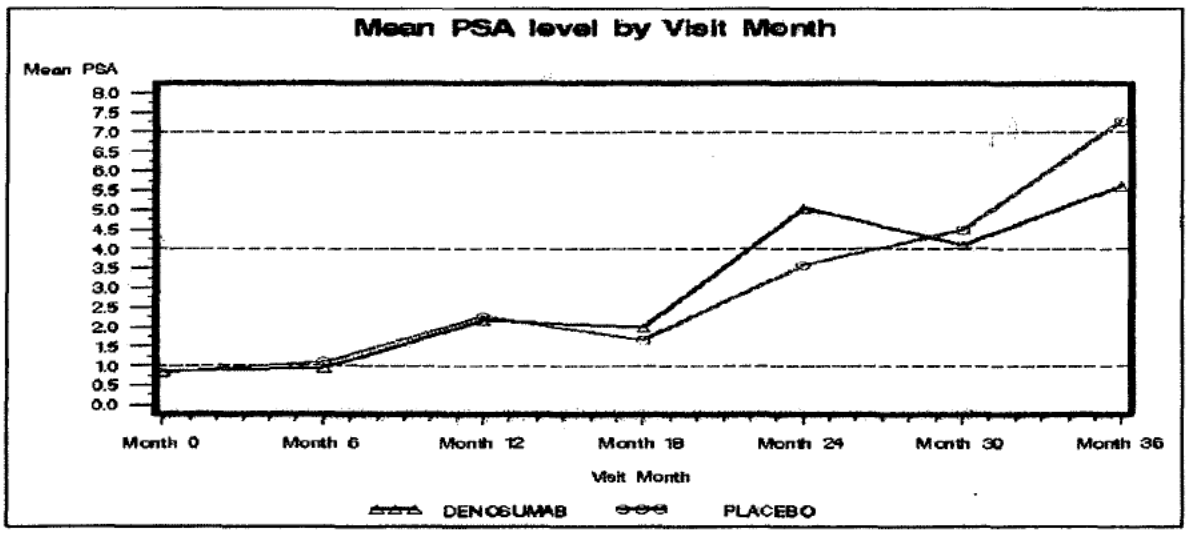


3.2 Evaluation of Safety

For a summary of the evaluation of safety refer the review by Dr. Suzanne Demko.

Prostate specific antigen (PSA) levels were examined overtime. Mean PSA levels by visit month from month 0 to month 36 are plotted by treatment group.

Figure 5 Mean Prostate Specific Antigen Levels by Visit Month



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Mean PSA levels from visit month 0 to visit month 18 were almost same for both groups. Denosumab group showed higher mean PSA levels at visit month 24, but placebo group showed higher mean PSA levels for visit months 30 and 36. Baseline mean PSA levels were 0.815 (n=734) and 0.861 (n=734), for placebo and denosumab, respectively.

PSA levels from visit month 6 to 36 were analyzed using an analysis of covariance (ANCOVA) approach adjusting for baseline PSA level, age group (< 70 years vs. ≥ 70 years), duration of ADT (≤ 6 months vs. > 6 months), and prostate cancer recurrence risk level as covariates.

Table 37 Least Squares Means for PSA Levels from Months 6 to Month 36 (Fullset Population)

	PSA			Difference from Placebo		
	n	LS mean	95% CI	LS mean	95% CI	p-value*
Month 6						
Placebo	688	1.229	(0.66, 1.79)			
Denosumab 60 mg Q6M	706	1.055	(0.49, 1.62)	-0.174	(-0.80, 0.45)	0.582
Month 12						
Placebo	667	2.825	(0.87, 4.78)			
Denosumab 60 mg Q6M	673	2.746	(0.80, 4.69)	-0.079	(-2.26, 2.10)	0.943
Month 18						
Placebo	600	1.231	(0.26, 2.21)			
Denosumab 60 mg Q6M	625	1.533	(0.55, 2.51)	0.302	(-0.79, 1.39)	0.588
Month 24						
Placebo	534	2.350	(-1.92, 6.62)			
Denosumab 60 mg Q6M	560	3.694	(-0.60, 7.98)	1.344	(-3.50, 6.19)	0.586
Month 30						
Placebo	463	3.369	(-0.08, 6.82)			
Denosumab 60 mg Q6M	499	2.771	(-0.69, 6.23)	-0.598	(-4.54, 3.35)	0.766
Month 36						
Placebo	451	8.048	(2.79, 13.30)			
Denosumab 60 mg Q6M	475	6.358	(1.05, 11.67)	-1.690	(-7.74, 4.36)	0.584
Month6-Month 36*						
Placebo		3.879	(1.72, 6.04)			
Denosumab 60 mg Q6M		4.077	(1.92, 6.23)	0.198	(-2.24, 2.64)	0.874

*: Proc mixed model (repeated measures) was used adjusting for baseline PSA level, age group (< 70 years vs. ≥ 70 years), duration of ADT (≤ 6 months vs. > 6 months), and prostate cancer recurrence risk level

Placebo group showed higher PSA level increases than the denosumab group at months 6, 12, 30 and 36. Denosumab group showed higher PSA level increases at months 18 and 24 compared to

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the placebo group. Overall from month 6 through 36, denosumab showed higher PSA levels than placebo, but there was no statistical difference between the two groups.

Incidence of subject's PSA rise to 2 ng/mL analysis was performed using ITT population. PSA rise was defined as a rise by ≥ 50% from the previous on-study PSA nadir to an absolute PSA ≥ 2.0 ng/mL while in a castrate state (serum testosterone level < 50 ng/dl). A logistic regression model was used by adjusting for age group, duration of ADT at study entry, prostate cancer risk level and the baseline PSA level.

Table 38 Incidence of PSA Rise (to 2ng/mL) Overtime (Fullset Population)

	Crude Incidence		Odd Ratio		
	n/N	%	Estimate	95%CI	p-value
Through Month 12					
Placebo	69/708	9.8			
Denosumab 60 mg Q6M	76/715	10.6	0.94	(0.66, 1.33)	0.708
Through Month 24					
Placebo	116/712	16.3			
Denosumab 60 mg Q6M	119/715	16.6	1.00	(0.75, 1.33)	0.997
Through Month 36					
Placebo	141/713	19.8			
Denosumab 60 mg Q6M	153/716	21.4	0.93	(0.71, 1.21)	0.575

There was no difference between the treatment groups in incidence of subjects' PSA rise to 2 ng/mL overtime. Generalized linear model (GEE) was performed for the mean of PSA rise 2 ng/mL response as a logistic regression with treatment arm, visit month, age group, duration of ADT at study entry, prostate cancer risk level and the baseline PSA level as independent variables using repeated statement. Estimates and 95% CI were -0.121 (-0.44, 0.20) (p=0.460). There was no difference between the two groups.

Incidence of subject's PSA rise analysis was performed using fullest population (ITT population). PSA rise was defined as a rise by ≥ 50% from the previous on-study PSA nadir to an absolute PSA ≥ 5.0 ng/mL while in a castrate state (serum testosterone level < 50 ng/dl). A logistic regression model was used by adjusting for age group, duration of ADT at study entry, prostate cancer risk level and the baseline PSA level.

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Table 39 Incidence of PSA Rise (to 5ng/mL) Overtime (Fullset Population)

	Crude Incidence		Odd Ratio		
	n/N	%	Estimate	95%CI	p-value
Through Month 12					
Placebo	40/708	5.7			
Denosumab 60 mg Q6M	42/715	5.9	1.00	(0.63, 1.58)	1.000
Through Month 24					
Placebo	74/712	10.4			
Denosumab 60 mg Q6M	73/715	10.2	0.95	(0.67, 1.34)	0.750
Through Month 36					
Placebo	92/713	12.9			
Denosumab 60 mg Q6M	98/716	13.7	1.04	(0.76, 1.42)	0.826

There was no difference between the treatment groups in incidence of subjects' PSA rise to 5 ng/mL overtime. Generalized linear model (GEE) was performed for the mean of PSA rise 5 ng/mL response as a logistic regression with treatment arm, visit month, age group, duration of ADT at study entry, prostate cancer risk level and the baseline PSA level as independent variables using repeated statement. The estimates and 95% CI were 0.06 (-0.31, 0.43) (p=-.751). There was no difference between the two groups.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Subgroup analyses for race and age group (<65 years versus ≤ 65 years) are summarized in Table 35. Majority are White or Caucasean (83.4%), Black or African American, Hispanic or Latino, Asian, American Indian or Alaska Native and Other are combined to Other than White or Caucasean in Table 40 below.

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Table 40 Subgroup Analyses for Race and Age.

	% Change from Baseline			Difference from Placebo		
	n/N	LS Mean	95% CI	LS Mean	95% CI	p-value
Caucasian						
Placebo	596/609	-0.9	(-1.2, -0.5)			
Denosumab	600/615	5.8	(5.4, 6.1)	6.7	(6.2, 7.1)	<0.0001
Other than White or Caucasean						
Placebo	120/125	-2.1	(-2.9, -1.3)			
Denosumab	114/119	4.7	(3.9, 5.6)	6.8	(5.7, 7.9)	<0.0001
<65 years*						
Placebo	53/55	-1.8	(-3.2, -0.5)			
Denosumab	47/49	6.6	(5.2, 8.0)	8.5	(6.6, 10.4)	<0.0001
≥65 years*						
Placebo	663/679	-1.0	(-1.3, -0.6)			
Denosumab	667/685	5.5	(5.2, 5.9)	6.5	(6.1, 7.0)	<0.0001

*:Significant interaction between treatment and the variable at 0.1

Age younger than 65 years group showed a greater percentage change in lumbar spine BMD from baseline to Month 24 as compared to age 65 years or 65 years older group.

4.2 Other Special/Subgroup Populations

Subgroup analyses results for stratification factors, age <70 years vs. ≥ 70 years and androgen deprivation therapy duration at study entry ≤6 months vs. > 6 months are summarized in Table 41.

Table 41 Subgroup Analyses for Stratification Factors

	% Change from Baseline			Difference from Placebo		
	n/N	LS Mean	95% CI	LS Mean	95% CI	p-value
<70 years*						
Placebo	121/124	-1.8	(-2.7,-0.8)			
Denosumab	122 /125	6.0	(5.1, 6.9)	7.7	(6.5, 8.9)	<0.0001
≥70 years*						
Placebo	595/610	-0.9	(-1.3,-0.6)			
Denosumab	592/609	5.5	(3.4, 5.3)	6.5	(6.0, 6.9)	<0.0001
≤ 6 months ADT duration*						
Placebo	169/175	-2.4	(-3.0,-1.7)			
Denosumab	171/175	5.1	(4.4, 5.8)	7.5	(6.5, 8.4)	<0.0001
>6 months ADT duration*						
Placebo	547/559	-0.6	(-1.0,-0.3)			
Denosumab	543/559	5.8	(5.4, 6.2)	6.5	(5.9, 6.9)	<0.0001

*:Significant interaction between treatment and the variable at 0.1

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Age younger than 70 years group showed a greater percentage change difference in lumbar spine BMD from baseline to Month 24 as compared to age 70 years or older than 70 years group.

Duration of androgen deprivation therapy at study entry less than equal to 6 months group showed a greater percentage change in lumbar spine BMD from baseline to Month 24 as compared to more than 6 months group.

Subgroup analyses for weight and BMI for the primary endpoint are summarized in Table 42 below

Table 42 Subgroup Analyses of Weight and BMI for Percentage Change in Lumbar Spine BMD

	% Change from Baseline			Difference from Placebo		
	n/N	LS Mean	95% CI	LS Mean	95% CI	p-value
Weight <75 kg*						
Placebo	188/190	-2.0	(-2.6, -1.4)			
Denosumab	174/180	6.2	(5.5, 6.8)	8.1	(7.3, 9.0)	<0.0001
Weight ≥75 kg*						
Placebo	528/543	-0.7	(-1.1, -0.3)			
Denosumab	539/553	5.4	(5.0, 5.8)	6.2	(5.6, 6.7)	<0.0001
< 26 kg/m² BMI*						
Placebo	244/250	-1.6	(-2.2,-1.1)			
Denosumab	218/223	6.1	(5.5, 6.7)	7.7	(6.9, 8.5)	<0.0001
≥ 26 kg/m² BMI*						
Placebo	472/483	-0.8	(-1.2,-0.3)			
Denosumab	495/510	5.4	(5.0, 5.8)	6.1	(5.6, 6.7)	<0.0001

*:Significant interaction between treatment and the variable at 0.1

Subjects with weight less than 75 kg and BMI less then 26 kg/m² showed a greater percentage change in lumbar spine from baseline to Month 24 as compared to weight greater than or equal to 75 kg and BMI greater than equal to 26 kg/m², respectively.

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Table 43 Subgroup Analyses of Prevalent Vertical Fracture and Study Region

	% Change from Baseline			Difference from Placebo		
	n/N	LS Mean	95% CI	LS Mean	95% CI	p-value
No prevalent vertebral fracture						
Placebo	494/504	-1.0	(-1.4, -0.6)			
Denosumab	524/531	5.5	(5.1, 5.9)	6.5	(6.0, 7.0)	<0.0001
Prevalent vertebral fracture						
Placebo	172/174	-1.0	(-1.7, -0.3)			
Denosumab	149/155	6.0	(5.2, 6.7)	7.0	(6.0, 8.0)	<0.0001
Europe*						
Placebo	176/179	-1.0	(-1.6, -0.3)			
Denosumab	175/178	6.6	(5.9, 7.2)	7.6	(6.7, 8.5)	<0.0001
North America*						
Placebo	540/555	-1.1	(-1.4, -0.7)			
Denosumab	539/540	5.3	(4.9, 5.7)	6.3	(5.8, 6.9)	<0.0001

*:Significant interaction between treatment and the variable at 0.1

Europe subjects showed a greater percentage change in lumbar spine from baseline to Month 24 as compared to that of North America.

Subgroup analyses of baseline type 1 C-telopeptide (CTX1) level and T-score are summarized in Table 44 below.

Table 44 Subgroup Analyses of Baseline CTX1 and BMD T-Score

	% Change from Baseline			Difference from Placebo		
	n/N	LS Mean	95% CI	LS Mean	95% CI	p-value
0.475 ug/L CTX1						
Placebo	224/231	-0.4	(-0.9, 0.2)			
Denosumab	217/221	4.7	(4.1, 5.3)	5.1	(4.3, 5.8)	<0.0001
0.475 ug/L- <0.764 ug/L CTX1						
Placebo	232/236	-1.3	(-1.9, -0.7)			
Denosumab	224/229	5.6	(5.0, 6.1)	6.9	(6.1, 7.6)	<0.0001
≥ 0.764 ug/L CTX1						
Placebo	214/216	-1.7	(-2.3, -1.1)			
Denosumab	234/240	6.7	(6.1, 7.4)	8.4	(7.6, 9.3)	<0.0001
≤ -1.0 T-score*						
Placebo	317/321	-1.4	(-2.0, -0.8)			
Denosumab	272/276	6.3	(5.7, 6.9)	7.7	(6.9, 8.4)	<0.0001
> -1.0 T-score*						
Placebo	399/408	-0.9	(-1.3, -0.5)			
Denosumab	442/ 451	5.1	(4.7, 5.5)	6.0	(5.4, 6.5)	<0.0001

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*:Significant interaction between treatment and the variable at 0.1

Subjects with higher baseline CTX1 value showed a greater percentage change difference in lumbar spine BMD from baseline to Month 24 than subjects with low baseline CTX1 value. Baseline T-score less than or equal to -1.0 subjects showed a greater percentage change difference in lumbar spine than subjects with baseline T-score greater than -1.0.

The number of subject in the baseline vitamin D levels of < 12 ng/mL, 12-20 ng/mL, 21-29 ng/mL and ≥30 ng/mL are summarized in Table 45 below.

Table 45 Number of Subjects for Baseline Vitamin D Levels

	<12 n/mL	12-20 ng/mL	21-29 ng/mL	≥30-ng/mL	Total
Denosumab	4 (0.6)	202 (30.1)	258 (38.4)	208 (31.0)	672
Placebo	7 (1.0)	197 (29.4)	263 (39.3)	203 (30.3)	670
Total	11(0.9)	399 (29.7)	521 (38.8)	411 (30.6)	1342

Subgroup analysis for baseline vitamin D levels is summarized in Table 46 below.

Table 46 Subgroup Analyses for Baseline Vitamin D Levels

	n/ N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1						
<20 ng/mL	399/410	-0.459	0.326	0.785	(0.25, 1.32)	0.0044
21-29 ng/mL	509/521	-0.132	1.384	1.516	(1.04, 2.00)	<.0001
≥30 ng/mL	400/411	-0.260	1.062	1.322	(0.82, 1.82)	<.0001
Month 3						
<20 ng/mL	399/410	-0.470	1.920	2.390	(1.83, 2.95)	0.0010
21-29 ng/mL	509/521	-0.078	2.457	2.536	(2.02, 3.06)	<.0001
≥30 ng/mL	400/411	-0.514	2.398	2.912	(2.34, 3.48)	<.0001
Month 6						
<20 ng/mL	399/410	-0.711	2.096	2.807	(2.18, 3.43)	<.0001
21-29 ng/mL	509/521	0.005	3.261	3.256	(2.73, 3.78)	<.0001
≥30 ng/mL	400/411	-0.663	2.874	3.536	(2.98, 4.09)	<.0001
Month 12						
<20 ng/mL	399/410	-1.373	3.475	4.848	(4.10, 5.60)	<.0001
21-29 ng/mL	509/521	-0.548	4.164	4.712	(4.09, 5.33)	<.0001
≥30-ng/mL	400/411	-1.103	3.839	4.942	(4.21, 5.67)	<.0001
Month 24						
<20 ng/mL	399/410	-2.116	4.619	6.735	(5.82, 7.65)	<.0001
21-29 ng/mL	509/521	-1.263	5.378	6.640	(5.90, 7.39)	<.0001
≥30-ng/mL	400/411	-1.125	5.161	6.286	(5.47, 7.10)	<.0001
Month 36						
<20 ng/mL	399/410	-1.774	5.916	7.690	(6.67, 8.71)	<.0001
21-29 ng/mL	509/521	-1.465	6.414	7.878	(7.01, 8.75)	<.0001
≥30-ng/mL	400/411	-1.402	6.540	7.942	(7.01, 8.87)	<.0001

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There was no association between baseline vitamin D levels and the percentage change in lumbar spine BMDs from baseline to month 24.

Conclusion:

Subgroup analyses consistently showed that denosumab group increased the percentage changes in lumbar spine BMDs from baseline to month 24 as compared to that of placebo.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- There was no adequate data to identify any potential for detrimental effects on progression free survival (PFS) and overall survival on how denosumab affects the primary disease of prostate cancer. In particular, the study was not designed to adequately comparing between study arms. There were no meaningful safety information about the primary disease progression or overall survival and no routine neoplastic disease assessment.

- The percentage of subjects with missing lumbar spine BMD scores for the denosumab group and the placebo group were 21% and 24%, respectively, at month 24 and 38% and 40%, respectively, at month 36. Last observation carried forward imputation method was used for the efficacy analyses. Sponsor performed sensitivity analyses including repeated measures model, ANCOVA model using the per protocol analysis set, ANCOVA model using subjects categorized by their actual stratum and univariate and multivariate covariate analyses to demonstrate the robustness of the primary results.

- There was no demonstrated reduction in the incidence of any fracture endpoints during 3-year treatment periods, but there was a demonstrated reduction in incidence of new vertebral fractures at month 36. Most of new vertebral fractures (70%) in denosumab were reported at year 3. Absolute rate difference (placebo-denosumab) for any fractures between the two treatments were 0 %, 1.9 %, and 0.9 % for year 1, 2, and 3, respectively. Absolute rate difference (placebo-denosumab) for new vertebral fractures between the two treatments were 0.7%, 1.5%, and 0.4 % for year 1, 2, and 3, respectively. Absolute risk reduction (placebo-denosumab) for any fractures during 2 years (cumulatively) and 3 years (cumulatively) were 1.8% and 2%, respectively. Absolute risk reduction (placebo-denosumab) for new vertebral fractures during 2 years (cumulatively) and 3 years (cumulatively) were 2.2%, and 2.4%, respectively.

- There is no estimated difference in overall survival (HR=0.97 (95% CI: 0.64- 1.49); p-value = 0.89) after 86 deaths. In addition, this study was not designed to adequately compare overall survival and progression free survival (PFS).

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- There was heterogeneity in the treatment effects on the percent change from baseline in lumbar spine BMD between Europe and North America region. The difference of the lumbar spine percentage change from baseline to month 24 between the two treatment groups for Europe and North America were 7.6% (95% CI: 6.7, 8.5) and 6.3% (95% CI: 5.8, 6.9), respectively.

- Subgroup analysis for age younger than 65 years group demonstrated a greater percentage change difference in lumbar spine BMD from baseline to month 24 as compared to age 65 years or older group, the percentage differences were 8.5% (95% CI: 6.6, 10.4) and 6.5% (95% CI:6.1, 7.0), respectively.

- Subgroup analyses for weight less than 75 kg and body mass index (BMI) less than 26 kg/m^2 subjects demonstrated a greater percentage change differences in lumbar spine BMD from baseline to month 24 as compared to weight greater than or equal to 75 kg and BMI greater or equal to 26 kg/m^2 subjects. The percentage differences for weight <75 kg vs. $\geq$ 75 kg and BMI <26 kg/m^2 vs. $\geq$ 26 kg/m^2 were 8.1% (95% CI 7.3, 9.00) vs. 6.2% (95% CI: 5.6, 6.7), and 7.7 % (95% CI: 6.9, 8.5) vs. 6.1% (95% CI: 5.6, 6.7), respectively.

- Subgroup analysis for subjects with higher baseline CTX1 values showed a greater percentage change difference in lumbar spine BMD from baseline to month 24 than subjects with lower baseline CTX1 values. Subjects with baseline T-scores less than or equal to -1.0 had a greater percentage change difference in lumbar spine BMD than subjects with baseline T-scores greater than -1.0.

- Subgroup analysis for subjects' baseline vitamin D levels showed no association between the baseline vitamin D levels and the percentage change in lumbar spine BMD from baseline to month 24.

5.2 Conclusions and Recommendations

The primary endpoint of percentage change in lumbar spine bone mineral density from baseline to month 24 demonstrated a statistically significant percentage change for the denosumab group as compared to the placebo group ($p < 0.0001$). The least squares mean estimate was 5.6% increase in denosumab and 1.0% decrease in placebo, the percentage difference between denosumab and placebo was 6.7% (95% CI: 6.2, 7.1) at month 24. The sensitivity analyses performed by the sponsor and by this reviewer confirmed the primary analysis.

The secondary endpoints for the percentage changes in femoral neck BMD and total hip BMD from baseline to month 24 and the percentage changes in lumbar spine, femoral neck and total hips BMDs from baseline to month 36 demonstrated statistically significant BMD percentage increases in the denosumab group as compared to the placebo group (all $p < 0.0001$). The sensitivity analyses results by the sponsor and by this reviewer were consistent.

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Denosumab failed to demonstrate a reduction in incidence of any fracture events at month 36 (OR=0.70; 95% CI: 0.46, 1.08) (p=0.1048), but the subject incidence in new vertebral fracture at month 36 demonstrated statistically significant results (p=0.0063, adjusted p=0.0125). Further testing for other fracture endpoints of steps 4 and 5 should be stopped at this point.

There is evidence that this study supports that denosumab 60 mg subcutaneously (SC) once every 6 months with a total of 6 doses over the 36-month treatment period as compared to placebo increases percentage change in lumbar spine BMD from baseline to month 24 for subjects with nonmetastatic prostate cancer who were undergoing ADT. However, safe use of denosumab has not been evaluated for these prostate cancer patients based on tumor related outcomes.

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number: BL STN 125332/0

Drug Name: PROLIA (denosumab)

Indication(s): Treatment of Bone Loss in Subjects Undergoing Aromatase Inhibitor Therapy for Nonmetastatic Breast Cancer

Applicant: Amgen, Incorporated

Date(s): Received Date: December 19, 2008
Application Review Due Date: October 19, 2009

Review Priority: Standard

Biometrics Division: Division of Biometrics V

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Clinical Team: Dr. Suzanne Demko, Clinical reviewer

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Keywords:

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1. EXECUTIVE SUMMARY

BLA 125332 (Study 20040135) is a submission to evaluate denosumab (AMG 162) in the treatment of bone loss in subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer.

The sponsor submitted four BLAs 125320, 125331, 125332, and 125333 for denosumab simultaneously. BLA 125333 consists of the results of Study 2004138 in subjects receiving hormone-ablative therapies for nonmetastatic prostate cancer. BLAs 125332 and 125333 are under review by the Division of Biologic Oncology Products (DBOP). BLA 125320 consists of the results of Study 2003216 in subjects with postmenopausal osteoporosis and BLA 125331 consists of the results of Study 20040132 in subjects with postmenopausal low bone mineral density. BLAs 125320 and 125331 are under review by the Division of Reproductive and Urologic Products (DRUP). Study 20030216 is the pivotal study for the treatment of postmenopausal osteoporosis (PMO) as the primary indication examining fracture risk reduction and increases in bone mineral density (BMD). This trial is to demonstrate the evidence of clinically relevant increases in BMD and reductions in fracture. Studies 20040132, 20040135 and 20040138 are pivotal trials supporting the treatment and prevention of PMO and bone loss associated with hormone ablation therapy for breast and prostate cancer, respectively, examining increases in BMD. The Advisory committee for the Reproductive Health Drugs met on August 13, 2009 for BLA submissions, 125320, 125331, 125332 and 125333.

Bone mineral density (BMD) and fracture endpoints are clinically relevant for women with postmenopausal osteoporosis. BMD is a major determinant of fracture risk, and increases in BMD have been associated with a reduction in fracture risk in patients. Although the fracture incidence rate among patients with low bone mass is known to be relatively low, the total number of fractures among patients with low bone mass is known to be greater than that among patients with osteoporosis. BMD decrease over time is indicative of bone loss, microarchitecture deterioration and potential fractures. Low BMD is used as a surrogate endpoint for the risk of developing fractures.

1.1 Conclusions and Recommendations

The primary endpoint of the percentage change in lumbar spine bone mineral density (BMD) from baseline to month 12 demonstrated a statistically significant percentage increase in the denosumab group as compared to the placebo group ($p < 0.0001$). The least squares mean estimate was a 4.8% increase in the denosumab arm and a 0.7% decrease in the placebo arm. The difference with percentage change between denosumab and placebo was 5.5% (95% CI: 4.8, 6.3) at month 12. The sensitivity analyses performed by the sponsor and by this reviewer were consistent with the results of the primary analysis.

Secondary endpoints for the percentage change in lumbar spine BMD from baseline to month 6 and the percentage changes in total hip and femoral neck BMDs from baseline to months 6 and 12 demonstrated a statistically significant percentage increases in the denosumab group as compared to the placebo group ($p<0.0001$).

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The data are not adequate to conclude whether denosumab affects breast cancer. In particular, the study was not designed to adequately compare disease free survival (DFS) and overall survival (OS) between study arms. There were no meaningful safety information about the primary disease free survival and overall survival and no routine neoplastic disease assessment.

There is evidence that this study supports that denosumab 60 mg subcutaneously (SC) once every 6 months over the 24-month treatment period increases the percentage change in lumbar spine BMD from baseline to month 12 for subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. However, safe use of denosumab has not been evaluated for these breast cancer patients based on tumor related outcomes.

1.2 Brief Overview of Clinical Studies

There are four pivotal trials for denosumab. These four pivotal trials are as follow;

Study 20040135 is a pivotal trial supporting the treatment and prevention of bone loss associated hormone ablation therapy for breast cancer. This study is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy of denosumab in subjects receiving adjuvant aromatase inhibitor therapy for nonmetastatic breast cancer. Subjects with BMD T-scores between -1.0 and -2.5, excluding women with osteoporosis and those with normal BMD were randomized in a 1:1 ratio to receive either 60 mg denosumab or placebo subcutaneously once every 6 months for 24 months with a total of 4 injections.

A total of 252 subjects were randomized into the study, 127 subjects to denosumab and 125 subjects to placebo. The stratification factor was duration of aromatase inhibitor therapy (≤ 6 months versus > 6 months) at study entry. Subjects were followed for 24 months after the last dose of investigational product (ie, the 24-month safety follow-up period).

The primary endpoint was the percentage change in lumbar spine BMD from baseline to month 12. The secondary endpoints were the percentage change in lumbar spine BMD from baseline to month 6 and percentage changes in total hip and femoral neck BMDs from baseline to months 6 and 12. The secondary efficacy endpoints analyses were contingent on rejection of the primary null hypothesis at a level of 0.05 and Hochberg procedure was used to adjust multiplicity at a level of 0.05.

Study 20040138 is a pivotal trial supporting the treatment and prevention of bone loss associated hormone ablation therapy for prostate cancer. This study is an international, multicenter, randomized, double-blind, placebo-controlled study in subjects with nonmetastatic prostate cancer who were undergoing ADT. A total of 1486 subjects were randomized (1:1) to receive either placebo or denosumab 60 mg subcutaneously (SC) once every 6 months with a total of 6 doses over 60 months study duration (36-month treatment period and a 24-month safety follow-up period.) Randomization stratification factors were age group (< 70 years vs. ≥ 70 years) and duration of ADT with gonadotropin-releasing hormone (GnRH) agonists or orchiectomy at study entry (≤ 6 months vs. > 6 months).

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The primary endpoint was the percentage change in lumbar spine BMD from baseline to month 24. Secondary efficacy endpoints were the percentage change in lumbar spine BMD from baseline to month 36, the percentage changes in femoral neck BMD and total hip BMD from baseline to month 24 and month 36, the incidence of any fracture (ie, osteoporotic fracture at any skeletal site, including vertebral, but excluding skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges), and the incidence of new vertebral fracture over the 36-month treatment period, time to first clinical fracture over the 36-month treatment period and the incidence of any fracture over the 24-month treatment period. The secondary efficacy endpoints analyses were contingent on rejection of the primary null hypothesis at a level of 0.05 and used the Hochberg procedure to adjust for multiplicity at level of 0.05. Denosumab demonstrated statistically significant percentage increases in lumbar spine, total hip, and femoral neck BMDs from baseline to months 24 and 36. Denosumab demonstrated a significant reduction on new vertebral fractures at month 36.

Study 20030216 is a pivotal study for the primary indication of the treatment of PMO. This study is an international, multicenter, randomized, double-blind, placebo-controlled study tested the clinical hypotheses that denosumab, as compared with placebo, is effective in reducing the risks of new vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis (BMD T-score < -2.5 at either the lumbar spine or the total hip, or at both locations, but ≥ -4.0 at both locations).

A total of 7808 subjects were randomized to receive either denosumab 60 mg (3902 subjects) or placebo (3906 subjects) every 6 months (Q6M) subcutaneously for 3 years (last dose at month 30; follow-up to month 36). Randomization was stratified by age at entry: 60 to 64 years, 65 to 69 years, 70 to 74 years; and $\geq$ 75 years.

The primary efficacy endpoint is the subject incidence of new vertebral fractures during the entire 36-month treatment period. Secondary efficacy endpoints are time to first nonvertebral fracture and time to first hip fracture. A fixed sequence testing procedure among these 3 endpoints was used for multiplicity adjustment to maintain the overall significance level at 0.05. Denosumab demonstrated significant reductions of risks in new vertebral, nonvertebral, and hip fractures at month 36. Denosumab demonstrated significant increases in percentage change in lumbar spine, total hip, and femoral neck BMDs from baseline to month 36.

Study 20040132 is a pivotal study for the prevention of PMO indication. This study is a multicenter, randomized, double-blind, 2-period, parallel group study enrolled postmenopausal women with lumbar spine BMD T-score between -1.0 and -2.5. A total of 332 subjects were randomized (1:1) to receive either denosumab 60 mg (166 subjects) or placebo (166 subjects) every 6 months (Q6M) subcutaneously for 2 years. Duration of study is approximately 50 months (2 months screening period, 24 months treatment period and 24 month follow-up period.) Randomization was stratified by time since onset of menopause ($\leq$ 5 years or $>$ 5 years).

The primary efficacy endpoint is the percent change from baseline in the lumbar spine BMD (by DXA) at 24 months of treatment. Secondary efficacy endpoints are percent change from baseline in BMD (by DXA) of the total hip, femoral neck, trochanter, distal 1/3 radius, and total body (without head) at 24 months and percent change from baseline in trabecular, cortical, and

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total volumetric BMD of the distal radius as measured by QCT at 24 months Multiplicity adjustments of both hierarchical testing strategy and Hochberg procedure were applied to one primary and secondary efficacy endpoints to maintain the overall type I error at ≤ 0.025 within each strata. Denosumab demonstrated significant increases in percentage change in lumbar spine, total hip, and femoral neck BMDs from baseline to month 24.

1.3 Statistical Issues and Findings

1.3.1 Issues and Findings

- There was no adequate data to identify any potential for detrimental effects on disease free survival (DFS) and overall survival on how denosumab affects the primary disease of breast cancer. In particular, the study was not designed to adequately comparing between study arms. There were no meaningful safety information about the primary disease free survival and overall survival and no routine neoplastic disease assessment.

- The percent of subjects with missing lumbar spine BMD scores were 9% and 15 % at months 12 and 24 in the denosumab group and 15%, and 19 % at months 12 and 24 in the placebo group. The placebo group had 4% to 6% more missing lumbar spine BMD scores than that of the denosumab group. Last observation carried forward imputation method was used for the efficacy analyses. Sponsor performed sensitivity analyses including repeated measures model, ANCOVA model using mean of the other group (MOTH) imputation methods and the per protocol analysis set, ANCOVA model using subjects categorized by their actual stratum and univariate and multivariate covariate analyses to demonstrate the robustness of the primary results.

- Overall survival data was not matured. There were only 4 deaths, two deaths in each group.

- The younger than 65 years old age group had a greater percentage increase in lumbar spine BMD as compared to that of age $\geq$ 65 years old group. Subjects in denosumab demonstrated percentage increases in lumbar spine BMD from baseline to month 1 throughout month 24.

- Prior chemotherapy group had a greater percentage change in lumbar spine BMD from baseline at month 12 than those subjects of the no prior chemotherapy group.

- Last menstrual period less than or equal to 5 years group had a greater percentage change in lumbar spine BMD as compare to that of the longer than 5 years group.

- The no prior selective estrogen receptor modulator (SERM) group had a greater percentage change in lumbar spine BMD than the prior SERM use group.

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- Subjects with weight 66-<75 kg and body mass index (BMI) 24-<26 kg/m^2 had the greatest percentage change and weight >85 kg and BMI ≥ 30 kg/m^2 had the least percentage change in lumbar spine BMD from baseline to month 12.

- Subjects with no osteoporosis criteria at baseline had a greater percentage change differences in the lumbar spine BMD from baseline to months 1, 3, 6, and 12 (but not month 24).

- Subjects with baseline vitamin D levels < 20 ng/mL had the greatest percentage change differences in lumbar spine BMD from baseline through months 24 compared to subjects with baseline vitamin D levels of 21-29 ng/mL and ≥ 30 ng/mL.

1.3.2 Advisory Committee Vote and Summary on Selected Questions

Questions and voting results of advisory committee meeting for reproductive health drugs held on August 13, 2009 are summarized below. The advisory committee meeting is for four BLA submissions, 125320, 125331, 125332 and 125333.

Question 1.a: Is there a population of postmenopausal women with osteoporosis in which the benefit of treatment with denosumab is likely to outweigh the risks? AC members vote: 15- yes, 0-No.

Question 2.a: Is there a population of postmenopausal women with low bone mineral density who do not meet the criteria for of osteoporosis in which the benefit of prevention of osteoporosis with denosumab is likely to outweigh the risks? AC members vote: 3- yes, 12-No.

Question 3.a: Is a favorable risk/benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors? AC members vote: 2- yes, 13-No.

Question 3.b: Is a favorable risk/benefit ratio demonstrated for denosumab for the prevention of bone loss associated with hormone ablation therapy in women with breast cancer receiving aromatase inhibitors? AC members vote: 0- yes, 14-No, 1-abstain.

Question 4.a: Is a favorable risk/benefit ratio demonstrated for denosumab for the treatment of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy? AC members vote: 9- yes, 4-No (all 3 oncologists voted No).)
Question 4.b: Is a favorable risk/benefit ratio demonstrated for denosumab for the prevention of bone loss associated with hormone ablation therapy in men with prostate cancer receiving androgen deprivation therapy? AC members vote: 3- yes, 11-No.

Question 6a: If approved, do you recommend that denosumab have a Risk Evaluation and Mitigation Strategy or REMS? AC members vote: 12- yes, 1-No.

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Summary of Committee Recommendation:

- Denosumab should be limited to PMO high risk patients (second-line).
- Denosumab should not be approved for PMO prevention.
- Denosumab should not be approved for treatment or prevention of bone loss in breast cancer population receiving aromatase inhibitors.
- Denosumab should be approved for treatment of bone loss in men with prostate cancer receiving androgen deprivation therapy.
- Denosumab should not be approved for prevention of bone loss in men with prostate cancer receiving androgen deprivation therapy.
- Denosumab should have a Risk Evaluation and Mitigation Strategy or REMS.

2. INTRODUCTION

2.1 Overview

Study 20040135 is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy of denosumab in subjects receiving adjuvant aromatase inhibitor therapy for nonmetastatic breast cancer.

The primary objective of the study was to determine whether denosumab, compared with placebo, preserved lumbar spine BMD during aromatase inhibitor therapy in subjects with nonmetastatic breast cancer after 12 months. Aromatase inhibitor therapy is believed to deplete estrogen in the body and increase the risk of osteoporosis. It is believed by the sponsor that bone mineral density status may be the most important factor in predicting fracture risk.

Subjects were randomized in a 1:1 ratio to receive either 60 mg denosumab or placebo subcutaneously once every 6 months for 24 months with a total of 4 injections. The stratification factor was duration of aromatase inhibitor therapy ($\leq$ 6 months versus > 6 months) at study entry. Subjects were followed for 24 months after the last dose of investigational product (ie., the 24-month safety follow-up period).

The enrolled subjects were women with low bone mass, BMD T-scores between -1.0 and -2.5, excluding women with osteoporosis and those with normal BMD.

There were 53 study centers in the United States and Canada. Two hundred and forty three subjects (96%) in 50 sites were enrolled from the United States and only 9 subjects (4%) in 3 sites were enrolled from Canada.

The first subject enrolled date was October 4, 2004 and the last subject completed 24-month treatment period and data cutoff date was May 11, 2007.

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BMDs for lumbar spine, hip (total hip, femoral neck, and trochanter), distal 1/3 radius, and total body were assessed by dual X-ray absorptiometry (DXA) at Months 1, 3, 6, 12 and 24 during the study. Two DXA machine types, Hologic and GE lunar, were used for BMD measurement.

An external data monitoring committee (DMC) monitored the study on an approximate semi-annual basis.

The primary endpoint was the percentage change in lumbar spine BMD from baseline to month 12. The secondary endpoints were the percentage change in lumbar spine BMD from baseline to month 6 and percentage changes in total hip and femoral neck BMD from baseline to months 6 and 12. The secondary efficacy endpoints analyses were contingent on rejection of the primary null hypothesis at a level of 0.05 (2-sided) and used the Hochberg procedure to adjust for multiplicity at level of 0.05.

2.2 Data Sources

The sponsor provided electronic datasets for this phase III Study 20040135. The data utilized for the review are as follows:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

This is a randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of denosumab for the preservation of lumbar spine BMD in women with nonmetastatic breast cancer who were receiving aromatase inhibitors.

The study included a treatment period (defined as baseline to month 24) and a safety follow-up period (defined as months 25 to 48). Subjects were randomized 1:1 to receive either 60 mg denosumab or placebo subcutaneously once every 6 months for 18 months (a total of 4 injections). Randomization was stratified by duration of aromatase inhibitor therapy ($\leq$ 6 months vs. > 6 months) at study entry. All subjects received supplemental calcium (1 gram/day) and vitamin D ($\geq$ 400 IU/day) during the study.

The primary analyses were conducted when all subjects had completed the 24-month treatment period and additional analyses will be conducted when all subjects have had the opportunity to complete their month-48 follow-up visit separately.

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Women with low bone mass, BMD T-scores between -1.0 and -2.5, were enrolled excluding women with osteoporosis and those with normal BMD for eligible criteria.

3.1.2 Study Endpoints

The primary efficacy endpoint is the percentage change in lumbar spine BMD from baseline to month 12.

Secondary endpoints are percentage change in lumbar spine BMD from baseline to month 6 and percentage changes in total hip and femoral neck BMD from baseline to months 6 and 12.

Safety endpoints are subject incidence of adverse events changes from baseline safety laboratory analyses at each visit, including 25(OH) vitamin D, serum chemistry, and hematology, subject incidence of anti-denosumab antibody formation by time point and at anytime during the study, changes in vital signs at each visit and serum denosumab levels at baseline and 1, 3, 6, 12, 15, 18, and 24 months.

Exploratory endpoints are percentage changes in lumbar spine, total hip, and femoral neck BMD from baseline to months 1, 3, and 24, percentage change in total body and distal 1/3 radius BMD from baseline to months 12 and 24, percentage change in trochanter BMD at months 1, 3, 6, 12, and 24, percentage change in serum CTX1 and serum P1NP from baseline to months 1, 6, 12, and 24, incidence rate of vertebral fractures and time to first nonvertebral fractures, including hip fractures and overall survival at month 24.

Primary efficacy analysis subset included all randomized subjects who had a nonmissing baseline and ≥ 1 nonmissing postbaseline evaluation at or prior to the time point under consideration according to their original randomized treatment assignment.

Per-protocol analysis set included subjects in the primary efficacy subset who were compliant with the protocol, as characterized by treatment compliance $\geq 50\%$ (received ≥ 2 doses of investigational product) and by the absence of deviations from the key entry criteria.

Full analysis subset included all randomized subjects according to their original randomized treatment assignment, regardless of the actual treatment received.

Safety subset included all randomized subjects who received at least one dose of investigational product according to their actual treatment received.

3.1.3 Statistical Methodologies

Sample Size Determination

The sample size of 166 subjects (83 subjects/group) provides at least 95% power to detect a 2% difference (SD = 3.5%) between the denosumab and the placebo groups in the percentage change

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from baseline in lumbar spine BMD after 12 months. The final analysis was performed at α= 0.05. Taking into account an expected loss to follow-up DXA assessment rate of 20% per year, the total of 208 subjects (104 subjects/group) was planned.

Analyses Methods

The primary analysis of the primary endpoint of percentage change from baseline to month 12 in lumbar spine BMD was based on an analysis of covariance (ANCOVA) model including treatment as the main effect and adjusting for duration of aromatase inhibitor therapy at study entry ($\leq$ 6 months vs. > 6 months), baseline BMD value, machine type (Hologic and GE lunar), and the interaction between baseline BMD and machine type as covariates. The point estimate for the least-squares mean and the 2-sided 95% confidence interval (CI) for the treatment difference (denosumab - placebo) at month 12 were used for primary conclusions for BMD efficacy in the final analysis. Missing 12-month BMD data were imputed using the last-observation-carried-forward (LOCF) method and missing baseline BMDs at any anatomical site were not imputed. Missing values were also imputed using mean of the other group (MOTH) values for sensitivity analyses.

The efficacy analyses of BMDs in different anatomical site (eg. femoral neck, total hip, total body, and 1/3 distal radius) used ANCOVA models with the last observation carried forward (LOCF) imputation as (the same method of that of primary endpoint).

Sponsor's sensitivity analyses for BMD endpoints were as follows;

1. Repeated measures model using no imputation of missing post-baseline measurements
2. An ANCOVA model using mean of the other group (MOTH)
   i. For a subject with missing post-baseline BMD value at an anatomical site at a particular time point, identify baseline characteristics of duration of AIT use ($\leq$ 6 months or > 6 months), age group (< 65 or $\geq$ 65), DXA machine type (hologic or lunar), and baseline BMD (< median or $\geq$ median)
   ii. The missing BMD value will be imputed by using the mean BMD value obtained from the same anatomical site at the same time point of those subjects in the other treatment group who match this subject's baseline characteristics.

   The baseline characteristics for MOTH imputation will be re-examined for appropriateness and may be re-categorized (due to small sample size) before unblinding the study.
3. An ANCOVA model using the per-protocol analysis set with no imputation
4. An ANCOVA model using actual strata rather than those used in the randomizattion (if > 5% error)

Statistical Changes in the Protocol Amendment:

There were 3 protocol amendments, June 18, 2004, October 17, 2005 and November 14, 2006. The statistical plan changes in the protocol amendments were as follows;

- The primary analysis model for all BMD endpoints was changed from a likelihood-based repeated-measures model to ANCOVA with LOCF in response to an FDA request for

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modification to the planned analyses for the primary endpoint and for consistency across denosumab studies.

- The percentage change in trochanter BMD at months 1, 3, 6, 12, and 24 was added as an exploratory endpoint.
- Age, baseline weight, and prior use of selective estrogen receptor modulators (SERM) were added as covariates; 4 previously specified covariates (prior estrogen use, prior tamoxifen use, alcohol consumption, and smoking history) were deleted.
- Three subgroup analyses (baseline BMI, baseline weight, and prior selective estrogen receptor modulator use), with clarification regarding how to categorize the subgroups, were added; subgroup analyses for safety endpoints were deleted.
- A sensitivity analysis to account for incorrect stratification was added.
- An analysis for overall survival was added.

Amendment 1 (June 18, 2004):
Patients with BMD T-scores > -1, (normal) and < -2.5 (osteoporotic) were excluded from the study because the results from a large, controlled clinical trial demonstrated that postmenopausal women with BMD T-scores ≥ -1.5 did not experience rapid bone loss after treatment with anastrozole and women with low bone mass may require active treatment in addition to calcium and vitamin D supplements.

Amendment 2 (October 17, 2005);
The BMD eligibility criteria were revised to clarify that only 1 of the 3 bone regions tested (lumbar spine, total hip, and femoral neck) must have had a BMD T-score between -1.0 and -2.5 and that patients with a BMD T-score < -2.5 in any of these 3 regions were ineligible for the study.

Amendment 3 (November 14, 2006);
A 24-month safety follow-up period was added, increasing the total study duration from 24 to 48 months.

The changes in Protocol Specified Analysis;

- Statistical testing of the fracture endpoints was not performed because of the small number of subjects who had fractures.

- Statistical testing of the overall survival endpoint and time-to-survival analyses were not performed because of the small number of subjects who died.

- Ad hoc analyses were conducted to summarize the proportion of subjects with a > 3% change from baseline in BMD and the proportion of subjects with a ≤ 0%, 0% to 3%, and > 3% change from baseline in BMD at month 24 at femoral neck, total hip, and lumbar spine.

- A subgroup analysis of the primary endpoint for time since last menstrual period was added.

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3.1.4 Study Results

The study start date was October 4, 2004. First subject enrolled and the study end date and last subject completed 24-month treatment period was May 11, 2007.

Total of 252 subjects were randomized, 127 subjects to denosumab and 125 subjects to placebo, 243 subjects (96%) at 50 study centers in United States and 9 subjects (4%) at 3 study centers in Canada.

Among 252 subjects, 249 subjects (125 denosumab, 124 placebo) received at least 1 dose of investigational product. Subject disposition and investigational product completion are summarized in Table 1 below.

Table 1 Subject Disposition and Investigational Product Completion (Randomized Subjects)

	Placebo (N = 125) n(%)	Denosumab 60 mg Q6M (N = 127) n(%)	All (N = 252) n(%)
Completed 24 months of study	99 (79)	106 (83)	205 (81)
Completed IP	96 (77)	101 (80)	197 (78)
Discontinued IP	3 (2)	5 (4)	8 (3)
Discontinued prior to 24 months of study	26 (21)	21 (17)	47 (19)
Completed IP	2 (2)	1 (1)	3 (1)
Discontinued IP	23 (18)	18 (14)	41 (16)
Never received IP	1 (1)	2 (2)	3 (1)

One hundred and six subjects (83%) in the denosumab group and 99 subjects (79%) in the placebo group completed the 24-month treatment period. Subject discontinuation is summarized in Table 2 below.

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Table 2 Reason for Study Discontinuation (Randomized Subjects)

	Placebo (N = 125) n (%)	Denosumab 60 mg Q6M (N = 127) n (%)	All (N = 252) n (%)
Completed study	99 (79)	106 (83)	205 (81)
Discontinued study	26 (21)	21 (17)	47 (19)
Ineligibility determined	4 (3)	4 (3)	8 (3)
Protocol deviation	0 (0)	0 (0)	0 (0)
Noncompliance	4 (3)	2 (2)	6 (2)
Adverse event	2 (2)	0 (0)	2 (1)
Consent withdrawn	9 (7)	11 (9)	20 (8)
Disease progression	3 (2)	1 (1)	4 (2)
Requirement for alternative therapy	0 (0)	0 (0)	0 (0)
Administrative decision	0 (0)	0 (0)	0 (0)
Lost to follow-up	3 (2)	0 (0)	3 (1)
Death	0 (0)	1 (1)	1 (0)
Pregnancy	0 (0)	0 (0)	0 (0)
Other	1 (1)	2 (2)	3 (1)

Consent withdrawn was the most common reason to discontinued study, 11 subjects (9%) from denosumab and 9 subjects (7%) from placebo. Six subjects (2 denosumab, 4 placebo) did not receive the treatment to which they had been randomized. Baseline demographics are summarized in Table 3 below.

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Table 3 Baseline Demographic (All Randomized Subjects)

	Placebo (N=125) n(%)	Denosumab 60 mg Q6M (N=127)	All (N=252)
Ethnic group / race - n (%)			
White or Caucasian	119 (95)	116 (91)	235 (93)
Black or African American	1 (1)	1 (1)	2 (1)
Hispanic or Latino	3 (2)	5 (4)	8 (3)
Asian	1 (1)	2 (2)	3 (1)
American Indian or Alaska Native	0 (0)	1 (1)	1 (0)
Native Hawaiian or Other Pacific Islander	1 (1)	0 (0)	1 (0)
Other	0 (0)	2 (2)	2 (1)
Age (years)			
Mean (SD)	59.7 (9.7)	59.2 (8.9)	59.5 (9.3)
Median	60.0	59.0	59.0
Q1, Q3	52.0, 67.0	52.0, 65.0	52.0, 66.0
Min, Max	35, 81	38, 84	35, 84
Age group - n (%)			
35 - < 45 years	4 (3)	1 (1)	5 (2)
45 - < 55 years	37 (30)	40 (31)	77 (31)
55 - < 65 years	43 (34)	51 (40)	94 (37)
65 - < 75 years	32 (26)	29 (23)	61 (24)
≥ 75 years	9 (7)	6 (5)	15 (6)
Geriatric age group - n (%)			
≥ 65 years	41 (33)	35 (28)	76 (30)
≥ 75 years	9 (7)	6 (5)	15 (6)
Years from last menstrual period - n (%)			
< 5 years	33 (26)	34 (27)	67 (27)
5 - 10 years	29 (23)	29 (23)	58 (23)
> 10 years	63 (50)	63 (50)	126 (50)
Unknown	0 (0)	1 (1)	1 (0)
Years from last menstrual period	125	126	251
Mean (SD)	13.1 (10.3)	12.8 (10.8)	12.9 (10.5)
Median	10.6	10.2	10.6
Q1, Q3	4.6, 20.7	3.9, 19.3	4.3, 19.8
Min, Max	1, 48	0, 48	0, 48
Duration of aromatase inhibitor therapy			
≤ 6 months	46 (37)	47 (37), 43 (34)	93 (37), 89 (35)
> 6 months	79 (63)	80 (63), 84 (66)	159 (63),163(65)

Actual verified number.

A median age was 59 years old. About 93% of the subjects were White or Caucasian. The baseline demographic characteristics were balanced between the two treatment groups.

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Fourteen subjects (6%) were assigned to the incorrect stratum: 4 subjects in the denosumab group to the ≤ 6 months of aromatase inhibitor therapy stratum, 5 subjects in the placebo group to the ≤ 6 months of aromatase inhibitor stratum, and 5 subjects in the placebo group to the > 6 months of aromatase inhibitor therapy stratum.

Breast cancer disease history is summarized in Table 4.

Table 4 Breast Cancer Disease History (All Randomized Subjects)

	Placebo (N=125) n (%)	Denosumab 60 mg Q6M (N=127) n (%)	All (N=252) n (%)
ECOG at study entry			
0	105 (84)	114 (90)	219 (87)
1	14 (11)	13 (10)	27 (11)
Unknown	6 (5)	0 (0)	6 (2)
Time from initial diagnosis			
< 2 years	55 (44)	51 (40)	106 (42)
2 - < 5 years	40 (32)	41 (32)	81 (32)
5 - < 10 years	26 (21)	34 (27)	60 (24)
≥ 10 years	4 (3)	1 (1)	5 (2)
Primary tumor			
T0	2 (2)	0 (0)	2 (1)
T1	72 (58)	71 (56)	143 (57)
T2	42 (34)	45 (35)	87 (35)
T3	7 (6)	11 (9)	18 (7)
T4	2 (2)	0 (0)	2 (1)
Regional lymph node			
N0	73 (58)	84 (66)	157 (62)
N1	46 (37)	36 (28)	82 (33)
N2	6 (5)	6 (5)	12 (5)
N3	0 (0)	1 (1)	1 (0)
Distant metastasis at diagnosis			
No	125 (100)	127 (100)	252 (100)
Disease stage at initial diagnosis			
I	53 (42)	55 (43)	108 (43)
IIA	37 (30)	42 (33)	79 (31)
IIB	24 (19)	17 (13)	41 (16)
IIIA	9 (7)	12 (9)	21 (8)
IIIB	2 (2)	0 (0)	2 (1)
IIIC	0 (0)	1 (1)	1 (0)

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There was little difference in the breast cancer disease history (ECOG, time from initial diagnosis, regional lymph node and disease stage at initial diagnosis) between the two treatment groups.

Table 5 Prior Cancer Treatment and Bisphosphonate Use (All Randomized Subjects)

	Placebo (N=125) n (%)	Denosumab 60 mg Q6M (N=127) n (%)	All (N=252) n (%)
Prior chemotherapy			
Yes	78 (62)	83 (65)	161 (64)
No	47 (38)	44 (35)	91 (36)
Prior hormone regimens excluding AIT			
Yes	56 (45)	63 (50)	119 (47)
No	69 (55)	64 (50)	133 (53)
Prior adjuvant radiotherapy			
Yes	82 (66)	84 (66)	166 (66)
No	43 (34)	43 (34)	86 (34)
Prior anti-neoadjuvant surgery			
Yes	123 (98)	126 (99)	249 (99)
No	2 (2)	1 (1)	3 (1)
Prior selective estrogen receptor modulator			
Yes	53 (42)	60 (47)	113 (45)
No	72 (58)	67 (53)	139 (55)
Prior Tamoxifen treatment			
Yes	53 (42)	60 (47)	113 (45)
No	72 (58)	67 (53)	139 (55)
Prior oral bisphosphonate			
Yes	7 (6)	3 (2)	10 (4)
No	118 (94)	124 (98)	242 (96)
Prior IV bisphosphonate			
No	125 (100)	127 (100)	252 (100)
Actual duration of AIT >6 months			
Yes	79 (63)	84 (66)	163 (65)
No	46 (37)	43 (34)	89 (35)

The majority of subjects (65% denosumab, 62% placebo) had received prior chemotherapy and 50% in the denosumab group and 45% of subjects in the placebo group had received prior hormonal therapy (excluding aromatase inhibitor therapy). The majority of subjects (66% of in both groups) had received prior adjuvant radiotherapy and almost all subjects in both groups (99% denosumab, 98% placebo) had undergone prior surgery for cancer. No subject had received prior IV bisphosphonates. Only 4% received prior oral bisphosphonate (6% placebo,

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2% denosumab). Prior cancer treatment and bisphosphonate use at enrollment were balanced across treatment groups.

Table 6 Baseline Bone Mineral Density T-Scores

	n	Mean	SD	Min	Q1	Median	Q3	Max
Lumbar spine								
Placebo (N=125)	125	-0.98	0.93	-2.9	-1.60	-1.20	-0.50	2.6
Denosumab 60 mg Q6M (N=127)	127	-1.13	0.87	-3.8	-1.70	-1.20	-0.60	1.9
All (N=252)	252	-1.06	0.90	-3.8	-1.70	-1.20	-0.60	2.6
Total hip								
Placebo (N=125)	125	-0.88	0.68	-2.4	-1.30	-0.80	-0.40	0.8
Denosumab 60 mg Q6M (N=127)	126	-1.02	0.63	-2.4	-1.50	-1.00	-0.50	0.9
All (N=252)	251	-0.95	0.66	-2.4	-1.40	-0.90	-0.50	0.9
Femoral neck								
Placebo (N=125)	125	-1.20	0.66	-3.0	-1.60	-1.20	-0.70	0.7
Denosumab 60 mg Q6M (N=127)	126	-1.33	0.66	-2.6	-1.70	-1.30	-1.00	1.2
All (N=252)	251	-1.27	0.66	-3.0	-1.70	-1.30	-0.90	1.2
Trochanter								
Placebo (N=125)	125	-0.67	0.72	-2.3	-1.10	-0.70	-0.20	1.1
Denosumab 60 mg Q6M (N=127)	126	-0.86	0.71	-2.3	-1.40	-0.90	-0.40	1.3
All (N=252)	251	-0.77	0.72	-2.3	-1.20	-0.80	-0.30	1.3
Distal 1/3 radius								
Placebo (N=125)	124	-1.93	1.45	-4.4	-3.00	-2.40	-0.70	1.8
Denosumab 60 mg Q6M (N=127)	126	-2.18	1.20	-5.0	-2.90	-2.45	-1.60	1.5
All (N=252)	250	-2.06	1.34	-5.0	-3.00	-2.40	-1.40	1.8
Ultradistal radius								
Placebo (N=125)	124	-2.36	1.50	-5.0	-3.50	-2.45	-1.30	1.0
Denosumab 60 mg Q6M (N=127)	126	-2.43	1.31	-5.6	-3.50	-2.50	-1.50	0.8
All (N=252)	250	-2.40	1.40	-5.6	-3.50	-2.50	-1.40	1.0
Total radius								
Placebo (N=125)	46	-0.77	1.21	-3.6	-1.60	-0.75	0.00	1.7
Denosumab 60 mg Q6M (N=127)	39	-1.05	0.94	-3.0	-1.80	-1.10	-0.40	1.0
All (N=252)	85	-0.90	1.10	-3.6	-1.70	-0.90	-0.20	1.7

All bone mineral density T-scores were better for placebo than denosumab in the baseline BMD T-scores.

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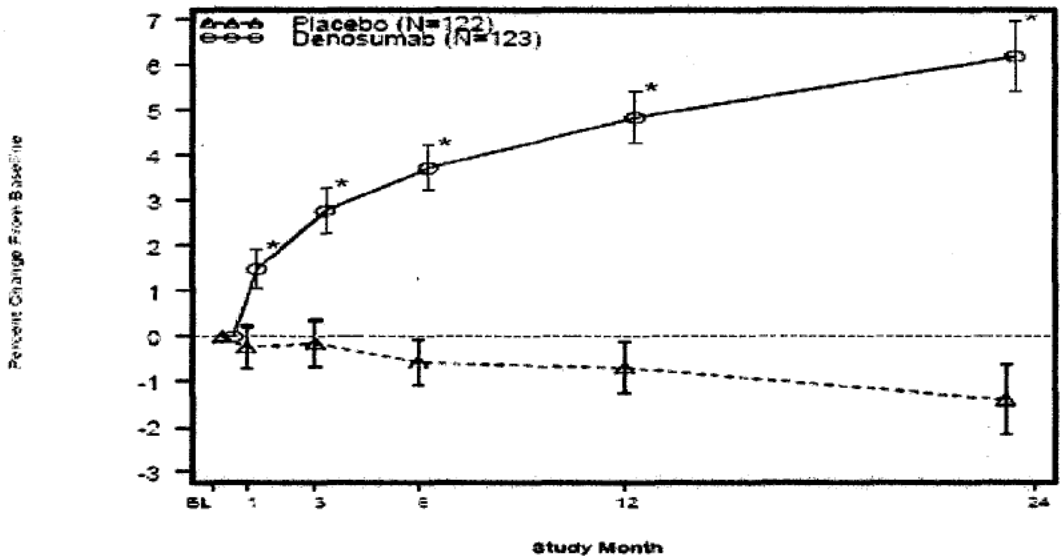
Sponsor's Efficacy Results

Table 7 Sponsor's Primary Efficacy Results

	Placebo		Denosumab 60 mg Q6M		Difference		
	n/N	Estimate	n/N	Estimate	Estimate	95% CI	p-value
Lumbar Spine Bone Mineral Density Percentage change From Baseline at Month 12[a]							
	122/122	-0.7	123/123	4.8	5.5	(4.8, 6.3)	<0.0001

a: Based on ANCOVA model adjusting for stratification variable, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction.

Figure 1 Lumbar Spine BMD Percentage Change From Baseline – Least squares Means and Confidence Intervals (LOCF Imputation, Primary Efficacy Subset)



Lumbar spine bone mineral density increased by 4.8% in denosumab and decreased by 0.7% in placebo, the percentage change difference between denosumab and placebo from baseline to month 12 was 5.5% (95% CI: 4.8, 6.3) (p<0.0001).

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Table 8 Sponsor's Secondary Efficacy Results

	Placebo		Denosumab 60 mg Q6M		Difference		
	n/N	Estimate	n/N	Estimate	Estimate	95% CI	p-value
Lumbar Spine Bone Mineral Density Percentage change From Baseline at Month 6							
	122/122	-0.6	123/123	3.7	4.3	(3.6, 5.0)	<0.0001
Total Hip Bone Mineral Density Percentage change From Baseline at Month 6 a							
	122/122	-0.4	123/123	2.3	2.7	(2.1, 3.3)	<0.0001
Femoral Neck Bone Mineral Density Percentage change From Baseline at Month 6[a]							
	122/122	-0.9	123/123	1.2	2.1	(1.3, 2.9)	<0.0001
Total Hip Bone Mineral Density Percentage change From Baseline at Month 12 [a]							
	122 /122	-0.7	123/123	3.1	3.7	(3.1, 4.4)	<0.0001
Femoral Neck Bone Mineral Density Percentage change From Baseline at Month 12[a]							
	122/122	-0.6	123/123	1.9	2.5	(1.6, 3.3)	<0.0001

a Based on ANCOVA model adjusting for treatment, stratification variable, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction. P-values for all secondary endpoints are adjusted with Hochberg's procedure for multiple comparisons.

The secondary endpoint, lumbar spine bone mineral density increased by 3.7% in denosumab and decreased by 0.6% in placebo from baseline to month 6, the percentage change difference between denosumab and placebo from baseline to month 6 was 4.3% (95% CI:3.6, 5.0) at month 6 ($p<0.0001$).

Secondary endpoints, total hip and femoral neck increased by 2.3 % and 1.2 %, respectively, in denosumab and decreased by 0.4 % and 0.9 %, respectively, in placebo from baseline to month 6, the percentage change differences between denosumab and placebo from baseline to month 6 were 2.7% (95% CI: 2.1, 3.3) and 2.1% (95% CI:1.3, 2.9), respectively (both $p<0.0001$).

Secondary endpoints, total hip and femoral neck BMDs increased by 3.1% and 1.9%, respectively, in denosumab and decreased by 0.7% and 0.6%, respectively, in placebo from baseline to 1 year, the percentage change differences between denosumab and placebo from baseline to month 12 were 3.7 % (95% CI: 3.1, 4.4) and 2.5 % (95% CI: 1.6, 3.3), respectively (both $p <0.0001$).

The sponsor performed sensitivity analyses and sponsor's sensitivity analyses are as follows;

1. ANCOVA model using mean of the other group (MOTH) imputation for missing 12-month BMD values
2. ANCOVA model using per protocol analysis
3. ANCOVA model with LOCF imputation using the actual strata rather than the as-randomized
4. A likelihood-based repeated-measures model

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Table 9 Sensitivity Analyses for Lumbar Spine Bone Mineral Density Percentage change From Baseline at Month 12

		% Change From Baseline		Difference from Placebo		
	n	LS mean	95% CI	LS Mean	95% CI	p-value
1. MOTH						
Placebo	122	0.1	(-0.7, 0.9)			
Denosumab 60 mg Q6M	123	4.3	(3.6, 5.1)	4.3	(3.2, 5.3)	<0.0001
2. Per protocol						
Placebo	99	-0.8	(-1.5, -0.2)			
Denosumab 60 mg Q6M	107	4.9	(4.3, 5.5)	5.8	(4.9, 6.6)	<0.0001
3. LOCF using actual strata						
Placebo	122	0.1	(-0.7, 0.9)			
Denosumab 60 mg Q6M	123	4.3	(3.6, 5.1)	4.3	(3.2, 5.3)	<0.0001
4. Repeated-measures model						
Placebo	103	-0.757	(-1.354, -0.159)			
Denosumab 60 mg Q6M	112	4.927	(4.350, 5.503)	5.683	(4.873, 6.494)	<0.0001

Number of subjects who had a non-missing baseline and at least 1 non-missing post-baseline data.: N = 122 for Placebo and N=123 for Denosumab; LS = Least squaress.
aBased on ANCOVA model adjusting for treatment, stratification variable, baseline BMD value, machine type, and baseline BMD value by- machine type interaction.

Sensitivity analyses for lumbar spine BMD percentage change from baseline to month 12 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Sensitivity analyses for secondary efficacy endpoints were performed. Results of sensitivity analyses for lumbar spine, total hip, and femoral neck BMDs percentage changes from baseline to month 6 and for total hip and femoral neck BMDs percentage changes from baseline to month 12 are summarized in Tables 10, 11, 12, 13, and 14 below.

Reference ID: 3168397

Table 10 Sensitivity Analyses for Lumbar Spine Bone Mineral Density Percentage Change From Baseline at Month 6

		% Change From Baseline		Difference from Placebo		
	n	LS mean	95% CI	LS Mean	95% CI	p-value
1. MOTH						
Placebo	122	-0.4	(-1.0, -0.3)			
Denosumab 60 mg Q6M	123	3.5	(2.8, 4.1)	3.8	(3.0, 4.7)	<0.0001
2. Per protocol						
Placebo	107	-0.7	(-1.3, -0.2)			
Denosumab 60 mg Q6M	112	3.7	(3.2, 4.2)	4.4	(3.7, 5.2)	<0.0001
3. LOCF using actual strata						
Placebo	122	-0.6	(-1.1, 0.0)			
Denosumab 60 mg Q6M	123	3.7	(3.2, 4.2)	4.3	(3.6, 5.0)	<0.0001
4. Repeated-measures model						
Placebo	113	-0.663	(-1.181, -0.146)			
Denosumab 60 mg Q6M	119	3.665	(3.161, 4.169)	4.328	(3.628, 5.028)	<0.0001

Sensitivity analyses for lumbar spine BMD percentage change from baseline to month 6 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Table 11 Sensitivity Analyses for Total Hip Bone Mineral Density Percentage Change From Baseline at Month 6

		% Change From Baseline		Difference from Placebo		
	n	LS mean	95% CI	LS Mean	95% CI	p-value
1. MOTH						
Placebo	122	-0.1	(-0.6, 0.4)			
Denosumab 60 mg Q6M	123	2.2	(1.7, 2.8)	2.3	(1.6, 3.1)	<0.0001
2. Per protocol						
Placebo	106	-0.5	(-0.9, 0.0)			
Denosumab 60 mg Q6M	111	2.6	(2.1, 3.0)	3.0	(2.4, 3.6)	<0.0001
3. LOCF using actual strata						
Placebo	122	-0.4	(-0.8, 0.1)			
Denosumab 60 mg Q6M	123	2.3	(1.9, 2.8)	2.7	(2.1, 3.3)	<0.0001

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4. Repeated-measures model						
Placebo	112	-0.416	(-0.854, 0.022)			
Denosumab 60 mg Q6M	118	2.402	(1.965, 2.839)	2.818	(2.209, 3.427)	<0.0001

Per protocol N=110 for placebo and N=115 for denosumab

Sensitivity analyses for total hip BMD percentage change from baseline to month 6 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Table 12 Sensitivity Analyses for Femoral Neck Bone Mineral Density Percentage Change From Baseline at Month 6

		% Change From Baseline		Difference from Placebo		
	n	LS mean	95% CI	LS Mean	95% CI	p-value
1. MOTH						
Placebo	122	-1.2	(-1.9, -0.4)			
Denosumab 60 mg Q6M	123	0.9	(0.1, 1.6)	2.0	(1.1, 2.9)	<0.0001
2. Per protocol						
Placebo	106	-1.1	(-1.8, -0.4)			
Denosumab 60 mg Q6M	111	1.4	(0.7, 2.0)	2.5	(1.7, 3.3)	<0.0001
3. LOCF using actual strata						
Placebo	122	-0.8	(-1.5, -0.1)			
Denosumab 60 mg Q6M	123	1.2	(0.5, 1.9)	2.0	(1.2, 2.8)	<0.0001
4. Repeated-measures model						
Placebo	112	-0.890	(-1.529, -0.251)			
Denosumab 60 mg Q6M	118	1.427	(0.807, 2.047)	2.317	(1.542, 3.093)	<0.0001

Per protocol N=110 for placebo and N=115 for denosumab

Sensitivity analyses for femoral neck BMD percentage change from baseline to month 6 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Reference ID: 3168397

Table 13 Sensitivity Analyses for Total Hip Bone Mineral Density Percentage Change From Baseline at Month 12

		% Change From Baseline		Difference from Placebo		
	n	LS mean	95% CI	LS Mean	95% CI	p-value
1. MOTH						
Placebo	121	0.2	(-0.4, 0.8)			
Denosumab 60 mg Q6M	123	2.9	(2.3, 3.6)	2.8	(1.9, 3.6)	<0.0001
2. Per protocol						
Placebo	97	-0.8	(-1.3, -0.3)			
Denosumab 60 mg Q6M	106	3.3	(2.8, 3.8)	4.1	(3.4, 4.7)	<0.0001
3. LOCF using actual strata						
Placebo	122	-0.7	(-1.1, -0.2)			
Denosumab 60 mg Q6M	123	3.1	(2.6, 3.5)	3.7	(3.0, 4.4)	<0.0001
4. Repeated-measures model						
Placebo	101	-0.718	(-1.181, -0.254)			
Denosumab 60 mg Q6M	111	3.116	(2.660, 3.572)	3.834	(3.193, 4.475)	<0.0001

Per protocol N=110 for placebo and N=115 for denosumab

Sensitivity analyses for total hip BMD percentage change from baseline to month 12 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Table 14 Sensitivity Analyses for Femoral Neck Bone Mineral Density Percentage Change From Baseline at Month 12

		% Change From Baseline		Difference from Placebo		
	n	LS mean	95% CI	LS Mean	95% CI	p-value
1. MOTH						
Placebo	121	-0.4	(-1.4, 0.5)			
Denosumab 60 mg Q6M	123	1.3	(0.4, 2.3)	1.8	(0.7, 2.9)	0.0011
2. Per protocol						
Placebo	97	-0.8	(-1.6, 0.0)			
Denosumab 60 mg Q6M	106	2.1	(1.3, 2.8)	2.9	(2.0, 3.8)	<0.0001
3. LOCF using actual strata						
Placebo	122	-0.6	(-1.4, 0.2)			
Denosumab 60 mg Q6M	123	1.8	(1.1, 2.6)	2.4	(1.6, 3.3)	<0.0001

Reference ID: 3168397

4. Repeated-measures model						
Placebo	101	-0.915	(-1.615, -0.215)			
Denosumab 60 mg Q6M	111	1.828	(1.055, 2.500)	2.642	(1.777, 3.508)	<0.0001

Sensitivity analyses for femoral neck BMD percentage change from baseline to month 12 demonstrated a significant increase in the denosumab group as compared to the placebo group.

Sensitivity analyses results were consistent to the primary analysis results.

Fracture Endpoints-Exploratory Endpoints

Eight subjects (6%) in the denosumab group and 8 subjects (6%) in the placebo group had nonveterbral fracture events. Kaplan-Meier estimates of the risk of nonvertebral fracture were 3.3% for the denosumab group and 3.5% for the placebo group at month 12 and 7.2% for both treatment groups at month 24. No vertebral fractures were reported during the 24-month treatment period.

Overall survival Analysis

The overall survival analysis was not performed because there were only two deaths (one of each group).

Summary of Efficacy Results

- Denosumab demonstrated a significant percentage change in lumbar spine BMD from baseline to Month 12.
- Denosumab demonstrated a significant percentage change in lumbar spine BMD from baseline to Month 6.
- Denosumab demonstrated significant percentage changes in total hip and femoral neck BMDs from baseline to Months 6, and 12.
- All sensitivity analyses for BMD efficacy endpoints were consistent to the primary analysis results.
- Meaningful fracture endpoints analyses could not be performed because of small events.
- A meaningful overall survival analysis could not be performed due to small number of death events.

Reviewer's Analyses

Among 252 randomized subjects, 245 subjects were involved in the efficacy population (122 subjects from the placebo group and 123 subjects from the denosumab group) had at least one postbaseline values. The number of subjects who missed lumbar BMD from month 1 through 24 is summarized Table 15 below.

Reference ID: 3168397

Table 15 Number of missing lumbar spine BMD by visit

	Month 1 n(%)	Month 3 n(%)	Month 6 n(%)	Month 12 n(%)	Month 24 n(%)	Total
Denosumab	4 (3.3)	7 (5.7)	4 (3.3)	11 (9.0)	18 (14.8)	122
Placebo	3 (2.4)	3 (2.4)	9 (7.3)	19 (15.4)	23 (18.7)	123
Total	7 (2.9)	10 (4.1)	13 (5.3)	30 (12.2)	41 (16.7)	245

There were missing lumbar spine BMDs, 12%, and 17 % at months 12 and 24. The placebo group had 4% to 6% more missing lumbar spine BMDs than that of the denosumab group.

Lumbar spine mean BMD T-scores and percentage changes from baseline are summarized in Table 16 by visit.

Table 16 Mean Lumbar Spine BMD and Percentage Change from Baseline BMD

	Placebo (N=125)			Denosumab (N=127)		
	Mean (SD)	N	%Change (SD)	Mean (SD)	N	%Change (SD)
Lumbar Spine						
Baseline	1.017 (0.124)	125		1.007 (0.113)	127	
Month 1	1.015 (0.123)	119	-0.353 (2.350)	1.023 (0.108)	119	1.456 (2.341)
Month 3	1.017 (0.125)	122	-0.122 (2.698)	1.039 (0.106)	116	2.850 (2.708)
Month 6	1.011 (0.122)	113	-0.793 (2.875)	1.042 (0.116)	119	3.607 (2.522)
Month12	1.008 (0.125)	103	-0.890 (3.132)	1.054 (0.116)	112	4.840 (3.040)
Month 24	1.006 (0.137)	99	-1.405 (4.411)	1.071 (0.120)	105	6.505 (3.995)

Mean changes of lumbar spine BMD T-score from baseline to months 12 and 24 were -0.009 and -0.011 in the placebo group and 0.047 and 0.064 in the denosumab group, respectively. The mean percentage changes from baseline to months 12 and 24 were -0.890 % and -1.405 % in the placebo group and 4.840 % and 6.505 % in the denosumab group.

Baseline lumbar spine BMD values were imputed for missing lumbar spine BMDs both placebo and denosumab for a sensitivity analysis by this reviewer. The results are summarized Table 17 below.

Table 17 Least squares Means for Percentage change from Baseline for Lumbar Spine BMD using BOCF (BMD population)

	N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	245	-0.348	1.338	1.686	(1.10, 2.27)	<.0001
Month 3	245	-0.182	2.551	2.733	(2.05, 3.41)	<.0001
Month 6	245	-0.584	3.612	4.195	(3.52, 4.87)	<.0001
Month 12	245	-0.617	4.462	5.079	(4.31, 5.85)	<.0001
Month 24	246	-1.181	5.522	6.703	(5.63, 7.77)	<.0001

Reference ID: 3168397

Sensitivity analysis results using baseline observations carried forward imputation method provided consistent results to the primary analysis.

For a worst case sensitivity analysis, this reviewer performed a sensitivity analysis by imputing baseline values for missing lumbar spine BMD values if subjects' last lumbar spine BMD values were decreased, otherwise imputing last observation carried forward lumbar spine BMD values in the placebo group and by imputing baseline values if subjects' last lumbar spine values were increased from the baseline value, otherwise imputing the last observation carried forward values in the denosumab group. The worst case sensitivity analysis results are summarized in Table 18 below.

Table 18 Least squares Means for Percentage change from Baseline for Lumbar Spine BMD with a worst case sensitivity analysis

	N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	245	-0.348	1.338	1.686	(1.10, 2.27)	<.0001
Month 3	245	-0.167	2.554	2.721	(2.04, 3.40)	<.0001
Month 6	245	-0.532	3.598	4.130	(3.45, 4.81)	<.0001
Month 12	245	-0.500	4.442	4.941	(4.16, 5.72)	<.0001
Month 24	245	-1.054	5.503	6.557	(5.48, 7.63)	<.0001

Sensitivity analysis results using the worst case imputation method were consistent to the primary analysis results.

The number of subjects whose BMD scores increase, same, or decrease compared to that of baseline by visit months are summarized Table 19 below.

Table 19 Number of Subjects' Lumbar Spine BMD values Increase, Same or Decrease from Baseline Lumbar Spine Value by Visit

From Baseline	Month1	Month3	Month 6	Month 12	Month24
Denosumab					
N	123	123	128	124	123
Increase	91 (74.0)	93 (75.6)	116 (90.6)	110 (88.7)	100 (81.3)
Same	3 (2.4)	2 (1.6)	0	0	0
Decrease	29 (23.6)	28 (22.8)	12 (9.4)	14 (11.3)	23 (18.7)
Placebo					
N	122	124	122	122	123
Increase	46 (37.7)	55 (25.6)	45 (36.9)	36 (29.5)	33 (26.8)
Same	**2 (1.6)**	**3(2.3)**	**3 (2.3)**	**1 (0.8)**	**1 (0.8)**
Decrease	74 (60.7)	66 (53.2)	74 (60.7)	85 (69.7)	89 (72.4)

Reference ID: 3168397

The number of subjects whose BMD scores decreased as compared to that of the baseline BMD scores was greater in the placebo group than in the denosumab group for 2 years.

Total hip mean BMD T-scores and percentage changes from baseline BMD are summarized in Table 20 by visit.

Table 20 Mean Total Hip BMD and Percentage Change from Baseline BMD

	Placebo (N=125)			Denosumab (N=127)		
	Mean (SD)	N	%Change (SD)	Mean (SD)	N	%Change (SD)
Total Hip						
Baseline	0.873 (0.086)	122		0.859 (0.084)	123	
Month 1	0.874 (0.087)	117	0.069 (1.738)	0.866 (0.086)	118	0.622 (2.321)
Month 3	0.872 (0.087)	118	-0.115 (2.118)	0.877 (0.085)	117	1.966 (2.218)
Month 6	0.868 (0.086)	112	-0.456 (2.053)	0.880 (0.087)	118	2.492 (2.479)
Month12	0.866 (0.088)	101	-0.770 (2.299)	0.887 (0.087)	111	3.214 (2.334)
Month 24	0.865 (0.084)	95	-1.120 (2.523)	0.900 (0.090)	101	4.089 (2.725)

Mean changes of total hip BMD T-scores from baseline to months 12 and 24 were -0.007 and -0.008 in the placebo group and 0.028 and 0.031 in the denosumab group. The mean percentage changes from baseline to months 12 and 24 were -0.770 % and -1.120 % in the placebo group and 3.214 % and 4.089 % in the denosumab group.

Baseline total hip BMD values were imputed for missing total hip BMDs both placebo and denosumab for a sensitivity analysis by this reviewer. The results are summarized Table 21 below.

Table 21 Least squares Means of Percentage Change in Total Hip BMD from Baseline through Month 24 with Baseline Observation Carried Forward Imputation: Sensitivity Analysis

	N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	245	0.063	0.564	0.501	(-0.01, 1.02)	0.056
Month 3	245	-0.057	1.914	1.972	(1.42, 2.52)	<.0001
Month 6	245	-0.440	2.377	2.817	(2.25, 3.39)	<.0001
Month 12	245	-0.719	2.839	3.559	(2.98, 4.13)	<.0001
Month 24	245	-0.946	3.256	4.202	(3.53, 4.87)	<.0001

Sensitivity analysis results using baseline observation carried forward imputation provided consistent results to the primary analysis.

Sensitivity analysis results using a worst case imputation are summarized in Table 22 below.

Reference ID: 3168397

Table 22 Least squares Means of Percentage Change in Total Hip BMD from Baseline through Month 24 with a Worst Case Imputation Method: Sensitivity Analysis

	N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	245	0.063	0.564	0.501	(-0.01, 1.02)	0.056
Month 3	245	-0.025	1.803	1.828	(1.23, 2.43)	<.0001
Month 6	245	-0.365	2.272	2.637	(2.01, 3.27)	<.0001
Month 12	245	-0.647	2.697	3.345	(2.71, 3.98)	<.0001
Month 24	245	-0.816	3.108	3.924	(3.19, 4.66)	<.0001

Sensitivity analysis results using the worst case imputation method provided consistent results to the primary analysis.

Table 23 Mean Femoral Neck BMD and Percentage Change in Femoral Neck BMD from Baseline BMD through Month 24

	Placebo (N=125)			Denosumab (N=127)		
	Mean (SD)	N	%Change (SD)	Mean (SD)	N	%Change (SD)
Femoral Neck						
Baseline	0.793 (0.108)	122		0.783 (0.104)	123	
Month 1	0.795 (0.111)	117	-0.004 (3.293)	0.788 (0.103)	118	0.358 (2.694)
Month 3	0.793 (0.111)	118	0.171 (3.947)	0.797 (0.104)	117	1.470 (3.021)
Month 6	0.785 (0.108)	112	-0.717 (3.153)	0.797 (0.105)	118	1.693 (2.860)
Month12	0.785 (0.107)	101	-0.770 (3.494)	0.803 (0.109)	111	2.146 (2.985)
Month 24	0.782 (0.109)	95	-1.300 (3.758)	0.812 (0.111)	101	3.111 (3.025)

Mean changes of femoral neck BMD T-score from baseline to months 12 and 24 were -0.008 and -0.011 in the placebo group and 0.020 and 0.029 in the denosumab group. The mean percentage changes from baseline to months 12 and 24 were -0.770 % and -1.300 % in the placebo group and 2.146 % and 3.111 % in the denosumab group.

Sensitivity analysis results for imputing baseline BMD values for the missing femoral neck BMD values are summarized in Table 24 below.

Table 24 Least squares Means of Percentage Change in Femoral Neck BMD from Baseline through Month 24 with Baseline Observation Carried Forward Imputation: Sensitivity Analysis

	N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	245	-0.526	-0.251	0.275	(-0.47, 1.02)	0.466
Month 3	245	-0.233	0.841	1.074	(0.21, 1.94)	0.015
Month 6	245	-1.292	0.884	2.176	(1.45, 2.90)	<.0001
Month 12	245	-0.922	1.617	2.539	(1.77, 3.31)	<.0001
Month 24	245	-1.126	2.447	3.573	(2.76, 4.38)	<.0001

Reference ID: 3168397

Sensitivity analysis results using baseline observation carried forward imputation provided consistent results to the primary analysis.

Sensitivity analysis results for a worst case using a worst case imputation method are summarized in Table 25 below.

Table 25 Least squares Means of Percentage Change in Femoral Neck BMD from Baseline though Month 24 with a Worst Case Imputation: Sensitivity Analysis

	N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	245	-0.526	-0.251	0.275	(-0.47, 1.02)	0.466
Month 3	245	-0.185	0.780	0.965	(0.09, 1.84)	0.030
Month 6	245	-1.170	0.644	1.814	(1.02, 2.61)	<.0001
Month 12	245	-0.668	1.339	2.007	(1.15, 2.86)	<.0001
Month 24	245	-0.661	2.156	2.817	(1.87, 3.76)	<.0001

Sensitivity analysis results using a worst case imputation method provided consistent results to the primary analysis.

The mean lumbar spine DXA T-scores and percentage changes are summarized table 26 below.

Table 26 Lumbar Spine DXA T-scores and Percentage change from the Baseline through Month 24

	Placebo (N=125)				Denosumab (N=127)			
	Mean (SD)	N	%Change (SD)	N	Mean (SD)	N	%Change (SD)	N
Lumbar Spine								
Baseline	-0.983 (0.933)	125			-1.129 (0.865)	127		
Month 1	-1.000 (0.941)	119	-5.867 (45.50)	119	-1.000 (0.832)	119	9.369 (56.42)	116
Month 3	-0.996 (0.963)	121	0.159 (79.63)	121	-0.855 (0.832)	116	24.109 (82.30)	113
Month 6	-1.014 (0.965)	113	-0.925 (47.88)	113	-0.875 (0.952)	124	29.774 (91.51)	121
Month12	-1.031 (0.968)	103	-3.752 (66.02)	103	-0.729 (0.910)	113	31.908 (114.8)	110
Month 24	-1.059 (1.055)	100	-1.952 (88.81)	100	-0.601 (0.983)	105	45.882 (172.5)	103

Mean changes of lumbar spine DXA T-score from baseline to months 12 and 24 were -1.031 and -1.059 in the placebo group and -0.729 and -0.621 in the denosumab group. The mean percentage changes from baseline to months 12 and 24 were -3.752 % and -1.925 % in the placebo group and 31.908 % and 45.882 % in the denosumab group.

Baseline lumbar spine DXA T-scores were imputed for missing lumbar spine DXA T-scores both placebo and denosumab for a sensitivity analysis by this reviewer. The results are summarized Table 27 below.

Reference ID: 3168397

Table 27 Least squares Means for Lumbar Spine DXA T-score Change from Baseline through Month 24

	N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	238	-1.088	-0.943	0.145	(0.09, 0.20)	<.0001
Month 3	237	-1.058	-0.804	0.255	(0.19, 0.32)	<.0001
Month 6	237	-1.142	-0.766	0.376	(0.31, 0.44)	<.0001
Month 12	216	-1.131	-0.647	0.484	(0.41, 0.56)	<.0001
Month 24	205	-1.173	-0.486	0.687	(0.59, 0.79)	<.0001

Sensitivity analysis of DXA T-scores results using LOCF imputation provided consistent results to the primary analysis.

Table 28 Least squares Means for Lumbar Spine DXA T-score Percentage change from Baseline through Month 24

	N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1	235	-6.254	8.181	14.436	(1.20, 27.67)	0.0326
Month 3	234	-2.426	21.583	24.009	(2.83, 45.19)	0.0265
Month 6	234	-2.481	29.978	32.459	(13.13, 51.79)	0.0011
Month 12	213	-4.903	30.658	35.561	(9.46, 61.66)	0.0078
Month 24	203	-4.522	43.620	48.141	(9.14, 87.14)	0.0158

Based on DXA t-scores, there was a statistically significant increase in lumbar spine BMD for the denosumab arm as compared to the placebo from baseline to month 24.

Conclusion:
Reviewer's sensitivity analyses using baseline observation carried forward imputation and a worst case imputation method showed the robustness of the results. Analysis based on DXA T-scores provided consistent results to those results of the primary and the secondary efficacy analyses.

In addition, Study20030216 which is designed to demonstrate the efficacy for the treatment and prevention of postmenopausal osteoporosis (PMO) and Study 20040138 which is designed for bone loss in subjects with nonmetastatic prostate cancer who were undergoing androgen deprivation therapy (ADT) showed the similar results for BMD endpoints. The BMD efficacy results are summarized in Table below.

Reference ID: 3168397

Change in BMD from baseline to Month 24 for Study 20030216, Study 20040132, Study 20040135, and Study 20040138

	Study 20030216	*Study 20040132*	*Study 20040135*	*Study 20040138*
Percent Change (least squares mean (95% CI))				
Lumbar Spine	*7.5 (6.6, 8.3)*	*6.5 (5.8, 7.1)*	*7.6 (6.6, 8.6)*	*6.7 (6.2, 7.1)*
Total Hip	*4.8 (4.2, 5.4)*	*3.4 (3.0, 3.8)*	*4.7 (4.0, 5.5)*	*4.8 (4.4, 5.1)*
Femoral Neck	*4.5 (3.7, 5.2)*	*2.8 (2.3, 3.4)*	*3.6 (2.7, 4.6)*	*3.9 (3.5, 4.4)*

3.2 Evaluation of Safety

For a summary of the evaluation of safety refer to the review by Dr. Suzanne Demko.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

All subjects were women. Among them, 93% were Caucasian.
Subgroup analysis results for age <65 versus ≥ 65 years are summarized in Table 29.

Table 29 Least squares Means for Percentage Change from Baseline to Month 12 for Lumbar BMD Using LOCF

	% Change from Baseline			Difference from Placebo		
	n/N	LS Mean	95% CI	LS Mean	95% CI	p-value
<65 years						
Placebo	81/81	-0.7	(-1.3,-0.1)			
Denosumab	89/89	5.1	(4.3, 5.4)	5.8	(4.8, 6.3)	<0.0001
≥65 years						
Placebo	41/41	-0.7	(-1.7, 0.2)			
Denosumab	34/34	4.3	(3.4, 5.3)	5.1	(3.7, 6.4)	<0.0001

The younger than 65 years old age group had a greater percentage increase in lumbar spine BMD as compared to the age ≥ 65 years old group. Denosumab demonstrated percentage increases in lumbar spine BMD from baseline to month 1 throughout month 24.

Reference ID: 3168397

4.2 Other Special/Subgroup Populations

Subgroup analysis for stratification factor of the duration of aromatase inhibitor therapy at study entry are summarized Table 30 below.

Table 30 Subgroup Analysis for Stratification Factor; Duration of Aromatase Inhibitor Therapy at Study Entry

	% Change from Baseline			Difference from Placebo		
	n/N	LS Mean	95% CI	LS Mean	95% CI	p-value
≤6 months AIT						
Placebo	43/43	-0.9	(-2.0, 0.2)			
Denosumab	47/47	4.5	(3.4, 5.5)	5.4	(3.9, 6.8)	<0.0001
>6 months AIT						
Placebo	79/79	-0.6	(-1.3, 0.1)			
Denosumab	76/76	5.1	(4.4, 5.8)	5.6	(4.7, 6.6)	<0.0001

There was no demonstrated difference in the percentage change in lumbar spine between aromatase inhibitor therapy duration of ≤6 months and aromatase inhibitor therapy duration of > 6 months at study entry.

Table 31 Subgroup Analyses; Prior Chemotherapy, Duration from Last Menstrual Period, and Prior Selective Estrogen Receptor Modulator (SERM) Use

	% Change from Baseline			Difference from Placebo		
	n/N	LS Mean	95% CI	LS Mean	95% CI	p-value
Prior Chemotherapy						
Placebo	75/75	-0.7	(-1.5, 0.1)			
Denosumab	80/80	5.2	(4.4, 5.9)	5.9	(4.9, 6.8)	<0.0001
No prior chemotherapy						
Placebo	47/47	-0.5	(-1.5, 0.4)			
Denosumab	43/43	4.4	(3.4, 5.3)	4.9	(3.6, 6.2)	<0.0001
≤5 years from Last Menstrual Period						
Placebo	33/33	-1.2	(-2.4, 0.0)			
Denosumab	32/32	5.7	(4.5, 6.9)	6.9	(5.3, 8.5)	<0.0001
>5 years from Last Menstrual Period						
Placebo	89/89	-0.5	(-1.1, 0.2)			
Denosumab	90/90	4.6	(4.0, 5.3)	5.1	(4.2, 6.0)	<0.0001
Prior SERM use						
Placebo	53/53	-0.7	(-1.6, 0.1)			
Denosumab	58/58	4.5	(3.6, 5.4)	5.2	(4.1, 6.4)	<0.0001

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No prior SERM use						
Placebo	69/69	-0.7	(-1.5, 0.4)			
Denosumab	65/65	5.1	(4.3, 5.9)	5.8	(4.7, 6.8)	<0.0001

The prior chemotherapy group had a greater percentage change in lumbar spine BMD from baseline to month 12 than those subjects of no prior chemotherapy group. Last menstrual period less than or equal to 5 years group had a greater percentage change as compare to that of longer than 5 years group. The no prior selective estrogen receptor modulator (SERM) group had a greater percentage change than those who had prior SERM use group.

Table 32 Subgroup analyses; Weight and Body Mass Index

	% Change from Baseline			Difference from Placebo		
	n/N	LS Mean	95% CI	LS Mean	95% CI	p-value
Weight <65 kg						
Placebo	30/30	-0.7	(-1.8, 0.4)			
Denosumab	46/46	4.7	(3.8, 5.6)	5.4	(4.1, 6.7)	<0.0001
Weight 66-<75 kg						
Placebo	36/36	-0.9	(-2.0, 0.2)			
Denosumab	38/38	5.2	(4.1, 6.2)	6.1	(4.6, 7.6)	<0.0001
Weight 75-<85 kg						
Placebo	36/36	-1.1	(-2.1, -0.1)			
Denosumab	20/20	4.5	(3.1, 5.8)	5.6	(4.0, 7.2)	<0.0001
Weight ≥85 kg						
Placebo	19/19	-0.1	(-2.3, -0.4)			
Denosumab	19/19	4.6	(2.8, 6.3)	4.7	(2.2, 7.2)	0.0006
BMI <22 kg/m²						
Placebo	12/12	-0.6	(-2.3, 1.2)			
Denosumab	18/18	4.5	(3.2, 5.8)	5.1	(3.0, 7.2)	<0.0001
BMI 22-<24 kg/m²						
Placebo	18/18	-1.0	(-2.5, 0.5)			
Denosumab	17/17	4.1	(2.3, 6.0)	5.1	(2.8, 7.4)	<0.0001
BMI 24-<26 kg/m²						
Placebo	16/23	-0.3	(-2.2, 1.5)			
Denosumab	23/23	6.9	(5.2, 8.5)	7.2	(4.9, 9.6)	<0.0001
BMI 26-<30 kg/m²						
Placebo	41/41	-1.4	(-2.3, -0.4)			
Denosumab	28/28	5.6	(3.8, 6.2)	6.4	(4.9, 7.8)	<0.0001
BMI ≥ 30 kg/m²						
Placebo	33/33	0.0	(-1.1, 0.2)			
Denosumab	36/36	4.4	(3.4, 5.5)	4.4	(2.9, 5.9)	<0.0001

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The weight 66-<75 kg and body mass index (BMI) 24-<26 kg/m² groups had the greatest percentage change and weight >85 kg and BMI ≥ 30 kg/m² had the least percentage change in lumbar spine BMD from baseline to month 12.

The criteria for osteoporosis was used as follow; T-score for osteoporosis or low bone mass are -4.0 ≤ T-score ≤ -1.8 for the lumbar spine and -3.5 ≤ T-score ≤ -1.8 for the total hip or femoral neck. Subjects with these osteoporosis criteria are examined by visit in Table below.

Table 33 Number of Osteoporosis Criteria Subjects by Visit

	Month 0 n(%)	Month 1 n(%)	Month 3 n(%)	Month 6 n(%)	Month 12 n(%)	Month 24 n(%)
Denosumab	30 (23.6)	24 (19.5)	13 (10.6)	14 (11.4)	7 (5.7)	9 (7.3)
Placebo	25 (20.0)	24 (19.7)	22 (18.0)	21 (17.2)	21 (17.2)	29 (23.8)
Total	55 (21.8)	48 (19.5)	35 (14.3)	35 (14.3)	28 (11.4)	38 (15.5)

The number of subjects in the osteoporosis criteria from baseline decreased in denosumab as compared to placebo at months 12 and 24, but not in the placebo.

Table 34 Subgroup analyses for baseline osteoporosis criteria (LOCF)

	N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1						
Osteoporosis	55	0.437	1.780	1.343	(-0.15, 2.83)	0.076
No osteoporosis	190	-0.512	1.280	1.792	(1.16, 2.43)	<.0001
Month 3						
Osteoporosis	55	0.382	2.507	2.124	(0.57, 3.68)	0.008
No osteoporosis	190	-0.431	2.658	3.809	(2.32, 3.86)	<.0001
Month 6						
Osteoporosis	55	0.017	3.537	3.520	(1.85, 5.19)	0.0001
No osteoporosis	190	-0.803	3.788	4.590	(3.86, 5.32)	<.0001
Month 12						
Osteoporosis	55	0.058	5.409	5.350	(3.19, 7.51)	<.0001
No osteoporosis	190	-0.994	4.621	5.615	(4.81, 6.42)	<.0001
Month 24						
Osteoporosis	55	-2.132	5.854	7.985	(5.14, 10.83)	<.0001
No osteoporosis	190	-1.379	5.995	7.374	(6.30, 8.45)	<.0001

Subjects with no osteoporosis criteria at baseline showed a greater percentage change differences in the lumbar spine from baseline to months 1, 3, 6, and 12 except month 24.

Baseline vitamin D level were examined by < 12 ng/mL, 12-20 ng/mL, 21-29 ng/mL and ≥ 30 ng/mL.

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Table 35 Number of Subjects in the Baseline Vitamin D Levels

	<12 ng/mL	12-20 ng/mL	21-29 ng/mL	≥30-ng/mL	Total
Denosumab	1(0.9)	16 (13.9	41 (35.7)	57 (49.6)	115
Placebo	2 (1.7)	27 (22.5)	32 (26.7)	59 (49.1)	120
Total	3 (1.4)	43 (18.3)	73 (31.1)	116 (49.4)	235

Majority (81%) women's baseline vitamin D levels were higher than 21 ng/mL. Subgroup analysis using baseline vitamin D levels were performed. The results are summarized in Table below.

Table 36 Subgroup analyses for baseline Vitamin D

	n/ N	Placebo	Denosumab	Difference	95% CI	p-value
Month 1						
<20 ng/mL	45/46	-0.494	2.217	2.711	(1.37, 4.06)	0.0002
21-29 ng/mL	69/73	-0.530	1.227	1.757	(0.39, 3.12)	0.0124
≥30-ng/mL	114/115	-0.116	1.499	1.615	(0.79, 2.44)	0.0002
Month 3						
<20 ng/mL	45/46	-0.318	3.195	3.513	(1.52,5.51)	0.0010
21-29 ng/mL	69/73	0.290	2.982	2.692	(1.28, 4.10)	0.0003
≥30-ng/mL	114/115	-0.457	2.587	3.044	(2.11, 3.98)	<.0001
Month 6						
<20 ng/mL	45/46	-0.996	4.160	5.156	(3.41, 6.90)	<.0001
21-29 ng/mL	69/73	-1.135	3.926	5.061	(3.58, 6.54)	<.0001
≥30-ng/mL	114/115	-0.348	3.485	3.833	(2.88, 4.78)	<.0001
Month 12						
<20 ng/mL	45/46	-0.494	6.014	6.508	(4.62, 8.40)	<.0001
21-29 ng/mL	69/73	0.124	4.685	4.561	(2.98, 6.14)	<.0001
≥30-ng/mL	114/115	-1.188	4.955	6.143	(5.05, 7.24)	<.0001
Month 24						
<20 ng/mL	45/46	-1.818	6.092	7.910	(5.48, 10.34)	<.0001
21-29 ng/mL	69/73	-1.310	6.460	7.770	(5.58, 9.96)	<.0001
≥30-ng/mL	114/115	-0.714	6.229	6.943	(5.44, 8.45)	<.0001

Subjects with baseline vitamin D levels < 20 ng/mL had the greatest percentage change differences in lumbar spine from baseline through months 24.

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- There was no adequate data to identify any potential for detrimental effects on disease free survival (DFS) and overall survival on how denosumab affects the primary disease of breast cancer. In particular, the study was not designed to adequately comparing between study arms. There were no meaningful safety information about the primary disease free survival and overall survival and no routine neoplastic disease assessment.

- The percentage of subjects with missing lumbar spine BMD scores were 9% and 15 % at months 12 and 24 in the denosumab group and 15%, and 19 % at months 12 and 24 in the placebo group. The placebo group had 4% to 6% more missing lumbar spine BMD scores than that of the denosumab group. Last observation carried forward imputation method was used for the efficacy analyses. Sponsor performed sensitivity analyses including repeated measures model, ANCOVA model using mean of the other group (MOTH) imputation methods and the per protocol analysis set, ANCOVA model using subjects categorized by their actual stratum and univariate and multivariate covariate analyses to demonstrate the robustness of the primary results.

- Overall survival data was not matured. There were only 4 deaths, two deaths in each group.

- The younger than 65 years old age group had a greater percentage increase in lumbar spine BMD as compared to that of age $\geq$ 65 years old group. Subjects in denosumab demonstrated percentage increases in lumbar spine BMD from baseline to month 1 throughout month 24.

- Prior chemotherapy group had a greater percentage change in lumbar spine BMD from baseline to month 12 than those subjects of the no prior chemotherapy group.

- Last menstrual period less than or equal to 5 years group had a greater percentage change in lumbar spine BMD as compare to that of longer than 5 years group.

- The no prior selective estrogen receptor modulator (SERM) group had a greater percentage change in lumbar spine BMD than the prior SERM use group.

- Subjects with weight 66-<75 kg and body mass index (BMI) 24-<26 kg/m^2 had the greatest percentage change and weight >85 kg and BMI $\geq$ 30 kg/m^2 had the least percentage change in lumbar spine BMD from baseline to month 12.

- Subjects with no osteoporosis criteria at baseline had a greater percentage change differences in the lumbar spine BMD from baseline to months 1, 3, 6, and 12 (but not month 24).

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- Subjects with baseline vitamin D levels < 20 ng/mL had the greatest percentage change differences in lumbar spine BMD from baseline through months 24 compared to subjects with baseline vitamin D levels of 21-29 ng/mL and ≥ 30 ng/mL.

5.2 Conclusions and Recommendations

The primary endpoint of the percentage change in lumbar spine BMD from baseline to month 12 demonstrated a statistically significant percentage increase in the denosumab group as compared to the placebo group ($p < 0.0001$). The least squares mean estimates were a 4.8% increase in denosumab and a 0.7% decrease in placebo, the percentage change difference between denosumab and placebo was 5.5% (95% CI: 4.8, 6.3) at month 12. The sensitivity analyses performed by the sponsor and by this reviewer were consistent with the results of the primary analysis.

Secondary endpoints for the percentage change in lumbar spine BMD from baseline to month 6 and the percentage changes in total hip and femoral neck BMDs from baseline to months 6 and 12 demonstrated statistically significant percentage increases in the denosumab group as compared to the placebo group ($p<0.0001$). The sensitivity analyses performed by the sponsor and by this reviewer were consistent with the results of the secondary efficacy analyses.

The data are not adequate on whether denosumab affects breast cancer. In particular, the study was not designed to adequately compare disease free survival (DFS) and overall survival (OS) between study arms. There were no meaningful safety information about the primary disease free survival and overall survival and no routine neoplastic disease assessment.

There is evidence that this study supports that denosumab 60 mg subcutaneously (SC) once every 6 months over the 24-month treatment period increases the percentage change in lumbar spine BMD from baseline to month 12 for subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. However, safe use of denosumab has not been evaluated for these breast cancer patients based on tumor related outcomes.

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

STATISTICAL REVIEW AND EVALUATION

BLA Number	125331, 125320, 125332, and 125333
Drug Name:	denosumab (PROLIA)
Indication(s):	- Prevention of osteoporosis in postmenopausal women - Treatment of osteoporosis in postmenopausal women - Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer - Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer
Applicant:	Amgen Inc.
Date submitted:	December 19, 2009
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Biometrics Division:	Quantitative Safety and Pharmacoepidemiology Division
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Keywords: serum calcium low, hypocalcemia, renal function, vitamin D, osteoporosis, bone loss, breast cancer, prostate cancer

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This review evaluates the incidence of adverse cardiovascular events reported during nine clinical trials of denosumab administered at a dose of 60 mg via the subcutaneous (SC) route once every six months (Q6M). Arms testing other doses and regimens of denosumab were included in Phase 1 and Phase 2 studies, but are not included in this safety evaluation since the sponsor only seeks marketing approval for the 60 mg Q6M dose at this time. The studies included in this analysis were of at least 12 months duration.

The data from nine studies suggest that the risk of bradyarrhythmia is approximately twice as high in subjects receiving denosumab than in subjects receiving placebo control. Additionally, the data suggest that the risk of events of ischaemic heart disease is approximately 1.3 to 1.8 times the risk in subjects receiving placebo control. There appeared to be no consistent effect of denosumab on events of myocardial infarction or any outcomes related to arrhythmia.

1.2 Statistical Issues and Findings

The goal of this review is to determine whether available data suggest that treatment with denosumab is associated with increased risk of adverse cardiovascular events. Adverse events were quantified with respect to subject incidence rate—the number of subjects reporting one or more occurrence of a given event divided by the total number of subjects receiving the treatment. Multiple occurrences of the same event were counted once per subject, and risk was quantified via computation of relative risk (RR), odds ratio (OR) and risk difference (RD).

An As-Treated analysis was performed using the safety population. Specifically, the analysis included subjects who received at least one dose of treatment and subjects were classified according to actual treatment received. The dataset included information on adverse event seriousness and severity, with severity graded as mild/1, moderate/2, severe/3, life-threatening/4, or fatal/5, and seriousness as a binary variable (serious vs. not serious). Serious is defined as in Sec. 312.32 ("IND safety reports") of 21 Code of Federal Regulations. Analyses were carried out to explore the following event characteristics: severity, seriousness, and time to event.

The cardiovascular adverse events from nine studies were analyzed using a classification system developed by the sponsor, and broad and narrow cardiovascular-related standardized MedDRA queries (SMQs). The sponsor developed a classification system to categorize various cardiovascular MedDRA Preferred Terms (PTs) into six categories: acute coronary syndromes, arrhythmia, congestive heart failure, death, other vascular disorders and stroke, and included a system for adjudicating the events themselves. An analysis of unadjudicated adverse event data was performed, as well.

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Three sets of analyses were performed, based on the following groupings of MedDRA preferred terms: (1) The sponsor's groupings, (2) Broad search of MedDRA SMQ terms (listed in Appendix III), and (3) Narrow search of MedDRA SMQ terms (listed in Appendix IV). These approaches were applied to four ways of grouping the nine studies in the database: (1) analyze all studies separately, (2) pool the two largest pivotal studies (HALT and PMO indications), (3) pool the placebo-controlled studies (PMO indication), and (4) pool all controlled studies (PMO indication).

One approach to identifying adverse event reports for which there was an imbalance between the denosumab and control arms was to sort on the p-value associated with estimates of risk. In this context, a p-value is not used for valid inference, but, rather, as one criteria to sort events in terms of difference in incidence. Once subject incidence and risk was computed for each of the different sets of pooled data according to the various approaches described above for grouping MedDRA terms, events with a p-value of 0.10 were selected for futher evaluation.

The events identified via this approach were then placed in the context of the incidence of the same event at all severity levels, regardless of p-value. That is, if risk of "moderate bradycardia" was observed to occur with $p<0.10$, then risk estimates for mild, moderate, severe, life-threatening, serious and severe or worse bradycardia were added to the table, regardless of their associated p-value.

In addition, events of a serious nature were selected for futher evaluation.

Risk of cardiovascular events was computed separately for each of nine studies, as well as for the studies pooled according to whether they were large, pivotal studies (PMO and HALT indications), placebo-controlled (PMO indication), or controlled studies in the PMO population. A broad and narrow SMQ search strategy was used to group terms for the analysis. Thus, there were eight assessments performed by the reviewer, i.e. 2 MedDRA approaches (broad and narrow) for each of four ways of grouping data (all studies separately, large, pivotal studies pooled, placebo-controlled studies pooled, PMO studies pooled).

Bradyarrhytmia and ischaemic heart disease are the only signals that appear consistently in the analysis of the data from the nine studies of denosumab in PMO and HALT populations.

Bradyarrhythmia had a consistent signal according to the broad MedDRA search strategy. In the analysis of all PMO studies pooled, relative risk was estimated as 2.9 for moderate events and 1.7 for all worse severity levels. This trend was observed in the analysis of study 20030216 alone (RR=3.5), which appears to have heavily influenced the pooled analysis.

Severe ischaemic heart disease was associated with relative risk estimates greater than one in all eight analyses, with RR ranging from 1.7 to 2.0. There was a consistent estimate of relative risk greater than one across all severity levels for the placebo-

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controlled and pooled PMO studies. Relative risk estimates ranging from 1.4 to 1.8 having p-values less than 0.05 were observed for all worse severity levels in the pooled placebo-controlled and PMO studies.

This review provides an exploratory statistical evaluation of adverse event reports. Ultimately, this information, along with clinical judgment will be used to determine the cardiovascular safety of denosumab.

2. INTRODUCTION

2.1 Class and Indication

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing individuals to an increased risk of fracture. Denosumab, a fully human monoclonal antibody which binds to and inhibits the action of receptor activator of nuclear factor κB (RANK) ligand, blocks the differentiation, activation, and survival of osteoclasts and thereby inhibits bone resorption. Denosumab has the potential to protect against bone loss and reduce the risk for fracture in disease settings in which bone loss occurs, such as postmenopausal osteoporosis (PMO) and bone loss associated with hormone ablation therapy (HALT).

2.2 Background on Drug Development

This marketing application includes thirty (30) clinical studies in normal volunteers and patients with osteoporosis (approximately 10,500 subjects), and in those with bone loss associated with hormone ablation therapy (approximately 1700 subjects), rheumatoid arthritis, or advanced cancer. The studies were performed between June 2001 and September 2008. Twelve studies were conducted in subjects with postmenopausal osteoporosis or low bone mass. Two studies were conducted in subjects with breast cancer or prostate cancer who had bone loss associated with hormone ablation therapy (aromatase inhibitor and androgen deprivation therapy, respectively). A third study is ongoing in subjects with breast cancer receiving aromatase inhibitor therapy. Nine additional studies, conducted in healthy subjects, provide biopharmaceutic and clinical pharmacology information as well as information on initial efficacy and tolerability of denosumab. The remaining studies were conducted in patient populations outside of the bone loss indications (i.e. inhibition of structural damage in subjects with rheumatoid arthritis, prevention of skeletal-related events in subjects with advanced cancer and bone metastases, and treatment of multiple myeloma).

2.3 Specific Studies Reviewed

The following nine studies contribute data to this review: protocols numbered 20030216, 20040132, 20050179, 20050234, 20050172, 20040135, 20040138, 20050141, and 20010223. These studies were selected since they enrolled the relevant PMO or HALT patient population, evaluated 60 mg denosumab dosed via the subcutaneous (SC) route once every six months (Q6M) for at least 12 months, and utilized randomization to treatment arm.

The PMO clinical development program is supported by two large, pivotal phase 3 studies (20030216 and 20040132). Study 20030216 is a three year, randomized, double-blind, placebo-controlled study in postmenopausal women with osteoporosis designed to determine whether denosumab treatment can reduce the incidence of new vertebral (primary endpoint), and nonvertebral and hip fractures (secondary endpoints) as compared with control. Study 20040132 is a randomized, double-blind, placebo-controlled study in postmenopausal women with low bone mass to determine whether denosumab treatment can prevent lumbar spine bone loss.

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Supportive phase 2 and phase 3 studies in PMO have been completed, including Studies 20010223, 20050141, 20050179, 20050172, and 20050234. Study 20010223 is a phase 2, randomized, double-blind, placebo-controlled dose ranging study in postmenopausal women with low BMD. Studies 20050141 and 20050179 examine the effect of denosumab compared with alendronate on BMD and bone turnover markers (BTMs), and Study 20050234 examines the effect of denosumab on BMD and BTMs in women who switch from alendronate to denosumab therapy compared to women continuing to receive alendronate. Study 20050172 is a Phase 2, randomized, double-blind, placebo-controlled, dose-response study in Japanese women with PMO.

The HALT clinical development program is supported by two large, pivotal phase 3 studies (20040138 and 20040135). Study 20040138 was a randomized, double-blind, placebo-controlled study in men undergoing androgen deprivation therapy for nonmetastatic prostate cancer to determine the treatment effect of denosumab on lumbar spine BMD compared with control. Study 20040138 also included prespecified endpoints for new vertebral and any fracture risk reduction. Study 20040135 was a randomized, double-blind, placebo-controlled study in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer to determine the treatment effect of denosumab on lumbar spine BMD compared with control. The primary analyses for Study 20040138 and Study 20040135 were performed at 3 years and 2 years, respectively, once all subjects had the opportunity to complete the treatment phase. Both studies included an ongoing 2-year extension phase in which no investigational product was administered to characterize the safety profile after cessation of denosumab treatment. An open-label extension study of Study 20040138 has initiated (Study 20080537), and eligible subjects were offered the choice to enroll into the extension study rather than continue in the follow-up phase of Study 20040138.

Table 1 and Table 2 provide a summary of the design and objectives of the PMO and HALT population studies, respectively, included in this safety review. All of the studies enrolled a denosumab 60 mg SC arm and occured over a period of 12 months or longer. All nine studies included a control arm and were conducted in a relevant patient population.

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Table 1. Features of PMO Studies Included in this Reviewer's Safety Analysis. Footnotes are on the following page.

	Objectives	Design	Test Product	Number Exposed	Key Entry Criteria	Duration
20030216	EFF (fracture), SAFE, TOL, BMD, PD, PK, bone histology, histomorphometry, fracture healing	Phase 3, RAND, DB, PC	DEN 60 mg SC Q6M or PLAC SC Q6M 6 doses total	3886 DEN 3876 PLAC	Women with PMO[1] Age: 60-90 yr	36 months
20040132	EFF (BMD), SAFE, TOL, PD	Phase 3, RAND, DB, PC	DEN 60 mg SC Q6M or PLAC SC Q6M 4 doses total	164 DEN 165 PLAC	Postmenopausal women with low BMD[2] Age: ≤ 90 yr	24 months treat 24 months off treatment extension
20050172	EFF (BMD), SAFE, TOL, dose selection, PK, PD	Phase 2, RAND, DB, PC, dose-response	DEN 60 mg[8] SC Q6M or PLAC SC Q6M 2 doses total	54 DEN 55 PLAC	Japanese women with PMO[3] Age: ≤ 80 yr	12 months
20010223	EFF (BMD), SAFE, TOL, dose selection	Phase 2, RAND, DB, PC, AC, dose-finding	DEN 60 mg[9, 10] SC Q6M or PLAC SC Q6M or ALEN 70 mg PO QW	47 DEN 46 PLAC 46 ALEN	Postmenopausal women with low BMD[4] Age: ≤ 80 yr	48 months
20050179	EFF (cortical thickness, BMD), PD, SAFE	Phase 2, RAND, DB, DD, PC, AC	DEN 60 mg SC Q6M (2 doses) plus PLAC for ALEN PO QW or PLAC for DEN SC Q6M (2 doses) plus ALEN 70 mg PO QW or PLAC for DEN SC Q6M (2 doses) plus PLAC for ALEN PO QW	83 DEN 82 ALEN 82 PLAC	Postmenopausal women with low BMD[5] Age: 50 to 70 yr	12 months
20050234	Comparative EFF (BMD), PD, SAFE, TOL	Phase 3b, RAND, DB, AC, DD, parallel-group	DEN 60 mg SC Q6M (2 doses) plus PLAC for ALEN PO QW or PLAC for DEN SC Q6M (2 doses) plus ALEN 70 mg PO QW	253 DEN 251 ALEN	Women with PMO[6] who received ALEN 70 mg QW or equivalent for ≥ 6 mo before screening Age: ≥ 55 yr	12 months
20050141	Comparative EFF (BMD), SAFE, TOL	Phase 3, RAND, DB, AC, DD, parallel group	DEN 60 mg SC Q6M (2 doses) plus PLAC for ALEN PO QW or PLAC for DEN SC Q6M (2 doses) plus ALEN 70 mg PO QW	594 DEN 595 ALEN	Postmenopausal women with low BMD[7]	12 months

AC=Active controlled, ALEN=Alendronate, BMD=Bone Mineral Density, DB=Double blind, DD=Double dummy, DEN=Denosumab, EFF=Efficacy, PC=Placebo controlled, PD=Pharmacodynamics, PK=Pharmacokinetics, PLAC=Placebo, PMO=Postmenopausal osteoporosis, RAND=randomized, Rx=Treatment, SAFE=Safety study, SC=Subcutaneous, Q6M=Every 6 months, QW=Every week, TOL=Tolerability study

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Footnotes for Table 1 (on previous):

[1]PMO = -4.0 ≤ T-score < -2.5 at the lumbar spine or total hip or both
[2]BMD = -2.5 < T-score < -1.0 at the lumbar spine
[3]PMO = -4.0 ≤ T-score ≤ -2.5 for lumbar spine or -3.5 ≤ T-score ≤ -2.5 for total hip or femoral neck
[4]BMD = -4.0 ≤ T-score ≤ -1.8 for lumbar spine or -3.5 ≤ T-score ≤ -1.8 for total hip or femoral neck
[5]BMD = -3.0 ≤ T-score ≤ -2.0 at the lumbar spine or total hip
[6]PMO = -4.0 ≤ T-score ≤ -2.0 at the lumbar spine or total hip
[7]BMD = T-score ≤ -2.0 at the lumbar spine or total hip
[8]In addition, 14mg and 100 mg doses were tested, but data from these arms are not included in this safety analysis.
[9]In addition, an arm in which DEN 6 mg, 14 mg, or 30 mg was dosed SC Q3M was tested, but not included in this analysis.
[10]Doses of 14mg, 100 mg, or 210 mg were administered SC Q6M, but not included in this analysis.

Table 2. Features of HALT Studies Included in this Reviewer's Safety Analysis.

	Objectives	Design	Test Product	Number Exposed	Key Entry Criteria	Duration*
20040135	EFF (BMD), SAFE, PK	Phase 3, RAND, DB, PC	DEN 60 mg SC Q6M or PLAC SC Q6M (4 doses)	125 DEN 124 PLAC	Women with nonmetastatic breast cancer receiving aromatase inhibitor therapy with low bone mass; BMD criteria[1]	24 months treatment + 24-month safety follow-up
20040138	EFF (BMD, vertebral and any fracture incidence), SAFE, PK	Phase 3, RAND, DB, PC	DEN 60 mg SC Q6M or Placebo SC Q6M (6 doses)	731 DEN 725 PLAC	Age: ≥ 18 yr Men with nonmetastatic prostate cancer receiving androgen-deprivation therapy; subjects with BMD criteria[2]	36 months treatment + 24-month safety follow-up or 2-year extension

AC=Active controlled, ALEN=Alendronate, BMD=Bone Mineral Density, DB=Double blind, DD=Double dummy, DEN=Denosumab, EFF=Efficacy, PC=Placebo controlled, PD=Pharmacodynamics, PK=Pharmacokinetics, PLAC=Placebo, PMO=Postmenopausal osteoporosis, RAND=randomized, Rx=Treatment, SAFE=Safety study, SC=Subcutaneous, Q6M=Every 6 months, QW=Every week, TOL=Tolerability study
*Duration: Includes follow up
[1]BMD criteria: -2.5 ≤ BMD, T-score ≤ -1.0 at the lumbar spine, femoral neck, or total hip (with none < -2.5)
[2]BMD criteria: BMD T-score < -4.0 at lumbar spine, total hip, or femoral neck excluded For those < 70 yrs of age (but not those ≥ 70 yrs): history of osteoporotic fracture or BMD T-score < -1.0 at the lumbar spine, total hip, or femoral neck

The following studies were not included in this safety analysis because they enrolled only healthy subjects, had a small number of patients, were shorter than 12 months in duration

(b) (4)

3. DATA SOURCES

The sponsor provided all data and study reports in electronic format. The model for the data structure was described as consistent with CDISC Study Data Tabulation Model (SDTM) and Analysis Dataset model (ADaM) guidelines (www.cdisc.org).

Appendix V lists the study reports reviewed and provides the path to their location in the electronic document room and chapter location in Global Summit Review.

Since the AAE dataset only includes subjects who reported an adverse event, the ASLINFO and demographics (DM) datasets were needed to determine the appropriate count of subjects (denominator) exposed to treatment or control.

Adverse events were coded using terminology standardized in the Medical Dictionary for Regulatory Activities (MedDRA). Appendix VI lists the version of MedDRA utilized to code events in each of the nine studies reviewed. The Integrated Summary of Safety (ISS) dataset harmonized these versions into single dataset with MedDRA version 11.0.

4. METHODS

This review evaluates the incidence of adverse cardiovascular events reported during nine clinical trials of denosumab 60 mg administered via the subcutaneous route once every six months. The trials were not designed to detect a statistically significant difference in adverse events, thus, the data analytic approaches described in this review are considered exploratory.

The goal of this review is to determine whether available data suggest that treatment with denosumab is associated with adverse cardiovascular events.

Questions to be explored include:
- Do significantly more subjects experience adverse cardiovascular events in the denosumab treatment group compared to the control group?
- Is the severity of cardiovascular events greater in the denosumab treatment group compared to the control group?
- Is the seriousness of cardiovascular events greater in the denosumab treatment group compared to the control group?
- Is the time to occurrence of cardiovascular events in the denosumab treatment group shorter than in the control group?

Statistical Methodologies

The safety dataset integrates data from all subjects who received at least one dose of investigational product. Adverse events were graded according to severity, specifically into the categories of "Mild", "Moderate", "Severe", "Life-threatening" and "Fatal". They were also flagged according to whether they were of a serious nature, as defined in Sec. 312.32 ("IND safety reports") of 21 Code of Federal Regulations:

> Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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Rationale for Pooling Data
Data from the nine studies described in Section 2.1.3 and Section 2.2 of this review were reviewed individually and also pooled according to the following groupings of interest. Note that although some studies tested several doses of denosumab, only the 60 mg denosumab arm was included in the analysis.

Large, Pivotal Trial Data
The data from Study 20030216 and Study 20040138 were pooled for analysis since both were large, placebo-controlled large, pivotal trials of 36 months in duration. The pooled data from studies 20030216 and 20040138 will be referred to as the large, pivotal dataset, and covers the PMO and HALT populations.

Placebo-Controlled Studies in PMO
Data from the denosumab and placebo arms were pooled from Study 20030216, 20040132, 20050172, 20050179, and 20010223, as these represent the placebo-controlled studies in patients with PMO.

All Controlled PMO Studies in PMO
Data from the denosumab, placebo and alendronate arms were pooled from Study 20030216, 20040132, 20050172, 20050179, 20010223, 20050234, and 20050141, as these represent any controlled studies of denosumab in the PMO population.

Data from Study 20040135 and Study 20040138 were not pooled for analysis because they were conducted in different populations (i.e. male vs. female; different age groups; different illness).

This analysis accepts the Sponsor's records of adverse events. That is, no attempt was made to evaluate the case report forms for agreement between information in the patient's record and values recorded in the dataset.

Definition of Safety Population
The incidence of adverse events reported in subjects receiving a 60 mg dose of denosumab every six months (Q6M) was compared to that in subjects administered control treatment – placebo and/or alendronate 70 mg dosed orally once weekly (QW). An As-Treated approach was taken to the analysis—the safety population included all subjects who received at least one dose of treatment (i.e. members of the SAFETY=T population) and according to actual treatment received (i.e. the TRTA or EXTRT variable). The dataset included information on adverse event seriousness and severity (variable name: AESEV or AETOXGR). Seriousness was indicated by the variable named AESER. Severity was denoted with the variable AESEV (mild, moderate, severe, life-threatening, fatal) or AETOXGR (Grade 1-Grade 5).

Metrics
Adverse events were quantified in terms of subject incidence rate—the number of subjects reporting one or more occurrence of a given event divided by the total number of

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subjects receiving the treatment. Multiple occurrences of same event were counted once per subject.

Relative risks (RR), odds ratios (OR) and risk differences (RD) were computed to quantify risk. Relative risk is the ratio of the probability of the event occurring in the experimental group versus in a control group. The odds ratio is the ratio of the odds of an event occurring in the experimental group to the odds it occurs in the control group. The risk difference computes the absolute change in risk attributable to experimental intervention and is calculated as risk in the experimental group minus risk in the control group. Risk differences allow for a risk estimate to be computed in the event that zero events occur in one of the arms since it involves taking differences, thus, does not involve division by zero.

P-values for risk estimates were computed and p-values for relative risk were used to prioritize/score adverse events. Since the nine studies analyzed were not designed for a causal analysis of safety, this use of a p-value is exploratory. Logistic regression was used to obtain two-sided p-values. When cell counts were less than or equal to 5, exact logistic regression was used to obtain the confidence interval and p-value of risk estimates. When cell counts were equal to zero, the point estimate was assigned as zero (no event in the denosumab group) but the confidence interval and p-value was computed using exact logistic regression.

In addition, time to event (i.e. SMQ category or one of the sponsor's six categories of adverse cardiovascular event) was computed. Time to event was not computed for individual preferred terms since the data were too sparse to support such an estimate.

MedDRA Term Search strategy

The reviewer performed an analysis of unadjudicated adverse event data. The unadjudicated data were examined since the sponsor only adjudicated adverse event data from two studies and it was of interest to evaluate outcomes from as many relevant trials as possible. In addition, adjudication has the potential to introduce subjectivity into data collection, thus, analysis of unadjudicated data seemed an important check to perform. Three sets of analyses were performed, based on the following groupings of MedDRA preferred terms: (1) the sponsor's groupings, (2) broad search of MedDRA SMQ terms listed in Appendix III, and (3) narrow search of MedDRA SMQ terms listed in Appendix IV.

For each of these three approaches to MedDRA term grouping, the following items were tabulated: the preferred term, the severity (i.e. AESEV or AETOXGR), the total number of events, the number of subjects that experienced at least one event, and the risk rate (at the subject level) for actual treatment received. These items were computed for all of the preferred terms separately, and with terms pooled under structured categories. RR, OR, RD and their corresponding 95% confidence intervals are provided.

MedDRA terms were also grouped according to System Organ Class (SOC), Higher Level Group Term (HLGT), High Level Term (HLT) and Preferred Term (PT) for each

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of the three pooled datasets of interest: pooled large, pivotal trials, pooled placebo-controlled PMO trials, pooled placebo- or active- controlled trials.

5. RESULTS

Tabulations of subject incidence, risk and their associated p-values were generated by grouping reported adverse events according to broad SMQ, narrow SMQ and the sponsor's MedDRA preferred term grouping strategy. Events with a relative risk having an associated p-value of less than 0.10 were selected for further evaluation. Given that none of the nine studies were designed to evaluate the incidence of cardiovascular adverse events, this approach of ranking reports of adverse events by p-value is considered an exploratory analysis.

Table 3 shows a cross-trial comparison of relative risk estimates for events having at least one relative risk estimate associated with a p-value less than 0.10. Note that columns of the table correspond to the trial or pooled dataset for which the relative risk estimates were computed—the first nine columns correspond to using a broad SMQ search strategy and the remaining columns correspond to a narrow SMQ search strategy. Relative Risk estimates are reported unless the relative risk cannot be computed due to the occurrence of zero events. In such instances, the number of subjects in each arm with the event is reported instead of RR. Highlighted entries are associated with a p-value less than 0.10, while non-highlighted RR values are not associated with a p-value less than 0.10. Empty cells indicate that a particular event did not occur in that particular dataset employing the given SMQ strategy.

Table 3 shows that there were 24 different terms whose relative risk estimate was associated with a p-value less than 0.10: Arrhythmia related investigations, Bradyarrhythmias, Cardiac Arrhythmias, Cardiac arrhythmia terms, Cardiac Failure, Cardiomyopathy, Conduction Defects, Disorders of Sinus Node Function, Embolic and Thrombotic Events, Embolic and Thrombotic Events—Arterial, Embolic and Thrombotic Events—Unspecified, Embolic and Thrombotic Events—Venous, Gastrointestinal Haemorrhage, Gastrointestinal Perforation, Ulceration, etc., Haemodynamic oedema, effusions, etc., Haemorrhages, Haemorrhage Terms (excl lab), Hypertension, Ischaemic Heart Disease, Myocardial Infarction, Pulmonary Hypertension, Thrombophlebitis, Torsade de Pointes/QT Prolongation, and Toxic-septic shock conditions.

Note that more detailed tabulations and a discussion of the results is provided in Appendix VII. Tables A1 – A42 in Appendix VII provide event counts, risk estimates, confidence intervals and p-values for all individual studies and pooled datasets using broad SMQ, narrow SMQ and the sponsor's grouping of terms.

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Table 3. Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison. Columns of the table correspond to the trial or pooled dataset on which the relative risk estimates were computed. The first nine columns correspond to using a broad SMQ search strategy and the remaining columns correspond to a narrow SMQ search strategy. Relative Risk estimates are reported unless it cannot be computed due to the occurrence of zero events. In such instances, the number of subjects in each arm with the event is reported instead of RR. Note that highlighted entries are associated with a p-value less than 0.10. Non-highlighted RR values are not associated with a p-value less than 0.10. Empty cells indicate that a particular event didn't occur in that particular dataset employing the given SMQ strategy.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Arrhythmia related investigations	Ser 1.08	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 1.32	Ser 0.99	Ser 0 Den 0 Alen	Ser 1.16	Ser 1.14	Ser 0.97									
	All 1.08	All 1.76	All 1.86	All 1.12	All 0.99	All 1.5	All 1.08	All 1.11	All 1.0									
	Mild 1.3	Mild 1.34	Mild 0.93	Mild 0.62	Mild 0.77	Mild 2.5	Mild 1.25	Mild 1.3	Mild 1.19									
	Fatal 0.3	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 1.98	Fatal 1 Den 0 Alen	Fatal 0 Den 0 Alen	Fatal 0.69	Fatal 0.3	Fatal 0.33									

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Bradyarrhythmias	Ser	Ser	Ser	Ser	Ser	Ser	Ser	Ser	Ser									
	1.9	0 Den 0 Plac	1 Den 0 Plac	1.74	1 Den 0 Alen	1 Den 0 Alen	1.9	1.9	1.75									
	All	All	All	All	All	All	All	All	All									
	1.3	1.01	1 Den 0 Plac	1.82	2.0	1 Den 0 Alen	1.4	1.29	1.15									
	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod									
	3.5	0 Den 0 Plac	0 Den 0 Plac	0.66	0 Den 1 Alen	0 Den 0 Alen	2.3	3.5	2.9									
	Sev	Sev	Sev	Sev	Sev	Sev	Sev	Sev	Sev									
	1.66	0 Den 0 Plac	1 Den 0 Plac	4.96	1 Den 0 Alen	1 Den 0 Alen	2.1	1.66	1.66									
	≥Sev	≥Sev	≥Sev	≥Sev	≥Sev	≥Sev	≥Sev	≥Sev	≥Sev									
	1.7	0 Den 0 Plac	1 Den 0 Plac	4.96	1 Den 0 Alen	1 Den 0 Alen	2.1	1.71	1.66									

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Reference ID: 3168397

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Cardiac Arrhythmias	Ser 1.11	Ser 0 Den 0 Plac	Ser 0.93	Ser 1.28	Ser 2.94	Ser 2.0	Ser 1.15	Ser 1.13	Ser 0.99									
	All 1.03	All 2.01	All 1.09	All 1.07	All 1.18	All 0.74	All 1.04	All 1.06	All 0.94									
	Sev 0.98	Sev 0 Den 1 Plac	Sev 2.79	Sev 2.0	Sev 1.96	Sev 0.98	Sev 1.16	Sev 0.96	Sev 0.85									
	Fatal 0.3	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 2.0	Fatal 1 Den 0 Alen	Fatal 0 Den 0 Alen	Fatal 0.69	Fatal 0.3	Fatal 0.33									
Cardiac arrhythmia terms	Ser 1.18	Ser 0 Den 0 Plac	Ser 0.93	Ser 1.49	Ser 2 Den 0 Alen	Ser 2.0	Ser 1.25	Ser 1.25	Ser 1.05									
	All 0.97	All 2.52	All 0.31	All 1.21	All 1.72	All 0.49	All 1.01	All 1.01	All 0.87									
	Mild 0.83	Mild 2.52	Mild 0 Den 1 Plac	Mild 0.85	Mild 1.96	Mild 0.66	Mild 0.83	Mild 0.83	Mild 0.77									

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Cardiac Failure	Ser	Ser	Ser	Ser	Ser	Ser	Ser	Ser	Ser	Ser		Ser	Ser		Ser	Ser	Ser	Ser
	0.95	0 Den 0 Plac	0 Den 1 Plac	0.76	0 Den 0 Alen	1 Den 0 Alen	0.89	0.89	0.81	0.92		0 Den 1 Plac	0.74		1 Den 0 Alen	0.87	0.92	0.79
	All	All	All	All	All	All	All	All	All	All		All	All		All	All	All	All
	1.13	0.56	1.33	0.95	1.32	1.57	1.09	1.09	0.99	1.14		0 Den 2 Plac	0.8		1 Den 0 Alen	1.06	1.14	0.96
	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild		Mild	Mild		Mild	Mild	Mild	Mild
	1.03	1.01	1.63	1.6	1.82	1.23	1.14	1.14	0.96	0.91		0 Den 0 Plac	2.5		0 Den 0 Alen	1.04	0.91	0.76
	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod		Mod	Mod		Mod	Mod	Mod	Mod
	1.3	0.25	0.62	0.31	0.50	0.98	1.01	1.01	1.03	1.43		0 Den 2 Plac	0.17		0 Den 0 Alen	1.22	1.43	1.19
	LT	LT	LT	LT	LT	LT	LT	LT	LT	LT		LT	LT		LT	LT	LT	LT
	0.6	0 Den 0 Plac	0 Den 0 Plac	0.17	0 Den 0 Alen	1 Den 0 Alen	0.36	0.36	0.66	0.6		0 Den 0 Plac	0.17		1 Den 0 Alen	0.36	0.6	0.66

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Reference ID: 3168397

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Cardiomyopathy	Ser 1.01	Ser 0 Den 0 Plac	Ser 0 Den 1 Plac	Ser 1.22	Ser 0 Den 2 Alen	Ser 0 Den 0 Alen	Ser 1.08	Ser 1.03	Ser 0.86	Ser 2.5	1	Ser 0 Den 0 Plac	Ser 2.0	Ser 0 Den 1 Alen		Ser 2.33	Ser 2.5	Ser 2.08
	All 0.97	All 1.51	All 1.14	All 0.97	All 0.81	All 1.23	All 0.97	All 0.98	All 0.88	All 1.0		All 1 Den 0 Plac	All 0.99	All 0 Den 1 Alen		All 1.0	All 1.0	All 0.83
	Mod 0.95	Mod 1.01	Mod 0.93	Mod 0.69	Mod 0.66	Mod 0 Den 2 Alen	Mod 0.89	Mod 0.97	Mod 0.84	Mod 1.33		Mod 1 Den 0 Plac	Mod 0.66	Mod 0 Den 1 Alen		Mod 1.0	Mod 1.33	Mod 1.11
	Fatal 0.4	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 1.79	Fatal 0 Den 0 Alen	Fatal 0 Den 0 Alen	Fatal 0.81	Fatal 0.36	Fatal 0.3	Fatal 1 Den 0 Plac		Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Alen		Fatal 1 Den 0 Plac	Fatal 1 Den 0 Plac	Fatal 1 Den 0 Plac
Conduction Defects	Ser 2.66	Ser 0 Den 0 Plac	Ser 1 Den 0 Plac	Ser 0.66	Ser 0 Den 0 Alen		Ser 1.66	Ser 2.66	Ser 2.22									
	All 1.1	All 1.01	All 1 Den 0 Plac	All 1.49	All 0.99		All 1.16	All 1.04	All 0.91									
	Sev 4.99	Sev 0 Den 0 Plac	Sev 1 Den 0 Plac	Sev 2.98	Sev 0 Den 0 Alen		Sev 4.0	Sev 4.99	Sev 4.16									

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Disorders of Sinus Node Function	Ser 1.57			Ser 2.48		Ser 1 Den 0 Alen	Ser 1.77	Ser 1.57	Ser 1.42									
	All 1.7			All 1.98		All 1 Den 0 Alen	All 1.8	All 1.8	All 1.58									
	Mod 3.7			Mod 0.99		Mod 0 Den 0 Alen	Mod 2.6	Mod 3.7	Mod 3.1									
Embolic and Thrombotic Events	Ser 1.14		Ser 2.79	Ser 1.17	Ser 0.25	Ser 0.98	Ser 1.15	Ser 1.14	Ser 0.96	Ser 1.1		Ser 2.8	Ser 1.27	Ser 0 Den 3 Alen	Ser 0 Den 0 Alen	Ser 1.15	Ser 1.09	Ser 0.91
	All 1.04		All 1.4	All 1.11	All 0.42	All 0.98	All 1.06	All 1.04	All 0.89	All 0.99		All 1.4	All 1.13	All 0.40	All 0.98	All 1.03	All 0.98	All 0.84
	Mod 0.93		Mod 0 Den 1 Plac	Mod 1.52	Mod 0.66	Mod 0.98	Mod 1.06	Mod 0.95	Mod 0.83	Mod 0.86		Mod 0 Den 1 Plac	Mod 2.1	Mod 0.50	Mod 0.98	Mod 1.07	Mod 0.86	Mod 0.76
	Sev 1.5		Sev 0.93	Sev 1.19	Sev 0 Den 1 Alen	Sev 0 Den 1 Alen	Sev 1.43	Sev 1.5	Sev 1.24	Sev 1.5		Sev 0.93	Sev 1.37	Sev 0 Den 1 Alen	Sev 0 Den 0 Alen	Sev 1.4	Sev 1.4	Sev 1.19

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Reference ID: 3168397

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Embolic and Thrombotic Events, Arterial	Ser 1.24		Ser 2.79	Ser 1.1	Ser 0 Den 2 Alen	Ser 0 Den 0 Alen	Ser 1.19	Ser 1.22	Ser 1.01	Ser 1.24		Ser 2.8	Ser 1.1	Ser 0 Den 2 Alen	Ser 0 Den 0 Alen	Ser 1.19	Ser 1.22	Ser 1.01
	All 1.22		All 2.79	All 1.11	All 0.99	All 0 Den 1 Alen	All 1.19	All 1.2	All 1.03	All 1.22		All 2.8	All 1.11	All 0.99	All 0 Den 1 Alen	All 1.19	All 1.2	All 1.03
	Sev 1.7		Sev 0.83	Sev 1.61	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 1.7	Sev 1.66	Sev 1.39	Sev 1.7		Sev 0.93	Sev 1.61	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 1.7	Sev 1.66	Sev 1.4
	LT 0.4		LT 2 Den 0 Plac	LT 0.58	LT 0 Den 0 Alen	LT 0 Den 0 Alen	LT 0.5	LT 0.4	LT 0.33	LT 0.4		LT 2 Den 0 Plac	LT 0.58	LT 0 Den 0 Alen	LT 0 Den 0 Alen	LT 0.5	LT 0.4	LT 0.33
Embolic and Thrombotic Events, Unspecified	Ser 1.32			Ser 0.93	Ser 0.99	Ser 0.98	Ser 1.2	Ser 1.35	Ser 1.17									
	All 1.29			All 0.84	All 0.50	All 0.98	All 1.15	All 1.31	All 1.12									
	Sev 1.8			Sev 0.99	Sev 0 Den 0 Alen	Sev 0 Den 1 Alen	Sev 1.52	Sev 1.8	Sev 1.45									
	≥Sev 1.6			≥Sev 0.86	≥Sev 0 Den 0 Alen	≥Sev 0.98	≥Sev 1.31	≥Sev 1.6	≥Sev 1.37									

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ							
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Embolic and Thrombotic Events, Venous	Ser 1.0		Ser 0 Den 0 Plac	Ser 2.73	Ser 0 Den 1 Alen	Ser 0 Den 0 Alen	Ser 1.26	Ser 1.0	Ser 0.83	Ser 1.0		Ser 0 Den 0 Plac	Ser 2.73	Ser 0 Den 1 Alen	Ser 0 Den 0 Alen	Ser 1.26	Ser 1.0	Ser 0.83
	All 0.75		All 0 Den 1 Plac	All 1.39	All 0 Den 3 Alen	All 1 Den 0 Alen	All 0.86	All 0.75	All 0.64	All 0.75		All 0 Den 1 Plac	All 1.39	All 0 Den 3 Alen	All 1 Den 0 Alen	All 0.86	All 0.75	All 0.64
	Mild 0.5		Mild 0 Den 0 Plac	Mild 0.5	Mild 0 Den 2 Alen	Mild 0 Den 0 Alen	Mild 0.5	Mild 0.5	Mild 0.42	Mild 0.5		Mild 0 Den 0 Plac	Mild 0.5	Mild 0 Den 2 Alen	Mild 0 Den 0 Alen	Mild 0.5	Mild 0.5	Mild 0.42
	Mod 0.59		Mod 0 Den 1 Plac	Mod 2.64	Mod 0 Den 0 Alen	Mod 1 Den 0 Alen	Mod 0.84	Mod 0.59	Mod 0.53	Mod 0.59		Mod 0 Den 1 Plac	Mod 2.64	Mod 0 Den 0 Alen	Mod 1 Den 0 Alen	Mod 0.84	Mod 0.59	Mod 0.53

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Reference ID: 3168397

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Gastrointestinal Haemorrhage	Ser 1.21	Ser 0 Den 0 Plac	Ser 1 Den 0 Plac	Ser 0.44	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 0.96	Ser 1.21	Ser 1.05									
	All 1.4	All 0.5	All 1.86	All 0.9	All 1.01	All 0.49	All 1.24	All 1.29	All 1.15									
	Mild 1.0	Mild 0.25	Mild 0.93	Mild 1.49	Mild 0 Den 4 Alen	Mild 0.98	Mild 1.11	Mild 0.94	Mild 0.81									
	Mod 2.1	Mod 1.01	Mod 0 Den 0 Plac	Mod 0.5	Mod 3 Den 0 Alen	Mod 0 Den 1 Alen	Mod 1.52	Mod 1.9	Mod 1.76									
Gastrointestinal Perforation, Ulceration, etc.	Ser 1.4	Ser 0 Den 0 Plac	Ser 1.86	Ser 0.47	Ser 0.99	Ser 0 Den 1 Alen	Ser 1.1	Ser 1.4	Ser 1.21									
	All 1.16	All 1.01	All 1.67	All 0.97	All 1.04	All 0.22	All 1.12	All 1.15	All 1.04									
	Mild 1.0	Mild 0.6	Mild 0.93	Mild 2.2	Mild 0.91	Mild 0.49	Mild 1.11	Mild 0.98	Mild 0.92									
	Mod 1.4	Mod 2.52	Mod 3 Den 0 Plac	Mod 0.78	Mod 1.2	Mod 0 Den 4 Alen	Mod 1.25	Mod 1.4	Mod 1.24									

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Haemodynamic oedema, effusions, etc.	Ser 1.63	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 1.16	Ser 0 Den 0 Alen	Ser 1 Den 0 Alen	Ser 1.47	Ser 1.63	Ser 1.44	Ser 1.63	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 1.16	Ser 0 Den 0 Alen	Ser 1 Den 0 Alen	Ser 1.47	Ser 1.63	Ser 1.44
	All 1.09	All 0.64	All 1.47	All 1.08	All 1.32	All 1.8	All 1.09	All 1.09	All 1.0	All 1.09	All 0.64	All 1.5	All 1.08	All 1.32	All 1.8	All 1.09	All 1.09	All 1.0
	Mild 1.02	Mild 1.51	Mild 1.34	Mild 1.5	Mild 1.5	Mild 1.38	Mild 1.1	Mild 1.05	Mild 0.98	Mild 1.02	Mild 1.5	Mild 1.34	Mild 1.5	Mild 1.50	Mild 1.38	Mild 1.1	Mild 1.05	Mild 0.98
Haemorrhages	Ser 0.86	Ser 0 Den 0 Plac	Ser 1 Den 0 Plac	Ser 0.73	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 0.82	Ser 0.86	Ser 0.73	Ser 0.86	Ser 0 Den 0 Plac	Ser 1 Den 0 Plac	Ser 0.73	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 0.82	Ser 0.86	Ser 0.73
	All 0.99	All 0.36	All 1.46	All 0.91	All 1.12	All 0.53	All 0.97	All 0.95	All 0.86	All 0.99	All 0.38	All 1.33	All 0.92	All 0.89	All 0.53	All 0.98	All 0.96	All 0.87
	Mild 0.95	Mild 0.22	Mild 1.2	Mild 1.08	Mild 1.9	Mild 0.84	Mild 0.97	Mild 0.9	Mild 0.83	Mild 0.95	Mild 0.23	Mild 1.06	Mild 1.08	Mild 0.52	Mild 0.84	Mild 0.98	Mild 0.91	Mild 0.84
	Mod 1.09	Mod 1.01	Mod 2 Den 0 Plac	Mod 0.67	Mod 0.29	Mod 0.16	Mod 0.99	Mod 1.1	Mod 0.99	Mod 1.1	Mod 1.01	Mod 2 Den 0 Plac	Mod 0.7	Mod 3.45	Mod 0.16	Mod 1.01	Mod 1.12	Mod 1.0
	Sev 0.82	Sev 0.5	Sev 1 Den 0 Plac	Sev 0.78	Sev None	Sev 0 Den 0 Alen	Sev 0.81	Sev 0.75	Sev 0.62	Sev 0.82	Sev 0.5	Sev 1 Den 0 Plac	Sev 0.84	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 0.83	Sev 0.75	Sev 0.62

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

Reference ID: 3168397

Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Haemorrhage Terms (excl lab)	Ser 0.86	Ser None	Ser 1 Den 0 Plac	Ser 0.73	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 0.82	Ser 0.86	Ser 0.73	Ser 0.86	Ser 0 Den 0 Plac	Ser 1 Den 0 Plac	Ser 0.73	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 0.82	Ser 0.86	Ser 0.73
	All 0.99	All 0.36	All 1.46	All 0.92	All 1.12	All 0.53	All 0.98	All 0.95	All 0.87	All 0.99	All 0.38	All 1.33	All 0.92	All 0.89	All 0.53	All 0.98	All 0.96	All 0.87
	Mild 0.96	Mild 0.22	Mild 1.2	Mild 1.08	Mild 1.9	Mild 0.84	Mild 0.98	Mild 0.9	Mild 0.83	Mild 0.95	Mild 0.23	Mild 1.06	Mild 1.08	Mild 0.52	Mild 0.84	Mild 0.98	Mild 0.91	Mild 0.84
	Mod 1.1	Mod 1.01	Mod 2 Den 0 Plac	Mod 0.7	Mod 0.29	Mod 0.16	Mod 1.01	Mod 1.12	Mod 1.0	Mod 1.1	Mod 1.01	Mod 2 Den 0 Plac	Mod 0.7	Mod 3.45	Mod 0.16	Mod 1.01	Mod 1.12	Mod 1.0
	Sev 0.82	Sev 0.5	Sev 1 Den 0 Plac	Sev 0.84	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 0.83	Sev 0.75	Sev 0.62	Sev 0.82	Sev 0 Den 0 Plac	Sev 1 Den 0 Plac	Sev 0.84	Sev 0 Den 0 Alen	Sev 0 Den 0 Alen	Sev 0.83	Sev 0.75	Sev 0.62
Hypertension	Ser 0.93	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 0.57	Ser 0 Den 1 Alen	Ser 1 Den 0 Alen	Ser 0.86	Ser 0.93	Ser 0.8	Ser 0.93	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 0.57	Ser 0 Den 1 Alen	Ser 1 Den 0 Alen	Ser 0.86	Ser 0.93	Ser 0.8
	All 0.99	All 0.4	All 0.58	All 1.06	All 0.61	All 1.07	All 0.99	All 0.98	All 0.86	All 0.99	All 0.4	All 0.58	All 1.06	All 1.64	All 1.07	All 0.99	All 0.98	All 0.86
	Mod 0.97	Mod 0.25	Mod 0 den 5 plac	Mod 0.82	Mod 0.51	Mod 0.98	Mod 0.95	Mod 0.96	Mod 0.83	Mod 0.97	Mod 0.25	Mod 0 den 5 plac	Mod 0.82	Mod 1.96	Mod 0.98	Mod 0.95	Mod 0.96	Mod 0.83

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Ischaemic Heart Disease	Ser 1.4	Ser 0 Den 0 Plac	Ser 1.86	Ser 0.8	Ser 0.33	Ser 0.98	Ser 1.18	Ser 1.4	Ser 1.18	Ser 1.4	Ser 0 Den 0 Plac	Ser 1.86	Ser 0.8	Ser 0.33	Ser 0.98	Ser 1.18	Ser 1.4	Ser 1.18
	All 1.14	All 0.34	All 1.86	All 1.01	All 0.59	All 0.33	All 1.11	All 1.13	All 0.96	All 1.15	All 0.34	All 1.86	All 0.99	All 0.59	All 0.33	All 1.11	All 1.13	All 0.96
	Sev 2.0	Sev 0 Den 1 Plac	Sev 0.93	Sev 1.28	Sev 0.50	Sev 0 Den 0 Alen	Sev 1.8	Sev 1.8	Sev 1.55	Sev 2.0	Sev 0 Den 1 Plac	Sev 0.93	Sev 1.28	Sev 0.50	Sev 0 Den 0 Alen	Sev 1.8	Sev 1.8	Sev 1.6
	≥Sev 1.7	≥Sev 0 Den 1 Plac	≥Sev 1.86	≥Sev 0.89	≥Sev 0.50	≥Sev 1 Den 0 Alen	≥Sev 1.4	≥Sev 1.6	≥Sev 1.4	≥Sev 1.7	≥Sev 0 Den 1 Plac	≥Sev 1.86	≥Sev 0.89	≥Sev 0.50	≥Sev 1 Den 0 Alen	≥Sev 1.4	≥Sev 1.6	≥Sev 1.4

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Myocardial Infarction	Ser 1.42		Ser 2 Den 0 Plac	Ser 0.8	Ser 0 Den 1 Alen		Ser 1.13	Ser 1.38	Ser 1.15	Ser 1.42		Ser 2 Den 0 Plac	Ser 0.8	Ser 0 Den 1 Alen		Ser 1.13	Ser 1.4	Ser 1.15
	All 1.36		All 2 Den 0 Plac	All 0.88	All 0.99		All 1.14	All 1.32	All 1.13	All 1.41		All 2 Den 0 Plac	All 0.88	All 0.99		All 1.16	All 1.36	All 1.16
	Mild 0		Mild 0 Den 0 Plac	Mild 0.5	Mild 0 Den 0 Alen		Mild 0.2	Mild 0 Den 3 Pla	Mild 0 Den 3 Pla	Mild 0 Den 2 Pla		Mild 0 Den 0 Plac	Mild 0 Den 1 Plac	Mild 0 Den 0 Alen		Mild 0 Den 3 Plac	Mild 0 Den 2 Plac	Mild 0 Den 2 Plac
	Sev 2.5		Sev 1 Den 0 Plac	Sev 2.48	Sev 0 Den 0 Alen		Sev 2.5	Sev 2.3	Sev 1.9	Sev 2.5		Sev 1 Den 0 Plac	Sev 2.48	Sev 0 Den 0 Alen		Sev 2.5	Sev 2.3	Sev 1.9
	≥Sev 1.5		≥Sev 2 Den 0 Plac	≥Sev 0.83	≥Sev 0 Den 0 Alen		≥Sev 1.18	≥Sev 1.48	≥Sev 1.23	≥Sev 1.5		≥Sev 2 Den 0 Plac	≥Sev 0.83	≥Sev 0 Den 0 Alen		≥Sev 1.18	≥Sev 1.5	≥Sev 1.23

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Pulmonary Hypertension	Ser 1.55	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 3.3	Ser 0 Den 0 Alen	Ser 0 Den 0 Alen	Ser 2.0	Ser 1.55	Ser 1.29	Ser 1 Den 0 Plac			Ser 0 Den 0 Plac			Ser 1 Den 0 Plac	Ser 1 Den 0 Plac	Ser 1 Den 0 Plac
	All 0.91	All 0 Den 2 Plac	All 1.3	All 1.09	All 0.99	All 1.48	All 0.96	All 0.91	All 0.81	All 1.5			All 0.33			All 1.0	All 1.5	All 1.25
	Mod 0.79	Mod 0 Den 1 Plac	Mod 2.79	Mod 0.76	Mod 1.96	Mod 0 Den 1 Alen	Mod 0.78	Mod 0.79	Mod 0.68	Mod 2 Den 0 Plac			Mod 0.99			Mod 3.0	Mod 2 Den 0 Plac	Mod 2 Den 0 Plac
	≥Sev 2.0	≥Sev 0 Den 0 Plac	≥Sev 0 Den 0 Plac	≥Sev 1.32	≥Sev 0 Den 0 Alen	≥Sev 1 Den 0 Alen	≥Sev 1.7	≥Sev 2.0	≥Sev 1.77	≥Sev 2 Den 0 Plac			≥Sev 0 Den 1 Plac			≥Sev 2.0	≥Sev 2 Den 0 Plac	≥Sev 2 Den 0 Plac

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Thrombophlebitis	Ser		Ser	Ser	Ser	Ser	Ser	Ser	Ser	Ser			Ser		Ser	Ser	Ser	Ser
	2.33		0 Den 0 Plac	1.49	0 Den 1 Alen	0 Den 0 Alen	2.0	2.33	1.94	3.0			0 Den 1 Plac		0 Den 0 Alen	1.5	3.0	2.5
	All		All	All	All	All	All	All	All	All			All		All	All	All	All
	1.06		0 Den 1 Plac	0.99	0.33	1 Den 0 Alen	1.05	1.08	0.93	0.6			0 Den 2 Plac		1 Den 0 Alen	0.53	0.6	0.55
	Mod		Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod			Mod		Mod	Mod	Mod	Mod
	0.91		0 Den 1 Plac	1.19	1 Den 0 Alen	1 Den 0 Alen	0.95	0.94	0.83	0.37			0 Den 1 Plac		1 Den 0 Alen	0.33	0.37	0.42
	Sev		Sev	Sev	Sev	Sev	Sev	Sev	Sev	Sev			Sev		Sev	Sev	Sev	Sev
	2.6		0 Den 0 Plac	0.6	0 Den 1 Alen	0 Den 0 Alen	1.59	2.6	2.16	3 Den 0 Plac			0 Den 1 Plac		0 Den 0 Alen	3.0	3 Den 0 Plac	3 Den 0 Plac
	≥Sev		≥Sev	≥Sev	≥Sev	≥Sev	≥Sev	≥Sev	≥Sev	≥Sev			≥Sev		≥Sev	≥Sev	≥Sev	≥Sev
	2.6		0 Den 0 Plac	0.79	0 Den 1 Alen	0 Den 0 Alen	1.69	2.6	2.16	3 Den 0 Plac			0 Den 1 Plac		0 Den 0 Alen	3.0	3 Den 0 Plac	3 Den 0 Plac

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Torsade de Pointes/QT Prolongation	Ser 1.03	Ser 0 Den 0 Plac	Ser 0 Den 0 Plac	Ser 1.45	Ser 1 Den 0 Alen	Ser 0 Den 0 Alen	Ser 1.16	Ser 1.06	Ser 0.91	Ser 2 Den 0 Plac			Ser 0.99			Ser 3.0	Ser 2 Den 0 Plac	Ser 2 Den 0 Plac
	All 0.92	All 2.01	All 2.79	All 1.39	All 0.99	All 0.98	All 1.0	All 0.96	All 0.88	All 2.0			All 2.0			All 2.0	All 2.0	All 1.66
	Mod 0.74	Mod 2 Den 0 Plac	Mod 1 Den 0 Plac	Mod 0.99	Mod 1.5	Mod 0.98	Mod 0.77	Mod 0.76	Mod 0.71	Mod 1 Den 1 Plac			Mod 1 Den 0 Plac			Mod 2.0	Mod 1.0	Mod 0.83
	Fatal 0.3	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 1.98	Fatal 1 Den 0 Alen	Fatal 0 Den 0 Alen	Fatal 0.69	Fatal 0.3	Fatal 0.33	Fatal 0 Den 0 Plac			Fatal 0 Den 0 Plac			Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac	Fatal 0 Den 0 Plac

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

(Table 3 continued on the next page.)

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Table 3 (*continued from the previous page*). Relative Risk Estimates for Events Having at Least One Relative Risk Estimate Associated with a P-value less than 0.10: A Cross-Trial Comparison.

	BROAD SMQ									NARROW SMQ								
Event	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**	**2003 0216**	**2004 0132**	**2004 0135**	**2004 0138**	**2005 0141**	**2005 0234**	**Large, pivotal**	**Placebo Controlled**	**Any PMO Controlled**
Toxic-septic shock conditions	Ser 1.16		Ser 1 Den 0 Plac	Ser 0.76	Ser 0 Den 1 Alen		Ser 0.96	Ser 1.16	Ser 0.97	Ser 3.0			Ser 0 den 4 plac			Ser 0.6	Ser 3.0	Ser 2 Den 0 Plac
	All 1.09		All 0.93	All 0.84	All 0.50		All 0.97	All 1.04	All 0.9	All 1.66			All 0 den 4 plac			All 0.71	All 1.66	All 1.66
	Mod 1.75		Mod 0 Den 0 Plac	Mod 0.87	Mod 0.99		Mod 1.16	Mod 1.75	Mod 1.66	Mod 0 Den 1 Plac			Mod 0 Den 0 Plac			Mod 0 Den 1 Plac	Mod 0 Den 1 Plac	Mod 0.83
	≥Sev 0.84		≥Sev 1 Den 0 Plac	≥Sev 0.63	≥Sev 0 Den 0 Alen		≥Sev 0.75	≥Sev 0.84	≥Sev 0.7	≥Sev 3.0			≥Sev 0 den 4 plac			≥Sev 3 Den 5 Plac	≥Sev 3 Den 1 Plac	≥Sev 1 Den 0 Plac

All = All severity levels pooled; DEN = Denosumab; Fatal = Fatal severity; LT = Life-threatening severity; Mild = Mild severity; Mod = Moderate severity; PLA = Placebo; Ser = Serious event; Sev = Severe severity; ≥Sev = Severe or worse severity

Of the 24 terms in Table 3 having at least one relative risk estimate associated with a p-value less than 0.10, relative risk estimates were close to 1.0 or scattered below and above 1.0, thus, not consistently suggesting an imbalance in incidence, for the following terms: arrhythmia related investigations, cardiac arrhythmias, cardiac arrhythmia terms, cardiac failure, cardiomyopathy, embolic and thrombotic events, embolic and thrombotic events—arterial, embolic and thrombotic events—unspecified, embolic and thrombotic events—venous, Haemodynamic oedema, effusions, etc., Haemorrhages, Haemorrhage Terms (excl lab), Hypertension, Torsade de Pointes/QT Prolongation and Toxic-septic shock conditions.

There appears to be an imbalance in the incidence of gastrointestinal haemorrrhage and gastrointestinal perforation, ulceration, etc. in trial 20030216 (see Table A1 in Appendix VII). The relative risk estimate for serious events of gastrointestinal perforation, ulceration, etc. in Study 20030216 was 1.4 (56 denosumab, 40 placebo) and associated with a p-value of 0.10. The relative risk of gastrointestinal haemorrhage across all levels of severity was 1.38 (69 denosumab, 50 placebo) and associated with a p-value of 0.08. In addition, the relative risk for moderate severity gastrointestinal haemorrages was 2.1 (31 denosumab, 15 placebo) in study 20030216, with a p-value of 0.018. In contrast, gastrointestinal haemorrhage and gastrointestinal perforation, ulceration, etc. was associated with a relative risk of 0.47 (9 denosumab, 19 placebo) for serious events in study 20040138, with a p-value of 0.054. Study 20040138 is a study in cancer patients, while 20030216 was conducted in the PMO population.

There appears to be an imbalance in the incidence of ischaemic heart disease in study 20030216 (see Table A1). The relative risk for serious or severe events of ischaemic heart disease was 1.4 (106 denosumab, 75 placebo) and 2.0 (68 denosumab, 34 placebo), respectively, with corresponding p-values of 0.02 and 0.002. However, no other trial suggests an imbalance in the incidence of ischemic heart disease.

There appears to be an imbalance in the incidence of myocardial infarction events in study 20030216. The relative risk for severe events of myocardial infarction was 2.5 (25 denosumab, 10 placebo), and associated p-value of 0.01. However, no other trial suggests an imbalance in the incidence of myocardial infarction.

There appears to be an imbalance in the incidence of thrombophlebitis in study 20030216. The relative risk for serious events of thrombophlebitis was 2.3 (14 denosumab, 6 placebo), and associated with a p-value of 0.07. However, no other trial suggests an imbalance in the incidence of thrombophlebitis.

The data suggest an imbalance in the incidence of bradyarrhythmias. In study 20030216, the relative risk for serious and moderate events was 1.9 (19 denosumab, 10 placebo) and 3.5 (14 denosumab, 4 placebo), respectively, with corresponding p-values of 0.095 and 0.03. Table A7 shows that the relative risk for serious, moderate, severe and severe or worse bradyarrhythmia events was 2.0 or greater in the analysis of the pooled large, pivotal trial data set, and associated with p-values ranging from 0.06 to 0.09. The relative risk for serious, all, and severe events in study 20040138 was 1.7, 1.8, and 5.0,

respectively, although none of these estimates was associated with a p-value less than 0.10.

The data suggest that there may have been an imbalance in the incidence of conduction defects. Table 3 shows that in study 20030216, the relative risk for serious and severe conduction defects was 2.7 and 5.0, respectively, although none of these estimates were associated with a p-value less than 0.10. In study 20040138, relative risk for all and severe events was 1.5 and 3.0, respectively, although none were associated with a p-value less than 0.10. Table A7 shows that in the pooled large, pivotal dataset, relative risk for severe events was 4.0 (8 denosumab, 2 placebo), with an associated p-value of 0.109.

The data suggest that there may have been an imbalance in disorders of sinus node function. Table A1 shows that in study 20030216, the relative risk for serious, all and moderate disorders of sinus node function was 1.6, 1.7, and 3.7 respectively, however, only moderate severity was associated with a p-value less than 0.10 (p=0.057). Table 3 shows that in study 20040138, relative risk for serious and all events was 2.5 and 2.0, respectively, although none were associated with a p-value less than 0.10. Table A7 shows that in the pooled large, pivotal dataset, relative risk for all and moderate events was 1.76 (23 denosumab, 13 placebo) and 2.6 (13 denosumab, 5 placebo), respectively, with associated p-values of 0.097 and 0.096.

The data suggest that there may have been an imbalance in the incidence of pulmonary hypertension. Table A4 shows that in study 20040138, the relative risk for serious events was 3.3 (10 denosumab, 3 placebo) and associated with a p-value of 0.09. Table 3 shows that the relative risk for serious events was 1.6 in study 20030216, although it was not associated with a p-value less than 0.10. Table A1 shows that the relative risk for severe or worse events was 2.0 (16 denosumab, 8 placebo) in study 20030216 and associated with a p-value of 0.10. Table A7 shows that in the pooled large, pivotal trial dataset, the relative risk for serious and severe or worse events was 2.0 (24 denosumab, 12 placebo) and 1.7 (24 denosumab, 14 placebo), respectively, with associated p-values of 0.05 and 0.106.

Based on the cross-study comparison of events in Table 3, this review will focus on the following adverse events:
•Conduction defects (child of "bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)" which is a child of "cardiac arrhythmias (SMQ)")
•Disorders of sinus node function (child of "bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)" which is a child of "cardiac arrhythmias (SMQ)")
•Bradyarrhythmia (child of "cardiac arrhythmias (SMQ)")
•Pulmonary hypertension

Table 4 tallies subjects experiencing conduction defects by Preferred Term in the pooled large, pivotal trial dataset. The greatest imbalance of subjects was in 'Atrioventricular block complete', with eight subjects receiving denosumab and four subjects receiving

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placebo. In addition, 'Bundle branch block right" had imbalance, as the event was recorded in eleven subjects receiving denosumab and seven receiving placebo.

Table 4. Conduction defects (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	Placebo
Atrioventricular block	1	2
Atrioventricular block complete	8	4
Atrioventricular block first degree	2	1
Atrioventricular block second degree	1	1
Bifascicular block	0	1
Bundle branch block	0	3
Bundle branch block left	6	6
Bundle branch block right	11	7
Electrocardiogram repolarisation abnormality	2	0
Trifascicular block	0	1
Wolff-Parkinson-White syndrome	1	0

Table 5 tallies subjects experiencing conduction defects by Preferred Term in the pooled placebo-controlled PMO studies dataset. It shows little imbalance in the incidence of conduction defects.

Table 5. Conduction defects (SMQ): Number of Subjects in the Placebo-Controlled PMO Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	Placebo
Atrioventricular block	1	1
Atrioventricular block complete	5	3
Atrioventricular block first degree	0	2
Atrioventricular block second degree	1	1
Bifascicular block	0	1
Bundle branch block	0	2
Bundle branch block left	6	6
Bundle branch block right	10	7
Electrocardiogram repolarisation abnormality	2	0
Wolff-Parkinson-White syndrome	1	0

Table 6 tallies subjects experiencing disorders of sinus node function by Preferred Term in the pooled large, pivotal trials dataset. It shows that the greatest imbalance of subjects was in 'Sick sinus syndrome', with sixteen subjects receiving denosumab and five subjects receiving placebo.

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Table 6. Disorders of sinus node function (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	Placebo
Sick sinus syndrome	16	5
Sinus arrhythmia	2	1
Sinus bradycardia	5	7

Table 7 tallies subjects experiencing disorders of sinus node function by Preferred Term in the pooled placebo-controlled PMO studies dataset. It shows the greatest imbalance for the incidence of sick sinus syndrome.

Table 7. Disorders of sinus node function (SMQ): Number of Subjects in the Placebo-Controlled PMO Studies: One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	Placebo
Sick sinus syndrome	11	4
Sinus arrhythmia	2	0
Sinus bradycardia	5	6

Table 8 tallies subjects experiencing Bradyarrhythmias by Preferred Term in the pooled large, pivotal studies dataset. It shows that the greatest imbalance of subjects was in 'Sick sinus syndrome', with sixteen subjects receiving denosumab and five subjects receiving placebo.

Table 8. Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	Placebo
Bradyarrhythmia	0	1
Bundle branch block left	6	6
Bundle branch block right	11	7
Electrocardioagram repolarisation abnormality	2	0
Sick sinus syndrome	16	5
Sinus arrhythmia	2	1
Sinus bradycardia	5	7
Trifascicular block	0	1
Wolff-Parkinson-White syndrome	1	0

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Table 9 tallies subjects experiencing Bradyarrhythmias by Preferred Term in the pooled placebo-controlled studies dataset. It shows the largest discrepany for sick sinus syndrome.

Table 9. Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ): Number of Subjects in the Placebo-Controlled PMO Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	**Placebo**
Bradyarrhythmia	0	1
Bundle branch block left	6	6
Bundle branch block right	10	7
Electrocardioagram repolarisation abnormality	2	0
Sick sinus syndrome	11	4
Sinus arrhythmia	2	0
Sinus bradycardia	5	6
Wolff-Parkinson-White syndrome	1	0

Table 10 tallies subjects experiencing Pulmonary Hypertension by Preferred Term. It shows little imbalance in the incidence of pulmonary hypertension.

Table 10. Pulmonary Hypertension (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	**Placebo**
Carotid pulse decreased	0	1
Dyspnoea	125	136
Emphysema	17	16
Hepatic cirrhosis	3	2
Pulmonary infarction	0	1

Table 11 tallies subjects experiencing Pulmonary Hypertension by Preferred Term in the pooled placebo controlled PMO studies dataset. It shows little imbalance in the Preferred Terms comprising pulmonary hypertension.

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Table 11. Pulmonary Hypertension (SMQ): Number of Subjects in the Placebo-Controlled PMO Studies with One or More Events According to a Broad MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	Placebo
Carotid pulse decreased	0	1
Dyspnoea	94	106
Emphysema	13	13
Hepatic cirrhosis	1	2
Pulmonary infarction	0	1

There is no narrow SMQ grouping of adverse events for bradyarrhythmia, conduction defects or disorders of sinus node function. Table 12 shows a tally of subjects experiencing Pulmonary Hypertension by Preferred Term using narrow SMQ grouping on the pooled large, pivotal trials dataset. It shows little imbalance in the incidence of pulmonary hypertension.

Table 12. Pulmonary Hypertension (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Narrow MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining large, pivotal studies 20030216 and 20040138.

	Denosumab 60 mg Q6M	Placebo
Pulmonary arterial hypertension	0	1
Pulmonary hypertension	6	5
Right atrial dilatation	0	1
Right ventricular failure	1	0

Table 13 tallies subjects experiencing Pulmonary Hypertension by Preferred Term on the pooled placebo-controlled PMO trial dataset. It shows little imbalance in the Preferred Terms comprising pulmonary hypertension.

Table 13. Pulmonary Hypertension (SMQ): Number of Subjects in the Large Pivotal Studies with One or More Events According to a Narrow MedDRA Classification of Preferred Terms. Analysis conducted on a pooled dataset combining studies 20030216, 20040132, 20050172, 20050179 and 20010223.

	Denosumab 60 mg Q6M	Placebo
Pulmonary arterial hypertension	0	1
Pulmonary hypertension	5	2
Right atrial dilatation	0	1
Right ventricular failure	1	0

The lists of preferred terms above are areas where one can statistically assess the imbalance.

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Analysis by MedDRA System Organ Class Hierarchy
To increase the likelihood of detecting potential signals, an alternative analysis of the data was performed. Adverse events were grouped according to MedDRA hierarchy. That is, in addition to evaluating results by SMQ, adverse events were analyzed by their System Organ Class (SOC), Higher Level Group Term (HLGT), Higher Level Term (HLT) and Preferred Term (PT).

Table 14, Table 15, and Table 16 show the groupings by HLGT, HLT and PT for events with a p-value less than 0.10 associated with their event counts and relative risk estimate for the pooled large, pivotal trial dataset. Table 17 shows that no signal (i.e. no $p<0.10$) was apparent at the SOC level.

At the HLGT level, the relative risk for pleural disorders was 1.9 (25 denosumab, 13 placebo, with a 95% confidence interval of 0.98 to 3.74 and a p-value of 0.052. The relative risk for administration site reactions was 3.3 (10 denosumab, 3 placebo), with a 95% confidence interval of 0.91 to 12.1, and a p-value of 0.053.

At the HLT level, two categories had relative risk estimates associated with a p-value less than 0.10: pneumothorax and pleural effusions NEC, and circulatory collapse and shock. Pneumothorax and pleural effusions was associated with a relative risk of 1.92 (25 denosumab, 13 placebo), with a 95% confidence interval of 0.98 to 3.7 and $p = 0.052$. Circulatory collapse and shock was associated with a relative risk of 3.0 (9 denosumab, 3 placebo), with a 95% confidence interval of 0.81 to 11.0 and $p=0.084$.

At the PT level, cardiac failure (RR=1.43 (0.96,2.13); p=0.073), pleural effusion (RR=2.3 (1.09,4.8); p=0.024), essential hypertension (RR=2.37 (1.04, 5.4); p=0.035), sick sinus syndrome (RR=3.2 (1.17, 8.7); p=0.017), and orthostatic hypotension (RR=3.0 (0.96, 9.26); p=0.046) were associated with a p-value less than 0.10. Event counts are provided in Table 14. Four events were associated with zero events in the placebo group and one or more events in the denosumab group: aortic dilatation (3 denosumab events), dilatation atrial (3 denosumab events), lower gastrointestinal haemorrhage (3 denosumab events), and pulse absent (3 denosumab events).

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Table 14. HLGT Grouping of Events for the Pooled Large, Pivotal Trial Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLGT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Coronary artery disorders	DEN	307	1.16	0.064	(0.99, 1.36)
	PLA	262			
Pleural disorders	DEN	25	1.92	0.052	(0.98, 3.74)
	PLA	13			
Administration site reactions	DEN	10	3.32	0.053	(0.91, 12.1)
	PLA	3			
Infections - pathogen unspecified	DEN	1	0.17	0.070	(0.02, 1.38)
	PLA	6			

Table 15. HLT Grouping of Events for the Pooled Large, Pivotal Trial Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Pneumothorax and pleural effusions NEC	DEN	25	1.92	0.052	(0.98, 3.74)
	PLA	13			
Cardiac disorders NEC	DEN	3	0.30	0.051	(0.082, 1.09)
	PLA	10			
Circulatory collapse and shock	DEN	9	3.0	0.084	(0.81, 11.0)
	PLA	3			
Eye injuries NEC	DEN	2	0.22	0.034	(0.048, 1.0)
	PLA	9			
Arterial inflammations*	DEN	0	0	0.062	NA
	PLA	4			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

Reference ID: 3168397

Table 16. PT Grouping of Events for the Pooled Large, Pivotal Trial Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

PT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Oedema peripheral	DEN	242	1.19	0.063	(0.99, 1.43)
	PLA	203			
Cardiac failure	DEN	59	1.43	0.073	(0.96, 2.13)
	PLA	41			
Pleural effusion	DEN	23	2.29	0.024	(1.09, 4.81)
	PLA	10			
Essential hypertension	DEN	19	2.37	0.035	(1.04, 5.40)
	PLA	8			
Sick sinus syndrome	DEN	16	3.19	0.017	(1.17, 8.70)
	PLA	5			
Orthostatic hypotension	DEN	12	2.99	0.046	(0.96, 9.26)
	PLA	4			
Periorbital haematoma	DEN	2	0.22	0.034	(0.048, 1.02)
	PLA	9			
Cardiomegaly	DEN	2	0.25	0.065	(0.053, 1.17)
	PLA	8			
Cardiac disorder	DEN	1	0.17	0.070	(0.02, 1.38)
	PLA	6			
Sinus tachycardia*	DEN	0	0	NA	NA
	PLA	5			
Temporal arteritis*	DEN	0	0	NA	NA
	PLA	4			
Aortic dilatation*	DEN	3	NA	NA	NA
	PLA	0			
Bundle branch block*	DEN	0	0	NA	NA
	PLA	3			
Dilatation atrial*	DEN	3	NA	NA	NA
	PLA	0			
Haemorrhagic stroke*	DEN	0	0	NA	NA
	PLA	3			
Lower gastrointestinal haemmorhage*	DEN	3	NA	NA	NA
	PLA	0			
Pulse absent*	DEN	3	NA	NA	NA
	PLA	0			
Vascular pseudo aneurysm*	DEN	0	0	NA	NA
	PLA	3			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

Table 17. SOC Grouping of Cardiac and Vascular Events for the Pooled Large, Pivotal Trial Dataset.

SOC	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Cardiac disorders	DEN	948	1.06	0.15	(0.98, 1.15)
	PLA	881			
Vascular disorders	DEN	1222	0.993	0.84	(0.93, 1.06)
	PLA	1222			

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Table 18, Table 19 and Table 20 show the groupings by HLGT, HLT and PT for events with a p-value less than 0.10 associated with relative risk estimates for the pooled placebo-controlled PMO trials dataset.

At the HLGT level, the relative risk estimate for administration site reactions and reproductive tract disorders NEC were associated with a p-value of 0.03 and 0.08, respectively. The relative risk for administrative site reactions was 3.66 (95% CI: 1.0, 13.1) with a p-value of 0.032. The relative risk for reproductive tract disorders NEC was 3.0 (95% CI: 0.81,11.1) with a p-value of 0.084. Event counts are provided in Table 18.

Table 18. HLGT Grouping of Events for the Pooled Placebo-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLGT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Coronary artery disorders	Den	244	1.18	0.069	(0.99, 1.42)
	Pla	205			
Administration site reactions	Den	11	3.66	0.032	(1.0, 13.1)
	Pla	3			
Reproductive tract disorders NEC	Den	9	3.0	0.084	(0.81, 11.05)
	Pla	3			

Den = Denosumab
Pla = Placebo

At the HLT level, the following had relative risk estimates greater than 1.0 that were associated with a p-value less than 0.10: myocardial disorders NEC (RR=1.83 (0.81,3.7); p = 0.087), reproductive tract disorders NEC (excl neoplasms) (RR=3.0 (0.81, 11.0); p=0.084), and injection and infusion site reactions (RR=4.5 (0.97, 20.8); p=0.035). Event counts are provided in Table 19.

Table 19. HLT Grouping of Events for the Pooled Placebo-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Myocardial disorders NEC	Den	22	1.83	0.087	(0.91, 3.7)
	Pla	12			
Reproductive tract disorders NEC (excl neoplasms)	Den	9	3.0	0.084	(0.81, 11.0)
	Pla	3			
Injection and infusion site reactions	Den	9	4.5	0.035	(0.97, 20.8)
	Pla	1			
Eye injuries NEC	Den	2	0.25	0.065	(0.053, 1.17)
	Pla	8			
Cardiac disorders NEC	Den	1	0.12	0.021	(0.016, 1.0)
	Pla	8			
Arterial inflammations*	Den	0	0	0.062	NA
	Pla	4			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

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At the PT level, tachycardia (RR=1.56 (0.94,2.6); p=0.08), essential hypertension (RR=2.37 (1.04, 5.4); p=0.03), aortic stenosis (RR=2.6 (0.93,7.3); p=0.06), acute myocardial infarction (RR=2.39 (0.84, 6.8); p=0.09), sick sinus syndrome (RR=2.74 (0.87, 8.6); p=0.07), pleural effusion (RR=3.33 (0.92, 12.1); p=0.05), and genital haemorrhage (RR=3.0 (0.81, 11.0); p=0.08). Event counts are provided in Table 20.

Table 20. PT Grouping of Events for the Pooled Placebo-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

PT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Haematoma	Den	38	0.68	0.06	(0.45, 1.0)
	Pla	56			
Tachycardia	Den	39	1.56	0.08	(0.94, 2.6)
	Pla	25			
Hot flush	Den	22	0.61	0.06	(0.36, 1.0)
	Pla	36			
Hypotension	Den	22	0.61	0.06	(0.36, 1.0)
	Pla	36			
Essential hypertension	Den	19	2.37	0.03	(1.0, 5.4)
	Pla	8			
Aortic stenosis	Den	13	2.59	0.06	(0.93, 7.3)
	Pla	5			
Acute myocardial infarction	Den	12	2.39	0.09	(0.84, 6.8)
	Pla	5			
Sick sinus syndrome	Den	11	2.74	0.07	(0.87, 8.6)
	Pla	4			
Pleural effusion	Den	10	3.33	0.05	(0.92, 12.1)
	Pla	3			
Genital haemorrhage	Den	9	3.0	0.08	(0.81, 11.0)
	Pla	3			
Periorbital haematoma	Den	2	0.25	0.06	(0.05, 1.17)
	Pla	8			
Cardiac disorder*	Den	0	0	0.03	NA
	Pla	5			
Sinus tachycardia*	Den	0	0	0.03	NA
	Pla	5			
Temporal arteritis*	Den	0	0	0.06	NA
	Pla	4			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

Table 21 shows that cardiac disorders and vascular disorders SOCs were not associated with relative risk estimates having a p-value less than 0.10.

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Table 21. SOC Grouping of Events for the Pooled Placebo-ControlledTrials Dataset.

SOC	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Cardiac disorders	Den	792	1.07	0.13	(0.98, 1.18)
	Pla	729			
Vascular disorders	Den	1074	0.98	0.50	(0.91, 1.05)
	Pla	1096			

Den = Denosumab
Pla = Placebo

Table 22, Table 23, Table 24 and Table 25 show the groupings by SOC, HLGT, HLT and PT for events with a p-value less than 0.10 for the pooled placebo- or active- controlled PMO trials dataset.

Table 22 shows that the relative risk for vascular disorders is less than 1.0, which does not suggest a signal at the SOC level.

Table 22. SOC Grouping of Events for the Pooled Placebo- or Active-ControlledTrials Dataset.

SOC	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Cardiac disorders	Den	819	0.93	0.14	(0.85, 1.02)
	Pla	729			
Vascular disorders	Den	1133	0.86	.000045	(0.80, 0.92)
	Pla	1096			

Den = Denosumab
Pla = Placebo

At the HLGT level, only administration site reactions were associated with relative risk greater than one (RR=3.0; 11 denosumab, 3 placebo; p-value=0.072).

Table 23. HLGT Grouping of Events for the Pooled Placebo- or Active-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLGT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Vascular hypertensive disorders	Den	706	0.86	0.0015	(0.78, 0.94)
	Pla	686			
Joint disorders	Den	71	0.75	0.070	(0.54, 1.0)
	Pla	79			
Cardiac valve disorders	Den	58	0.73	0.078	(0.51, 1.0)
	Pla	66			
Vascular haemorrhagic disorders	Den	47	0.67	0.041	(0.46, 0.99)
	Pla	58			
Administration site reactions	Den	11	3.0	0.072	(0.85, 10.9)
	Pla	3			

Den = Denosumab
Pla = Placebo

Table 24 shows that at the HLT level, there was no suggestion of increased risk.

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Table 24. HLT Grouping of Events for the Pooled Placebo- or Active-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

HLT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Vascular hypertensive disorders NEC	Den	692	0.86	0.0023	(0.78, 0.95)
	Pla	669			
Haemorrhages NEC	Den	47	0.67	0.041	(0.46, 0.99)
	Pla	58			
Vascular hypotensive disorders	Den	31	0.64	0.062	(0.40, 1.03)
	Pla	40			
Cardiac valve disorders NEC	Den	3	0.31	0.077	(0.08, 1.17)
	Pla	8			
Eye injuries NEC	Den	2	0.21	0.051	(0.04, 0.98)
	Pla	8			
Cardiac disorders NEC	Den	1	0.10	0.014	(0.01, 0.83)
	Pla	8			
Arterial inflammations*	Den	0	0	0.042	NA
	Pla	4			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

Table 25 shows that at the PT level, there was no suggestion of increased risk.

Table 25. PT Grouping of Events for the Pooled Placebo- or Active-ControlledTrials Dataset: Events with Relative Risk Estimates Having a P-value Less than 0.10.

PT	Arm	Number of Events	RR	p-value	95% Confidence Interval for RR
Hypertension	Den	669	0.84	.00066	(0.76, 0.93)
	Pla	660			
Haematoma	Den	41	0.61	0.014	(0.41, 0.91)
	Pla	56			
Hypotension	Den	23	0.53	0.015	(0.31, 0.89)
	Pla	36			
Extrasystoles	Den	20	0.57	0.051	(0.32, 1.0)
	Pla	29			
Cardiac Failure Congestive	Den	16	0.58	0.087	(0.31, 1.1)
	Pla	23			
Periorbital haematoma	Den	2	0.21	0.051	(0.04, 0.98)
	Pla	8			
Cardiac disorder*	Den	0	0	0.019	NA
	Pla	5			
Sinus tachycardia*	Den	0	0	0.019	NA
	Pla	5			
Temporal arteritis*	Den	0	0	0.042	NA
	Pla	4			
Vascular pseudoaneurysm*	Den	0	0	0.093	NA
	Pla	3			

*One arm is associated with zero events
Den = Denosumab
Pla = Placebo

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According to this MedDRA SOC analysis, it appears that administration site reactions are the only consistent signal in the trials.

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6. DISCUSSION

This report describes three approaches to grouping MedDRA terms for analyzing cardiovascular adverse events – the sponsor's approach, SMQ term grouping, and MedDRA SOC grouping. It considers adjudicated and non-adjudicated data.

Risk of cardiovascular events was computed separately for each of nine studies, as well as for the studies pooled according to whether they were large pivotal studies, placebo-controlled, or controlled studies in the PMO population. A broad and narrow MedDRA search strategy was used to group terms for the analysis. Thus, there were eight assessments performed by the reviewer, i.e. 2 MedDRA approaches (broad and narrow) for each of four ways of grouping data (all studies separately, large, pivotal studies pooled, placebo-controlled studies pooled, PMO studies pooled).

Given that the SMQ grouping was developed by a panel of experts representing different viewpoints, the results of that grouping holds more weight in this review. In addition, the analysis of non-adjudicated data is of greater interest since it permits the use of data from more studies and does not rely on an unvetted grouping of MedDRA terms.

An analysis of the adverse event data by SMQ suggested an imbalance in conduction defects, disorders of sinus node function, bradyarrhythmia and pulmonary hypertension. The Preferred Terms comprising these SMQs were explored in greater detail to determine the source of the imbalance.

The relative risk for conduction defects estimated in each pooled dataset explored (pooled large, pivotal trails, pooled placebo-controlled PMO trials, pooled placebo- or active-controlled PMO trials) ranged from 1.66-2.66 for serious events, although none of these RR estimates was associated with $p<0.10$. The relative risk for severe events was greater than or equal to 4.0, with $p<0.10$ for the pooled large, pivotal trial dataset. The relative risk estimate was close to 1.0 when data from all severity levels were pooled.

The imbalance in conduction defects was due to events of atrioventricular block complete (8 subjects denosumab, 4 subjects placebo) and bundle branch block right (11 subjects denosumab vs 7 subjects placebo) in the pooled large, pivotal trials dataset. Similarly, in the pooled placebo-controlled PMO study dataset, atrioventricular block complete (5 denosumab vs. 3 placebo) and bundle branch block right (10 denosumab vs. 7 placebo) were associated with the imbalance in conduction defects.

The relative risk for disorders of sinus node function estimated in each pooled dataset explored ranged from 1.42-1.77 for serious events, although none of these estimates were associated with $p<0.10$. The analysis of all severity levels grouped together in the pooled large, pivotal trials dataset yielded a relative risk estimate of 1.8, and was associated with $p<0.10$. Moderately severe disorders of sinus node function had relative risk estimates ranging from 2.7-3.7 in all of the pooled datasets explored, and these estimates were associated with $p<0.10$.

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The imbalance in disorders of sinus node function are due to reports of sick sinus syndrome—16 denosumab vs. 5 placebo in the pooled large, pivotal trial dataset, and 11 denosumab vs. 4 placebo in the pooled placebo-controlled PMO trial dataset.

The relative risk for serious events of bradyarrhythmia was 1.9 for the pooled large, pivotal trial dataset, as well as the pooled placebo-controlled PMO trial dataset. Each of these estimates of RR was associated with $p<0.10$. Relative risk for moderate events in all pooled datasets explored ranged from 2.3-3.5, and were associated with $p<0.10$. Relative risk for severe events in the pooled large, pivotal trial dataset was 2.1, and associated with $p<0.10$.

Bradyarrhythmia is a parent SMQ for conduction defects and disorders of sinus node function. When examined at the preferred term level, it was apparent that the terms associated with the imbalance in conduction defects and disorders of sinus node function were driving the imbalance in bradyarrhythmia, specifically, atrioventricular block complete, bundle branch block right and sick sinus syndrome.

The relative risk for serious events of pulmonary hypertension was 2.0 in the pooled large, pivotal trial dataset, and associated with a $p<0.10$. The relative risk for events of a severe or worse nature ranged from 1.7-2.0 in the pooled large, pivotal and pooled placebo-controlled datasets, and were associated with $p<0.10$.

The analysis of preferred terms in pulmonary hypertension showed that in the narrow SMQ terms list, pulmonary hypertension was observed in 5 subjects receiving denosumab and 2 receiving placebo.

7. CONCLUSION

Bradyarrhytmia and ischaemic heart disease are the only signals that appear consistently in this exploratory analysis of the data from the nine studies of denosumab in PMO and HALT populations.

Bradyarrhythmia had a consistent signal according to the broad MedDRA search strategy. In the analysis of all PMO studies pooled, relative risk was estimated as 2.9 for moderate events and 1.7 for all worse severity levels. This trend was observed in the analysis of study 20030216 alone (RR=3.5), which appears to have heavily influenced the pooled analysis. Figure 1 shows this graphically in a Forest Plot of odds ratio estimates in each of the nine trials evaluated.

Severe ischaemic heart disease was associated with relative risk estimates greater than one in several analyses, with RR ranging from 1.7 to 2.0. There was a consistent estimate of relative risk greater than one across all severity levels for the placebo-controlled and pooled PMO studies. Relative risk estimates ranging from 1.4 to 1.8 having p-values less than 0.10 were observed for all worse severity levels in the pooled placebo-controlled and PMO studies. Figure 2 shows this graphically in a Forest Plot of odds ratio estimates in each of the nine trials evaluated.

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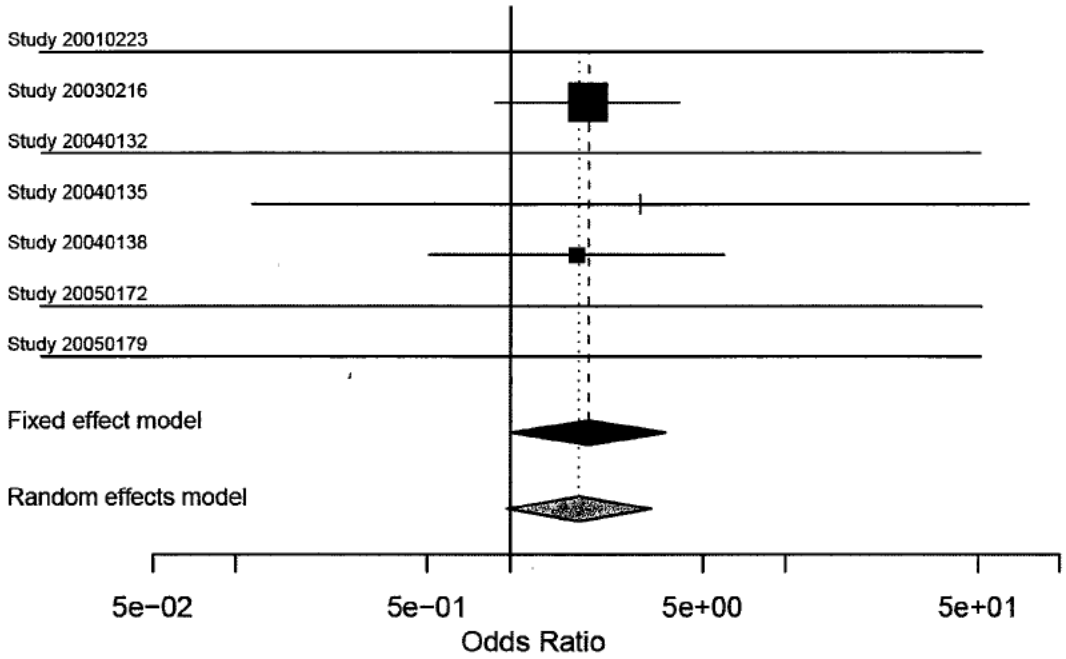
This exploratory result will be discussed with the review team to evaluate clinical relevance.

Figure 1. Forest Plot of Odds Ratio for Bradyarrhythmias: Serious Adverse Events.



Denosumab vs. Placebo

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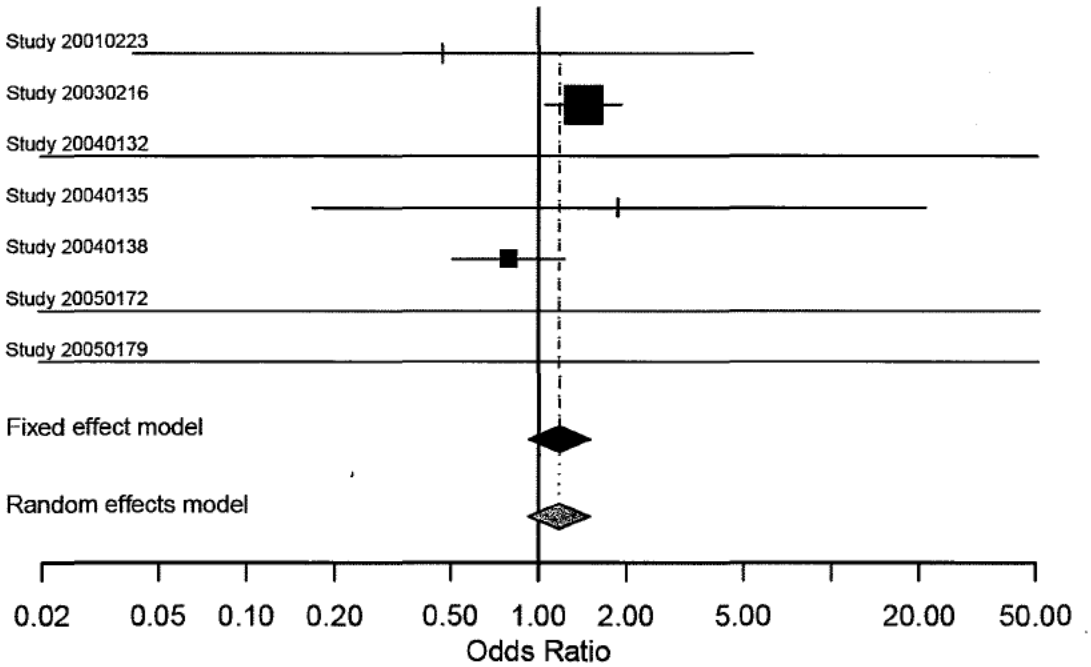
Figure 2. Forest Plot of Odds Ratio for Ischaemic Heart Disease: Serious Adverse Events.



Denosumab vs. Placebo

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APPENDICES

Appendix I Sponsor's Procedure for Adjudicating Adverse Events

The sponsor's procedure for adjudicating cardiovascular adverse events in studies 20030216 and 20040138 is described in this section.

An adjudication committee was formed to define and apply standard criteria for consistent, independent, and unbiased review of serious adverse event (SAE) reports. The adjudication committee (i.e. the San Francisco Coordinating Center; SFCC) adjudicated any serious adverse cardiovascular events in Study 20030216 and 20040138 that were sent to the SFCC by the sponsor. The SFCC was blinded to treatment arm.

The sponsor received all Serious Adverse Event (SAE) reports consistent with their global SAE reporting processes. The sponsor's Safety team screened all SAE Reports for deaths and potential cardiovascular (CV) events according to predefined MedDRA preferred terms approved by the SFCC. The sponsor was blinded to treatment arm while screening the SAEs. All SAEs matching predefined MedDRA preferred terms within those categories were sent to SFCC for review and adjudication.

Two cardiologists from the SFCC blindly reviewed and independently assessed events to determine an adjudicated diagnosis according to the event definitions classification criteria. An Event Specialist compared adjudication forms from each assigned cardiologist to determine if the classification was concordant or discordant. If the codes were discordant, the case was sent to a third Cardiologist for review. Cases which were concordant in two of the three adjudications were reviewed by a Physician Adjudicator to determine if the case warranted holding for discussion or if the case should be considered complete and the majority decision reflected on a Final Decision Summary Form. The Oncologist, upon the request of a Cardiologist, assessed deaths that occurred in the Study 20040138 to determine if they were cancer-related.

Only events confirmed positive by the adjudication committee to meet cardiovascular event definition criteria were included in the sponsor's analysis. In addition, each non-fatal event code that had a corresponding fatal event code within the same event category (ACS, stroke, other vascular event, arrhythmia, or CHF) and with the same serious adverse event number and the same date of onset was flagged and excluded from the analysis. Only the corresponding fatal event was included in the sponsor's analysis.

The sponsor analyzed time to first adjudicated positive cardiovascular event using a Cox proportional hazards model stratifying by study with treatment group and the baseline cardiovascular risk level as the independent variable (defined in Appendix II).

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Appendix II Criteria for determining baseline cardiovascular risk

A total cardiovascular risk assessment score was computed for each subject at baseline by summing the points from each individual risk factor based on the modified Raloxifene Use for the Heart (RUTH) criteria used in the Multiple Outcomes of Raloxifene (MORE) study as listed in the table provided below. Subjects with a total cardiovascular risk assessment score of ≥4 points were considered at high risk for cardiovascular events, and subjects with <4 points were considered at low risk for cardiovascular events.

Modified RUTH Criteria for Defining a Population at High-Risk for Cardiovascular Events.

Cardiovascular risk factor	Points
Prior myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgery	4
Diabetes mellitus	3
Age ≥70 years	2
Age 65-69 years	1
Former/current smoker[a]	1
Hypertension[a]	1
High cholesterol[a]	1

RUTH = Raloxifene Use for the Heart

[a]An extra point is added if all 3 criteria "former/current smoker", "hypertension", and "high cholesterol" were met (i.e. yielding a total of 4 points).

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Appendix III Details on Reviewer's Broad MedDRA SMQ Search Strategy

Cardiac arrhythmias (SMQ)
  Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)
  Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)
    Conduction defects (SMQ)
    Disorders of sinus node function (SMQ)
  Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)
    Supraventricular tachyarrhythmias (SMQ)
    Ventricular tachyarrhythmias (SMQ)
  Congenital and neonatal arrhythmias (SMQ)
  Arrhythmia related investigations, signs and symptoms (SMQ)
Cardiac Failure (SMQ)
Cardiomyopathy (SMQ)
Cerebrovascular disorders (SMQ)
  Central nervous system haemorrhages and cerebrovascular accidents (SMQ)
    Haemorrhagic cerebrovascular conditions (SMQ)
    Ischaemic cerebrovascular conditions (SMQ)
Embolic and thrombotic events (SMQ)
  Embolic and thrombotic event, arterial (SMQ)
  Embolic and thrombotic event, venous (SMQ)
  Embolic and thrombotic event, vessel type unspecified and mixed arterial venous (SMQ)
Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)
  Gastrointestinal haemorrhage (SMQ)
Haemodynamic oedema, effusions and fluid overload (SMQ)
Haemolytic disorders (SMQ)
Haemorrhages (SMQ)
  Haemorrhage laboratory terms (SMQ)
  Haemorrhage terms (excl laboratory terms) (SMQ)
Hypertension (SMQ)
Ischaemic heart disease (SMQ)
  Myocardial infarction (SMQ)
Pulmonary hypertension (SMQ)
Shock (SMQ)
  Anaphylactic/anaphylactoid shock conditions (SMQ)
  Hypoglycaemic and neurogenic shock conditions (SMQ)
  Hypovolaemic shock conditions (SMQ)
  Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)
  Torsade de pointes, shock-associated conditions (SMQ)
  Toxic-septic shock conditions (SMQ)
Thrombophlebitis (SMQ)
Torsade de pointes / QT prolongation (SMQ)

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Appendix IV Details on Reviewer's Narrow MedDRA SMQ Search Strategy

Cardiac Failure (SMQ)
Cardiomyopathy (SMQ)
Cerebrovascular disorders (SMQ)
  Central nervous system haemorrhages and cerebrovascular accidents (SMQ)
    Haemorrhagic cerebrovascular conditions (SMQ)
    Ischaemic cerebrovascular conditions (SMQ)
Embolic and thrombotic events (SMQ)
  Embolic and thrombotic event, arterial (SMQ)
  Embolic and thrombotic event, venous (SMQ)
Haemodynamic oedema, effusions and fluid overload (SMQ)
Haemolytic disorders (SMQ)
Haemorrhages (SMQ)
  Haemorrhage laboratory terms (SMQ)
  Haemorrhage terms (excl laboratory terms) (SMQ)
Hypertension (SMQ)
Ischaemic heart disease (SMQ)
  Myocardial infarction (SMQ)
Pulmonary hypertension (SMQ)
Shock (SMQ)
  Anaphylactic/anaphylactoid shock conditions (SMQ)
  Hypoglycaemic and neurogenic shock conditions (SMQ)
  Hypovolaemic shock conditions (SMQ)
  Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)
  Torsade de pointes, shock-associated conditions (SMQ)
  Toxic-septic shock conditions (SMQ)
Thrombophlebitis (SMQ)
Torsade de pointes / QT prolongation (SMQ)

Reference ID: 3168397

Appendix V Location of Data and Reports Utilized in this Review

Description	Location
Adverse Events Analysis Data	**5.3.5.3 iss – Integrated Summary of Safety** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis**aae.xpt**
Cardiovascular Events Analysis Data	**5.3.5.3 iss – Integrated Summary of Safety** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis**acecv.xpt**
Subject Level Information Analysis Data	**5.3.5.3 iss – Integrated Summary of Safety** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis**aslinfo.xpt**
Clinical Overview	**2.5 Clinical Overview** cbsap58\M\eCTD_Submissions\STN125320\0000\m2\25-clin-over**clinical-overview.pdf**
Reviewer's Guide to Data Conventions	**5.3.5.3.25.3.3 Analysis Data Definition** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis\ **crtreviewersguide.pdf**
CV Event Adjudication Manual of Operations	**Section 5.3.5.3.28 Integrated analysis of safety – integrated summary of safety report** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pmo\5353-rep-analys-data-more-one-stud\iss**cv-manual-procedures.pdf**
Definitions and links to ADaM datasets	**5.3.5.3.25.3.3 Analysis Data Definition** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\iss\analysis**define.xml**
Statistical Analysis Plan for the Summary of Safety	**5.3.5.3.12 Statistical Methods Interim Analysis Plan** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pmo\5353-rep-analys-data-more-one-stud\iss**isap.pdf**
Integrated Analysis of Safety	**Section 5.3.5.3.28 Integrated analysis of safety – integrated summary of safety report** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pmo\5353-rep-analys-data-more-one-stud**iss.pdf**
MedDRA coding conventions	**Section 5.3.5.3.28 Integrated analysis of safety – integrated summary of safety report** cbsap58\M\eCTD_Submissions\STN125320\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pmo\5353-rep-analys-data-more-one-stud\iss**medra-coding-guidelines.pdf**
Synopses of individual studies	**Section 2.7.6 Synopses of Individual Studies** cbsap58\M\eCTD_Submissions\STN125320\0000\m2\27-clin-sum**synopses-indiv-studies.pdf**
Summary of Clinical Safety	**Section 2.7.4 Summary of Clinical Safety** cbsap58\M\eCTD_Submissions\STN125320\0000\m2\27-clin-sum**summary-clin-safety-pdf**

Appendix VI MedDRA Version Utilized in Each Clinical Trial Reviewed.

Note that the Integrated Summary of Safety dataset harmonized version on MedDRA version 11.0.

Study	MedDRA version
20030216	11.0
20040132	9.0
20040135	9.0
20040138	11.0
20050172	10.0
20050179	10.0
20050234	10.0
20010223	9.0
20050141	10.0

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Appendix VII Additional Details on Reviewer's Analysis

Broad Search Criteria: All Studies Analyzed Separately

Table A1 and Table A2 list the adverse cardiovascular events for which a p-value associated with relative risk estimates is equal to or less than 0.10 for at least one severity level when a broad MedDRA SMQ search strategy was employed to analyze each of the nine studies separately.

The events identified were placed in the context with the same event of all severity levels, regardless of statistical significance. That is, if risk of "moderate bradycardia" was observed to occur with $p<0.10$, then the risk estimates for mild, moderate, severe, life-threatening, serious and severe or worse bradycardia were added to the table regardless of whether they occurred with $p<0.10$.

Table A1 shows the estimated relative risk for moderate bradyarrhythmia was 3.5 ($p=0.031$) in subjects receiving denosumab in study 20030216. Relative risk estimates were all greater than one for severe (RR=1.66), life-threatening (RR=2.0), serious (RR=1.9) and severe (RR=1.71) bradyarrhythmia, but none of these estimates were associated with a p-value less than 0.10. No subject experienced a fatal bradyarrhythmia in study 20030216. The relative risk for moderate disorders of sinus node function was 3.66 ($p=0.057$). The relative risk of serious events was 1.57, but this estimate was associated with a p-value of 0.348. Relative risk was unity for severe events (RR=1). The relative risk (RR=1.52) for severe embolic and thrombotic events had a p-value of less than 0.05 ($p=0.018$), but the relative risk of mild, moderate, life-threatening or fatal events was unity. There was a statistically significant ($p=0.032$) relative risk of 1.73 for severe arterial embolic and thrombotic events, but estimated relative risk for the fatal (RR=1.28) and serious (RR=1.24) categories was not associated with a p-value less than 0.05. The relative risk of having an arterial embolic or thrombotic event of category severe or worse was 1.32 with a p-value of 0.179.

The relative risk for moderate gastrointestinal haemorrhage was 2.0 ($p=0.018$). Although no other level of gastrointestinal haemorrhage severity was associated with a p-value less than 0.10, there was trend toward relative risk greater than unity for the severe (RR=1.33) and serious (RR=1.21) categories. One subject experienced a fatal gastrointestinal haemorrhage in study 20030216, and that subject received denosumab.

P-values less than 0.10 were observed for severe (RR=2.0, $p=0.0007$), severe or worse (RR=1.72, $p=0.002$), and serious (RR=1.41, $p=0.021$) ischaemic heart disease events in subjects receiving denosumab in study 20030216. In this study, 9 subjects receiving denosumab and 7 receiving placebo had a fatal event, yielding a relative risk of 1.28 ($p=0.62$). The relative risk of severe myocardial infarction was 2.5 ($p=0.011$). The relative risk of life-threatening or fatal events was approximately unity. The relative risk of serious events was 1.52, but this was associated with a p-value of 0.147.

Table A2 shows the relative risk for severe cardiac arrhythmias was 1.52 ($p=0.056$), however, no other level of arrhythmia severity was associated with a p-value less than

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0.10 in study 20040138. The estimated relative risk for fatal cardiac arrhythmias was 1.98 (p=0.507), and for serious cardiac arrhythmias 1.28 (p=0.323). Although one estimate of relative risk was associated with a p-value less than 0.10 for one category of severity for each of the following adverse events – cardiac failure, gastrointestinal perforation, or haemodynamic oedema – estimates of relative risk were above and below unity for the remaining severity levels.

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Table A1. Broad Search Criteria With All Studies Analyzed Separately: Study 20030216 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Arrhythmia related investigations								
	All pooled	206	191	1.08	(0.89, 1.3)	3.73	(-6.07, 13.5)	0.455
	Mild/1	125	96	1.3	(1.0, 1.7)	7.40	(0.0020, 15)	0.05
	Moderate/2	66	75	0.88	(0.6, 1.2)	-2.37	(-8.31, 3.58)	0.435
	Severe/3	20	19	1.05	(0.6, 2.0)	0.245	(-2.90, 3.39)	0.879
	Life-threatening/4	5	1	4.99	(0.6, 43)	1.03	(-0.207, 2.3)	0.219
	Fatal/5	3	10	0.3	(0.08, 1.1)	-1.81	(-3.6, 0.012)	0.057
	≥Severe/3	28	30	0.93	(0.56, 1.6)	-0.535	(-4.37, 3.30)	0.785
	Serious	38	35	1.08	(0.69, 1.7)	0.749	(-3.55, 5.04)	0.733
Bradyarrhythmias								
	All pooled	38	29	1.31	(0.81, 2.1)	2.30	(-1.82, 6.41)	0.274
	Mild/1	14	21	0.66	(0.34, 1.3)	-1.82	(-4.80, 1.17)	0.233
	Moderate/2	14	4	3.49	(1.2, 10.6)	2.57	(0.433, 4.71)	0.031
	Severe/3	10	6	1.66	(0.60, 4.6)	1.03	(-0.99, 3.04)	0.319
	Life-threatening/4	2	1	1.99	(0.18, 22)	0.257	(-0.617, 1.1)	1
	Fatal/5	0	0		N.A.		N.A.	.
	≥Severe/3	12	7	1.71	(0.67, 4.3)	1.28	(-0.916, 3.5)	0.253
	Serious	19	10	1.9	(0.88, 4.1)	2.31	(-0.404, 5.0)	0.095
Cardiac Arrhythmias								
	All pooled	377	365	1.03	(0.90, 1.18)	2.85	(-10.2, 15.9)	0.6699
	Mild/1	205	189	1.08	(0.89, 1.31)	3.99	(-5.77, 13.8)	0.4231
	Moderate/2	155	149	1.04	(0.83, 1.29)	1.45	(-7.19, 10.1)	0.7421
	Severe/3	50	51	0.98	(0.66, 1.44)	-0.291	(-5.33, 4.75)	0.9099
	Life-threatening/4	7	5	1.4	(0.44, 4.40)	0.511	(-1.24, 2.26)	0.7742
	Fatal/5	3	10	0.3	(0.08, 1.09)	-1.81	(-3.6, 0.012)	0.0569
	≥Severe/3	60	64	0.94	(0.66, 1.33)	-1.07	(-6.65, 4.51)	0.7065
	Serious	97	87	1.11	(0.84, 1.48)	2.52	(-4.25, 9.28)	0.4664
Cardiac Failure								
	All pooled	268	236	1.13	(0.96, 1.34)	8.08	(-2.88, 19.0)	0.1487
	Mild/1	140	135	1.03	(0.82, 1.30)	1.20	(-7.03, 9.42)	0.7755
	Moderate/2	116	90	1.29	(0.98, 1.69)	6.63	(-0.52, 13.8)	0.0692
	Severe/3	26	24	1.08	(0.62, 1.88)	0.499	(-3.06, 4.06)	0.7836
	Life-threatening/4	3	5	0.6	(0.14, 2.50)	-0.518	(-1.95, 0.91)	0.5071
	Fatal/5	6	8	0.75	(0.26, 2.15)	-0.520	(-2.41, 1.37)	0.5893
	≥Severe/3	33	36	0.91	(0.57, 1.46)	-0.796	(-4.97, 3.38)	0.7088
	Serious	39	41	0.95	(0.61, 1.47)	-0.542	(-5.04, 3.95)	0.8132
Cardiomyopathy								
	All pooled	358	368	0.97	(0.84, 1.11)	-2.82	(-15.8, 1.0.1)	0.6699
	Mild/1	194	185	1.05	(0.86, 1.27)	2.19	(-7.40, 11.8)	0.6539
	Moderate/2	156	163	0.95	(0.77, 1.18)	-1.91	(-10.7, 6.92)	0.6718
	Severe/3	43	42	1.02	(0.67, 1.56)	0.229	(-4.40, 4.86)	0.9226
	Life-threatening/4	5	5	1	(0.29, 3.44)	-0.00332	(-1.60, 1.59)	1
	Fatal/5	4	11	0.36	(0.12, 1.14)	-1.81	(-3.76, 0.15)	0.0762
	≥Severe/3	50	57	0.87	(0.60, 1.28)	-1.84	(-7.03, 3.35)	0.4872
	Serious	67	66	1.01	(0.72, 1.42)	0.214	(-5.56, 5.99)	0.9422

(Table A1 is continued on the next page.)

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Table A1 (continued from the previous page). Broad Search Criteria With All Studies Analyzed Separately: Study 20030216 Results.

Disorders of Sinus Node Function								
	All pooled	17	10	1.7	(0.78, 3.7)	1.79	(-0.824, 4.4)	0.179
	Mild/1	2	3	0.66	(0.11, 4.0)	-0.259	(-1.39, 0.87)	0.687
	Moderate/2	11	3	3.66	(1.02, 13)	2.06	(0.171, 3.94)	0.057
	Severe/3	5	5	1	(0.29, 3.4)	-0.0033	(-1.60, 1.59)	1
	Life-threatening/4	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	6	5	1.2	(0.37, 3.92)	0.254	(-1.42, 1.93)	1
	Serious	11	7	1.57	(0.61, 4.04)	1.02	(-1.11, 3.16)	0.348
Embolic and thrombotic events								
	All pooled	184	176	1.04	(0.85, 1.28)	1.94	(-7.41, 11.3)	0.684
	Mild/1	41	45	0.91	(0.60, 1.38)	-1.06	(-5.72, 3.60)	0.656
	Moderate/2	59	63	0.93	(0.66, 1.33)	-1.07	(-6.61, 4.46)	0.7044
	Severe/3	79	52	1.52	(1.07, 2.14)	6.91	(1.19, 12.6)	0.018
	Life-threatening/4	15	17	0.88	(0.44, 1.76)	-0.526	(-3.38, 2.33)	0.718
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.267	(-2.89, 2.35)	0.842
	≥Severe/3	101	81	1.24	(0.93, 1.66)	5.09	(-1.64, 11.8)	0.138
	Serious	128	112	1.14	(0.89, 1.46)	4.04	(-3.66, 11.7)	0.304
Embolic and thrombotic events, arterial								
	All pooled	93	76	1.22	(0.90, 1.65)	4.32	(-2.17, 10.8)	0.192
	Mild/1	18	16	1.12	(0.57, 2.20)	0.504	(-2.43, 3.44)	0.737
	Moderate/2	25	22	1.13	(0.64, 2.01)	0.757	(-2.69, 4.21)	0.667
	Severe/3	40	23	1.73	(1.04, 2.89)	4.36	(0.370, 8.35)	0.032
	Life-threatening/4	4	10	0.4	(0.13, 1.27)	-1.55	(-3.44, 0.34)	0.118
	Fatal/5	9	7	1.28	(0.48, 3.44)	0.510	(-1.51, 2.53)	0.620
	≥Severe/3	53	40	1.32	(0.88, 1.99)	3.32	(-1.52, 8.16)	0.179
	Serious	67	54	1.24	(0.87, 1.77)	3.31	(-2.20, 8.82)	0.239
Embolic and thrombotic events, unspecified								
	All pooled	70	54	1.29	(0.91, 1.84)	4.08	(-1.50, 9.66)	0.1516
	Mild/1	17	15	1.13	(0.57, 2.26)	0.505	(-2.35, 3.36)	0.7286
	Moderate/2	23	19	1.21	(0.66, 2.21)	1.02	(-2.25, 4.28)	0.5415
	Severe/3	28	16	1.75	(0.95, 3.22)	3.08	(-0.26, 6.42)	0.071
	Life-threatening/4	6	3	1.99	(0.50, 7.97)	0.770	(-0.74, 2.28)	0.5076
	Fatal/5	3	4	0.75	(0.17, 3.34)	-0.260	(-1.60, 1.08)	0.7261
	≥Severe/3	37	23	1.6	(0.96, 2.69)	3.59	(-0.31, 7.48)	0.0712
	Serious	49	37	1.32	(0.86, 2.02)	3.06	(-1.59, 7.72)	0.1973

(Table A1 is continued on the next page.)

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Table A1 (continued from the previous page). Broad Search Criteria With All Studies Analyzed Separately: Study 20030216 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Gastrointestinal haemorrhage								
	All pooled	69	50	1.38	(0.96, 1.98)	4.86	(-0.61, 10.3)	0.082
	Mild/1	27	27	1	(0.59, 1.70)	-0.0179	(-3.72, 3.68)	0.992
	Moderate/2	31	15	2.06	(1.11, 3.81)	4.11	(0.695, 7.52)	0.018
	Severe/3	12	9	1.33	(0.56, 3.15)	0.766	(-1.54, 3.08)	0.516
	Life-threatening/4	1	1	1	(0.06, 15.9)	-0.00066	(-0.72, 0.71)	1
	Fatal/5	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	≥Severe/3	14	10	1.4	(0.62, 3.14)	1.02	(-1.45, 3.49)	0.417
	Serious	23	19	1.21	(0.66, 2.21)	1.02	(-2.25, 4.28)	0.542
Gastrointestinal perforation, ulceration, etc.								
	All pooled	195	168	1.16	(0.95, 1.42)	6.84	(-2.56, 16.2)	0.1538
	Mild/1	86	86	1	(0.74, 1.34)	-0.0571	(-6.61, 6.49)	0.9864
	Moderate/2	87	64	1.36	(0.98, 1.87)	5.88	(-0.27, 12.0)	0.0609
	Severe/3	36	27	1.33	(0.81, 2.19)	2.30	(-1.69, 6.29)	0.2592
	Life-threatening/4	2	3	0.66	(0.11, 3.98)	-0.259	(-1.39, 0.87)	0.687
	Fatal/5	1	1	1	(0.06, 15.9)	-0.00066	(-0.72, 0.71)	1
	≥Severe/3	38	30	1.26	(0.78, 2.03)	2.04	(-2.11, 6.18)	0.3352
	Serious	56	40	1.4	(0.93, 2.09)	4.09	(-0.83, 9.0)	0.103
Ischaemic heart disease								
	All pooled	198	173	1.14	(0.94, 1.39)	6.32	(-3.17, 15.8)	0.192
	Mild/1	61	65	0.94	(0.66, 1.32)	-1.07	(-6.70, 4.55)	0.709
	Moderate/2	93	77	1.2	(0.89, 1.62)	4.07	(-2.44, 10.6)	0.221
	Severe/3	68	34	1.99	(1.32, 3.00)	8.73	(3.67, 13.8)	.0007
	Life-threatening/4	11	8	1.37	(0.55, 3.41)	0.767	(-1.43, 2.96)	0.494
	Fatal/5	9	7	1.28	(0.48, 3.44)	0.510	(-1.51, 2.53)	0.620
	≥Severe/3	83	48	1.72	(1.21, 2.45)	8.97	(3.25, 14.7)	0.002
	Serious	106	75	1.41	(1.05, 1.89)	7.93	(1.22, 14.6)	0.021
Myocardial Infarction								
	All pooled	41	30	1.36	(0.85, 2.18)	2.81	(-1.42, 7.05)	0.193
	Mild/1	0	3	0	N.A.	-0.774	(-1.65, 0.10)	0.125
	Moderate/2	5	3	1.66	(0.40, 6.95)	0.513	(-0.91, 1.94)	0.726
	Severe/3	25	10	2.49	(1.20, 5.18)	3.85	(0.875, 6.83)	0.011
	Life-threatening/4	6	7	0.85	(0.29, 2.54)	-0.262	(-2.08, 1.56)	0.778
	Fatal/5	8	7	1.14	(0.41, 3.14)	0.253	(-1.70, 2.21)	0.800
	≥Severe/3	37	24	1.54	(0.92, 2.57)	3.33	(-0.60, 7.26)	0.097
	Serious	40	28	1.42	(0.88, 2.30)	3.07	(-1.08, 7.21)	0.147
Pulmonary Hypertension								
	All pooled	121	132	0.91	(0.72, 1.17)	-2.92	(-10.8, 4.98)	0.4691
	Mild/1	63	62	1.01	(0.72, 1.44)	0.216	(-5.38, 5.82)	0.9397
	Moderate/2	53	67	0.79	(0.55, 1.13)	-3.65	(-9.14, 1.84)	0.1928
	Severe/3	15	8	1.87	(0.79, 4.41)	1.80	(-0.62, 4.21)	0.1455
	Life-threatening/4	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	16	8	1.99	(0.85, 4.66)	2.05	(-0.42, 4.52)	0.1033
	Serious	14	9	1.55	(0.67, 3.58)	1.28	(-1.14, 3.70)	0.2993

(Table A1 is continued on the next page.)

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Table A1. (continued from the previous page). Broad Search Criteria With All Studies Analyzed Separately: Study 20030216 Results.

Thrombophlebitis								
	All pooled	65	61	1.06	(0.75, 1.50)	0.989	(-4.63, 6.61)	0.7303
	Mild/1	25	26	0.96	(0.55, 1.66)	-0.275	(-3.87, 3.32)	0.881
	Moderate/2	31	34	0.91	(0.56, 1.48)	-0.795	(-4.85, 3.26)	0.7009
	Severe/3	13	5	2.59	(0.93, 7.27)	2.06	(-0.083, 4.2)	0.0959
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	13	5	2.59	(0.93, 7.27)	2.06	(-0.083, 4.2)	0.0959
	Serious	14	6	2.33	(0.90, 6.05)	2.05	(-0.20, 4.31)	0.0742
Torsade de Pointes / QT Prolongation								
	All pooled	95	103	0.92	(0.70, 1.21)	-2.13	(-9.14, 4.89)	0.5523
	Mild/1	41	37	1.11	(0.71, 1.72)	1.00	(-3.43, 5.44)	0.6572
	Moderate/2	34	46	0.74	(0.47, 1.15)	-3.12	(-7.61, 1.38)	0.1738
	Severe/3	16	13	1.23	(0.59, 2.55)	0.763	(-1.95, 3.48)	0.5815
	Life-threatening/4	5	2	2.49	(0.48, 12.8)	0.771	(-0.56, 2.11)	0.4529
	Fatal/5	3	10	0.3	(0.08, 1.09)	-1.81	(-3.6, 0.012)	0.0569
	≥Severe/3	24	25	0.96	(0.55, 1.67)	-0.274	(-3.80, 3.25)	0.8789
	Serious	31	30	1.03	(0.63, 1.70)	0.237	(-3.69, 4.17)	0.9057

Reference ID: 3168397

Table A2. Broad Search Criteria With All Studies Analyzed Separately: Study 20040132 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=164) n	Placebo Exposed Subjects (N=165) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Haemorrhages								
	All pooled	6	17	0.36	(0.14, 0.88)	-66.4	(-121, -11.9)	0.0181
	Mild/1	3	14	0.22	(0.06, 0.74)	-66.6	(-114, -19.3)	0.0106
	Moderate/2	2	2	1.01	(0.14, 7.06)	0.0739	(-23.6, 23.8)	1
	Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Serious	0	0	_	N.A.	_	N.A.	.
Haemorrhage Terms (excl lab)								
	All pooled	6	17	0.36	(0.14, 0.88)	-66.4	(-121, -11.9)	0.0181
	Mild/1	3	14	0.22	(0.06, 0.74)	-66.6	(-114, -19.3)	0.0106
	Moderate/2	2	2	1.01	(0.14, 7.06)	0.0739	(-23.6, 23.8)	1
	Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Serious	0	0	_	N.A.	_	N.A.	.
Hypertension								
	All pooled	6	15	0.4	(0.16, 1.01)	-54.3	(-107, -1.89)	0.0439
	Mild/1	4	7	0.57	(0.17, 1.93)	-18.0	(-56.8, 20.7)	0.5418
	Moderate/2	2	8	0.25	(0.05, 1.17)	-36.3	(-73, 0.054)	0.104
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

Reference ID: 3168397

Table A3. Broad Search Criteria With All Studies Analyzed Separately: Study 20040135 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=129) n	Placebo Exposed Subjects (N=120) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Hypertension								
	All pooled	5	8	0.58	(0.20, 1.73)	-27.9	(-83.6, 27.8)	0.3982
	Mild/1	4	5	0.74	(0.20, 2.71)	-10.7	(-57.3, 36.0)	0.7419
	Moderate/2	0	5	0	N.A.	-41.7	(-77.4, -5.9)	0.0249
	Severe/3	1	0	_	N.A.	7.75	(-7.38, 22.9)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	7.75	(-7.38, 22.9)	1
	Serious	0	0	_	N.A.	_	N.A.	.

Reference ID: 3168397

Table A4. Broad Search Criteria With All Studies Analyzed Separately: Study 20040138 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=731) n	Placebo Exposed Subjects (N=725) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Cardiac Arrhythmias								
	All pooled	70	65	1.07	(0.77, 1.47)	6.10	(-23.7, 35.9)	0.688
	Mild/1	17	21	0.8	(0.43, 1.51)	-5.71	(-22.1, 10.7)	0.494
	Moderate/2	29	32	0.9	(0.55, 1.47)	-4.47	(-25.1, 16.1)	0.671
	Severe/3	22	11	1.98	(0.97, 4.06)	14.9	(-0.33, 30.2)	0.056
	Life-threatening/4	5	8	0.62	(0.20, 1.89)	-4.19	(-13.9, 5.48)	0.420
	Fatal/5	6	3	1.98	(0.50, 7.90)	4.07	(-3.97, 12.1)	0.507
	≥Severe/3	32	21	1.51	(0.88, 2.60)	14.8	(-4.40, 34.0)	0.131
	Serious	36	28	1.28	(0.79, 2.07)	10.6	(-10.4 , 31.7)	0.323
Cardiac failure								
	All pooled	77	80	0.95	(0.71, 1.28)	-5.01	(-36.9, 26.9)	0.758
	Mild/1	50	31	1.6	(1.03, 2.47)	25.6	(2.15, 49.1)	0.033
	Moderate/2	11	35	0.31	(0.16, 0.61)	-33.2	(-51.2, -15)	.0003
	Severe/3	12	14	0.85	(0.40, 1.83)	-2.89	(-16.5, 10.7)	0.677
	Life-threatening/4	1	6	0.17	(0.02, 1.37)	-6.91	(-14.0, 0.21)	0.069
	Fatal/5	5	2	2.48	(0.48, 12.7)	4.08	(-3.01, 11.2)	0.452
	≥Severe/3	18	22	0.81	(0.44, 1.50)	-5.72	(-22.5, 11.1)	0.504
	Serious	13	17	0.76	(0.37, 1.55)	-5.66	(-20.3, 8.93)	0.447
Cardiomyopathy								
	All pooled	100	102	0.97	(0.75, 1.26)	-3.89	(-39.4, 31.6)	0.83
	Mild/1	41	41	0.99	(0.65, 1.51)	-0.464	(-24.1, 23.2)	0.9694
	Moderate/2	34	49	0.69	(0.45, 1.05)	-21.1	(-44.9, 2.74)	0.0829
	Severe/3	25	18	1.38	(0.76, 2.50)	9.37	(-8.00, 26.7)	0.2909
	Life-threatening/4	6	8	0.74	(0.26, 2.13)	-2.83	(-12.9, 7.20)	0.580
	Fatal/5	9	5	1.79	(0.60, 5.30)	5.42	(-4.59, 15.4)	0.4217
	≥Severe/3	39	31	1.25	(0.79, 1.98)	10.6	(-11.4, 32.6)	0.3448
	Serious	38	31	1.22	(0.77, 1.93)	9.22	(-12.6, 31.0)	0.4075
Gastrointestinal perforation, ulceration, etc.								
	All pooled	37	38	0.97	(0.62, 1.50)	-1.80	(-24.5, 20.9)	0.877
	Mild/1	20	9	2.2	(1.01, 4.81)	14.9	(0.635, 29.3)	0.041
	Moderate/2	11	14	0.78	(0.36, 1.71)	-4.26	(-17.6, 9.09)	0.531
	Severe/3	7	14	0.5	(0.20, 1.22)	-9.73	(-22.0, 2.52)	0.119
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	1	1	0.99	(0.06, 15.8)	-0.0113	(-3.82, 3.79)	1
	≥Severe/3	8	15	0.53	(0.23, 1.24)	-9.75	(-22.6, 3.07)	0.136
	Serious	9	19	0.47	(0.21, 1.03)	-13.9	(-28, 0.216)	0.054
Haemodynamic oedema, effusions, etc.								
	All pooled	83	76	1.08	(0.81, 1.45)	8.72	(-23.3, 40.7)	0.594
	Mild/1	54	36	1.49	(0.99, 2.24)	24.2	(-0.47, 48.9)	0.055
	Moderate/2	24	34	0.7	(0.42, 1.17)	-14.1	(-34.2, 6.03)	0.17
	Severe/3	7	7	0.99	(0.35, 2.81)	-0.0792	(-10.1, 9.95)	0.988
	Life-threatening/4	2	2	0.99	(0.14, 7.02)	-0.0226	(-5.40, 5.35)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	9	9	0.99	(0.40, 2.48)	-0.102	(-11.5, 11.2)	0.986
	Serious	7	6	1.16	(0.39, 3.43)	1.30	(-8.36, 11.0)	0.792

(Table A4 is continued on the next page.)

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Table A4 (continued from the previous page). Broad Search Criteria With All Studies Analyzed Separately: Study 20040138 Results.

Pulmonary Hypertension								
	All pooled	45	41	1.09	(0.72, 1.64)	5.01	(-19.2, 29.2)	0.6853
	Mild/1	21	14	1.49	(0.76, 2.90)	9.42	(-6.30, 25.1)	0.2408
	Moderate/2	20	26	0.76	(0.43, 1.35)	-8.50	(-26.5, 9.47)	0.3537
	Severe/3	6	6	0.99	(0.32, 3.06)	-0.0679	(-9.36, 9.22)	0.9886
	Life-threatening/4	2	0	_	N.A.	2.74	(-1.05, 6.52)	0.4997
	Fatal/5	1	0	_	N.A.	1.37	(-1.31, 4.05)	1
	≥Severe/3	8	6	1.32	(0.46, 3.79)	2.67	(-7.35, 12.7)	0.6019
	Serious	10	3	3.31	(0.91, 12.0)	9.54	(-0.088, 19)	0.0909

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Table A5. Broad Search Criteria With All Studies Analyzed Separately: Study 20040141 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=593) n	Alendronate Exposed Subjects (N=586) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Gastrointestinal Haemorrhage								
	All pooled	4	4	4	4	0.0806	(-9.29, 9.45)	1
	Mild/1	0	4	0	0	6.83	(0.16, 13.5)	0.0607
	Moderate/2	3	0	3	3	-5.06	(-10.8, 0.65)	0.2494
	Severe/3	0	0	0	0	_	N.A.	.
	Life-threatening/4	1	0	1	1	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	0	0	_	N.A.	.
	≥Severe/3	1	0	1	1	-1.69	(-4.99, 1.62)	1
	Serious	1	0	1	1	-1.69	(-4.99, 1.62)	1
Haemorrhages								
	All pooled	18	20	1.12	(0.60, 2.10)	3.78	(-16.4 , 23.9)	0.7136
	Mild/1	10	19	1.92	(0.90, 4.10)	15.6	(-2.13, 33.3)	0.0846
	Moderate/2	7	2	0.29	(0.06, 1.39)	-8.39	(-18.3, 1.50)	0.1781
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Serious	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
Haemorrhage Terms (excl lab)								
	All pooled	18	20	1.12	(0.60, 2.10)	3.78	(-16.4, 23.9)	0.7136
	Mild/1	10	19	1.92	(0.90, 4.10)	15.6	(-2.13, 33.3)	0.0846
	Moderate/2	7	2	0.29	(0.06, 1.39)	-8.39	(-18.3, 1.50)	0.178
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Serious	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
Hypertension								
	All pooled	28	17	0.61	(0.34, 1.11)	-18.2	(-40.0, 3.61)	0.1028
	Mild/1	19	11	0.59	(0.28, 1.22)	-13.3	(-31.2, 4.67)	0.148
	Moderate/2	10	5	0.51	(0.17, 1.47)	-8.33	(-21.1, 4.43)	0.2988
	Severe/3	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497
	Serious	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497

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Table A6. Broad Search Criteria With All Studies Analyzed Separately: Study 20050234 Results.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=253) n	Alen-dronate (N=249) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Gastrointestinal Perforation, Ulceration, etc.								
	All pooled	2	9	0.22	(0.05, 1.00)	-28.2	(-54, -2.6)	0.0353
	Mild/1	2	4	0.49	(0.09, 2.66)	-8.16	(-27.2, 10.9)	0.4471
	Moderate/2	0	4	0	N.A.	-16.1	(-32, -0.45)	0.0598
	Severe/3	0	1	0	N.A.	-4.02	(-11.9, 3.84)	0.496
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	-4.02	(-11.9, 3.84)	0.496
	Serious	0	1	0	N.A.	-4.02	(-11.9, 3.84)	0.496
Haemorrhages								
	All pooled	7	13	0.53	(0.22, 1.31)	-24.5	(-58.8, 9.69)	0.1598
	Mild/1	6	7	0.84	(0.29, 2.47)	-4.40	(-32.2, 23.4)	0.7565
	Moderate/2	1	6	0.16	(0.02, 1.35)	-20.1	(-40.7, 0.41)	0.0666
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Haemorrhage Terms (excl lab)								
	All pooled	7	13	0.53	(0.22, 1.31)	-0.245	(-58.8, 9.69)	0.1598
	Mild/1	6	7	0.84	(0.29, 2.47)	-4.40	(-32.2, 23.4)	0.7565
	Moderate/2	1	6	0.16	(0.02, 1.35)	-0.201	(-40.7, 0.41)	0.0666
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

Table A7 shows the tabulation of cardiovascular adverse events having at one relative risk estimate associated with a p-value of less than 0.10 when a broad MedDRA SMQ search strategy was employed to a pooled dataset consisting of the two large, pivotal studies.

According to this analysis, the relative risk for serious bradyarrhythmia events was 1.85 (p=0.0587). In addition, p-values were less than 0.10 for several other severity categories (Moderate: RR=2.28, p=0.06; Severe: RR=2.14, p=0.09; Severe or worse: RR=2.12, p=0.0729). However, no one suffered a fatal bradyarrhythmia in either of the two large, pivotal studies.

Although severe embolic and thrombotic events in the large, pivotal studies were associated with a relative risk of 1.43 (p=0.02), relative risk estimates for the remaining severity categories approached unity. Likewise, only severe arterial embolic and thrombotic events in the large, pivotal studies were associated with a p-value less than 0.10 for a relative risk greater than unity (RR=1.7; p=0.02). Severe events of ischaemic heart disease in the large, pivotal studies were associated with a relative risk of 1.76

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(p=0.001), and severe or worse events were associated with a relative risk of 1.35 (p=0.03). However, the relative risk was not consistently estimated above one for the remaining severity categories. Severe events of myocardial infarction in the large, pivotal studies were associated with a relative risk of 2.49 (p=0.003), however, there does not appear to be a consistent estimate of relative risk greater than one across the other categories of myocardial infarction severity. Serious events of pulmonary hypertension were associated with a relative risk of 2.0 (p=0.05) in the large, pivotal studies. There was a trend toward increased relative risk of pulmonary hypertension events for other severity categories (Severe events: RR=1.49; Severe events or worse: RR=1.71), however, none of these were associated with a p-value less than 0.10.

Kaplan-Meier estimates were computed for instances in which the p-value was less than 0.10. The upper graph on each plot shows the Kaplan-Meier estimators for the greatment groups, along with equal-precision 95% confidence bands. P-values are obtained using the log rank test.

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Table A7. Broad Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

	Severity	Denosumab Subjects (N=4617)	Placebo Subjects (N=4601)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Adverse Event Grouping		**n**	**n**					
Arrhythmia Related Investigations								
	All pooled	242	223	1.08	(0.91, 1.29)	3.95	(-4.99, 12.9)	0.3866
	Mild/1	130	104	1.25	(0.97, 1.61)	5.55	(-0.87, 12.0)	0.0901
	Moderate/2	77	88	0.87	(0.64, 1.18)	-2.45	(-7.86, 2.96)	0.3753
	Severe/3	32	25	1.28	(0.76, 2.15)	1.50	(-1.70, 4.70)	0.3592
	Life-threatening/4	7	6	1.16	(0.39, 3.46)	0.212	(-1.32, 1.74)	0.7862
	Fatal/5	9	13	0.69	(0.30, 1.61)	-0.876	(-2.87, 1.12)	0.3887
	≥Severe/3	48	43	1.11	(0.74, 1.68)	1.05	(-2.99, 5.09)	0.61
	Serious	58	50	1.16	(0.79, 1.68)	1.70	(-2.70, 6.09)	0.4495
Bradyarrhythmia								
	All pooled	49	35	1.4	(0.91, 2.15)	3.01	(-0.87, 6.88)	0.1289
	Mild/1	18	23	0.78	(0.42, 1.44)	-1.10	(-3.82, 1.62)	0.4273
	Moderate/2	16	7	2.28	(0.94, 5.53)	1.94	(-0.091, 4.0)	0.0614
	Severe/3	15	7	2.14	(0.87, 5.23)	1.73	(-0.26, 3.72)	0.0892
	Life-threatening/4	2	1	1.99	(0.18, 22.0)	0.216	(-0.52, 0.95)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	17	8	2.12	(0.91, 4.90)	1.94	(-0.18, 4.06)	0.0729
	Serious	26	14	1.85	(0.97, 3.54)	2.59	(-0.093, 5.3)	0.0587
Cardiac Failure								
	All pooled	345	316	1.09	(0.94, 1.26)	6.04	(-4.49, 16.6)	0.2608
	Mild/1	190	166	1.14	(0.93, 1.40)	5.07	(-2.79, 12.9)	0.2063
	Moderate/2	127	125	1.01	(0.79, 1.29)	0.339	(-6.32, 7.00)	0.9205
	Severe/3	38	38	1	(0.64, 1.56)	-0.0286	(-3.72, 3.66)	0.9879
	Life-threatening/4	4	11	0.36	(0.12, 1.14)	-1.52	(-3.17, 0.12)	0.0761
	Fatal/5	11	10	1.1	(0.47, 2.58)	0.209	(-1.74, 2.16)	0.8333
	≥Severe/3	51	58	0.88	(0.60, 1.27)	-1.56	(-5.97, 2.85)	0.4885
	Serious	52	58	0.89	(0.62, 1.30)	-1.34	(-5.78, 3.09)	0.5526
Conduction Defects								
	All pooled	28	24	1.16	(0.68, 2.00)	0.848	(-2.21, 3.91)	0.5866
	Mild/1	16	19	0.84	(0.43, 1.63)	-0.664	(-3.18, 1.85)	0.6042
	Moderate/2	3	3	1	(0.20, 4.93)	-0.00226	(-1.04, 1.04)	1
	Severe/3	8	2	3.99	(0.85, 18.8)	1.30	(-0.044, 2.6)	0.1092
	Life-threatening/4	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	9	3	2.99	(0.81, 11.0)	1.30	(-0.17, 2.77)	0.1457
	Serious	10	6	1.66	(0.60, 4.57)	0.862	(-0.84, 2.56)	0.3203
Disorders of Sinus Node Function								
	All pooled	23	13	1.76	(0.89, 3.48)	2.16	(-0.39, 4.70)	0.097
	Mild/1	4	4	1	(0.25, 3.98)	-0.00301	(-1.21, 1.20)	1
	Moderate/2	13	5	2.59	(0.92, 7.26)	1.73	(-0.072, 3.5)	0.0959
	Severe/3	7	5	1.4	(0.44, 4.39)	0.429	(-1.04, 1.90)	0.7743
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	8	5	1.59	(0.52, 4.87)	0.646	(-0.89, 2.18)	0.5808
	Serious	16	9	1.77	(0.78, 4.00)	1.51	(-0.61, 3.63)	0.1636

(Table A7 is continued on the next page.)

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Table A7 (continued from the previous page). Broad Search Criteria With Two Pivotal Studies (20030216 and 20040138) Pooled.

Embolic and thrombotic events								
	All pooled	251	236	1.06	(0.89, 1.26)	3.07	(-6.06, 12.2)	0.5099
	Mild/1	46	51	0.9	(0.60, 1.34)	-1.12	(-5.29, 3.05)	0.5978
	Moderate/2	85	80	1.06	(0.78, 1.43)	1.02	(-4.39, 6.44)	0.7112
	Severe/3	103	72	1.43	(1.06, 1.92)	6.66	(1.09, 12.2)	0.0191
	Life-threatening/4	26	32	0.81	(0.48, 1.36)	-1.32	(-4.55, 1.91)	0.4216
	Fatal/5	21	24	0.87	(0.49, 1.56)	-0.668	(-3.51, 2.18)	0.6455
	≥Severe/3	142	124	1.14	(0.90, 1.45)	3.81	(-3.03, 10.6)	0.2752
	Serious	181	157	1.15	(0.93, 1.42)	5.08	(-2.59, 12.8)	0.1944
Embolic and thrombotic events, arterial								
	All pooled	130	109	1.19	(0.92, 1.53)	4.47	(-2.02, 11.0)	0.1773
	Mild/1	20	18	1.11	(0.59, 2.09)	0.420	(-2.20, 3.04)	0.7532
	Moderate/2	37	28	1.32	(0.81, 2.15)	1.93	(-1.49, 5.34)	0.2686
	Severe/3	53	31	1.7	(1.10, 2.65)	4.74	(0.865, 8.62)	0.0166
	Life-threatening/4	11	22	0.5	(0.24, 1.03)	-2.40	(-4.84, 0.04)	0.0538
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.227	(-2.43, 1.98)	0.8401
	≥Severe/3	77	67	1.15	(0.83, 1.58)	2.12	(-2.95, 7.18)	0.4128
	Serious	98	82	1.19	(0.89, 1.59)	3.40	(-2.24, 9.05)	0.2377
Embolic and thrombotic events, venous								
	All pooled	51	59	0.86	(0.59, 1.25)	-1.78	(-6.21, 2.66)	0.4321
	Mild/1	8	16	0.5	(0.21, 1.16)	-1.74	(-3.83, 0.34)	0.1003
	Moderate/2	21	25	0.84	(0.47, 1.49)	-0.885	(-3.76, 1.99)	0.5465
	Severe/3	21	18	1.16	(0.62, 2.18)	0.636	(-2.01, 3.29)	0.638
	Life-threatening/4	7	4	1.74	(0.51, 5.95)	0.647	(-0.76, 2.06)	0.548
	Fatal/5	1	3	0.33	(0.03, 3.19)	-0.435	(-1.29, 0.42)	0.3741
	≥Severe/3	28	24	1.16	(0.68, 2.00)	0.848	(-2.21, 3.91)	0.5866
	Serious	33	26	1.26	(0.76, 2.11)	1.50	(-1.76, 4.75)	0.3677
Ischaemic heart disease								
	All pooled	254	228	1.11	(0.93, 1.32)	5.46	(-3.63, 14.5)	0.2391
	Mild/1	72	71	1.01	(0.73, 1.40)	0.163	(-4.88, 5.21)	0.9495
	Moderate/2	110	94	1.17	(0.89, 1.53)	3.39	(-2.61, 9.40)	0.268
	Severe/3	90	51	1.76	(1.25, 2.47)	8.41	(3.40, 13.4)	0.001
	Life-threatening/4	22	25	0.88	(0.50, 1.55)	-0.669	(-3.58, 2.24)	0.6522
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.227	(-2.43, 1.98)	0.8401
	≥Severe/3	118	87	1.35	(1.03, 1.78)	6.65	(0.631, 12.7)	0.0304
	Serious	143	121	1.18	(0.93, 1.50)	4.67	(-2.13, 11.5)	0.1786
Myocardial infarction								
	All pooled	65	57	1.14	(0.80, 1.62)	1.69	(-2.98, 6.35)	0.4778
	Mild/1	1	5	0.2	(0.02, 1.71)	-0.870	(-1.91, 0.17)	0.1243
	Moderate/2	8	6	1.33	(0.46, 3.83)	0.429	(-1.16, 2.02)	0.5972
	Severe/3	35	14	2.49	(1.34, 4.62)	4.54	(1.57, 7.50)	0.0027
	Life-threatening/4	13	20	0.65	(0.32, 1.30)	-1.53	(-3.97, 0.91)	0.2184
	Fatal/5	12	14	0.85	(0.40, 1.84)	-0.444	(-2.61, 1.72)	0.6879
	≥Severe/3	57	48	1.18	(0.81, 1.73)	1.91	(-2.42, 6.24)	0.3868
	Serious	61	54	1.13	(0.78, 1.62)	1.48	(-3.06, 6.01)	0.5234

(Table A7 is continued on the next page.)

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Table A7 (continued from the previous page). Broad Search Criteria With Two Pivotal Studies (20030216 and 20040138) Pooled.

Pulmonary hypertension								
	All pooled	166	173	0.96	(0.78, 1.18)	-1.65	(-9.33, 6.04)	0.6745
	Mild/1	84	76	1.1	(0.81, 1.50)	1.68	(-3.66, 7.01)	0.538
	Moderate/2	73	93	0.78	(0.58, 1.06)	-4.40	(-9.83, 1.03)	0.1121
	Severe/3	21	14	1.49	(0.76, 2.94)	1.51	(-1.00, 4.02)	0.2399
	Life-threatening/4	3	0	_	N.A.	0.650	(-0.085, 1.4)	0.2499
	Fatal/5	1	0	_	N.A.	0.217	(-0.208,0.64)	1
	≥Severe/3	24	14	1.71	(0.88, 3.30)	2.16	(-0.46, 4.77)	0.1063
	Serious	24	12	1.99	(1.00, 3.98)	2.59	(0.046, 5.13)	0.0462
Thrombophlebitis								
	All pooled	75	71	1.05	(0.76, 1.45)	0.813	(-4.28, 5.91)	0.7546
	Mild/1	26	27	0.96	(0.56, 1.64)	-0.237	(-3.32, 2.85)	0.8804
	Moderate/2	37	39	0.95	(0.60, 1.48)	-0.463	(-4.15, 3.23)	0.806
	Severe/3	16	10	1.59	(0.72, 3.51)	1.29	(-0.87, 3.46)	0.2422
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	17	10	1.69	(0.78, 3.70)	1.51	(-0.70, 3.71)	0.1802
	Serious	20	10	1.99	(0.93, 4.25)	2.16	(-0.17, 4.48)	0.0689

Table A8 shows the tabulation of cardiovascular adverse events for which at least one severity level was associated relative risk having a p-value less than 0.10 when a broad MedDRA SMQ search strategy was employed to a pooled dataset consisting of all placebo-controlled studies.

Moderate bradyarrhythmia was associated with a relative risk of 3.49 (p=0.03). There was a consistent pattern of relative risk estimates greater than one for all other higher levels of severity (Severe: RR=1.66; Life-threatening: RR=2.0; Severe or worse: RR=1.7; Serious: RR=1.9), however, none of these increases were associated with a p-value less than 0.10.

The estimate of relative risk for moderate disorders of sinus node function was 3.66 (p=0.057). Relative risk estimates were greater than one for severe or worse (RR=1.2) and serious (RR=1.6) disorders of sinus node function, however none of these levels of severity were associated with a p-value less than 0.10. Severe embolic and thrombotic events were associated with a relative risk of 1.49 (p=0.02), but relative risk estimates associated with all other severity categories were not consistently greater than one. Likewise, severe arterial embolic and thrombotic events were associated with a relative risk of 1.7 (p=0.05), but relative risk observed across the other severity categories was unity.

Relative risk associated with events of moderate gastroinstestinal haemorrhage was 1.9 (p=0.02), but the relative risk estimates for other levels of severity were not very different from one and were not associated with a p-value less than 0.10. Likewise, only relative risk of moderate gastrointestinal perforation (RR=1.4, p=0.03) was associated with a p-value less than 0.10.

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When all of the placebo-controlled studies were pooled, relative risk of severe (RR=1.83, p=0.002), severe or worse (RR=1.62, p=0.006), and serious (RR=1.39, p=0.03) events of ischaemic heart disease were associated with a p-value less than 0.10. There was also a trend toward higher risk for life threatening (RR=1.37, p=0.494) and fatal (RR=1.28, p=0.620) events. The relative risk for severe myocardial infarction (RR=2.27, p=0.02) was associated with a p-value less than 0.10, and there was a trend toward relative risk greater than one for events of a severe or worse nature (RR=1.48, p=0.129) and for serious events (RR=1.38, p=0.187).

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Table A8. Broad Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=4604 % (n/N)	Placebo Subjects n	Placebo Subjects N=4224 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Arrhythmia related investigations										
	All pooled	223	5.27	201	4.76	1.11	(0.92, 1.3)	5.0	(-4.23, 14)	0.285
	Mild/1	137	3.24	104	2.46	1.31	(1.02, 1.7)	7.73	(0.64, 14.8)	0.033
	Moderate/2	71	1.68	78	1.85	0.91	(0.66, 1.3)	-1.70	(-7.3, 3.9)	0.552
	Severe/3	20	0.47	20	0.47	1	(0.54, 1.9)	-0.012	(-2.9, 2.9)	0.993
	Life-threatening/4	5	0.12	1	0.02	4.99	(0.58 , 43)	0.945	(-0.19, 2.1)	0.219
	Fatal/5	3	0.07	10	0.24	0.3	(0.08, 1.1)	-1.66	(-3.3, .011)	0.057
	≥Severe/3	28	0.66	31	0.73	0.9	(0.54, 1.5)	-0.728	(-4.3, 2.82)	0.688
	Serious	40	0.95	35	0.83	1.14	(0.73, 1.8)	1.16	(-2.8, 5.16)	0.570
Brady-arrhythmia										
	All pooled	40	0.95	31	0.73	1.29	(0.81, 2.1)	2.11	(-1.78, 6.0)	0.288
	Mild/1	16	0.38	23	0.54	0.69	(0.37, 1.3)	-1.67	(-4.6, 1.22)	0.258
	Moderate/2	14	0.33	4	0.09	3.49	(1.2, 10.6)	2.36	(0.40, 4.3)	0.031
	Severe/3	10	0.24	6	0.14	1.66	(0.60, 4.6)	0.941	(-0.91, 2.8)	0.319
	Life-threatening/4	2	0.05	1	0.02	1.99	(0.18 , 22)	0.236	(-0.57, 1.0)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	12	0.28	7	0.17	1.71	(0.67, 4.3)	1.18	(-0.84, 3.2)	0.253
	Serious	19	0.45	10	0.24	1.9	(0.88, 4.1)	2.12	(-0.37, 4.6)	0.096
Cardiac Arrhythmias										
	All pooled	404	9.55	381	9.03	1.06	(0.93, 1.2)	5.20	(-7.2, 17.6)	0.410
	Mild/1	225	5.32	202	4.79	1.11	(0.92, 1.3)	5.31	(-4.0 , 14.6)	0.265
	Moderate/2	162	3.83	153	3.62	1.06	(0.85, 1.3)	2.03	(-6.0, 10.1)	0.622
	Severe/3	50	1.18	52	1.23	0.96	(0.65, 1.4)	-0.505	(-5.2, 4.2)	0.832
	Life-threatening/4	7	0.17	5	0.12	1.4	(0.44, 4.4)	0.47	(-1.1, 2.07)	0.774
	Fatal/5	3	0.07	10	0.24	0.3	(0.08, 1.1)	-1.66	(-3.3, .011)	0.057
	≥Severe/3	60	1.42	65	1.54	0.92	(0.65, 1.3)	-1.22	(-6.4, 3.92)	0.642
	Serious	99	2.34	87	2.06	1.13	(0.85, 1.5)	2.78	(-3.5, 9.0)	0.383
Cardio-myopathy										
	All pooled	372	8.79	379	8.98	0.98	(0.85, 1.1)	-1.89	(-14, 10.2)	0.760
	Mild/1	202	4.77	196	4.64	1.03	(0.85, 1.3)	1.30	(-7.7, 10.3)	0.778
	Moderate/2	161	3.8	165	3.91	0.97	(0.79, 1.2)	-1.05	(-9.3, 7.2)	0.803
	Severe/3	44	1.04	43	1.02	1.02	(0.67, 1.6)	0.210	(-4.1, 4.5)	0.924
	Life-threatening/4	5	0.12	5	0.12	1	(0.29, 3.4)	-.0031	(-1.5, 1.5)	1
	Fatal/5	4	0.09	11	0.26	0.36	(0.12, 1.1)	-1.66	(-3.5, 0.13)	0.076
	≥Severe/3	51	1.21	58	1.37	0.88	(0.60, 1.3)	-1.69	(-6.5, 3.1)	0.491
	Serious	68	1.61	66	1.56	1.03	(0.73, 1.4)	0.432	(-4.9, 5.8)	0.874

(Table A8 is continued on the next page.)

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Table A8 (continued from the previous page). Broad Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Disorders of Sinus Node Function										
	All pooled	18	0.43	10	0.24	1.8	(0.83, 3.9)	1.88	(-0.56, 4.3)	0.132
	Mild/1	3	0.07	3	0.07	1	(0.20, 4.9)	-.0019	(-1.1, 1.13)	1
	Moderate/2	11	0.26	3	0.07	3.66	(1.02, 13)	1.89	(0.16, 3.62)	0.057
	Severe/3	5	0.12	5	0.12	1	(0.29, 3.4)	-.0031	(-1.5, 1.5)	1
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.236	(-0.23, 0.7)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	6	0.14	5	0.12	1.2	(0.37, 3.9)	0.233	(-1.3, 1.8)	1
	Serious	11	0.26	7	0.17	1.57	(0.61, 4.0)	0.941	(-1.0, 2.9)	0.348
Embolic and Thrombotic Events										
	All pooled	185	4.37	177	4.19	1.04	(0.85, 1.3)	1.78	(-6.9, 10.4)	0.686
	Mild/1	41	0.97	45	1.07	0.91	(0.60, 1.4)	-0.973	(-5.3, 3.3)	0.656
	Moderate/2	60	1.42	63	1.49	0.95	(0.67, 1.4)	-0.748	(-5.9, 4.4)	0.774
	Severe/3	79	1.87	53	1.26	1.49	(1.05, 2.1)	6.11	(8.28, 11.4)	0.024
	Life-threatening/4	15	0.35	17	0.4	0.88	(0.44, 1.8)	-0.483	(-3.1, 2.1)	0.718
	Fatal/5	13	0.31	14	0.33	0.93	(0.44, 2.0)	-0.245	(-2.7, 2.2)	0.842
	≥Severe/3	101	2.39	82	1.94	1.23	(0.92, 1.6)	4.44	(-1.8, 10.6)	0.161
	Serious	129	3.05	113	2.68	1.14	(0.89, 1.5)	3.71	(-3.4 , 10.8)	0.306
Embolic and Thrombotic Events, arterial										
	All pooled	93	2.2	77	1.82	1.2	(0.89, 1.6)	3.73	(-2.3, 9.72)	0.222
	Mild/1	18	0.43	16	0.38	1.12	(0.57, 2.2)	0.463	(-2.2, 3.16)	0.737
	Moderate/2	25	0.59	22	0.52	1.13	(0.64, 2.0)	0.695	(-2.5, 3.9)	0.667
	Severe/3	40	0.95	24	0.57	1.66	(1.00, 2.8)	3.77	(0.072, 7.5)	0.046
	Life-threatening/4	4	0.09	10	0.24	0.4	(0.13, 1.3)	-1.42	(-3.2, 0.31)	0.118
	Fatal/5	9	0.21	7	0.17	1.28	(0.48, 3.4)	0.468	(-1.4, 2.32)	0.620
	≥Severe/3	53	1.25	41	0.97	1.29	(0.86, 1.9)	2.81	(-1.7, 7.28)	0.218
	Serious	67	1.58	55	1.3	1.22	(0.85, 1.7)	2.80	(-2.3, 7.9)	0.280
Embolic and Thrombotic Events, Unsp										
	All pooled	71	1.68	54	1.28	1.31	(0.92, 1.9)	3.98	(-1.2, 9.1)	0.129
	Mild/1	17	0.4	15	0.36	1.13	(0.57, 2.3)	0.463	(-2.2, 3.1)	0.729
	Moderate/2	24	0.57	19	0.45	1.26	(0.69, 2.3)	1.17	(-1.9, 4.2)	0.450
	Severe/3	28	0.66	16	0.38	1.75	(0.95, 3.2)	2.83	(-0.24, 5.9)	0.071
	Life-threatening/4	6	0.14	3	0.07	1.99	(0.5, 8.0)	0.707	(-0.68 , 2.1)	0.508
	Fatal/5	3	0.07	4	0.09	0.75	(0.17, 3.3)	-0.239	(-1.5, 0.99)	0.726
	≥Severe/3	37	0.87	23	0.54	1.6	(0.96, 2.7)	3.29	(-0.28, 6.9)	0.071
	Serious	50	1.18	37	0.88	1.35	(0.88, 2.1)	3.05	(-1.3, 7.4)	0.165

(Table A8 is continued on the next page.)

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Table A8 (continued from the previous page). Broad Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=4604 % (n/N)	Placebo Subjects n	Placebo Subjects N=4224 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Gastro-intestinal haemorrhage										
	All pooled	74	1.75	57	1.35	1.29	(0.92, 1.8)	3.98	(-1.3, 9.3)	0.138
	Mild/1	31	0.73	33	0.78	0.94	(0.57, 1.5)	-0.493	(-4.2, 3.2)	0.794
	Moderate/2	33	0.78	17	0.4	1.94	(1.1, 3.5)	3.77	(0.50, 7.04)	0.024
	Severe/3	12	0.28	9	0.21	1.33	(0.56, 3.2)	0.703	(-1.4, 2.8)	0.516
	Life-threatening/4	1	0.02	1	0.02	1	(0.06, 16)	-0.0006	(-0.7, 0.7)	1
	Fatal/5	1	0.02	0	0	_	N.A.	0.236	(-0.23, 0.7)	1
	≥Severe/3	14	0.33	10	0.24	1.4	(0.62, 3.1)	0.939	(-1.3, 3.2)	0.417
	Serious	23	0.54	19	0.45	1.21	(0.66, 2.2)	0.933	(-2.06, 3.9)	0.542
Gastro-intestinal perforation, ulceration, etc.										
	All pooled	220	5.2	191	4.52	1.15	(0.95, 1.4)	6.73	(-2.43, 16)	0.15
	Mild/1	104	2.46	106	2.51	0.98	(0.75, 1.3)	-0.538	(-7.2, 6.1)	0.874
	Moderate/2	94	2.22	67	1.59	1.4	(1.03, 1.9)	6.34	(0.51, 12.2)	0.033
	Severe/3	39	0.92	29	0.69	1.34	(0.83, 2.2)	2.35	(-1.5, 6.15)	0.228
	Life-threatening/4	2	0.05	3	0.07	0.66	(0.11, 4.0)	-0.238	(-1.3, 0.80)	0.687
	Fatal/5	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.7, 0.66)	1
	≥Severe/3	41	0.97	32	0.76	1.28	(0.81, 2.0)	2.11	(-1.8, 6.05)	0.295
	Serious	56	1.32	40	0.95	1.4	(0.93, 2.1)	3.76	(-0.76, 8.3)	0.103
Ischaemic heart disease										
	All pooled	203	4.8	179	4.24	1.13	(0.93, 1.4)	5.56	(-3.3, 0.14)	0.219
	Mild/1	62	1.47	66	1.56	0.94	(0.66, 1.3)	-0.986	(-6.19, 4.2)	0.711
	Moderate/2	97	2.29	80	1.9	1.21	(0.90, 1.6)	3.97	(-2.1, 10.1)	0.203
	Severe/3	68	1.61	37	0.88	1.83	(1.23, 2.7)	7.30	(2.58, 12.0)	0.002
	Life-threatening/4	11	0.26	8	0.19	1.37	(0.55, 3.4)	0.704	(-1.3, 2.7)	0.494
	Fatal/5	9	0.21	7	0.17	1.28	(0.48, 3.4)	0.468	(-1.4, 2.3)	0.620
	≥Severe/3	83	1.96	51	1.21	1.62	(1.15, 2.3)	7.5	(2.21, 12.9)	0.006
	Serious	107	2.53	77	1.82	1.39	(1.04, 1.9)	7.04	(0.82, 13.3)	0.027
Myocardial infarction										
	All pooled	41	0.97	31	0.73	1.32	(0.83, 2.1)	2.34	(-1.6, 6.3)	0.241
	Mild/1	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .009)	0.125
	Moderate/2	5	0.12	3	0.07	1.66	(0.40, 7.0)	0.471	(-0.84, 1.8)	0.726
	Severe/3	25	0.59	11	0.26	2.27	(1.12, 4.6)	3.30	(0.53, 6.08)	0.020
	Life-threatening/4	6	0.14	7	0.17	0.85	(0.29, 2.5)	-0.241	(-1.9, 1.4)	0.778
	Fatal/5	8	0.19	7	0.17	1.14	(0.41, 3.1)	0.232	(-1.6, 2.0)	0.8
	≥Severe/3	37	0.87	25	0.59	1.48	(0.89, 2.5)	2.82	(-0.82, 6.5)	0.129
	Serious	40	0.95	29	0.69	1.38	(0.85, 2.2)	2.58	(-1.25, 6.4)	0.187

(Table A8 is continued on the next page.)

Reference ID: 3168397

Table A8 (continued from the previous page). Broad Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Pulmonary Hypertension										
	All pooled	122	2.88	134	3.17	0.91	(0.7 , 1.2)	-2.92	(-10.2 , 4.4)	0.434
	Mild/1	63	1.49	63	1.49	1	(0.7 , 1.4)	-0.039	(-5.2, 5.1)	0.988
	Moderate/2	54	1.28	68	1.61	0.79	(0.56, 1.1)	-3.35	(-8.4, 1.74)	0.197
	Severe/3	15	0.35	8	0.19	1.87	(0.79, 4.4)	1.65	(-0.57, 39)	0.146
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.236	(-.23, 0.70)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	16	0.38	8	0.19	1.99	(0.85, 4.7)	1.89	(-0.38 , 4.2)	0.103
	Serious	14	0.33	9	0.21	1.55	(0.67, 3.6)	1.18	(-1.04 , 3.4)	0.299
Thrombo-phlebitis										
	All pooled	66	1.56	61	1.45	1.08	(0.76, 1.5)	1.14	(-4.04, 6.3)	0.666
	Mild/1	25	0.59	26	0.62	0.96	(0.55, 1.7)	-0.252	(-3.6, 3.05)	0.881
	Moderate/2	32	0.76	34	0.81	0.94	(0.58, 1.5)	-0.49	(-4.25, 3.4)	0.797
	Severe/3	13	0.31	5	0.12	2.59	(0.93, 7.3)	1.89	(-.077, 3.9)	0.096
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	13	0.31	5	0.12	2.59	(0.93, 7.3)	1.89	(-.077, 3.9)	0.096
	Serious	14	0.33	6	0.14	2.33	(0.90, 6.1)	1.89	(-0.18, 4.0)	0.074
Torsade de Pointes / QT Prolongation										
	All pooled	101	2.39	105	2.49	0.96	(0.73, 1.3)	-1.01	(-7.6, 5.56)	0.763
	Mild/1	45	1.06	38	0.9	1.18	(0.77, 1.8)	1.63	(-2.57, 5.8)	0.447
	Moderate/2	36	0.85	47	1.11	0.76	(0.50, 1.2)	-2.63	(-6.8, 1.58)	0.221
	Severe/3	16	0.38	13	0.31	1.23	(0.59, 2.6)	0.701	(-1.8, 3.19)	0.582
	Life-threatening/4	5	0.12	2	0.05	2.49	(0.48, 13)	0.708	(-0.52, 1.9)	0.453
	Fatal/5	3	0.07	10	0.24	0.3	(0.08, 1.1)	-1.66	(-3.3, .011)	0.057
	≥Severe/3	24	0.57	25	0.59	0.96	(0.55, 1.7)	-0.252	(-3.5, 2.99)	0.879
	Serious	32	0.76	30	0.71	1.06	(0.65, 1.8)	0.454	(-3.2, 4.09)	0.807

Table A9 shows the results of the analysis of a dataset in which all PMO studies (placebo and active controlled) were pooled and analyzed using broad MedDRA SMQ criteria.

Moderate bradyarrhythmia was associated with a relative risk of 2.9 (p=0.058). Relative risk for additional severity categories was greater than one (Severe: RR=1.66; Life-threatening: RR=1.66, p=1; Severe or worse: RR=1.66, p=0.267; Serious: RR=1.75, p=0.141), however none of these estimates were associated with a p-value less than 0.10. Moderate gastrointestinal haemorrhage was associated with a relative risk of 1.76 (p=0.05), but relative risk estimates among the remaining severity levels was not consistently greater than one.

Severe ischaemic heart disease was associated with a relative risk of 1.55 (p=0.03). Risk estimates were greater than one in other severity categories (Life-threatening: RR=1.25, p=0.628; Severe or worse: RR=1.39, p=0.063; Serious: RR=1.18, p=0.269), but none were associated with a p-value less than 0.10.

Reference ID: 3168397

Table A9. Broad Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, and 20050141) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=5451 % (n/N)	Placebo Subjects n	Placebo Subjects N=4224 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Arrhythmia Related Investigations										
	All pooled	242	4.77	201	4.76	1	(0.83, 1.2)	0.0375	(-8.7, 8.7)	0.993
	Mild/1	149	2.93	104	2.46	1.19	(0.93, 1.5)	4.70	(-1.9, 11.3)	0.165
	Moderate/2	77	1.52	78	1.85	0.82	(0.60, 1.1)	-3.32	(-8.6, 1.96)	0.214
	Severe/3	20	0.39	20	0.47	0.83	(0.45, 1.5)	-0.80	(-3.5, 1.89)	0.558
	Life-threatening/4	5	0.1	1	0.02	4.16	(0.49, 36)	0.748	(-0.23, 1.7)	0.231
	Fatal/5	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2, .076)	0.061
	≥Severe/3	29	0.57	31	0.73	0.78	(0.47, 1.3)	-1.63	(-4.9, 1.67)	0.327
	Serious	41	0.81	35	0.83	0.97	(0.62, 1.5)	-0.218	(-3.9, 3.46)	0.908
Brady-arrhythmias										
	All pooled	43	0.85	31	0.73	1.15	(0.73, 1.8)	1.1	(-2.5, 4.73)	0.544
	Mild/1	17	0.33	23	0.54	0.61	(0.33, 1.2)	-2.10	(-4.8, 0.63)	0.123
	Moderate/2	14	0.28	4	0.09	2.91	(0.96, 8.8)	1.81	(0.094, 3.5)	0.058
	Severe/3	12	0.24	6	0.14	1.66	(0.62, 4.4)	0.942	(-0.81, 2.7)	0.304
	Life-threatening/4	2	0.04	1	0.02	1.66	(0.15, 18)	0.157	(-.56, 0.87)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	14	0.28	7	0.17	1.66	(0.67, 4.1)	1.10	(-0.80, 3.0)	0.267
	Serious	21	0.41	10	0.24	1.75	(0.82, 3.7)	1.77	(-0.53, 4.1)	0.141
Cardiac Arrhythmias										
	All pooled	432	8.51	381	9.03	0.94	(0.83, 1.1)	-5.19	(-16.7, 6.4)	0.378
	Mild/1	242	4.77	202	4.79	1	(0.83, 1.2)	-0.199	(-8.9, 8.5)	0.964
	Moderate/2	171	3.37	153	3.62	0.93	(0.75, 1.2)	-2.57	(-10.1, 4.9)	0.501
	Severe/3	53	1.04	52	1.23	0.85	(0.58, 1.2)	-1.88	(-6.2, 2.5)	0.392
	Life-threatening/4	7	0.14	5	0.12	1.16	(0.37, 3.7)	0.194	(-1.3, 1.65)	1
	Fatal/5	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2, .076)	0.061
	≥Severe/3	64	1.26	65	1.54	0.82	(0.58, 1.2)	-2.80	(-7.6, 2.02)	0.251
	Serious	104	2.05	87	2.06	0.99	(0.75, 1.3)	-0.131	(-5.9, 5.66)	0.965
Cardiac Arrhythmia Terms										
	All pooled	221	4.35	210	4.98	0.87	(0.73, 1.1)	-6.23	(-14.9 , 2.4)	0.155
	Mild/1	102	2.01	110	2.61	0.77	(0.59, 1.0)	-5.97	(-12, 0.19)	0.055
	Moderate/2	99	1.95	81	1.92	1.02	(0.76, 1.4)	0.306	(-5.31, 5.9)	0.915
	Severe/3	34	0.67	32	0.76	0.88	(0.55, 1.4)	-0.886	(-4.3, 2.6)	0.613
	Life-threatening/4	3	0.06	4	0.09	0.62	(0.14, 2.8)	-0.357	(-1.5, 0.79)	0.709
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	37	0.73	34	0.81	0.9	(0.57, 1.4)	-0.769	(-4.34, 2.8)	0.672
	Serious	68	1.34	54	1.28	1.05	(0.73, 1.5)	0.598	(-4.04, 5.2)	0.801

(Table A9 is continued on the next page.)

Reference ID: 3168397

Table A9 (continued from the previous page). Broad Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, and 20050141) Pooled.

Cardio-myopathy										
	All pooled	400	7.88	379	8.98	0.88	(0.77, 1.0)	-11.0	(-22, 0.035)	0.056
	Mild/1	223	4.39	196	4.64	0.95	(0.78, 1.1)	-2.52	(-11.0, 6.0)	0.560
	Moderate/2	167	3.29	165	3.91	0.84	(0.68, 1.0)	-6.20	(-13.8, 1.4)	0.109
	Severe/3	44	0.87	43	1.02	0.85	(0.56, 1.3)	-1.52	(-5.5, 2.44)	0.448
	Life-threatening/4	6	0.12	5	0.12	1	(0.30, 3.3)	-0.003	(-1.41, 1.4)	1
	Fatal/5	4	0.08	11	0.26	0.3	(0.1, 0.95)	-1.82	(-3.5,-.098)	0.037
	≥Severe/3	52	1.02	58	1.37	0.75	(0.51, 1.1)	-3.50	(-8.0, 0.97)	0.120
	Serious	68	1.34	66	1.56	0.86	(0.61, 1.2)	-2.25	(-7.1, 2.7)	0.366
Disorders of Sinus Node Function										
	All pooled	19	0.37	10	0.24	1.58	(0.74, 3.4)	1.37	(-0.86, 3.6)	0.237
	Mild/1	3	0.06	3	0.07	0.83	(0.17, 4.1)	-0.120	(-1.2, 0.93)	1
	Moderate/2	11	0.22	3	0.07	3.05	(.85, 10.9)	1.46	(-0.055,3.0)	0.105
	Severe/3	6	0.12	5	0.12	1	(0.30, 3.3)	-0.003	(-1.4, 1.4)	1
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.197	(-.19, 0.58)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	7	0.14	5	0.12	1.16	(0.37, 3.7)	0.194	(-1.3, 1.65)	1
	Serious	12	0.24	7	0.17	1.42	(0.56, 3.6)	0.705	(-1.1, 2.5)	0.454
Embolic and Thrombotic Events, Arterial										
	All pooled	95	1.87	77	1.82	1.03	(0.76, 1.4)	0.466	(-5.03, 6.0)	0.868
	Mild/1	19	0.37	16	0.38	0.99	(0.51, 1.9)	-0.049	(-2.55, 2.5)	0.969
	Moderate/2	26	0.51	22	0.52	0.98	(0.56, 1.7)	-0.092	(-3.02, 2.8)	0.951
	Severe/3	40	0.79	24	0.57	1.39	(0.84, 2.3)	2.19	(-1.13 , 5.5)	0.203
	Life-threatening/4	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2,0.076)	0.061
	Fatal/5	9	0.18	7	0.17	1.07	(0.40, 2.9)	0.114	(-1.57, 1.8)	0.895
	≥Severe/3	53	1.04	41	0.97	1.07	(0.72, 1.6)	0.724	(-3.35, 4.8)	0.728
	Serious	67	1.32	55	1.3	1.01	(0.71, 1.4)	0.164	(-4.48, 4.8)	0.945
Embolic and Thrombotic Events, Venous										
	All pooled	38	0.75	49	1.16	0.64	(0.42, 1.0)	-4.13	(-8.1,-0.12)	0.040
	Mild/1	7	0.14	14	0.33	0.42	(0.17, 1.0)	-1.94	(-4.0, .074)	0.050
	Moderate/2	14	0.28	22	0.52	0.53	(0.27, 1.0)	-2.46	(-5.06,0.15)	0.058
	Severe/3	15	0.3	13	0.31	0.96	(0.46, 2.0)	-0.126	(-2.37, 2.1)	0.912
	Life-threatening/4	5	0.1	4	0.09	1.04	(0.28, 3.9)	0.037	(-1.23, 1.3)	1
	Fatal/5	1	0.02	3	0.07	0.28	(0.03, 2.7)	-0.514	(-1.4, 0.38)	0.336
	≥Severe/3	21	0.41	19	0.45	0.92	(0.49, 1.7)	-0.366	(-3.05, 2.3)	0.788
	Serious	22	0.43	22	0.52	0.83	(0.46, 1.5)	-0.88	(-3.7, 1.95)	0.538

(Table A9 is continued on the next page.)

Reference ID: 3168397

Table A9 (continued from the previous page). Broad Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, and 20050141) Pooled.

Gastro-intestinal haemorrhage										
	All pooled	79	1.56	57	1.35	1.15	(0.82, 1.6)	2.05	(-2.8, 6.92)	0.412
	Mild/1	32	0.63	33	0.78	0.81	(0.50, 1.3)	-1.52	(-4.95, 1.9)	0.382
	Moderate/2	36	0.71	17	0.4	1.76	(0.99, 3.1)	3.06	(.066, 6.06)	0.051
	Severe/3	12	0.24	9	0.21	1.11	(0.47, 2.6)	0.231	(-1.7, 2.16)	0.815
	Life-threatening/4	2	0.04	1	0.02	1.66	(0.15, 18)	0.157	(-.56, 0.87)	1
	Fatal/5	1	0.02	0	0	_	N.A.	0.197	(-.19, 0.58)	1
	≥Severe/3	15	0.3	10	0.24	1.25	(0.56, 2.8)	0.585	(-1.5, 2.68)	0.588
	Serious	24	0.47	19	0.45	1.05	(0.58, 1.9)	0.225	(-2.5, 2.99)	0.874
Haemorrhages										
	All pooled	289	5.69	278	6.59	0.86	(0.74, 1.0)	-8.95	(-19, 0.88)	0.073
	Mild/1	165	3.25	166	3.93	0.83	(0.67, 1.0)	-6.83	(-14.5,0.79)	0.077
	Moderate/2	111	2.19	93	2.2	0.99	(0.76, 1.3)	-0.174	(-6.16, 5.8)	0.955
	Severe/3	24	0.47	32	0.76	0.62	(0.37, 1.0)	-2.85	(-6.1, 0.37)	0.077
	Life-threatening/4	3	0.06	1	0.02	2.49	(0.26, 24)	0.354	(-0.46, 1.2)	0.631
	Fatal/5	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9, 0.99)	0.561
	≥Severe/3	32	0.63	38	0.9	0.7	(0.44, 1.1)	-2.70	(-6.3, 0.89)	0.134
	Serious	45	0.89	51	1.21	0.73	(0.49, 1.1)	-3.22	(-7.4, 0.96)	0.126
Haemorrhage Terms (excl lab)										
	All pooled	289	5.69	276	6.54	0.87	(0.74, 1.0)	-8.48	(-18.3, 1.3)	0.089
	Mild/1	165	3.25	165	3.91	0.83	(0.67, 1.0)	-6.60	(-14.2, 1.0)	0.087
	Moderate/2	111	2.19	92	2.18	1	(0.76, 1.3)	0.063	(-5.90, 6.0)	0.983
	Severe/3	24	0.47	32	0.76	0.62	(0.37, 1.1)	-2.85	(-6.08, 3.7)	0.077
	Life-threatening/4	3	0.06	1	0.02	2.49	(0.26, 24)	0.354	(-0.46, 1.2)	0.631
	Fatal/5	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9, 0.99)	0.561
	≥Severe/3	32	0.63	38	0.9	0.7	(0.44, 1.1)	-2.70	(-6.3, 0.89)	0.134
	Serious	45	0.89	51	1.21	0.73	(0.49, 1.1)	-3.22	(-7.4, 0.96)	0.126
Hypertension										
	All pooled	746	14.69	719	17.03	0.86	(.79,0.95)	-23.4	(-38, -8.5)	0.002
	Mild/1	377	7.42	349	8.27	0.9	(0.78, 1.0)	-8.44	(-19.4, 2.6)	0.131
	Moderate/2	383	7.54	385	9.12	0.83	(.72,0.95)	-15.8	(-27, -4.5)	0.006
	Severe/3	34	0.67	39	0.92	0.72	(0.46, 1.2)	-2.54	(-6.2, 1.11)	0.166
	Life-threatening/4	0	0	0	0	_	N.A.		N.A.	.
	Fatal/5	1	0.02	0	0	_	N.A.	0.197	(-0.19,-.58)	1
	≥Severe/3	35	0.69	39	0.92	0.75	(0.47, 1.2)	-2.35	(-6.02, 1.3)	0.205
	Serious	29	0.57	30	0.71	0.8	(0.48, 1.3)	-1.40	(-4.7, 1.88)	0.399
Ischaemic heart disease										
	All pooled	207	4.08	179	4.24	0.96	(0.79, 1.2)	-1.64	(-9.8, 6.51)	0.693
	Mild/1	63	1.24	66	1.56	0.79	(0.56, 1.1)	-3.23	(-8.05, 1.6)	0.185
	Moderate/2	98	1.93	80	1.9	1.02	(0.76, 1.4)	0.346	(-5.24, 5.9)	0.904
	Severe/3	69	1.36	37	0.88	1.55	(1.04, 2.3)	4.82	(0.57, 9.07)	0.029
	Life-threatening/4	12	0.24	8	0.19	1.25	(0.51, 3.1)	0.468	(-1.4, 2.34)	0.628
	Fatal/5	9	0.18	7	0.17	1.07	(0.40, 2.9)	0.114	(-1.57, 1.8)	0.895
	≥Severe/3	85	1.67	51	1.21	1.39	(0.98, 2.0)	4.66	(-0.17, 9.5)	0.063
	Serious	109	2.15	77	1.82	1.18	(0.88, 1.6)	3.22	(-2.45, 8.9)	0.269

(Table A9 is continued on the next page.)

Reference ID: 3168397

Table A9 (continued from the previous page). Broad Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, and 20050141) Pooled.

Myocardial Infarction										
	All pooled	42	0.83	31	0.73	1.13	(0.71, 1.8)	0.927	(-2.66, 4.5)	0.614
	Mild/1	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .093)	0.094
	Moderate/2	6	0.12	3	0.07	1.66	(0.42, 6.6)	0.471	(-0.77, 1.7)	0.524
	Severe/3	25	0.49	11	0.26	1.89	(0.93, 3.8)	2.32	(-0.15, 4.8)	0.073
	Life-threatening/4	6	0.12	7	0.17	0.71	(0.24, 2.1)	-0.477	(-2.0, 1.1)	0.540
	Fatal/5	8	0.16	7	0.17	0.95	(0.34, 2.6)	-0.083	(-1.7, 1.56)	0.921
	≥Severe/3	37	0.73	25	0.59	1.23	(0.74, 2.0)	1.36	(-1.9, 4.65)	0.421
	Serious	40	0.79	29	0.69	1.15	(0.71, 1.9)	1.01	(-2.47, 4.5)	0.573
Pulmonary Hypertension										
	All pooled	131	2.58	134	3.17	0.81	(0.64, 1.0)	-5.95	(-13, 0.91)	0.086
	Mild/1	69	1.36	63	1.49	0.91	(0.65, 1.3)	-1.34	(-6.2, 3.5)	0.587
	Moderate/2	56	1.1	68	1.61	0.68	(0.48, 1.0)	-5.08	(-9.8,-0.32)	0.033
	Severe/3	15	0.3	8	0.19	1.56	(0.66, 3.7)	1.06	(-0.93, 3.1)	0.306
	Life-threatening/4	2	0.04	0	0	_	N.A.	0.394	(-0.15, 0.9)	0.504
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	17	0.33	8	0.19	1.77	(0.76, 4.1)	1.45	(-0.61, 3.5)	0.178
	Serious	14	0.28	9	0.21	1.29	(0.56, 3.0)	0.625	(-1.38, 2.6)	0.546
Torsade de Pointes / QT Prolongation										
	All pooled	111	2.19	105	2.49	0.88	(0.68, 1.1)	-3.02	(-9.2, 3.17)	0.336
	Mild/1	50	0.98	38	0.9	1.09	(0.72, 1.7)	0.844	(-3.09, 4.8)	0.676
	Moderate/2	40	0.79	47	1.11	0.71	(0.46, 1.1)	-3.26	(-7.3, 0.73)	0.104
	Severe/3	16	0.32	13	0.31	1.02	(0.49, 2.1)	0.071	(-2.2, 2.34)	0.951
	Life-threatening/4	5	0.1	2	0.05	2.08	(0.40, 11)	0.511	(-0.57, 1.59)	0.467
	Fatal/5	4	0.08	10	0.24	0.33	(0.10, 1.0)	-1.58	(-3.2, .076)	0.061
	≥Severe/3	25	0.49	25	0.59	0.83	(0.48, 1.4)	-1.00	(-4.01,2.01)	0.512
	Serious	33	0.65	30	0.71	0.91	(0.56, 1.5)	-0.609	(-4.0, 2.75)	0.722

Table A10, A11, A12, A13, A14 and A15 show the results of the analysis of all studies separately using narrow MedDRA SMQ search criteria.

In Study 20030216, severe embolic and thrombotic arterial events were associated with a relative risk of 1.73 (p=0.03), and relative risk estimates tended to be greater than one for the remaining severity levels (Fatal: RR=1.38, p=0.620; Severe or worse: RR=1.32, p=0.179; Serious: RR=1.24, p=0.239). Estimates of relative risk for severe (RR=2.0, p=0.0007), severe or worse (RR=1.72, p=0.002), and serious (RR=1.41, p=0.02) ischaemic heart disease was associated with p-values less than 0.10. There was a trend toward increased risk of life-threatening (RR=1.37, p=0.494) and fatal (RR=1.28, p=0.62) events, although these estimates were not associated with p-values less than 0.10. Severe myocardial infarction was associated with a relative risk of 2.5 (p=0.01). Events of severe or worse and severe myocardial infarction events (RR=1.54 and 1.42, respectively) were associated with relative risk estimates greater than one, however, these events were not associated with a p-value less than 0.10 (p=0.097 and 0.147, respectively).

Reference ID: 3168397

Table A10. Narrow Search Criteria With All Studies Analyzed Separately: Study 20030216.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Embolic and thrombotic events								
	All pooled	124	125	0.99	(0.77, 1.26)	-0.34	(-8.18, 7.50)	0.9322
	Mild/1	25	30	0.83	(0.49, 1.41)	-1.31	(-5.04, 2.43)	0.4926
	Moderate/2	38	44	0.86	(0.56, 1.33)	-1.57	(-6.12, 2.98)	0.4979
	Severe/3	53	36	1.47	(0.96, 2.24)	4.35	(-0.38, 9.09)	0.0718
	Life-threatening/4	9	14	0.64	(0.28, 1.48)	-1.30	(-3.71, 1.12)	0.2936
	Fatal/5	10	10	1	(0.42, 2.39)	-0.00664	(-2.26, 2.25)	0.9954
	≥Severe/3	69	59	1.17	(0.83, 1.65)	2.53	(-3.13, 8.20)	0.3807
	Serious	84	76	1.1	(0.81, 1.50)	2.01	(-4.31, 8.33)	0.5335
Embolic and thrombotic events, arterial								
	All pooled	93	76	1.22	(0.90, 1.65)	4.32	(-2.17, 10.8)	0.192
	Mild/1	18	16	1.12	(0.57, 2.20)	0.504	(-2.43, 3.44)	0.737
	Moderate/2	25	22	1.13	(0.64, 2.01)	0.757	(-2.69, 4.21)	0.667
	Severe/3	40	23	1.73	(1.04, 2.89)	4.36	(0.370, 8.35)	0.032
	Life-threatening/4	4	10	0.4	(0.13, 1.27)	-1.55	(-3.44, 0.34)	0.118
	Fatal/5	9	7	1.28	(0.48, 3.44)	0.510	(-1.51, 2.53)	0.620
	≥Severe/3	53	40	1.32	(0.88, 1.99)	3.32	(-1.52, 8.16)	0.179
	Serious	67	54	1.24	(0.87, 1.77)	3.31	(-2.20, 8.82)	0.239
Ischaemic heart disease								
	All pooled	198	172	1.15	(0.94, 1.40)	6.58	(-2.90, 16.1)	0.174
	Mild/1	61	64	0.95	(0.67, 1.35)	-0.814	(-6.42, 4.79)	0.776
	Moderate/2	93	77	1.2	(0.89, 1.62)	4.07	(-2.44, 10.6)	0.221
	Severe/3	68	34	1.99	(1.32, 3.00)	8.73	(3.67, 13.8)	.0007
	Life-threatening/4	11	8	1.37	(0.55, 3.41)	0.767	(-1.43, 2.96)	0.494
	Fatal/5	9	7	1.28	(0.48, 3.44)	0.510	(-1.51, 2.53)	0.620
	≥Severe/3	83	48	1.72	(1.21, 2.45)	8.97	(3.25, 14.7)	0.002
	Serious	106	75	1.41	(1.05, 1.89)	7.93	(1.22, 14.6)	0.021
Myocardial infarction								
	All pooled	41	29	1.41	(0.88, 2.26)	3.07	(-1.14, 7.27)	0.153
	Mild/1	0	2	0	N.A.	-0.516	(-1.23, 0.20	0.249
	Moderate/2	5	3	1.66	(0.40, 6.95)	0.513	(-0.91, 1.94)	0.726
	Severe/3	25	10	2.49	(1.20, 5.18)	3.85	(0.875, 6.83)	0.011
	Life-threatening/4	6	7	0.85	(0.29, 2.54)	-0.262	(-2.08, 1.56)	0.778
	Fatal/5	8	7	1.14	(0.41, 3.14)	0.253	(-1.70, 2.21)	0.80
	≥Severe/3	37	24	1.54	(0.92, 2.57)	3.33	(-0.60, 7.26)	0.097
	Serious	40	28	1.42	(0.88, 2.30)	3.07	(-1.08, 7.21)	0.147

Reference ID: 3168397

Table A11. Narrow Search Criteria With All Studies Analyzed Separately: Study 20040132.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Haemorrhages								
	All pooled	6	16	0.38	(0.15, 0.94)	-60.4	(-11.4, -6.9)	0.0284
	Mild/1	3	13	0.23	(0.07, 0.80)	-60.5	(-10.6,-14.6)	0.0183
	Moderate/2	2	2	1.01	(0.14, 7.06)	0.0739	(-23.6, 23.8)	1
	Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Serious	0	0	_	N.A.	_	N.A.	.
Haemorrhage Terms (excl lab)								
	All pooled	6	16	0.38	(0.15, 0.94)	-60.4	(-11.4,-6.87)	0.0284
	Mild/1	3	13	0.23	(0.07, 0.80)	-60.5	(-106, -14.6)	0.0183
	Moderate/2	2	2	1.01	(0.14, 7.06)	0.0739	(-23.6, 23.8)	1
	Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	2	0.5	(0.05, 5.49)	-6.02	(-26.5, 14.5)	1
	Serious	0	0	_	N.A.	_	N.A.	.
Hypertension								
	All pooled	6	15	0.4	(0.16, 1.01)	-54.3	(-107, -1.89)	0.0439
	Mild/1	4	7	0.57	(0.17, 1.93)	-18.0	(-56.8, 20.7)	0.5418
	Moderate/2	2	8	0.25	(0.05, 1.17)	-36.3	(-73.1, 0.54)	0.104
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

Reference ID: 3168397

Table A12. Narrow Search Criteria With All Studies Analyzed Separately: Study 20040135.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=129) n	Placebo Exposed Subjects (N=120) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Hypertension								
	All pooled	5	8	0.58	(0.20, 1.73)	-27.9	(-83.6, 27.8)	0.3982
	Mild/1	4	5	0.74	(0.20, 2.71)	-10.7	(-57.3, 36.0)	0.7419
	Moderate/2	0	5	0	N.A.	-41.7	(-77.4,-5.91)	0.0249
	Severe/3	1	0	_	N.A.	7.75	(-7.38, 22.9)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	7.75	(-7.38, 22.9)	1
	Serious	0	0	_	N.A.	_	N.A.	.

In Study 20040138, moderate embolic and thrombotic events were associated with a relative risk of 2.1 (p=0.059), but results were mixed for the remaining severity categories. Likewise, mild haemodynamic oedema and effusions were associated with a relative risk of 1.5 (p=0.055), but risk was approximately unity for the remaining categories of severity.

Note that none of the cardiovascular adverse events in the following studies were associated with a relative risk having a p-value less than 0.10: Study 20010223 (smallest p-value: 0.1278), Study 20040132 (smallest p-value: 0.4985), Study 20040135 (smallest p-value: 0.258), Study 20050141 (smallest p-value: 0.0846), Study 20050172 (smallest p-value: 0.3632), Study 20050179 (smallest p-value: 0.2424), Study 20050234 (smallest p-value: 0.23).

Reference ID: 3168397

Table A13. Narrow Search Criteria With All Studies Analyzed Separately: Study 20040138.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=731) n	Placebo Exposed Subjects (N=725) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Cardiac Failure								
	All pooled	21	26	0.8	(0.45, 1.41)	-7.13	(-25.3, 11.0)	0.4412
	Mild/1	5	2	2.48	(0.48, 12.7)	4.08	(-3.01, 11.2)	0.452
	Moderate/2	1	6	0.17	(0.02, 1.37)	-6.91	(-14.0, 0.21)	0.0686
	Severe/3	9	11	0.81	(0.34, 1.95)	-2.86	(-14.8, 9.10)	0.6392
	Life-threatening/4	1	6	0.17	(0.02, 1.37)	-6.91	(-14.0, 0.21)	0.0686
	Fatal/5	5	2	2.48	(0.48, 12.7)	4.08	(-3.01, 11.2)	0.452
	≥Severe/3	15	19	0.78	(0.40, 1.53)	-5.69	(-21.2, 9.83)	0.4725
	Serious	12	16	0.74	(0.35, 1.56)	-5.65	(-19.8, 8.46)	0.4323
Embolic and thrombotic events								
	All pooled	49	43	1.13	(0.76, 1.68)	7.72	(-17.3, 32.7)	0.545
	Mild/1	3	4	0.74	(0.17, 3.31)	-1.41	(-8.52, 5.70)	0.725
	Moderate/2	19	9	2.09	(0.95, 4.60)	13.6	(-0.49, 27.6)	0.059
	Severe/3	18	13	1.37	(0.68, 2.78)	6.69	(-8.12, 21.5)	0.3764
	Life-threatening/4	9	12	0.74	(0.32, 1.75)	-4.24	(-16.5, 8.01)	0.498
	Fatal/5	4	7	0.57	(0.17, 1.93)	-4.18	(-13.1, 4.72)	0.384
	≥Severe/3	30	32	0.93	(0.57, 1.51)	-3.10	(-23.8, 17.6)	0.770
	Serious	41	32	1.27	(0.81, 1.99)	11.9	(-10.5, 34.3)	0.296
Haemo-dynamic oedema, effusions, etc.								
	All pooled	83	76	1.08	(0.81, 1.45)	8.72	(-23.3, 40.7)	0.594
	Mild/1	54	36	1.49	(0.99, 2.24)	24.2	(-0.47, 48.9)	0.055
	Moderate/2	24	34	0.7	(0.42, 1.17)	-14.1	(-34.2, 6.03)	0.17
	Severe/3	7	7	0.99	(0.35, 2.81)	-0.0792	(-10.1, 9.95)	0.988
	Life-threatening/4	2	2	0.99	(0.14, 7.02)	-0.0226	(-5.40, 5.35)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	9	9	0.99	(0.40, 2.48)	-0.102	(-11.5, 11.2)	0.986
	Serious	7	6	1.16	(0.39, 3.43)	1.30	(-8.36, 11.0)	0.792
Toxic-septic shock conditions								
	All pooled	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
	Mild/1	0	0	_	N.A.	_	N.A.	.
	Moderate/2	0	0	_	N.A.	_	N.A.	.
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	3	0	N.A.	-4.14	(-8.81, 0.54)	0.1232
	Fatal/5	0	1	0	N.A.	-1.38	(-4.08, 1.32)	0.4979
	≥Severe/3	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
	Serious	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612

Reference ID: 3168397

Table A14. Narrow Search Criteria With All Studies Analyzed Separately: Study 20050141.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=593) n	Alendronate Exposed Subjects (N=586) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Haemorrhages								
	All pooled	18	20	1.12	(0.60, 2.10)	3.78	(-16.4, 23.9)	0.7136
	Mild/1	10	19	1.92	(0.90, 4.10)	15.6	(-2.13, 33.3)	0.0846
	Moderate/2	7	2	0.29	(0.06, 1.39)	-8.39	(-18.3, 1.50)	0.1781
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Serious	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
Haemorrhage Terms (excl lab)								
	All pooled	18	20	1.12	(0.60, 2.10)	3.78	(-16.4, 23.9)	0.7136
	Mild/1	10	19	1.92	(0.90, 4.10)	15.6	(-2.13, 33.3)	0.0846
	Moderate/2	7	2	0.29	(0.06, 1.39)	-8.39	(-18.3, 1.50)	0.1781
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
	Serious	1	0	_	N.A.	-1.69	(-4.99, 1.62)	1
Hypertension								
	All pooled	28	17	0.61	(0.34, 1.11)	-18.2	(-40.0, 3.61)	0.1028
	Mild/1	19	11	0.59	(0.28, 1.22)	-13.3	(-31.2, 4.67)	0.148
	Moderate/2	10	5	0.51	(0.17, 1.47)	-8.33	(-21.1, 4.43)	0.2988
	Severe/3	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497
	Serious	0	1	0	N.A.	1.71	(-1.64, 5.05)	0.497

Reference ID: 3168397

Table A15. Narrow Search Criteria With All Studies Analyzed Separately: Study 20050234.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=253) n	Alendronate Exposed Subjects (N=249) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Haemorrhages								
	All pooled	7	13	0.53	(0.22, 1.31)	-24.5	(-58.8, 9.69)	0.1598
	Mild/1	6	7	0.84	(0.29, 2.47)	-4.40	(-32.2, 23.4)	0.7565
	Moderate/2	1	6	0.16	(0.02, 1.35)	-20.1	(-40.7, 0.41)	0.0666
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Haemorrhage Terms (excl lab)								
	All pooled	7	13	0.53	(0.22, 1.31)	-24.5	(-58.8, 9.69)	0.1598
	Mild/1	6	7	0.84	(0.29, 2.47)	-4.40	(-32.2, 23.4)	0.7565
	Moderate/2	1	6	0.16	(0.02, 1.35)	-20.1	(-40.7, 0.41)	0.0666
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

Table A16 shows the results of a cardiovascular adverse event analysis using narrow MedDRA SMQ search criteria in a pooled dataset of the two large, pivotal trials, Study 20030216 and 20040138.

The relative risk for severe embolic and thrombotic events was 1.44 (p=0.05), however, the relative risk for events in all other severity categories was approximately one. Likewise, only severe arterial embolic and thrombotic events was associated with a relative risk of 1.7 (p=0.02); the relative risk of events in the remaining severity categories approached one. Severe ischaemic heart disease was associated with a relative risk of 1.76 (p=0.001), and severe or worse events were associated with a relative risk of 1.35 (p=0.03). However, the relative risk for fatal and life-threatening ischaemic heart disease was approximately equal to one. Relative risk for severe myocardial infarction was 2.5 (p=0.003), however, a relative risk greater than one was not observed in the other categories of severity.

Reference ID: 3168397

Table A16. Narrow Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects (N=4617)	Placebo Subjects (N=4601)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
		n	n					
Cardiac Failure								
	All pooled	107	101	1.06	(0.81, 1.38)	1.22	(-4.84, 7.29)	0.6925
	Mild/1	25	24	1.04	(0.59, 1.81)	0.199	(-2.77, 3.17)	0.8957
	Moderate/2	44	36	1.22	(0.79, 1.89)	1.71	(-2.08, 5.49)	0.3774
	Severe/3	31	31	1	(0.61, 1.64)	-0.0233	(-3.36, 3.31)	0.9891
	Life-threatening/4	4	11	0.36	(0.12, 1.14)	-1.52	(-3.17, 0.12)	0.0761
	Fatal/5	11	10	1.1	(0.47, 2.58)	0.209	(-1.74, 2.16)	0.8333
	≥Severe/3	44	51	0.86	(0.58, 1.28)	-1.55	(-5.68, 2.57)	0.46
	Serious	49	56	0.87	(0.60, 1.28)	-1.56	(-5.89, 2.77)	0.4808
Embolic and thrombotic events								
	All pooled	173	168	1.03	(0.83, 1.26)	0.956	(-6.75, 8.66)	0.8078
	Mild/1	28	34	0.82	(0.50, 1.35)	-1.33	(-4.66, 2.01)	0.4364
	Moderate/2	57	53	1.07	(0.74, 1.55)	0.826	(-3.61, 5.26)	0.7148
	Severe/3	71	49	1.44	(1.01, 2.07)	4.73	(0.103, 9.35)	0.0452
	Life-threatening/4	18	26	0.69	(0.38, 1.26)	-1.75	(-4.57, 1.06)	0.2223
	Fatal/5	14	17	0.82	(0.41, 1.66)	-0.663	(-3.03, 1.70)	0.5827
	≥Severe/3	99	91	1.08	(0.82, 1.44)	1.66	(-4.14, 7.46)	0.5739
	Serious	125	108	1.15	(0.89, 1.49)	3.60	(-2.81, 10.0)	0.2708
Embolic and thrombotic events, arterial								
	All pooled	130	109	1.19	(0.92, 1.53)	4.47	(-2.02, 11.0)	0.1773
	Mild/1	20	18	1.11	(0.59, 2.09)	0.420	(-2.20, 3.04)	0.7532
	Moderate/2	37	28	1.32	(0.81, 2.15)	1.93	(-1.49, 5.34)	0.2686
	Severe/3	53	31	1.7	(1.10, 2.65)	4.74	(0.865, 8.62)	0.0166
	Life-threatening/4	11	22	0.5	(0.24, 1.03)	-2.40	(-4.84, 0.04)	0.0538
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.227	(-2.43, 1.98)	0.8401
	≥Severe/3	77	67	1.15	(0.83, 1.58)	2.12	(-2.95, 7.18)	0.4128
	Serious	98	82	1.19	(0.89, 1.59)	3.40	(-2.24, 9.05)	0.2377
Embolic and thrombotic events, venous								
	All pooled	51	59	0.86	(0.59, 1.25)	-1.78	(-6.21, 2.66)	0.4321
	Mild/1	8	16	0.5	(0.21, 1.16)	-1.74	(-3.83, 0.34)	0.1003
	Moderate/2	21	25	0.84	(0.47, 1.49)	-0.885	(-3.76, 1.99)	0.5465
	Severe/3	21	18	1.16	(0.62, 2.18)	0.636	(-2.01, 3.29)	0.638
	Life-threatening/4	7	4	1.74	(0.51, 5.95)	0.647	(-0.76, 2.06)	0.5486
	Fatal/5	1	3	0.33	(0.03, 3.19)	-0.435	(-1.29, 0.42)	0.3741
	≥Severe/3	28	24	1.16	(0.68, 2.00)	0.848	(-2.21, 3.91)	0.5866
	Serious	33	26	1.26	(0.76, 2.11)	1.50	(-1.76, 4.75)	0.3677
Ischaemic heart disease								
	All pooled	252	226	1.11	(0.93, 1.32)	5.46	(-3.59, 14.5)	0.2371
	Mild/1	70	69	1.01	(0.73, 1.41)	0.165	(-4.81, 5.14)	0.9483
	Moderate/2	110	94	1.17	(0.89, 1.53)	3.39	(-2.61, 9.40)	0.268
	Severe/3	90	51	1.76	(1.25, 2.47)	8.41	(3.40, 13.4)	0.001
	Life-threatening/4	22	25	0.88	(0.50, 1.55)	-0.669	(-3.58, 2.24)	0.6522
	Fatal/5	13	14	0.93	(0.44, 1.97)	-0.227	(-2.43, 1.98)	0.8401
	≥Severe/3	118	87	1.35	(1.03, 1.78)	6.65	(0.631, 12.7)	0.0304
	Serious	143	121	1.18	(0.93, 1.50)	4.67	(-2.13, 11.5)	0.1786

(Table A16 is continued on the next page.)

Reference ID: 3168397

Table A16 (continued from the previous page). Narrow Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Myocardial infarction								
	All pooled	64	55	1.16	(0.81, 1.66)	1.91	(-2.70, 6.52)	0.4172
	Mild/1	0	3	0	N.A.	-0.652	(-1.4, 0.086)	0.1243
	Moderate/2	8	6	1.33	(0.46, 3.83)	0.429	(-1.16, 2.02)	0.5972
	Severe/3	35	14	2.49	(1.34, 4.62)	4.54	(1.57, 7.50)	0.0027
	Life-threatening/4	13	20	0.65	(0.32, 1.30)	-1.53	(-3.97, 0.91)	0.2184
	Fatal/5	12	14	0.85	(0.40, 1.84)	-0.444	(-2.61, 1.72)	0.6879
	≥Severe/3	57	48	1.18	(0.81, 1.73)	1.91	(-2.42, 6.24)	0.3868
	Serious	61	54	1.13	(0.78, 1.62)	1.48	(-3.06, 6.01)	0.5234
Thrombophlebitis								
	All pooled	9	17	0.53	(0.24, 1.18)	-1.75	(-3.91, 0.42)	0.1141
	Mild/1	4	7	0.57	(0.17, 1.94)	-0.655	(-2.07, 0.76)	0.3866
	Moderate/2	3	9	0.33	(0.09, 1.23)	-1.31	(-2.78, 0.17)	0.0915
	Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Serious	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1

Table A17 shows the result of an analysis of placebo-controlled trials using narrow MedDRA SMQ search criteria to evaluate the risk for cardiovascular adverse events.

Severe arterial embolic and thrombotic events were associated with a relative risk of 1.66 (p=0.05). The relative risk for fatal (RR=1.28), severe or worse (RR=1.29) and serious (RR=1.22) events were all greater than one, however, none of these estimates were associated with a p-value less than 0.10. Estimates of relative risk for severe (RR=1.83, p=0.002), severe or worse (RR=1.62, p=0.006), and serious (RR=1.39, p=0.03) ischaemic heart disease were all greater than one. Life-threatening (RR=1.37) and fatal (RR=1.28) events were also associated with a relative risk estimate greater than one, however these estimates did not have a p-value less than 0.10.

Relative risk for severe myocardial infarction was greater than one (RR=2.27, p=0.02). Myocardial infarction events of a severe or worse nature (RR=1.48) and events of a serious nature (RR=1.38) also had relative risk estimates greater than one, but these estimates were not associated with a p-value less than 0.10. Events of a life-threatening or fatal nature were associated with relative risk estimates approaching unity.

Reference ID: 3168397

Table A17. Narrow Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=4232 % (n/N)	Placebo Subjects n	Placebo Subjects N=4221 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Embolic and thrombotic events										
	All pooled	124	2.93	126	2.99	0.98	(0.77, 1.3)	-0.55	(-7.8, 6.7)	0.881
	Mild/1	25	0.59	30	0.71	0.83	(0.49, 1.4)	-1.20	(-4.63, 2.2)	0.493
	Moderate/2	38	0.9	44	1.04	0.86	(0.56, 1.3)	-1.44	(-5.6, 2.73)	0.498
	Severe/3	53	1.25	37	0.88	1.43	(0.94, 2.2)	3.76	(-0.62, 8.1)	0.092
	Life-threatening/4	9	0.21	14	0.33	0.64	(0.28, 1.5)	-1.19	(-3.4, 1.03)	0.294
	Fatal/5	10	0.24	10	0.24	1	(0.42, 2.4)	-0.006	(-2.08, 2.1)	0.995
	≥Severe/3	69	1.63	60	1.42	1.15	(0.81, 1.6)	2.09	(-3.14, 7.3)	0.433
	Serious	84	1.98	77	1.82	1.09	(0.80, 1.5)	1.61	(-4.2, 7.43)	0.589
Embolic and thrombotic events, arterial										
	All pooled	93	2.2	77	1.82	1.2	(0.89, 1.62)	3.73	(-2.25, 9.72)	0.222
	Mild/1	18	0.43	16	0.38	1.12	(0.57, 2.20)	0.463	(-2.24, 3.16)	0.737
	Moderate/2	25	0.59	22	0.52	1.13	(0.64, 2.01)	0.695	(-2.47, 3.87)	0.667
	Severe/3	40	0.95	24	0.57	1.66	(1.00, 2.75)	3.77	(0.072, 7.46)	0.046
	Life-threatening/4	4	0.09	10	0.24	0.4	(0.13, 1.27)	-1.42	(-3.16, 0.31)	0.118
	Fatal/5	9	0.21	7	0.17	1.28	(0.48, 3.44)	0.468	(-1.38, 2.32)	0.620
	≥Severe/3	53	1.25	41	0.97	1.29	(0.86, 1.93)	2.81	(-1.66, 7.28)	0.218
	Serious	67	1.58	55	1.3	1.22	(0.85, 1.73)	2.80	(-2.28, 7.89)	0.280
Ischaemic heart disease										
	All pooled	201	4.75	178	4.22	1.13	(0.92, 1.37)	5.33	(-3.50, 14.1)	0.237
	Mild/1	62	1.47	65	1.54	0.95	(0.67, 1.34)	-0.749	(-5.94, 4.44)	0.777
	Moderate/2	95	2.24	80	1.9	1.18	(0.88, 1.59)	3.50	(-2.57, 9.56)	0.259
	Severe/3	68	1.61	37	0.88	1.83	(1.23, 2.73)	7.30	(2.58, 12.0)	0.002
	Life-threatening/4	11	0.26	8	0.19	1.37	(0.55, 3.41)	0.704	(-1.31, 2.72)	0.494
	Fatal/5	9	0.21	7	0.17	1.28	(0.48, 3.44)	0.468	(-1.38, 2.32)	0.620
	≥Severe/3	83	1.96	51	1.21	1.62	(1.15, 2.29)	7.53	(2.21, 12.9)	0.006
	Serious	107	2.53	77	1.82	1.39	(1.04, 1.85)	7.04	(0.823, 13.3)	0.027
Myocardial infarction										
	All pooled	41	0.97	30	0.71	1.36	(0.85, 2.18)	2.58	(-1.31, 6.47)	0.194
	Mild/1	0	0	2	0.05	0	N.A.	-0.474	(-1.13, 0.18)	0.249
	Moderate/2	5	0.12	3	0.07	1.66	(0.40, 6.95)	0.471	(-0.84, 1.78)	0.726
	Severe/3	25	0.59	11	0.26	2.27	(1.12, 4.60)	3.30	(0.527, 6.08)	0.020
	Life-threatening/4	6	0.14	7	0.17	0.85	(0.29, 2.54)	-0.241	(-1.91, 1.43)	0.778
	Fatal/5	8	0.19	7	0.17	1.14	(0.41, 3.14)	0.232	(-1.56, 2.03)	0.8
	≥Severe/3	37	0.87	25	0.59	1.48	(0.89, 2.45)	2.82	(-0.82, 6.46)	0.129
	Serious	40	0.95	29	0.69	1.38	(0.85, 2.21)	2.58	(-1.25, 6.42)	0.187

Table A18 shows the results of the application of narrow MedDRA SMQ search criteria applied to a dataset of all PMO studies pooled.

Here, severe ischaemic heart disease was the only adverse event associated with a p-value less than 0.10 (RR=1.55, p=0.03). There was no clear trend with regard to risk estimates of any other severity category for ischaemic heart disease.

Reference ID: 3168397

Table A18. Narrow Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=5078 % (n/N)	Placebo Subjects n	Placebo Subjects N=4221 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Embolic and Thrombotic Events, Arterial										
	All pooled	95	1.87	77	1.82	1.03	(0.76, 1.4)	0.466	(-5.0, 6.0)	0.868
	Mild/1	19	0.37	16	0.38	0.99	(0.51, 1.9)	-0.049	(-2.55, 2.5)	0.969
	Moderate/2	26	0.51	22	0.52	0.98	(0.56, 1.7)	-0.092	(-3.0, 2.8)	0.951
	Severe/3	40	0.79	24	0.57	1.39	(0.84, 2.3)	2.19	(-1.13, 5.5)	0.203
	Life-threatening/4	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2,0.076)	0.061
	Fatal/5	9	0.18	7	0.17	1.07	(0.40, 2.9)	0.114	(-1.57, 1.8)	0.895
	≥Severe/3	53	1.04	41	0.97	1.07	(0.72, 1.6)	0.724	(-3.35, 4.8)	0.728
	Serious	67	1.32	55	1.3	1.01	(0.71, 1.4)	0.164	(-4.48, 4.8)	0.945
Embolic and Thrombotic Events, Venous										
	All pooled	38	0.75	49	1.16	0.64	(0.42, 1.0)	-4.13	(-8.1,-0.12)	0.040
	Mild/1	7	0.14	14	0.33	0.42	(0.17, 1.0)	-1.94	(-4.0,0.074)	0.050
	Moderate/2	14	0.28	22	0.52	0.53	(0.27, 1.0)	-2.46	(-5.06,0.15)	0.058
	Severe/3	15	0.3	13	0.31	0.96	(0.46, 2.0)	-0.126	(-2.37,2.12)	0.912 1
	Life-threatening/4	5	0.1	4	0.09	1.04	(0.28, 3.9)	0.037	(-1.23, 1.3)	1
	Fatal/5	1	0.02	3	0.07	0.28	(0.03, 2.7)	-0.514	(-1.4, 0.38)	0.336
	≥Severe/3	21	0.41	19	0.45	0.92	(0.49, 1.7)	-0.366	(-3.05, 2.3)	0.788
	Serious	22	0.43	22	0.52	0.83	(0.46, 1.5)	-0.880	(-3.7, 1.95)	0.538
Haemorrhages										
	All pooled	287	5.65	273	6.47	0.87	(0.74, 1.0)	-8.16	(-17.9 , 1.6)	0.10
	Mild/1	163	3.21	162	3.84	0.84	(0.68, 1.0)	-6.28	(-13.8,1.28)	0.101
	Moderate/2	111	2.19	92	2.18	1	(0.76, 1.3)	0.063	(-5.9, 6.03)	0.983
	Severe/3	24	0.47	32	0.76	0.62	(0.37, 1.0)	-2.85	(-6.1, 0.37)	0.077
	Life-threatening/4	3	0.06	1	0.02	2.49	(0.26, 24)	0.354	(-0.46, 1.2)	0.631
	Fatal/5	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9, 0.99)	0.561
	≥Severe/3	32	0.63	38	0.9	0.7	(0.44, 1.1)	-2.70	(-6.3, 0.89)	0.134
	Serious	45	0.89	51	1.21	0.73	(0.49, 1.1)	-3.22	(-7.4, 0.96)	0.126
Haemorrhage Terms (excl lab)										
	All pooled	287	5.65	273	6.47	0.87	(0.74, 1.0)	-8.16	(-17.9, 1.6)	0.10
	Mild/1	163	3.21	162	3.84	0.84	(0.68, 1.0)	-6.28	(-13.8, 1.3)	0.101
	Moderate/2	111	2.19	92	2.18	1	(0.76, 1.3)	0.063	(-5.9, 6.03)	0.983
	Severe/3	24	0.47	32	0.76	0.62	(0.37, 1.1)	-2.85	(-6.1, 0.37)	0.077
	Life-threatening/4	3	0.06	1	0.02	2.49	(0.26, 24)	0.354	(-0.46, 1.2)	0.631
	Fatal/5	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9, 0.99)	0.561
	≥Severe/3	32	0.63	38	0.9	0.7	(0.44, 1.1)	-2.70	(-6.3, 0.89)	0.134
	Serious	45	0.89	51	1.21	0.73	(0.49, 1.1)	-3.22	(-7.4, 0.96)	0.126

(Table A18 continued on the next page.)

Reference ID: 3168397

Table A18 (continued from the previous page). Narrow Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Hypertension										
	All pooled	746	14.69	719	17.03	0.86	(0.79, 1.0)	-23.4	(-38.4,-8.5)	0.002
	Mild/1	377	7.42	349	8.27	0.9	(0.78, 1.0)	-8.44	(-19.4, 2.6)	0.131
	Moderate/2	383	7.54	385	9.12	0.83	(0.72, 1.0)	-15.8	(-27, -4.5)	0.006
	Severe/3	34	0.67	39	0.92	0.72	(0.46, 1.2)	-2.54	(-6.2, 1.11)	0.166
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	1	0.02	0	0	_	N.A.	0.197	(-0.19,0.58)	1
	≥Severe/3	35	0.69	39	0.92	0.75	(0.47, 1.2)	-2.35	(-6.0, 1.33)	0.205
	Serious	29	0.57	30	0.71	0.8	(0.48, 1.3)	-1.40	(-4.7, 1.88)	0.399
Ischaemic heart disease										
	All pooled	205	4.04	178	4.22	0.96	(0.79, 1.17)	-1.80	(-9.93, 6.33)	0.664
	Mild/1	63	1.24	65	1.54	0.81	(0.57, 1.14)	-2.99	(-7.80, 1.81)	0.218
	Moderate/2	96	1.89	80	1.9	1	(0.74, 1.34)	-0.0478	(-5.61, 5.52)	0.987
	Severe/3	69	1.36	37	0.88	1.55	(1.04, 2.31)	4.82	(0.574, 9.07)	0.029
	Life-threatening/4	12	0.24	8	0.19	1.25	(0.51, 3.05)	0.468	(-1.40, 2.34)	0.628
	Fatal/5	9	0.18	7	0.17	1.07	(0.40, 2.87)	0.114	(-1.57, 1.80)	0.895
	≥Severe/3	85	1.67	51	1.21	1.39	(0.98, 1.96)	4.66	(-0.17, 9.48)	0.063
	Serious	109	2.15	77	1.82	1.18	(0.88, 1.57)	3.22	(-2.45, 8.90)	0.269
Myocardial Infarction										
	All pooled	42	0.83	30	0.71	1.16	(0.73, 1.9)	1.16	(-2.39, 4.7)	0.524
	Mild/1	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Moderate/2	6	0.12	3	0.07	1.66	(0.42, 6.6)	0.471	(-0.77, 1.7)	0.524
	Severe/3	25	0.49	11	0.26	1.89	(0.93, 3.8)	2.32	(-0.15, 4.8)	0.073
	Life-threatening/4	6	0.12	7	0.17	0.71	(0.24, 2.1)	-0.477	(-2.0, 1.07)	0.540
	Fatal/5	8	0.16	7	0.17	0.95	(0.34, 2.6)	-0.083	(-1.73, 1.6)	0.921
	≥Severe/3	37	0.73	25	0.59	1.23	(0.74, 2.0)	1.36	(-1.93, 4.7)	0.421
	Serious	40	0.79	29	0.69	1.15	(0.71, 1.9)	1.01	(-2.5, 4.5)	0.573
Shock-associated Circulatory or Cardiac Conditions										
	All pooled	20	0.39	18	0.43	0.92	(0.49, 1.7)	-0.326	(-2.94, 2.3)	0.806
	Mild/1	5	0.1	2	0.05	2.08	(0.4, 10.7)	0.511	(-0.57, 1.6)	0.467
	Moderate/2	0	0	3	0.07	0	N.A.	-0.711	(-1.5,0.093)	0.094
	Severe/3	3	0.06	0	0	_	N.A.	0.591	(-0.08, 1.3)	0.256
	Life-threatening/4	5	0.1	2	0.05	2.08	(0.4, 10.7)	0.511	(-0.57, 1.6)	0.467
	Fatal/5	9	0.18	11	0.26	0.68	(0.28, 1.6)	-0.834	(-2.76, 1.1)	0.388
	≥Severe/3	15	0.3	13	0.31	0.96	(0.46, 2.0)	-0.126	(-2.4, 2.12)	0.912
	Serious	15	0.3	13	0.31	0.96	(0.46, 2.0)	-0.126	(-2.4, 2.12)	0.912

Table A19, A20 and A21 show the results of applying the sponsor's Preferred Term grouping strategy to each of the nine studies separately.

In study 20030216, severe (RR=1.87, p=0.001), severe or worse (RR=1.53, p=0.01), and serious (RR=1.33, p=0.04) events of acute coronary syndromes/all preferred terms pooled were associated with a relative risk greater than one and a p-value less than 0.10. Relative risk for life-threatening events was also greater than one (RR=1.38, p=0.494), but was not associated with a p-value less than 0.10. Severe acute coronary syndomes/acute myocardial infarction was associated with a relative risk of 4.5 (p=0.065). The relative risk estimates associated with the remaining categories of acute coronary

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syndromes/myocardial infarction severity, however, were not consistently greater than one. Serious acute coronary syndromes/angina pectoris was associated with a relative risk of 1.83 (p=0.04). There was a trend toward relative risk estimates greater than one for severe (RR=1.8, p=0.11) and severe or worse (RR=1.75, p=0.118) events, but they were not associated with p-values less than 0.10. Mild arrhythmia/bradycardia was associated with a relative risk of 4.65 (p=0.01), but relative risk was not consistently greater than one for the remaining severity categories. Relative risk for moderate arrhythmia/tachycardia was 2.49 (p=0.05), but relative risk estimates were not greater than one for the remaining severity levels. Relative risk for severe events of other vascular disorders/All PTs was 1.65 (p=0.055). There was no a consistent trend toward relative risk estimates greater than one for the remaining severity categories and none were associated with a p-value less than 0.10. Risk difference for serious vascular disorders/skin ulcers was 0.00154 (p=0.031). The risk difference had to be computed since six (6) serious events were observed in the denosumab arm, but zero (0) in the control arm. The relative risk for severe events was 5.0, but this was not associated with a p-value less than 0.10 (p=0.219).

In study 20040138, the relative risk for severe arrhythmia/all PTs was 1.98 (p=0.056). There was a consistent trend of relative risk estimates greater than one for the remaining categories of severity, with RR=1.32 for fatal arrhythmia, RR=1.46 for severe or worse arrhythmia, and RR=1.2 for serious arrhythmia. None of these estimates, however, were associated with a p-value less than 0.10, with p=1, p=0.167 and p=0.463, respectively. Relative risk for mild congestive heart failure with all preferred terms pooled was1.61 (p=0.01), however, there was no consistent trend with respect to relative risk for the remaining severity categories. Relative risk for mild congestive heart failure/oedema peripheral was 1.65 (p=0.04), however, relative risk for the remaining severity categories was not greater than one. The risk difference of life-threatening vascular disorders with all terms pooled was 0.0109 (p=0.008). Risk difference had to be computed since there were eight events in the denosumab arm and zero in the control arm. Severe or worse (RR=1.37, p=0.376) and serious (RR=1.53, p=0.227) vascular disorders had relative risk estimates greater than one, but none were associated with p-values less than 0.10.

Note that the following studies did not have any events with a significant p-value: Study 20010223 (smallest p-value: 0.5754), Study 20040132 24 months (smallest p-value: 0.1421), Study 20040135 (smallest p-value: 0.116), Study 20050141 (smallest p-value: 0.374), Study 20050172 (smallest p-value: 0.6179), Study 20050179 (smallest p-value: 0.497, Study 20050234 (smallest p-value: 0.2486).

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Table A19. Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20030216.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Acute coronary syndromes: All PTs								
	All pooled	232	209	1.11	(0.92, 1.33)	5.78	(-4.52, 16.1)	0.271
	Mild/1	80	86	0.93	(0.69, 1.25)	-1.60	(-8.04, 4.84)	0.626
	Moderate/2	104	85	1.22	(0.92, 1.62)	4.83	(-2.02, 11.7)	0.167
	Severe/3	73	39	1.87	(1.27, 2.75)	8.72	(3.42, 14.0)	0.001
	Life-threatening/4	11	8	1.37	(0.55, 3.41)	0.767	(-1.43, 2.96)	0.494
	Fatal/5	10	13	0.77	(0.34, 1.75)	-0.781	(-3.20, 1.64)	0.527
	≥Severe/3	89	58	1.53	(1.10, 2.12)	7.94	(1.88, 14.0)	0.010
	Serious	111	83	1.33	(1.01, 1.77)	7.15	(0.208, 14.1)	0.044
Acute coronary syndromes: Acute myocardial infarction								
	All pooled	12	5	2.39	(0.84, 6.79)	1.80	(-0.28, 3.88)	0.143
	Mild/1	0	0	_	N.A.	_	N.A.	.
	Moderate/2	2	0	_	N.A.	0.515	(-0.20, 1.23)	0.500
	Severe/3	9	2	4.49	(0.97, 20.8)	1.80	(0.128, 3.47)	0.065
	Life-threatening/4	0	2	0	N.A.	-0.516	(-1.23, 0.20)	0.249
	Fatal/5	1	1	1	(0.06, 15.9)	-0.0007	(-0.72, 0.71)	1
	≥Severe/3	10	5	1.99	(0.68, 5.83)	1.28	(-0.67, 3.24)	0.301
	Serious	12	5	2.39	(0.84, 6.79)	1.80	(-0.28, 3.88)	0.143
Acute coronary syndromes: Angina pectoris								
	All pooled	101	87	1.16	(0.87, 1.54)	3.54	(-3.29, 10.4)	0.310
	Mild/1	39	33	1.18	(0.74, 187)	1.52	(-2.74, 5.79)	0.484
	Moderate/2	54	45	1.2	(0.81, 1.77)	2.29	(-2.71, 7.28)	0.370
	Severe/3	20	11	1.81	(0.87, 3.78)	2.31	(-0.50, 5.11)	0.107
	Life-threatening/4	1	1	1	(0.06, 15.9)	-0.0007	(-0.72, 0.71)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	21	12	1.75	(0.86, 3.54)	2.31	(-0.59, 5.20)	0.118
	Serious	33	18	1.83	(1.03, 3.24)	3.85	(0.26, 7.44)	0.036
Acute coronary syndromes: Cardiac disorder								
	All pooled	0	5	0	N.A.	-1.29	(-2.4, -0.16)	0.031
	Mild/1	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Moderate/2	0	1	0	N.A.	-0.258	(-0.76, 0.25)	0.4994
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

(Table A19 is continued on the next page.)

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Table A19 (continued from the previous page). Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20030216.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=3886) n	Placebo Exposed Subjects (N=3876) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Other vascular disorders: All PTs								
	All pooled	179	162	1.1	(0.90, 1.36)	4.27	(-4.85, 0.13)	0.359
	Mild/1	71	76	0.93	(0.68, 1.28)	-1.34	(-7.40, 4.73)	0.67
	Moderate/2	76	68	1.11	(0.81, 1.54)	2.01	(-3.99, 8.02)	0.511
	Severe/3	38	23	1.65	(0.98, 2.76)	3.84	(-0.082, 7.8)	0.055
	Life-threatening/4	7	6	1.16	(0.39, 3.46)	0.253	(-1.57, 2.07)	0.785
	Fatal/5	2	3	0.66	(0.11, 3.98)	-0.259	(-1.39, 0.87)	0.687
	≥Severe/3	46	30	1.53	(0.97, 2.42)	4.10	(-0.28, 8.48)	0.067
	Serious	50	38	1.31	(0.86, 2.00)	3.06	(-1.65, 7.77)	0.203
Other vascular disorder: Aortic Aneurysm								
	All pooled	6	8	0.75	(0.26, 2.15)	-0.520	(-2.41, 1.37)	0.5893
	Mild/1	1	1	1	(0.06, 15.9)	-0.00066	(-0.72, 0.71)	1
	Moderate/2	5	3	1.66	(0.40, 6.95)	0.513	(-0.91, 1.94)	0.7264
	Severe/3	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Serious	1	5	0.2	(0.02, 1.71)	-1.03	(-2.3, 0.20)	0.1244
Other vascular disorder: Aortic stenosis								
	All pooled	13	5	2.59	(0.93, 7.27)	2.06	(-0.083, 4.2)	0.0959
	Mild/1	8	4	1.99	(0.60, 6.62)	1.03	(-0.72, 2.77)	0.3873
	Moderate/2	3	0	_	N.A.	0.772	(-0.10, 1.65)	0.2499
	Severe/3	2	1	1.99	(0.18, 22.0)	0.257	(-0.62, 1.13)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	1	1.99	(0.18, 22.0)	0.257	(-0.62, 1.13)	1
	Serious	3	0	_	N.A.	0.772	(-0.10, 1.65)	0.2499
Other vascular disorders: Skin ulcer								
	All pooled	34	28	1.21	(0.74, 1.99)	1.53	(-2.43, 5.49)	0.450
	Mild/1	15	16	0.94	(0.46, 1.89)	-0.268	(-3.07, 2.54)	0.852
	Moderate/2	19	14	1.35	(0.68, 2.70)	1.28	(-1.62, 4.17)	0.387
	Severe/3	5	1	4.99	(0.58, 42.7)	1.03	(-0.21, 2.26)	0.219
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	1	4.99	(0.58, 42.7)	1.03	(-0.21, 2.26)	0.219
	Serious	6	0	_	N.A.	1.54	(0.310, 2.78)	0.031

(Table A19 is continued on the next page.)

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Table A19 (continued from the previous page). Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20030216.

Stroke: Cerebral Thrombosis								
	All pooled	3	5	0.6	(0.14, 2.50)	-0.518	(-1.95, 0.91)	0.5071
	Mild/1	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Moderate/2	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Severe/3	2	1	1.99	(0.18, 22.0)	0.257	(-0.62, 1.13)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	1	1.99	(0.18, 22.0)	0.257	(-0.62, 1.13)	1
	Serious	3	3	1	(0.20, 4.94)	-0.0020	(-1.24, 1.23)	1
Acute coronary syndromes: Myocardial Ischaemia								
	All pooled	37	31	1.19	(0.74, 1.91)	1.52	(-2.62, 5.67)	0.4714
	Mild/1	14	20	0.7	(0.35, 1.38)	-1.56	(-4.50, 1.38)	0.2989
	Moderate/2	16	11	1.45	(0.67, 3.12)	1.28	(-1.34, 3.90)	0.3385
	Severe/3	5	1	4.99	(0.58, 42.7)	1.03	(-0.21, 2.3)	0.2186
	Life-threatening/4	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Fatal/5	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	≥Severe/3	7	1	6.98	(0.86, 56.7)	1.54	(0.12, 2.97)	0.0702
	Serious	12	5	2.39	(0.84, 6.79)	1.80	(-0.28, 3.9)	0.143
Arrhythmia: Bradycardia								
	All pooled	18	12	1.5	(0.72, 3.10)	1.54	(-1.22, 4.30)	0.276
	Mild/1	14	3	4.65	(1.34, 16.2)	2.83	(0.75, 4.91)	0.013
	Moderate/2	2	5	0.4	(0.08, 2.06)	-0.775	(-2.11, 0.56)	0.288
	Severe/3	3	4	0.75	(0.17, 3.34)	-0.260	(-1.60, 1.08)	0.726
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	4	0.75	(0.17, 3.34)	-0.260	(-1.60, 1.08)	0.726
	Serious	4	3	1.33	(0.30, 5.94)	0.255	(-1.08, 1.59)	1
Arrhythmia: Sick Sinus Syndrome								
	All pooled	11	4	2.74	(0.87, 8.61)	1.80	(-0154, 3.75)	0.1181
	Mild/1	1	1	1	(0.06, 15.9)	-0.00066	(-0.72, 0.71)	1
	Moderate/2	7	1	6.98	(0.86, 56.7)	1.54	(0.12, 2.97)	0.0702
	Severe/3	4	3	1.33	(0.30, 5.94)	0.255	(-1.08, 1.59)	1
	Life-threatening/4	1	0	_	N.A.	0.257	(-0.25, 0.76)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	3	1.66	(0.40, 6.95)	0.513	(-0.91, 1.94)	0.7264
	Serious	9	4	2.24	(0.69, 7.28)	1.28	(-0.53, 3.1)	0.2664
Arrhythmia: Sinus tachycardia								
	All pooled	0	5	0	N.A.	-1.29	(-2.4, -0.16)	0.031
	Mild/1	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Moderate/2	0	1	0	N.A.	-0.258	(-0.76, 0.25)	0.4994
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.

(Table A19 is continued on the next page.)

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Table A19 (continued from the previous page). Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20030216.

Arrhythmia: Supraventricular tachycardia								
	All pooled	9	9	1	(0.40, 2.5)	-0.006	(-2.15, 2.13)	0.9956
	Mild/1	0	6	0	N.A.	-1.55	(-2.79,-0.31)	0.0155
	Moderate/2	6	3	1.99	(0.50, 7.97)	0.77	(-0.74, 2.28)	0.5076
	Severe/3	3	2	1.5	(0.25, 8.95)	0.256	(-0.87, 1.38)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	2	1.5	(0.25, 8.95)	0.256	(-0.87, 1.38)	1
	Serious	7	2	3.49	(0.73, 16.8)	1.29	(-0.23, 2.80)	0.1794
Arrhythmia: Tachycardia								
	All pooled	38	24	1.58	(0.95, 2.63)	3.59	(-0.37, 7.55)	0.076
	Mild/1	25	17	1.47	(0.79, 2.71)	2.05	(-1.22, 5.31)	0.219
	Moderate/2	15	6	2.49	(0.97, 6.42)	2.31	(0.0027, 4.6)	0.050
	Severe/3	0	2	0	N.A.	-0.516	(-1.23, 0.20)	0.250
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	2	0	N.A.	-0.516	(-1.23, 0.20)	0.249
	Serious	1	1	1	(0.06, 15.9)	-0.0007	(-0.72, 0.71)	1
Congestive Heart Failure: Cardiac Failure Congestive								
	All pooled	16	23	0.69	(0.37, 1.31)	-1.82	(-4.96, 1.33)	0.2577
	Mild/1	1	7	0.14	(0.02, 1.16)	-1.55	(-3.0, -0.12)	0.0387
	Moderate/2	11	9	1.22	(0.51, 2.94)	0.509	(-1.75, 2.76)	0.6585
	Severe/3	5	7	0.71	(0.23, 2.24)	-0.519	(-2.27, 1.23)	0.5803
	Life-threatening/4	0	1	0	N.A.	-0.258	(-0.76, 0.25)	0.499
	Fatal/5	0	1	0	N.A.	-0.258	(-0.76, 0.25)	0.4994
	≥Severe/3	5	9	0.55	(0.19, 1.65)	-1.04	(-2.92, 0.85)	0.3007
	Serious	10	13	0.77	(0.34, 1.75)	-0.781	(-3.20, 1.64)	0.527
Congestive Heart Failure: Oedema								
	All pooled	3	8	0.37	(0.10, 1.41)	-1.29	(-2.97, 0.38)	0.1452
	Mild/1	0	4	0	N.A.	-1.03	(-2.0,-0.021)	0.0621
	Moderate/2	3	4	0.75	(0.17, 3.34)	-0.260	(-1.6, 1.08)	0.7261
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Congestive Heart Failure: Oedema Peripheral								
	All pooled	189	155	1.22	(0.99, 1.50)	8.65	(-0.51, 17.8)	0.0642
	Mild/1	121	105	1.15	(0.89, 1.49)	4.05	(-3.43, 11.5)	0.2889
	Moderate/2	74	56	1.32	(0.93, 1.86)	4.59	(-1.11, 10.3)	0.1147
	Severe/3	4	4	1	(0.25, 3.99)	-0.0027	(-1.43, 1.43)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	4	4	1	(0.25, 3.99)	-0.0027	(-1.43, 1.43)	1
	Serious	3	0	_	N.A.	0.772	(-0.10, 1.65)	0.2499

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Table A20. Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20040138.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=731) n	Placebo Exposed Subjects (N=725) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Acute Coronary Syndromes: Angina Pectoris								
	All pooled	17	8	2.11	(0.92, 4.85)	12.2	(-1.09, 25.5)	0.0727
	Mild/1	5	3	1.65	(0.40, 6.89)	2.70	(-4.88, 10.3)	0.7258
	Moderate/2	10	4	2.48	(0.78, 7.87)	8.16	(-1.84, 18.2)	0.1775
	Severe/3	3	1	2.98	(0.31, 28.5)	2.72	(-2.64, 8.09)	0.6245
	Life-threatening/4	2	1	1.98	(0.18, 21.8)	1.36	(-3.29, 6.01)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	4	2	1.98	(0.36, 10.8)	2.71	(-3.86, 9.28)	0.6869
	Serious	4	4	0.99	(0.25, 3.95)	-0.0453	(-7.64, 7.55)	1
Acute Coronary Syndromes: Chest Pain								
	All pooled	8	10	0.79	(0.31, 2.00)	-2.85	(-14.2, 8.51)	0.6228
	Mild/1	3	3	0.99	(0.20, 4.90)	-0.034	(-6.62, 6.55)	1
	Moderate/2	5	6	0.83	(0.25, 2.70)	-1.44	(-10.3, 7.46)	0.7727
	Severe/3	0	1	0	N.A.	-1.38	(-4.08, 1.32)	0.4979
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	-1.38	(-4.08, 1.32)	0.4979
	Serious	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
Acute Coronary Syndromes: Coronary Artery Disease								
	All pooled	15	17	0.88	(0.44, 1.74)	-2.93	(-18.0, 12.1)	0.7031
	Mild/1	2	0	_	N.A.	2.74	(-1.05, 6.52)	0.4997
	Moderate/2	2	7	0.28	(0.06, 1.36)	-6.92	(-15.0, 1.14)	0.107
	Severe/3	9	8	1.12	(0.43, 2.88)	1.28	(-9.76, 12.3)	0.8205
	Life-threatening/4	2	2	0.99	(0.14, 7.02)	-0.0226	(-5.40, 5.35)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	11	10	1.09	(0.47, 2.55)	1.25	(-11.0, 13.5)	0.8409
	Serious	9	11	0.81	(0.34, 1.95)	-2.86	(-14.8, 9.10)	0.6392
Acute Coronary Syndromes: Myocardial Ischaemia								
	All pooled	5	7	0.71	(0.23, 2.22)	-2.82	(-12.1, 6.48)	0.578
	Mild/1	2	1	1.98	(0.18, 21.8)	1.36	(-3.29, 6.01)	1
	Moderate/2	2	3	0.66	(0.11, 3.95)	-1.40	(-7.42, 4.61)	0.6858
	Severe/3	1	1	0.99	(0.06, 15.8)	-0.011	(-3.82, 3.79)	1
	Life-threatening/4	0	2	0	N.A.	-2.76	(-6.58, 1.06)	0.2478
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	3	0.33	(0.03, 3.17)	-2.77	(-8.16, 2.62)	0.3724
	Serious	0	6	0	N.A.	-8.28	(-14.9, -1.7)	0.0151

(Table A20 is continued on the next page.)

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Table A20 (continued from previous page). Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20040138.

Arrhythmia: All PTs								
	All pooled	69	66	9.1	(0.75, 1.43)	3.36	(-26.4, 33.2)	0.825
	Mild/1	17	22	3.03	(0.41, 1.43)	-7.09	(-23.7, 9.50)	0.402
	Moderate/2	29	32	4.41	(0.55, 1.47)	-4.47	(-25.1, 16.1)	0.671
	Severe/3	22	11	1.52	(0.97, 4.06)	14.9	(-0.33, 30.2)	0.056
	Life-threatening/4	5	8	1.1	(0.20, 1.89)	-4.19	(-13.9, 5.48)	0.420
	Fatal/5	4	3	0.41	(0.30, 5.89)	1.33	(-5.77, 8.44)	1
	≥Severe/3	31	21	2.9	(0.85, 2.52)	13.4	(-5.60, 32.5)	0.167
	Serious	35	29	4	(0.74, 1.94)	7.88	(-13.2, 28.9)	0.463
Congestive heart failure: All PTs								
	All pooled	108	106	14.62	(0.79, 1.29)	1.54	(-34.8, 37.9)	0.934
	Mild/1	65	40	5.52	(1.10, 2.36)	33.7	(7.25, 60.2)	0.013
	Moderate/2	28	57	7.86	(0.31, 0.76)	-40.3	(-64.3,-16.3)	0.001
	Severe/3	19	20	2.76	(0.51, 1.75)	-1.59	(-18.2, 15.0)	0.851
	Life-threatening/4	3	7	0.97	(0.11, 1.64)	-5.55	(-14.0, 2.94)	0.223
	Fatal/5	9	3	0.41	(0.81, 11.0)	8.17	(-1.09, 17.4)	0.144
	≥Severe/3	30	29	4	(0.62 1.69)	1.04	(-19.2, 21.3)	0.920
	Serious	27	21	2.9	(0.73, 2.23)	7.97	(-10.4, 26.3)	0.394
Congestive heart failure: Oedema peripheral								
	All pooled	53	48	6.62	(0.75, 1.60)	6.30	(-19.8, 32.4)	0.636
	Mild/1	40	24	3.31	(1.01, 2.71)	21.6	(0.61, 0.43)	0.044
	Moderate/2	10	23	3.17	(0.21, 0.90)	-18.0	(-33.3,-2.76)	0.021
	Severe/3	3	3	0.41	(0.20, 4.90)	-0.034	(-6.62, 6.55)	1
	Life-threatening/4	0	0	0	N.A.	_	N.A.	.
	Fatal/5	0	0	0	N.A.	_	N.A.	.
	≥Severe/3	3	3	0.41	(0.20, 4.90)	-0.034	(-6.62, 6.55)	1
	Serious	1	2	0.28	(0.05, 5.46)	-1.39	(-6.05, 3.27)	0.623
Congestive Heart Failure: Pulmonary Oedema								
	All pooled	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
	Mild/1	0	0	_	N.A.	_	N.A.	.
	Moderate/2	0	0	_	N.A.	_	N.A.	.
	Severe/3	0	2	0	N.A.	-2.76	(-6.58, 1.06)	0.2478
	Life-threatening/4	0	2	0	N.A.	-2.76	(-6.58, 1.06)	0.2478
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	4	0	N.A.	-5.52	(-10.9,-0.13)	0.0612
	Serious	0	3	0	N.A.	-4.14	(-8.81, 0.54)	0.1232
Other vascular disorders: All PTs								
	All pooled	50	48	6.62	(0.70, 1.51)	2.19	(-23.5, 27.9)	0.867
	Mild/1	23	22	3.03	(0.58, 1.84)	1.12	(-16.7, 18.9)	0.902
	Moderate/2	18	17	2.34	(0.55, 2.02)	1.18	(-14.6, 16.9)	0.884
	Severe/3	13	12	1.66	(0.49, 2.34)	1.23	(-12.1, 14.6)	0.856
	Life-threatening/4	8	0	0	N.A.	10.9	(3.40, 18.5)	0.008
	Fatal/5	1	1	0.14	(0.06, 15.8)	-0.0113	(-3.82, 3.79)	1
	≥Severe/3	18	13	1.79	(0.68, 2.78)	6.69	(-8.12, 21.5)	0.376
	Serious	20	13	1.79	(0.76, 3.04)	9.43	(-5.84, 24.7)	0.227

(Table A20 is continued on the next page.)

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Table A20 (continued from previous page). Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20040138.

Stroke: All PTs								
	All pooled	40	36	1.1	(0.71, 1.71)	5.06	(-17.8, 27.9)	0.664
	Mild/1	6	6	0.99	(0.32, 3.06)	-0.068	(-9.36, 9.22)	0.9886
	Moderate/2	18	13	1.37	(0.68, 2.78)	6.69	(-8.12, 21.5)	0.3764
	Severe/3	13	14	0.92	(0.44, 1.95)	-1.53	(-15.4, 12.3)	0.8291
	Life-threatening/4	1	6	0.17	(0.02, 1.37)	-6.91	(-14.0, 0.21)	0.0686
	Fatal/5	7	3	2.31	(0.60, 8.91)	5.44	(-3.03, 13.9)	0.3421
	≥Severe/3	20	23	0.86	(0.48, 1.56)	-4.36	(-21.8, 13.0)	0.6228
	Serious	30	24	1.24	(0.73, 2.10)	7.94	(-11.5, 27.3)	0.423

Table A21. Sponsor's Search Criteria With All Studies Analyzed Separately: Study 20050141.

Adverse Event Grouping	Severity	Denosumab Exposed Subjects (N=593) n	Alendronate Exposed Subjects (N=586) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Acute Coronary Syndromes: All PTs								
	All pooled	8	16	0.49	(0.21, 1.15)	-13.8	(-29.9, 2.32)	0.0931
	Mild/1	4	6	0.66	(0.19, 2.32)	-3.49	(-14.0, 6.99)	0.5449
	Moderate/2	2	8	0.25	(0.05, 1.16)	-10.3	(-20.8, 0.21)	0.0629
	Severe/3	1	2	0.49	(0.04, 5.43)	-1.73	(-7.49, 4.04)	0.6225
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	1	0	_	N.A.	1.69	(-1.62, 4.99)	1
	≥Severe/3	2	2	0.99	(0.14, 6.99)	-0.0403	(-6.68, 6.60)	1
	Serious	2	4	0.49	(0.09, 2.69)	-3.45	(-11.6, 4.68)	0.4494
Acute Coronary Syndromes: Chest Pain								
	All pooled	2	10	0.2	(0.04, 0.90)	-13.7	(-25.2,-2.21)	0.0211
	Mild/1	1	4	0.25	(0.03, 2.20)	-5.14	(-12.6, 2.30)	0.2152
	Moderate/2	1	6	0.16	(0.02, 1.36)	-8.55	(-17.3, 0.24)	0.068
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	1	0	N.A.	-1.71	(-5.05, 1.64)	0.497

Table A22 shows the results of an analysis of data pooled from the two large, pivotal studies when analyzed according to the sponsor's categorization of MedDRA preferred terms.

The estimate of relative risk for severe acute coronary syndromes / all PTs pooled was 1.62 (p=0.0035). Estimates of relative risk were not consistently greater than one for the remaining levels of severity. The estimate of risk difference for severe acute coronary syndromes / acute coronary syndromes was 1.30 (p=0.03). The risk difference had to be computed because zero subjects receiving placebo had an event, but six subjects receiving denosumab reported an event. Relative risk for severe or worse (RR=3.5, p=0.1795) and serious (RR=2.33, p=0.3435) acute coronary syndromes were greater than one, but they were not associated with p-values less than 0.10. Estimates of relative risk for angina pectoris were associated with p-values less than 0.10 for several categories of

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severity—severe angina was observed with a relative risk of 1.91 (p=0.0639); severe or worse angina had a relative risk of 1.78 (p=0.0794) and serious angina had a relative risk of 1.68 (p=0.0517). Mild bradycardia was associated with a relative risk of 5.0 (p=0.0075), but no other severity category was associated with a p-value less than 0.10. Sick sinus syndrome had a relative risk of 3.19 for all severity levels pooled (p=0.03). Relative risk for sick sinus syndrome was greater than one for all severity levels (Mild: RR=2.0, p=1; Moderate: RR=4.5, p=0.065; Severe: RR=2.0, p=0.5076; Severe or worse: RR=2.33, p=0.3435; Serious: RR=2.79, p=0.0633), but none were associated with a p-value less than 0.10. Vascular disorders/All PTs events of grade severe or worse were associated with a relative risk of 1.48 (p=0.043) and of grade life-threatening were associated with a relative risk of 2.49 (p=0.05). Relative risk for severe events was 1.45 (p=0.0859) and for serious events was 1.37 (p=0.0855). Risk difference for serious skin ulcers was 1.3 (p=0.0312). Risk difference is reported because there were zero events in the placebo group, and six events in the denosumab arm. Relative risk for severe events was greater than one (RR=5.0, p=0.2186), but the associated p-value was not less than 0.10.

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Table A22. Sponsor's Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects (N=4617) n	Placebo Subjects (N=4601) n	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
Acute coronary syndromes: All PTs								
	All pooled	298	270	1.1	(0.94, 1.29)	5.86	(-3.95, 15.7)	0.242
	Mild/1	94	95	0.99	(0.74, 1.31)	-0.288	(-6.07, 5.50)	0.9222
	Moderate/2	126	106	1.18	(0.92, 1.53)	4.25	(-2.14, 10.6)	0.1925
	Severe/3	94	58	1.62	(1.17, 2.23)	7.75	(2.56, 12.9)	0.0035
	Life-threatening/4	22	25	0.88	(0.50, 1.55)	-0.669	(-3.58, 2.24)	0.6522
	Fatal/5	18	22	0.82	(0.44, 1.52)	-0.883	(-3.57, 1.80)	0.519
	≥Severe/3	127	100	1.27	(0.98, 1.64)	5.77	(-0.55, 12.1)	0.0738
	Serious	151	135	1.11	(0.89, 1.40)	3.36	(-3.71, 10.4)	0.3517
Acute coronary syndromes: Acute coronary syndrome								
	All pooled	8	3	2.66	(0.71, 10.0)	1.08	(-0.33, 2.49)	0.2263
	Mild/1	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Moderate/2	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Severe/3	6	0	_	N.A.	1.30	(0.26, 2.34)	0.0312
	Life-threatening/4	1	2	0.5	(0.05, 5.49)	-0.218	(-0.96, 0.52)	0.6243
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	7	2	3.49	(0.72, 16.8)	1.08	(-0.19, 2.36)	0.1795
	Serious	7	3	2.33	(0.60, 8.99)	0.864	(-0.48, 2.21)	0.3435
Acute Coronary Syndromes: Angina Pectoris								
	All pooled	118	95	1.24	(0.95, 1.62)	4.91	(-1.22, 11.0)	0.1167
	Mild/1	44	36	1.22	(0.79, 1.89)	1.71	(-2.08, 5.49)	0.3774
	Moderate/2	64	49	1.3	(0.90, 1.88)	3.21	(-1.28, 7.70)	0.1611
	Severe/3	23	12	1.91	(0.95, 3.83)	2.37	(-0.14, 4.88)	0.0639
	Life-threatening/4	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	25	14	1.78	(0.93, 3.42)	2.37	(-0.28, 5.02)	0.0794
	Serious	37	22	1.68	(0.99, 2.84)	3.23	(-0.022, 6.5)	0.0517
Acute Coronary Syndromes: Cardiac Disorder								
	All pooled	1	6	0.17	(0.02, 1.38)	-1.09	(-2.2, 0.038)	0.0698
	Mild/1	0	4	0	N.A.	-0.869	(-1.7,-0.018)	0.062
	Moderate/2	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	Severe/3	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Serious	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991

(Table A22 is continued on the next page.)

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Table A22 (continued from the previous page). Sponsor's Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Acute Coronary Syndromes: Coronary Artery Stenosis								
	All pooled	5	1	4.98	(0.58, 42.6)	0.866	(-0.17, 1.91)	0.2186
	Mild/1	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Moderate/2	0	0	_	N.A.	_	N.A.	.
	Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	4	1	3.99	(0.45, 35.7)	0.649	(-0.30, 1.60)	0.3749
	Serious	5	0	_	N.A.	1.08	(0.13, 2.03)	0.0624
Arrhythmia: Bradycardia								
	All pooled	26	16	1.62	(0.87, 3.01)	2.15	(-0.59, 4.90)	0.1247
	Mild/1	15	3	4.98	(1.44, 17.20)	2.60	(0.797, 4.4)	0.0075
	Moderate/2	7	7	1	(0.35, 2.84)	-0.0053	(-1.60, 1.58)	0.9948
	Severe/3	5	6	0.83	(0.25, 2.72)	-0.221	(-1.63, 1.19)	0.7739
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	6	0.83	(0.25, 2.72)	-0.221	(-1.63, 1.19)	0.7739
	Serious	8	6	1.33	(0.46, 3.83)	0.429	(-1.16, 2.02)	0.5972
Arrhythmia: Sick sinus syndrome								
	All pooled	16	5	3.19	(1.17, 8.70)	2.38	(0.435, 4.32)	0.0264
	Mild/1	2	1	1.99	(0.18, 22.0)	0.216	(-0.52, 0.95)	1
	Moderate/2	9	2	4.48	(0.97, 20.7)	1.51	(0.107, 2.92)	0.0653
	Severe/3	6	3	1.99	(0.50, 7.96)	0.648	(-0.63, 1.92)	0.5076
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	7	3	2.33	(0.60, 8.99)	0.864	(-0.48, 2.21)	0.3435
	Serious	14	5	2.79	(1.01, 7.74)	1.95	(0.096, 3.80)	0.0633
Arrhythmia: Sinus tachycardia								
	All pooled	0	5	0	N.A.	-1.09	(-2.0, -0.14)	0.0309
	Mild/1	0	4	0	N.A.	-0.869	(-1.7,-0.018)	0.062
	Moderate/2	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Arrhythmia: Supraventricular tachycardia								
	All pooled	9	9	1	(0.40, 2.51)	-0.0068	(-1.81, 1.80)	0.9941
	Mild/1	0	6	0	N.A.	-1.30	(-2.4, -0.26)	0.0154
	Moderate/2	6	3	1.99	(0.50, 7.96)	0.648	(-0.63, 1.92)	0.5076
	Severe/3	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1
	Serious	7	2	3.49	(0.72, 16.8)	1.08	(-0.19, 2.36)	0.1795

(Table A22 is continued on the next page.)

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Table A22 (continued from the previous page). Sponsor's Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Arrhythmia: Syncope								
	All pooled	81	81	1	(0.73, 1.35)	-0.0610	(-5.43, 5.30)	0.9822
	Mild/1	37	32	1.15	(0.72, 1.85)	1.06	(-2.46, 4.58)	0.5554
	Moderate/2	27	40	0.67	(0.41, 1.09)	-2.85	(-6.31, 0.62)	0.1078
	Severe/3	18	14	1.28	(0.64, 2.57)	0.856	(-1.54, 3.26)	0.4849
	Life-threatening/4	2	1	1.99	(0.18, 21.97)	0.216	(-0.52, 0.95)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	20	15	1.33	(0.68, 2.59)	1.07E-03	(-1.44, 3.58)	0.4029
	Serious	22	18	1.22	(0.65, 2.27)	8.53E-04	(-1.83, 3.54)	0.5334
Arrhythmia: Tachycardia								
	All pooled	39	29	1.34	(0.83, 2.16)	2.14E-03	(-1.35, 5.64)	0.229
	Mild/1	26	20	1.3	(0.72, 2.32)	1.28E-03	(-1.59, 4.16)	0.3815
	Moderate/2	15	7	2.14	(0.87, 5.23)	1.73E-03	(-0.26, 3.72)	0.0892
	Severe/3	0	2	0	N.A.	-0.435	(-1.04, 0.17)	0.2491
	Life-threatening/4	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	3	0	N.A.	-0.652	(-1.39, .086)	0.1243
	Serious	1	2	0.5	(0.05, 5.49)	-0.218	(-0.96, 0.52)	0.6243
Congestive Heart Failure: All PTs								
	All pooled	482	455	1.06	(0.93, 1.19)	5.51	(-6.83, 17.8)	0.3818
	Mild/1	270	232	1.16	(0.98, 1.38)	8.06	(-1.21, 17.3)	0.0883
	Moderate/2	188	202	0.93	(0.76, 1.13)	-3.18	(-11.4, 5.03)	0.4476
	Severe/3	56	51	1.09	(0.75, 1.60)	1.04	(-3.33, 5.42)	0.6397
	Life-threatening/4	7	15	0.47	(0.19, 1.14)	-1.74	(-3.74, 0.25)	0.0862
	Fatal/5	17	15	1.13	(0.56, 2.26)	0.422	(-1.98, 2.82)	0.7306
	≥Severe/3	77	78	0.98	(0.72, 1.34)	-0.275	(-5.53, 4.97)	0.9181
	Serious	83	77	1.07	(0.79, 1.46)	1.24	(-4.09, 6.57)	0.6481
Congestive Heart Failure: Cardiac Failure								
	All pooled	59	41	1.43	(0.96, 2.13)	3.87	(-0.36, 8.10)	0.0731
	Mild/1	17	11	1.54	(0.72, 3.28)	1.29	(-0.96, 3.54)	0.26
	Moderate/2	27	18	1.49	(0.82, 2.71)	1.94	(-0.91, 4.78)	0.1824
	Severe/3	13	7	1.85	(0.74, 4.63)	1.29	(-0.60, 3.19)	0.1818
	Life-threatening/4	1	2	0.5	(0.05, 5.49)	-0.218	(-0.96, 0.52)	0.6243
	Fatal/5	3	6	0.5	(0.12, 1.99)	-0.654	(-1.93, 0.62)	0.3427
	≥Severe/3	17	15	1.13	(0.56, 2.26)	0.422	(-1.98, 2.82)	0.7306
	Serious	20	17	1.17	(0.61, 2.24)	0.637	(-1.94, 3.22)	0.6287
Congestive Heart Failure: Cardiac Failure Congestive								
	All pooled	29	41	0.7	(0.44, 1.13)	-2.63	(-6.17, 0.92)	0.1459
	Mild/1	5	9	0.55	(0.19, 1.65)	-0.873	(-2.46, 0.72)	0.3006
	Moderate/2	12	14	0.85	(0.40, 1.84)	-0.444	(-2.61, 1.72)	0.6879
	Severe/3	12	16	0.75	(0.35, 1.58)	-0.878	(-3.13, 1.37)	0.4435
	Life-threatening/4	0	4	0	N.A.	-0.869	(-1.72,-.018)	0.062
	Fatal/5	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	≥Severe/3	13	21	0.62	(0.31, 1.23)	-1.75	(-4.22, 0.73)	0.1662
	Serious	16	23	0.69	(0.37, 1.31)	-1.53	(-4.18, 1.12)	0.2567

(Table A22 is continued on the next page.)

Reference ID: 3168397

Table A22 (continued from the previous page). Sponsor's Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Congestive Heart Failure: Cardiomegaly								
	All pooled	2	8	0.25	(0.05, 1.17)	-1.31	(-2.65, 0.04)	0.0648
	Mild/1	1	4	0.25	(0.03, 2.23)	-0.653	(-1.60, 0.30)	0.2178
	Moderate/2	0	3	0	N.A.	-0.652	(-1.39,0.086)	0.1243
	Severe/3	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	1	1	(0.06, 15.9)	-0.00075	(-0.60, 0.60)	1
	Serious	0	1	0	N.A.	-0.217	(-0.64, 0.21)	0.4991
Congestive Heart Failure: Dyspnoea								
	All pooled	125	136	0.92	(0.72, 1.16)	-2.48	(-9.26, 4.29)	0.472
	Mild/1	62	55	1.12	(0.78, 1.61)	1.47	(-3.10, 6.04)	0.5271
	Moderate/2	60	79	0.76	(0.54, 1.06)	-4.17	(-9.15, 0.80)	0.1001
	Severe/3	13	11	1.18	(0.53, 2.63)	0.425	(-1.66, 2.51)	0.689
	Life-threatening/4	2	0	_	N.A.	0.433	(-0.17, 1.03)	0.4999
	Fatal/5	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	≥Severe/3	16	11	1.45	(0.67, 3.12)	1.07	(-1.13, 3.28)	0.3398
	Serious	19	11	1.72	(0.82, 3.61)	1.72	(-0.60, 4.05)	0.1461
Congestive Heart Failure: Oedema								
	All pooled	6	13	0.46	(0.17, 1.21)	-1.53	(-3.38, 0.33)	0.1063
	Mild/1	3	6	0.5	(0.12, 1.99)	-0.654	(-1.93, 0.62)	0.3427
	Moderate/2	3	7	0.43	(0.11, 1.65)	-0.872	(-2.22, 0.47)	0.2255
	Severe/3	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	_	N.A.	_	N.A.	.
Congestive Heart Failure: Oedema Peripheral								
	All pooled	242	203	1.19	(0.99, 1.43)	8.29	(-0.45, 17.0)	0.0632
	Mild/1	161	129	1.24	(0.99, 1.56)	6.83	(-0.29, 14.0)	0.0602
	Moderate/2	84	79	1.06	(0.78, 1.44)	1.02	(-4.36, 6.40)	0.7093
	Severe/3	7	7	1	(0.35, 2.84)	-0.0053	(-1.60, 1.58)	0.9948
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	7	7	1	(0.35, 2.84)	-0.0053	(-1.60, 1.58)	0.9948
	Serious	4	2	1.99	(0.37, 10.9)	0.432	(-0.61, 1.47)	0.6874

(Table A22 is continued on the next page.)

Reference ID: 3168397

Table A22 (continued from the previous page). Sponsor's Search Criteria With Two Large, pivotal Studies (20030216 and 20040138) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects (N=4617)	Placebo Subjects (N=4601)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	p value
		n	n					
Other vascular disorders: All PTs								
	All pooled	229	210	1.09	(0.91, 1.30)	3.96	(-4.74, 12.7)	0.3724
	Mild/1	94	98	0.96	(0.72, 1.26)	-0.940	(-6.77, 4.89)	0.752
	Moderate/2	94	85	1.1	(0.82, 1.47)	1.89	(-3.75, 7.52)	0.5119
	Severe/3	51	35	1.45	(0.95, 2.23)	3.44	(-0.48, 7.36)	0.0859
	Life-threatening/4	15	6	2.49	(0.97, 6.42)	1.94	(.00013, 3.9)	0.0502
	Fatal/5	3	4	0.75	(0.17, 3.34)	-0.220	(-1.34, 0.91)	0.726
	≥Severe/3	64	43	1.48	(1.01, 2.18)	4.52	(0.145, 8.89)	0.043
	Serious	70	51	1.37	(0.96, 1.96)	4.08	(-0.57, 8.72)	0.0855
Other vascular disorders: Aortic aneurysm								
	All pooled	12	17	0.7	(0.34, 1.47)	-1.10	(-3.38, 1.19)	0.3476
	Mild/1	4	4	1	(0.25, 3.98)	-0.00301	(-1.21, 1.20)	1
	Moderate/2	6	7	0.85	(0.29, 2.54)	-0.222	(-1.75, 1.31)	0.7766
	Severe/3	1	6	0.17	(0.02, 1.38)	-1.09	(-2.21,0.038)	0.0698
	Life-threatening/4	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	6	0.33	(0.07, 1.64)	-0.871	(-2.07, 0.33)	0.1788
	Serious	3	8	0.37	(0.10, 1.41)	-1.09	(-2.50, 0.32)	0.1451
Other vascular disorders: Skin ulcer								
	All pooled	40	29	1.37	(0.85, 2.21)	2.36	(-1.16, 5.88)	0.1886
	Mild/1	18	16	1.12	(0.57, 2.20)	0.421	(-2.05, 2.90)	0.7388
	Moderate/2	22	15	1.46	(0.76, 2.81)	1.50	(-1.08, 4.09)	0.2532
	Severe/3	5	1	4.98	(0.58, 42.6)	0.866	(-0.17, 1.91)	0.2186
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	1	4.98	(0.58, 42.6)	0.866	(-0.17, 1.91)	0.2186
	Serious	6	0	_	N.A.	1.30	(0.26, 2.34)	0.0312
Other vascular disorders: Thrombophlebitis								
	All pooled	9	17	0.53	(0.24, 1.18)	-1.75	(-3.91, 0.42)	0.1141
	Mild/1	4	7	0.57	(0.17, 1.94)	-0.655	(-2.07, 0.76)	0.3866
	Moderate/2	3	9	0.33	(0.09, 1.23)	-1.31	(-2.78, 0.17)	0.0915
	Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	1	2.99	(0.31, 28.7)	0.432	(-0.42, 1.28)	0.6249
	Serious	3	2	1.49	(0.25, 8.94)	0.215	(-0.74, 1.17)	1
Stroke: Cerebral Thrombosis								
	All pooled	3	5	0.6	(0.14, 2.50)	-0.437	(-1.64, 0.77)	0.5069
	Mild/1	1	0	_	N.A.	0.217	(-0.21, 0.64)	1
	Moderate/2	0	4	0	N.A.	-0.869	(-1.72,-.018)	0.062
	Severe/3	2	1	1.99	(0.18, 22.0)	0.216	(-0.52, 0.95)	1
	Life-threatening/4	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	1	1.99	(0.18, 22.0)	0.216	(-0.52, 0.95)	1
	Serious	3	3	1	(0.20, 4.93)	-0.00226	(-1.04, 1.04)	1

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Table A23 shows the results of the analysis of a dataset in which all placebo-controlled studies were pooled and analyzed using the sponsor's grouping of MedDRA terms.

Acute coronary events were associated with a relative risk greater than one for events of grade severe (RR=1.76, p=0.003), severe or worse (RR=1.47, p=0.018) and serious (RR=1.31, p=0.054). Events of grade life-threatening had a relative risk of 1.37, but were not associated with a p-value less than 0.10 (p=0.494). Relative risk for serious angina pectoris was 1.73 (p=0.053). Severe angina was associated with a relative risk of 1.53 (p=0.225), but its p-value was not less than 0.10. Relative risk for mild bradycardia was 5.0 (p=0.008), but the remaining severity levels were not consistently associated with relative risk estimates greater than one. Relaitve risk for moderate tachycardia was 2.66 (p=0.03), but the remaining severity levels for tachycardia were not associated with a relative risk estimate greater than one. Severe vascular disorders – all PTs pooled was associated with a relative risk of 1.65 (p=0.055) and severe or worse vascular disorders were associated with a relative risk of 1.53 (p=0.067). However, the remaining categories of severity were not associated with consistent estimates of relative risk greater than one. The estimate of risk difference for serious skin ulcers was 1.42 (p=0.031). Risk difference had to be computed since there were zero events in the placebo arm and six events in the treatment arm. Relative risk for severe skin ulcers was 5.0 (p=0.219), but the associated p-value was not less than 0.10.

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Table A23. Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Deno-sumab Subjects N=4232 n	Deno-sumab Subjects % (n/N)	Placebo Subjects N=4221 n	Placebo Subjects % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Acute coronary syndromes: All PTs										
	All pooled	242	5.72	219	5.19	1.1	(0.92, 1.3)	5.30	(-4.4, 15.0)	0.283
	Mild/1	84	1.98	90	2.13	0.93	(0.69, 1.3)	-1.47	(-7.5, 4.58)	0.633
	Moderate/2	109	2.58	91	2.16	1.19	(0.91, 1.6)	4.20	(-2.3, 10.7)	0.204
	Severe/3	74	1.75	42	1	1.76	(1.21, 2.6)	7.54	(2.58, 12.5)	0.003
	Life-threatening/4	11	0.26	8	0.19	1.37	(0.55, 3.4)	0.704	(-1.31, 2.7)	0.494
	Fatal/5	10	0.24	13	0.31	0.77	(0.34, 1.8)	-0.717	(-2.9, 1.50)	0.527
	≥Severe/3	90	2.13	61	1.45	1.47	(1.07, 2.0)	6.81	(1.17, 12.5)	0.018
	Serious	112	2.65	85	2.01	1.31	(0.99, 1.7)	6.33	(-0.10,12.8)	0.054
Acute coronary syndromes: Acute myocardial infarction										
	All pooled	12	0.28	5	0.12	2.39	(0.84, 6.8)	1.65	(-0.26 , 3.6)	0.143
	Mild/1	0	0	0	0	_	N.A.	_	N.A.	.
	Moderate/2	2	0.05	0	0	_	N.A.	0.473	(-0.18 , 1.1)	0.500
	Severe/3	9	0.21	2	0.05	4.49	(0.97, 21)	1.65	(0.12, 3.19)	0.065
	Life-threatening/4	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.249
	Fatal/5	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.66, .66)	1
	≥Severe/3	10	0.24	5	0.12	1.99	(0.68, 5.8)	1.18	(-0.62, 3.0)	0.301
	Serious	12	0.28	5	0.12	2.39	(0.84, 6.8)	1.65	(-0.26, 3.6)	0.143
Acute coronary syndromes: Angina pectoris										
	All pooled	103	2.43	91	2.16	1.13	(0.85,1.5)	2.78	(-3.6, 9.16)	0.394
	Mild/1	40	0.95	33	0.78	1.21	(0.76, 1.9)	1.63	(-2.3, 5.58)	0.417
	Moderate/2	55	1.3	48	1.14	1.14	(0.78, 1.7)	1.62	(-3.05, 6.3)	0.496
	Severe/3	20	0.47	13	0.31	1.53	(0.76,3.1)	1.65	(-1.01, 4.3)	0.225
	Life-threatening/4	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.66, .66)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	21	0.5	14	0.33	1.5	(0.76,2.9)	1.65	(-1.09,4.38)	0.239
	Serious	33	0.78	19	0.45	1.73	(0.99, 3.0)	3.30	(-0.035,6.6)	0.053

(Table A23 continued on the next page.)

Reference ID: 3168397

Table A23 (continued from the previous page). Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Acute coronary syndromes: Cardiac disorder										
	All pooled	0	0	5	0.12	0	N.A.	-1.18	(-2.2,-0.15)	0.031
	Mild/1	0	0	4	0.09	0	N.A.	-0.95	(-1.9,-.019)	0.062
	Moderate/2	0	0	1	0.02	0	N.A.	-0.24	(-0.70,0.23)	0.499
	Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	0	0	_	N.A.	_	N.A.	.
Acute coronary syndromes: Myocardial ischaemia										
	All pooled	37	0.87	31	0.73	1.19	(0.74, 1.9)	1.40	(-2.41, 5.2)	0.472
	Mild/1	14	0.33	20	0.47	0.7	(0.35, 1.4)	-1.43	(-4.1, 1.3)	0.299
	Moderate/2	16	0.38	11	0.26	1.45	(0.67, 3.1)	1.17	(-1.23, 3.6)	0.339
	Severe/3	5	0.12	1	0.02	4.99	(0.58, 43)	0.945	(-0.19 , 2.1)	0.219
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.236	(-0.23 , 0.7)	1
	Fatal/5	1	0.02	0	0	_	N.A.	0.236	(-0.23, 0.7)	1
	≥Severe/3	7	0.17	1	0.02	6.98	(0.86, 57)	1.42	(0.11, 2.7)	0.070
	Serious	12	0.28	5	0.12	2.39	(0.84, 6.8)	1.65	(-0.26, 3.6)	0.143
Arrhythmia Bradycardia										
	All pooled	19	0.45	12	0.28	1.58	(0.77, 3.3)	1.65	(-0.93,4.22)	0.210
	Mild/1	15	0.35	3	0.07	4.99	(1.4, 17.2)	2.83	(0.87, 4.80)	0.008
	Moderate/2	2	0.05	5	0.12	0.4	(0.08, 2.0)	-0.712	(-1.94,0.52)	0.288
	Severe/3	3	0.07	4	0.09	0.75	(0.17,3.3)	-0.239	(-1.47,0.99)	0.726
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	0.07	4	0.09	0.75	(0.17,3.3)	-0.239	(-1.47,0.99)	0.726
	Serious	4	0.09	3	0.07	1.33	(0.30,5.9)	0.234	(-0.99,1.46)	1
Arrhythmia Sick Sinus Syndrome										
	All pooled	11	0.26	4	0.09	2.74	(0.87, 8.6)	1.65	(-0.14, 3.4)	0.118
	Mild/1	1	0.02	1	0.02	1	(0.06, 16	-.0006	(-0.66,0.66)	1
	Moderate/2	7	0.17	1	0.02	6.98	(0.86, 57)	1.42	(0.11, 2.73)	0.070
	Severe/3	4	0.09	3	0.07	1.33	(0.30, 5.9)	0.234	(-0.99, 1.5)	1
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.236	(-0.23,0.70)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	0.12	3	0.07	1.66	(0.40, 7.0	0.471	(-0.84, 1.8)	0.726
	Serious	9	0.21	4	0.09	2.24	(0.69, 7.3	1.18	(-0.49, 2.9)	0.267

(Table A23 is continued on the next page.)

Reference ID: 3168397

Table A23 (continued from the previous page). Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Arrhythmia Supra-ventricular tachycardia										
	All pooled	9	0.21	9	0.21	1	(0.40, 2.5)	-.0055	(-2.0, 2.0)	1.0
	Mild/1	0	0	6	0.14	0	N.A.	-1.42	(-2.6,-0.29)	0.016
	Moderate/2	6	0.14	3	0.07	1.99	(0.50, 8.0	0.707	(-0.68, 2.1)	0.508
	Severe/3	3	0.07	2	0.05	1.5	(0.25, 9.0	0.235	(-0.8, 1.27)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	0.07	2	0.05	1.5	(0.25, 9.0	0.235	(-0.80, 1.3)	1
	Serious	7	0.17	2	0.05	3.49	(0.73, 17	1.18	(-0.21, 2.6)	0.180
Arrhythmia Tachycardia										
	All pooled	40	0.95	25	0.59	1.6	(0.97,2.6)	3.53	(-0.19,7.25)	0.063
	Mild/1	26	0.61	18	0.43	1.44	(0.79,2.6)	1.88	(-1.19,4.95)	0.230
	Moderate/2	16	0.38	6	0.14	2.66	(1.04,6.8)	2.36	(0.19, 4.53)	0.033
	Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.13,0.18)	0.249
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.13,0.18)	0.249
	Serious	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.66,0.66)	1
Congestive Heart Failure: Cardiac Failure Congestive										
	All pooled	16	0.38	23	0.54	0.69	(0.37, 1.3)	-1.67	(-4.6, 1.22)	0.258
	Mild/1	1	0.02	7	0.17	0.14	(0.02, 1.2)	-1.42	(-2.7,-0.11)	0.039
	Moderate/2	11	0.26	9	0.21	1.22	(0.51, 2.9)	0.47	(-1.6, 2.54)	0.659
	Severe/3	5	0.12	7	0.17	0.71	(0.23, 2.2)	-0.48	(-2.08,1.13)	0.580
	Life-threatening/4	0	0	1	0.02	0	N.A.	-0.24	(-0.70,0.23)	0.499
	Fatal/5	0	0	1	0.02	0	N.A.	-0.24	(-0.70,0.23)	0.499
	≥Severe/3	5	0.12	9	0.21	0.55	(0.19, 1.7)	-0.95	(-2.68,0.78)	0.301
	Serious	10	0.24	13	0.31	0.77	(0.34, 1.8)	-0.72	(-2.94,1.50)	0.527
Congestive Heart Failure: Rales										
	All pooled	8	0.19	2	0.05	3.99	(0.85, 19)	1.42	(-0.048,2.9)	0.109
	Mild/1	5	0.12	2	0.05	2.49	(0.48, 13)	0.71	(-0.52,1.93)	0.453
	Moderate/2	3	0.07	0	0	_	N.A.	0.71	(-0.093,1.5)	0.250
	Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	0	0	_	N.A.	_	N.A.	.

(Table A23 is continued on the next page.)

Reference ID: 3168397

Table A23 (continued from the previous page). Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Adverse Event Grouping	Severity	Deno-sumab Subjects n	Deno-sumab Subjects N=4232 % (n/N)	Placebo Subjects n	Placebo Subjects N=4221 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Other vascular disorders: All PTs										
	All pooled	180	4.25	166	3.93	1.08	(0.88,1.3)	3.21	(-5.24,11.7)	0.457
	Mild/1	72	1.7	78	1.85	0.92	(0.67,1.3)	-1.47	(-7.09,4.16)	0.610
	Moderate/2	76	1.8	70	1.66	1.08	(0.78, 1.5)	1.37	(-4.18,6.93)	0.628
	Severe/3	38	0.9	23	0.54	1.65	(0.98,2.8)	3.53	(-0.077,7.1)	0.055
	Life-threatening/4	7	0.17	6	0.14	1.16	(0.39,3.5)	0.233	(-1.44,1.90)	0.785
	Fatal/5	2	0.05	3	0.07	0.66	(0.11, 4.0)	-0.238	(-1.28,0.80)	0.687
	≥Severe/3	46	1.09	30	0.71	1.53	(0.97, 2.4)	3.76	(-0.26,7.78)	0.067
	Serious	50	1.18	38	0.9	1.31	(0.86, 2.0)	2.81	(-1.51,7.14)	0.203
Other vascular disorders: Aortic aneurysm										
	All pooled	6	0.14	9	0.21	0.66	(0.24, 1.9)	-0.714	(-2.51,1.08)	0.435
	Mild/1	1	0.02	1	0.02	1	(0.06, 16)	-.0006	(-0.66,0.66)	1
	Moderate/2	5	0.12	4	0.09	1.25	(0.34, 4.6)	0.234	(-1.2, 1.6)	1
	Severe/3	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.062
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.062
	Serious	1	0.02	5	0.12	0.2	(0.02, 1.7)	-0.948	(-2.1, 0.19)	0.124
Other vascular disorders: Aortic stenosis										
	All pooled	13	0.31	5	0.12	2.59	(0.93, 7.3)	1.89	(-0.077,3.9)	0.096
	Mild/1	8	0.19	4	0.09	1.99	(0.60, 6.6)	0.943	(-0.66, 2.6)	0.387
	Moderate/2	3	0.07	0	0	_	N.A.	0.709	(-0.093,1.5)	0.250
	Severe/3	2	0.05	1	0.02	1.99	(0.18, 22)	0.236	(-0.57,1.04)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	0.05	1	0.02	1.99	(0.18, 22)	0.236	(-0.57,1.04)	1
	Serious	3	0.07	0	0	_	N.A.	0.709	(-0.093,1.5)	0.250

(Table A23 is continued on the next page.)

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Table A23 (continued from the previous page). Sponsor's Search Criteria With Placebo Controlled Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223) Pooled.

Other vascular disorders: Skin ulcer										
	All pooled	34	0.8	28	0.66	1.21	(0.74,2.0)	1.40	(-2.24,5.04)	0.451
	Mild/1	15	0.35	16	0.38	0.94	(0.46, 1.9)	-0.246	(-2.82,2.33)	0.852
	Moderate/2	19	0.45	14	0.33	1.35	(0.68, 2.7)	1.17	(-1.49,3.83)	0.387
	Severe/3	5	0.12	1	0.02	4.99	(0.58, 43)	0.945	(-0.19,2.08)	0.219
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	0.12	1	0.02	4.99	(0.58, 43)	0.945	(-0.19,2.08)	0.219
	Serious	6	0.14	0	0	_	N.A.	1.42	(0.28, 2.55)	0.031
Stroke: Cerebral Thrombosis										
	All pooled	3	0.07	5	0.12	0.6	(0.14, 2.5)	-0.476	(-1.8, 0.84)	0.507
	Mild/1	1	0.02	0	0	_	N.A.	0.236	(-0.23,0.70)	1
	Moderate/2	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.062
	Severe/3	2	0.05	1	0.02	1.99	(0.18, 22)	0.236	(-0.57,1.04)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	0.05	1	0.02	1.99	(0.18, 22)	0.236	(-0.57,1.04)	1
	Serious	3	0.07	3	0.07	1	(0.20, 4.9)	-.0019	(-1.1, 1.1)	1

Table A24 shows the results of the analysis of all PMO studies pooled and analyzed according to the sponsor's grouping of MedDRA terms

Severe acute coronary syndromes was associated with a relative risk of 1.5 (p=0.04), however, there was no consistent trend with respect to relative risk estimates for the remaining severity levels. Mild bradycardia was associated with a relative risk of 4.16 (p=0.02), but there was no consistent trend with regard to relative risk estimates for the remaining severity levels. Risk difference for serious skin ulcers was 1.18 (p=0.035). Serious skin ulcers were associated with a relative risk of 4.16 (p=0.231), but the associated p-value was not less than 0.10.

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Table A24. Sponsor's Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Adverse Event Grouping	Severity	Denosumab Subjects n	Denosumab Subjects N=5451 % (n/N)	Placebo Subjects n	Placebo Subjects N=4224 % (n/N)	RR	95% CI RR	RD ($x10^{-3}$)	95% CI RD ($x10^{-3}$)	P value
Acute coronary syndromes: All PTs										
	All pooled	254	5	219	5.19	0.96	(0.81, 1.15)	-1.86	(-10.8, 7.12)	0.684
	Mild/1	91	1.79	90	2.13	0.84	(0.63, 1.12)	-3.40	(-9.09, 2.28)	0.237
	Moderate/2	111	2.19	91	2.16	1.01	(0.77, 1.33)	0.30	(-5.65, 6.25)	0.921
	Severe/3	75	1.48	42	1	1.48	(1.02, 2.16)	4.82	(0.35, 9.29)	0.038
	Life-threatening/4	12	0.24	8	0.19	1.25	(0.51, 3.05)	0.468	(-1.40, 2.34)	0.628
	Fatal/5	11	0.22	13	0.31	0.7	(0.32, 1.57)	-0.914	(-3.02, 1.19)	0.387
	≥Severe/3	93	1.83	61	1.45	1.27	(0.92, 1.75)	3.86	(-1.29, 9.02)	0.146
	Serious	115	2.26	85	2.01	1.12	(0.85, 1.48)	2.51	(-3.38, 8.40)	0.406
Acute coronary syndromes: Cardiac Disorder										
	All pooled	0	0	5	0.12	0	N.A.	-1.18	(-2.2,-0.15)	0.019
	Mild/1	0	0	4	0.09	0	N.A.	-0.95	(-1.9,-.019)	0.042
	Moderate/2	0	0	1	0.02	0	N.A.	-0.24	(-0.70,0.23)	0.454
	Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	0	0	_	N.A.	_	N.A.	.
Acute coronary syndromes: Myocardial ischaemia										
	All pooled	37	0.73	31	0.73	0.99	(0.62, 1.6)	-0.058	(-3.5, 3.42)	0.974
	Mild/1	14	0.28	20	0.47	0.58	(0.29, 1.2)	-1.98	(-4.5, 0.54)	0.115
	Moderate/2	16	0.32	11	0.26	1.21	(0.56, 2.6)	0.55	(-1.6, 2.72)	0.627
	Severe/3	5	0.1	1	0.02	4.16	(0.49, 36)	0.75	(-0.23, 1.7)	0.231
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.20	(-0.19,0.58)	1
	Fatal/5	1	0.02	0	0	_	N.A.	0.20	(-0.19,0.58)	1
	≥Severe/3	7	0.14	1	0.02	5.82	(0.72, 47)	1.14	(0.02, 2.3)	0.078
	Serious	12	0.24	5	0.12	1.99	(0.70, 5.7)	1.18	(-0.05, 2.9)	0.227
Arrhythmia: Bradycardia										
	All pooled	19	0.37	12	0.28	1.32	(0.64, 2.7)	0.899	(-1.43,3.22)	0.454
	Mild/1	15	0.3	3	0.07	4.16	(1.2, 14.4)	2.24	(0.55, 3.94)	0.016
	Moderate/2	2	0.04	5	0.12	0.33	(0.06, 1.7)	-0.791	(-2.0, 0.38)	0.257
	Severe/3	3	0.06	4	0.09	0.62	(0.14, 2.8)	-0.357	(-1.5, 0.79)	0.709
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	0.06	4	0.09	0.62	(0.14, 2.8)	-0.357	(-1.5, 0.79)	0.709
	Serious	4	0.08	3	0.07	1.11	(0.25, 5.0)	0.077	(-1.0, 1.2)	1

(Table A24 continued on the next page.)

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Table A24 (continued from the previous page). Sponsor's Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Arrhythmia: Extrasystoles										
	All pooled	21	0.41	29	0.69	0.6	(0.34, 1.1)	-2.73	(-5.8, 0.32)	0.073
	Mild/1	17	0.33	20	0.47	0.71	(0.37, 1.4)	-1.39	(-4.0, 1.22)	0.289
	Moderate/2	4	0.08	10	0.24	0.33	(0.10, 1.1)	-1.58	(-3.2, .076)	0.061
	Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-.07, 0.23)	0.454
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Serious	0	0	0	0	_	N.A.	_	N.A.	.
Arrhythmia: Sick Sinus Syndrome										
	All pooled	12	0.24	4	0.09	2.49	(0.80, 7.7)	1.42	(-0.21, 3.0)	0.132
	Mild/1	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64,0.56)	1
	Moderate/2	7	0.14	1	0.02	5.82	(0.72, 47)	1.14	(0.02, 2.3)	0.080
	Severe/3	5	0.1	3	0.07	1.39	(0.33, 5.8)	0.274	(-0.91, 1.5)	0.736
	Life-threatening/4	1	0.02	0	0	_	N.A.	0.197	(-0.19,0.58)	1
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	6	0.12	3	0.07	1.66	(0.42, 6.6)	0.471	(-0.77, 1.7)	0.524
	Serious	10	0.2	4	0.09	2.08	(0.65, 6.6)	1.02	(-0.51 2.55)	0.285
Arrhythmia: Sinus Bradycardia										
	All pooled	5	0.1	6	0.14	0.69	(0.21, 2.3)	-0.437	(-1.9 , 0.99)	0.561
	Mild/1	2	0.04	2	0.05	0.83	(0.12, 5.9)	-0.080	(-0.93,0.77)	1
	Moderate/2	3	0.06	2	0.05	1.25	(0.21, 7.5)	0.12	(-0.82 , 1.1)	1
	Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Serious	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .093)	0.094
Arrhythmia: Sinus Tachycardia										
	All pooled	1	0.02	5	0.12	0.17	(0.02, 1.4)	-0.988	(-2.1, 0.12)	0.098
	Mild/1	1	0.02	4	0.09	0.21	(0.02, 1.9)	-0.751	(-1.8, 0.26)	0.184
	Moderate/2	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	0	0	_	N.A.	_	N.A.	.
	Serious	0	0	0	0	_	N.A.	_	N.A.	.
Arrhythmia: Supra-ventricular Tachycardia										
	All pooled	9	0.18	9	0.21	0.83	(0.33, 2.1)	-0.360	(-2.17,1.45)	0.694
	Mild/1	0	0	6	0.14	0	N.A.	-1.42	(-2.6,-0.29)	0.009
	Moderate/2	6	0.12	3	0.07	1.66	(0.42, 6.6)	0.471	(-0.77, 1.7)	0.524
	Severe/3	3	0.06	2	0.05	1.25	(0.21, 7.5)	0.117	(-0.82, 1.1)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	3	0.06	2	0.05	1.25	(0.21, 7.5)	0.117	(-0.82, 1.1)	1
	Serious	7	0.14	2	0.05	2.91	(0.60, 14)	0.905	(-0.31, 2.1)	0.196

(Table A24 continued on the next page.)

Reference ID: 3168397

Table A24 (continued from the previous page). Sponsor's Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Arrhythmia: Tachy-arrhythmia										
	All pooled	1	0.02	3	0.07	0.28	(0.03, 2.7)	-0.514	(-1.41,0.38)	0.336
	Mild/1	1	0.02	0	0	_	N.A.	0.197	(-0.19,0.58)	1
	Moderate/2	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Life-threatening/4	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Serious	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .093)	0.094
Arrhythmia: Tachycardia										
	All pooled	42	0.83	25	0.59	1.4	(0.85, 2.3)	2.35	(-1.1, 5.8)	0.183
	Mild/1	27	0.53	18	0.43	1.25	(0.69, 2.3)	1.05	(-1.8, 3.9)	0.467
	Moderate/2	17	0.33	6	0.14	2.36	(0.93, 6.0)	1.93	(-.027, 3.9)	0.063
	Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Serious	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64,0.56)	1
Congestive Heart Failure: Cardiac Failure										
	All pooled	53	1.04	38	0.9	1.16	(0.77, 1.8)	1.43	(-2.6, 5.4)	0.484
	Mild/1	16	0.32	11	0.26	1.21	(0.56, 2.6)	0.545	(-1.6, 2.7)	0.627
	Moderate/2	27	0.53	17	0.4	1.32	(0.72, 2.4)	1.29	(-1.5, 4.1)	0.367
	Severe/3	11	0.22	7	0.17	1.31	(0.51, 3.4)	0.508	(-1.3, 2.3)	0.579
	Life-threatening/4	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Fatal/5	1	0.02	5	0.12	0.17	(0.02, 1.4)	-0.988	(-2.1, 0.12)	0.098
	≥Severe/3	12	0.24	13	0.31	0.77	(0.35, 1.7)	-0.717	(-2.9, 1.4)	0.506
	Serious	16	0.32	15	0.36	0.89	(0.44, 1.8)	-0.403	(-2.8, 2.0)	0.737
Congestive Heart Failure: Cardiac Failure Chronic										
	All pooled	5	0.1	8	0.19	0.52	(0.17, 1.6)	-0.911	(-2.5, 0.66)	0.274
	Mild/1	2	0.04	3	0.07	0.55	(0.09, 3.3)	-0.317	(-1.3, 0.66)	0.664
	Moderate/2	3	0.06	4	0.09	0.62	(0.14, 2.8)	-0.357	(-1.5, 0.79)	0.709
	Severe/3	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64,0.56)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64,0.56)	1
	Serious	1	0.02	5	0.12	0.17	(0.02, 1.4)	-0.988	(-2.1 , 0.12)	0.098

(Table A24 continued on the next page.)

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Table A24 (continued from the previous page). Sponsor's Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Congestive Heart Failure: Cardiac Failure Congestive										
	All pooled	16	0.32	23	0.54	0.58	(0.31, 1.1)	-2.30	(-5.0, 0.41)	0.088
	Mild/1	1	0.02	7	0.17	0.12	(0.01, 1.0)	-1.46	(-2.8,-0.18)	0.027
	Moderate/2	11	0.22	9	0.21	1.02	(0.42, 2.5)	0.0340	(-1.9, 1.9)	0.972
	Severe/3	5	0.1	7	0.17	0.59	(0.19, 1.9)	-0.674	(-2.2, 0.83)	0.398
	Life-threatening/4	0	0	1	0.02	0	N.A.	-0.237	(-0.70, .23)	0.454
	Fatal/5	0	0	1	0.02	0	N.A.	-0.237	(-0.70, .23)	0.454
	≥Severe/3	5	0.1	9	0.21	0.46	(0.15, 1.4)	-1.15	(-2.8, 0.49)	0.184
	Serious	10	0.2	13	0.31	0.64	(0.28, 1.5)	-1.11	(-3.2, 0.96)	0.283
Congestive Heart Failure: Dyspnoea										
	All pooled	101	1.99	106	2.51	0.79	(0.60, 1.0)	-5.22	(-11.3,0.86)	0.089
	Mild/1	53	1.04	46	1.09	0.96	(0.65, 1.4)	-0.461	(-4.7, 3.7)	0.829
	Moderate/2	48	0.95	58	1.37	0.69	(0.47, 1.0)	-4.29	(-8.7, 0.12)	0.052
	Severe/3	9	0.18	6	0.14	1.25	(0.44, 3.5)	0.351	(-1.3, 2.0)	0.675
	Life-threatening/4	2	0.04	0	0	_	N.A.	0.394	(-0.15, .94)	0.504
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	11	0.22	6	0.14	1.52	(0.56, 4.1)	0.745	(-0.97 , 2.5)	0.403
	Serious	11	0.22	8	0.19	1.14	(0.46, 2.8)	0.271	(-1.6, 2.1)	0.773
Other vascular disorders: Aortic Aneurysm										
	All pooled	6	0.12	9	0.21	0.55	(0.20, 1.6)	-0.951	(-2.6, 0.73)	0.255
	Mild/1	1	0.02	1	0.02	0.83	(0.05, 13)	-0.040	(-0.64, .56)	1
	Moderate/2	5	0.1	4	0.09	1.04	(0.28, 3.9)	0.037	(-1.2, 1.3)	1
	Severe/3	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.042
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.042
	Serious	1	0.02	5	0.12	0.17	(0.02, 1.4)	-0.988	(-2.1, 0.12)	0.098
Other vascular disorders: Skin ulcer										
	All pooled	34	0.67	28	0.66	1.01	(0.61, 1.66)	0.0621	(-3.26, 3.38)	0.971
	Mild/1	15	0.3	16	0.38	0.78	(0.39, 1.57)	-0.837	(-3.22, 1.54)	0.486
	Moderate/2	19	0.37	14	0.33	1.13	(0.57, 2.25)	0.425	(-1.99, 2.84)	0.732
	Severe/3	5	0.1	1	0.02	4.16	(0.49, 35.6)	0.748	(-0.23, 1.73)	0.231
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	5	0.1	1	0.02	4.16	(0.49, 35.6)	0.748	(-0.23, 1.73)	0.231
	Serious	6	0.12	0	0	_	N.A.	1.18	(0.237, 2.13)	0.035

(Table A24 continued on the next page.)

Reference ID: 3168397

Table A24 (continued from the previous page). Sponsor's Search Criteria With All Controlled PMO Studies (20030216, 20040132 24 month, 20050172, 20050179, 20010223, 20050234, 20050141) Pooled.

Other vascular disorders: Vascular Pseudo-aneurysm										
	All pooled	0	0	3	0.07	0	N.A.	-0.711	(-1.5, .093)	0.094
	Mild/1	0	0	0	0	_	N.A.	_	N.A.	.
	Moderate/2	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
	Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	0	0	1	0.02	0	N.A.	-0.237	(-0.70,0.23)	0.454
	Serious	0	0	2	0.05	0	N.A.	-0.474	(-1.1, 0.18)	0.206
Stroke: Cerebral Thrombosis										
	All pooled	3	0.06	5	0.12	0.5	(0.12, 2.1)	-0.594	(-1.8, 0.64)	0.481
	Mild/1	1	0.02	0	0	_	N.A.	0.197	(-0.19, .58)	1
	Moderate/2	0	0	4	0.09	0	N.A.	-0.948	(-1.9,-.019)	0.042
	Severe/3	2	0.04	1	0.02	1.66	(0.15, 18)	0.157	(-0.56,0.87)	1
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	2	0.04	1	0.02	1.66	(0.15, 18)	0.157	(-0.56,0.87)	1
	Serious	3	0.06	3	0.07	0.83	(0.17, 4.1)	-0.120	(-1.2, 0.93)	1
Stroke: Vertebro-basilar insufficiency										
	All pooled	11	0.22	12	0.28	0.76	(0.34, 1.7)	-0.677	(-2.7, 1.4)	0.513
	Mild/1	6	0.12	6	0.14	0.83	(0.27, 2.6)	-0.240	(-1.7, 1.2)	0.748
	Moderate/2	4	0.08	7	0.17	0.47	(0.14, 1.6)	-0.871	(-2.3, 0.58)	0.243
	Severe/3	1	0.02	2	0.05	0.42	(0.04, 4.6)	-0.277	(-1.0, 0.49)	0.594
	Life-threatening/4	0	0	0	0	_	N.A.	_	N.A.	.
	Fatal/5	0	0	0	0	_	N.A.	_	N.A.	.
	≥Severe/3	1	0.02	2	0.05	0.42	(0.04, 4.6)	-0.277	(-1.0, 0.49)	0.594
	Serious	3	0.06	8	0.19	0.31	(0.08, 1.2)	-1.30	(-2.8, 0.17)	0.077

Reference ID: 3168397

Table A25 shows the events in Study 20030216 with whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Table A25. Events in Study 20030216 with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Acute coronary syndromes: All PTs	Severe	1.9	0.001
	≥Severe	1.5	0.01
Acute coronary syndromes: Acute myocardial infarction	Severe	4.5	0.065
Acute coronary syndromes: Angina pectoris	Severe	1.8	0.107
	Serious	1.8	0.036
Acute coronary syndromes: Cardiac disorder**	All	0 DEN 5 PLA	0.031
	Mild	0 DEN 4 PLA	0.062
Acute coronary syndromes: Myocardial Ischaemia	≥Severe	7.0	0.0702
Arrhythmia: Bradycardia	Mild	4.7	0.013
Arrhythmia: Sick Sinus Syndrome	Moderate	7.0	0.070
Arrhythmia: Sinus tachycardia**	All pooled	0 DEN 5 PLA	0.031
	Mild	0 DEN 4 PLA	0.062
Arrhythmia: Supraventricular tachycardia**	Mild	0 DEN 6 PLA	0.016
Arrhythmia: Tachycardia	All pooled	1.6	0.076
	Moderate	2.5	0.050
Congestive Heart Failure: Cardiac Failure Congestive	Mild	0.14	0.039
Congestive Heart Failure: Oedema**	Mild	0 DEN 4 PLA	0.062
Congestive Heart Failure: Oedema Peripheral	All pooled	1.22	0.064
Other vascular disorders: All PTs	Severe	1.7	0.055
	≥Severe	1.5	0.067
Other vascular disorder: Aortic Aneurysm**	Severe	0 DEN 4 PLA	0.062
	≥Severe	0 DEN 4 PLA	0.062
Other vascular disorder: Aortic stenosis	All pooled	2.6	0.096
Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Stroke: Cerebral Thrombosis**	Moderate	0 DEN 4 PLA	0.052

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled, DEN = Denosumab, LT = Life-threatening severity, PLA = Placebo

Reference ID: 3168397

Table A26 shows the events in individual studies whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Table A26. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Study	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
20040138	Acute Coronary Syndromes: Angina Pectoris	All pooled	2.1	0.073
20040138	Acute Coronary Syndromes: Chest Pain**	Serious	0 DEN 4 PLA	0.061
20040138	Acute Coronary Syndromes: Coronary Artery Disease	Moderate	0.28	0.107
20040138	Acute Coronary Syndromes: Myocardial Ischaemia**	Serious	0 DEN 6 PLA	0.015
20040138	Arrhythmia: All PTs	Severe	1.5	0.056
20040138	Congestive heart failure: All PTs	Mild	4.4	0.013
		Moderate	7.9	0.001
20040138	Congestive heart failure: Oedema peripheral	Mild	3.3	0.044
		Moderate	3.2	0.021
20040138	Congestive Heart Failure: Pulmonary Oedema**	All	0 DEN 4 PLA	0.0612
		≥Severe	0 DEN 4 PLA	0.0612
20040138	Other vascular disorders: All PTs**	LT	8 DEN 0 PLA	0.008
20040138	Stroke: All PTs	LT	0.17	0.069
20050141	Acute Coronary Syndromes: All PTs	All	0.49	0.093
		Moderate	0.25	0.063
20050141	Acute Coronary Syndromes: Chest Pain	All	0.2	0.021
		Moderate	0.16	0.068

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening severity
PLA = Placebo

Table A27 shows the events in the pooled large, pivotal studies dataset whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Reference ID: 3168397

Table A27. Events in the Pooled Large, pivotal Dataset with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Acute coronary syndromes: All PTs	Severe	1.6	0.004
	≥ Severe	1.3	0.074
Acute coronary syndromes: Acute coronary syndrome**	Severe	6 DEN 0 PLA	0.031
Acute Coronary Syndromes: Angina Pectoris	Severe	1.9	0.064
	≥ Severe	1.8	0.079
	Serious	1.7	0.052
Acute Coronary Syndromes: Cardiac Disorder**	All	0.17	0.070
	Mild	0 DEN 4 PLA	0.062
Acute Coronary Syndromes: Coronary Artery Stenosis**	Serious	5 DEN 0 PLA	0.062
Arrhythmia: Bradycardia	Mild	5.0	0.0075
Arrhythmia: Sick sinus syndrome	All	3.2	0.026
	Moderate	4.5	0.065
	Serious	2.8	0.063
Arrhythmia: Sinus tachycardia**	All	0 DEN 5 PLA	0.031
	Mild	0 DEN 4 PLA	0.062
Arrhythmia: Supraventricular tachycardia**	Mild	0 DEN 6 PLA	0.015
Arrhythmia: Syncope	Moderate	0.67	0.108
Arrhythmia: Tachycardia	Moderate	2.1	0.089
Congestive Heart Failure: All PTs	Mild	1.2	0.088
	LT	0.47	0.086
Congestive Heart Failure: Cardiac Failure	All	1.4	0.073
Congestive Heart Failure: Cardiac Failure Congestive**	LT	0 DEN 4 PLA	0.062
Congestive Heart Failure: Cardiomegaly	All	0.25	0.0648
Congestive Heart Failure: Dyspnoea	Moderate	0.76	0.100
Congestive Heart Failure: Oedema	All	0.46	0.106
Congestive Heart Failure: Oedema Peripheral	All	1.2	0.063
	Mild	1.2	0.060
Other vascular disorders: All PTs	Severe	1.5	0.086
	LT	2.5	0.050
	≥Severe	1.5	0.043
	Serious	1.4	0.086
Other vascular disorders: Aortic aneurysm	Severe	0.17	0.070
Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Other vascular disorders: Thrombophlebitis	Moderate	0.33	0.092
Stroke: Cerebral Thrombosis**	Moderate	0 DEN 4 PLA	0.062

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled, DEN = Denosumab, LT = Life-threatening severity, PLA = Placebo

Reference ID: 3168397

Table A28 shows the events in the pooled placebo-controlled studies dataset whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Table A28. Events in the Pooled Placebo-Controlled PMO Dataset with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Acute coronary syndromes: All PTs	Severe	1.8	0.003
	≥Severe	1.3	0.054
Acute coronary syndromes: Acute myocardial infarction	Severe	4.5	0.065
Acute coronary syndromes: Angina pectoris	Serious	1.7	0.053
Acute coronary syndromes: Cardiac disorder**	All	0 DEN 5 PLA	0.031
	Mild	0 DEN 4 PLA	0.062
Acute coronary syndromes: Myocardial ischaemia	≥Severe	7.0	0.070
Arrhythmia: Bradycardia	Mild	5.0	0.008
Arrhythmia: Sick Sinus Syndrome	Moderate	7.0	0.070
Arrhythmia: Supraventricular tachycardia**	Mild	0 DEN 6 PLA	0.016
Arrhythmia: Tachycardia	All	1.6	0.063
	Moderate	2.7	0.033
Congestive Heart Failure: Cardiac Failure Congestive	Mild	0.14	0.039
Congestive Heart Failure: Rales	All	4.0	0.109
Other vascular disorders: All PTs	Severe	1.7	0.055
	≥Severe	1.5	0.067
Other vascular disorders: Aortic aneurysm**	Severe	0 DEN 4 PLA	0.062
	≥Severe	0 DEN 4 PLA	0.062
Other vascular disorders: Aortic stenosis	All	2.6	0.096
Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Stroke: Cerebral Thrombosis**	Moderate	0 DEN 4 PLA	0.062

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening severity
PLA = Placebo

Reference ID: 3168397

Table A29 shows the events in the pooled placebo- or active- controlled PMO studies dataset whose relative risk estimate is associated with a p-value less than 0.10 when analyzed using the sponsor's grouping of preferred terms.

Table A29. Events in the Pooled Any-Controlled PMO Dataset with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using the Sponsor's Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Acute coronary syndromes: All PTs	Severe	1.5	0.038
Acute coronary syndromes: Cardiac Disorder**	All	0 DEN 5 PLA	0.019
	Mild	0 DEN 4 PLA	0.042
Acute coronary syndromes: Myocardial ischaemia	≥Severe	5.8	0.078
Arrhythmia: Bradycardia	Mild	4.2	0.016
Arrhythmia: Extrasystoles	All	0.6	0.073
	Moderate	0.33	0.061
Arrhythmia: Sick Sinus Syndrome	Moderate	5.8	0.080
Arrhythmia: Sinus Bradycardia**	Serious	0 DEN 3 PLA	0.094
Arrhythmia: Sinus Tachycardia	All	0.17	0.098
Arrhythmia: Supraventricular Tachycardia**	Mild	0 DEN 6 PLA	0.009
Arrhythmia: Tachyarrhythmia**	Serious	0 DEN 3 PLA	0.094
Arrhythmia: Tachycardia	Moderate	2.4	0.063
Congestive Heart Failure: Cardiac Failure	Fatal	0.17	0.098
Congestive Heart Failure: Cardiac Failure Chronic	Serious	0.17	0.098
Congestive Heart Failure: Cardiac Failure Congestive	All	0.58	0.088
	Mild	0.12	0.027
Congestive Heart Failure: Dyspnoea	All	0.79	0.089
	Moderate	0.69	0.052
Other vascular disorders: Aortic Aneurysm**	Severe	0 DEN 4 PLA	0.042
	≥Severe	0 DEN 4 PLA	0.042
	Serious	0.17	0.098
Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.035
Other vascular disorders: Vascular Pseudo-aneurysm**	All	0 DEN 3 PLA	0.094
Stroke: Cerebral Thrombosis**	Moderate	0 DEN 4 PLA	0.042
Stroke: Vertebrobasilar insufficiency	Serious	0.42	0.077

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening severity
PLA = Placebo

Reference ID: 3168397

Table A30 shows the serious, life-threatening and fatal events whose relative risk estimate is associated with a p-value less than 0.10 using broad SMQ criteria.

Table A30. Events Recorded as Serious, Life-Threatening or Fatal Having a Relative Risk Associated with a P-value of Less Than 0.10: Broad SMQ Criteria.

Analysis	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Study 20030216	Arrhythmia Related Investigations	Fatal	0.3	0.057
Study 20030216	Bradyarrhythmias	Serious	1.9	0.095
Study 20030216	Cardiac Arrhythmias	Fatal	0.3	0.057
Study 20030216	Cardiomyopathy	Fatal	0.36	0.076
Study 20030216	Gastrointestinal Perforation, Ulceration, etc.	Serious	1.4	0.103
Study 20030216	Ischaemic Heart Disease	Serious	1.4	0.021
Study 20030216	Thrombophlebitis	Serious	2.3	0.074
Study 20030216	Torsade de Pointes/QT Prolongation	Fatal	0.3	0.057
Study 20040138	Cardiac Failure	LT	0.17	0.069
Study 20040138	Gastrointestinal Perforation, ulceration, etc.	Serious	0.47	0.054
Study 20040138	Pulmonary Hypertension	Serious	3.3	0.091
Pool large, pivotal studies	Bradyarrhythmia	Serious	1.9	0.059
Pool large, pivotal studies	Cardiac Failure	LT	0.36	0.076
Pool large, pivotal studies	Embolic and Thrombotic Events, Arterial	LT	0.5	0.054
Pool large, pivotal studies	Pulmonary Hypertension	Serious	2.0	0.046
Pool large, pivotal studies	Thrombophlebitis	Serious	2.0	0.069
Pool placebo-controlled	Arrhythmia related investigations	Fatal	0.3	0.057
Pool placebo-controlled	Bradyarrhythmia	Serious	1.9	0.096
Pool placebo-controlled	Cardiac arrhythmias	Fatal	0.3	0.057
Pool placebo-controlled	Cardiomyopathy	Fatal	0.36	0.076
Pool placebo-controlled	Gastrointestinal Perforation, Ulceration, etc.	Serious	1.4	0.103
Pool placebo-controlled	Ischaemic Heart Disease	Serious	1.4	0.027
Pool placebo-controlled	Thrombophlebitis	Serious	2.3	0.074
Pool placebo-controlled	Torsade de Pointes / QT Prolongation	Fatal	0.3	0.057
Pool any controlled	Arrhythmia related investigations	Fatal	0.33	0.061
Pool any controlled	Cardiac arrhythmias	Fatal	0.33	0.061
Pool any controlled	Cardiomyopathy	Fatal	0.3	0.037
Pool any controlled	Embolic and Thrombotic Events, Arterial	LT	0.33	0.061
Pool any controlled	Torsade de Pointes / QT Prolongation	Fatal	0.33	0.061

*Relative Risk estimates are reported, unless otherwise noted.
LT = Life-threatening

In each of the following studies, no cardiovascular adverse event was associated with a relative risk having a p-value less than 0.05: Study 20010223 (smallest p-value: 0.1278), Study 20040132 (smallest p-value: 0.1421), Study 20040135 (smallest p-value: 0.248), Study 20050141 (smallest p-value: 0.0846), Study 20050172 (smallest p-value: 0.243), Study 20050179 (smallest p-value: 0.2102), Study 20050234 (smallest p-value: 0.23).

Table A31 shows the serious, life-threatening and fatal events whose relative risk estimate is associated with a p-value less than 0.10 using narrow SMQ criteria.

Reference ID: 3168397

Table A31. Events Recorded as Serious, Life-Threatening or Fatal Having a Relative Risk Associated with a P-value of Less Than 0.10: Narrow SMQ Criteria.
Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Analysis	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Study 20030216	Ischaemic Heart Disease	Serious	1.4	0.021
Study 20040138	Cardiac Failure	LT	0.17	0.069
Study 20040138	Toxic-septic shock conditions**	Serious	0 DEN 4 PLA	0.061
Pool large, pivotal studies	Cardiac Failure	LT	0.36	0.076
Pool large, pivotal studies	Embolic and Thrombotic Events, Arterial	LT	0.5	0.054
Pool placebo-controlled	Ischaemic Heart Disease	Serious	1.4	0.027
Pool any controlled	Embolic and Thrombotic Events, Arterial	LT	0.33	0.061

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
DEN = Denosumab
LT = Life-threatening
PLA = Placebo

Table A32 shows the serious, life-threatening and fatal events whose relative risk estimate is associated with a p-value less than 0.10 using the Sponsor's preferred term grouping.

Reference ID: 3168397

Table A32. Events Recorded as Serious, Life-Threatening or Fatal Having a Relative Risk Associated with a P-value of Less Than 0.10: Sponsor's Preferred Term Grouping. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Analysis	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Study 20030216	Acute coronary syndromes: Angina pectoris	Serious	1.8	0.036
Study 20030216	Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Study 20040138	Acute Coronary Syndromes: Chest Pain**	Serious	0 DEN 4 PLA	0.061
Study 20040138	Acute Coronary Syndromes: Myocardial Ischaemia**	Serious	0 DEN 6 PLA	0.015
Study 20040138	Other vascular disorders: All PTs**	LT	8 DEN 0 PLA	0.008
Study 20040138	Stroke: All PTs	LT	0.17	0.069
Pool large, pivotal studies	Acute Coronary Syndromes: Angina Pectoris	Serious	1.7	0.052
Pool large, pivotal studies	Acute Coronary Syndromes: Coronary Artery Stenosis**	Serious	5 DEN 0 PLA	0.0624
Pool large, pivotal studies	Arrhythmia: Sick sinus syndrome	Serious	2.8	0.063
Pool large, pivotal studies	Congestive Heart Failure: All PTs	LT	0.47	0.086
Pool large, pivotal studies	Congestive Heart Failure: Cardiac Failure Congestive**	LT	0 DEN 4 PLA	0.062
Pool large, pivotal studies	Congestive Heart Failure: All PTs	LT	0.47	0.086
Pool large, pivotal studies	Congestive Heart Failure: Cardiac Failure Congestive**	LT	0 DEN 4 PLA	0.062
Pool large, pivotal studies	Other vascular disorders: All PTs	LT	2.5	0.050
Pool large, pivotal studies	Other vascular disorders: All PTs	Serious	1.4	0.086
Pool large, pivotal studies	Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Pool placebo-controlled	Acute coronary syndromes: Angina pectoris	Serious	1.7	0.053
Pool placebo-controlled	Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.031
Pool any controlled	Arrhythmia: Sinus Bradycardia**	Serious	0 DEN 3 PLA	0.094
Pool any controlled	Arrhythmia: Tachyarrhythmia**	Serious	0 DEN 3 PLA	0.094
Pool any controlled	Congestive Heart Failure: Cardiac Failure	Fatal	0.17	0.098
Pool any controlled	Congestive Heart Failure: Cardiac Failure Chronic	Serious	0.17	0.098
Pool any controlled	Other vascular disorders: Aortic Aneurysm	Serious	0.17	0.098
Pool any controlled	Other vascular disorders: Skin ulcer**	Serious	6 DEN 0 PLA	0.035
Pool any controlled	Stroke: Vertebrobasilar insufficiency	Serious	0.42	0.077

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
DEN = Denosumab
LT = Life-threatening
PLA = Placebo

Reference ID: 3168397

Table A33 shows the events for which relative risk was associated with a p-value less than 0.10 when all severity levels were pooled in the broad SMQ analysis.

Table A33. Events for which Relative Risk was Associated with a P-value of Less Than 0.10 when All Severity Levels were Pooled in the Analysis: Broad SMQ Criteria.

Analysis	Events with Relative Risk Having p<0.10	Risk*	p-value
20030216	Gastrointestinal Haemorrhage	1.4	0.082
20040132	Haemorrhages	0.36	0.018
20040132	Haemorrhage Terms (excl lab)	0.36	0.018
20040132	Hypertension	0.4	0.044
20040141	Hypertension	0.61	0.103
20050234	Gastrointestinal Perforation, Ulceration, etc.	0.22	0.035
Pool large, pivotal studies	Disorders of Sinus Node Function	1.8	0.097
Pool any controlled PMO	Cardiomyopathy	0.88	0.056
Pool any controlled PMO	Embolic and Thrombotic Events, Venous	0.64	0.040
Pool any controlled PMO	Haemorrhages	0.86	0.073
Pool any controlled PMO	Haemorrhage Terms (excl lab)	0.87	0.089
Pool any controlled PMO	Hypertension	0.86	0.002
Pool any controlled PMO	Pulmonary Hypertension	0.81	0.086

*Relative Risk estimates are reported, unless otherwise noted.

Table A34 shows the events for which relative risk was associated with a p-value less than 0.10 when all severity levels were pooled in the narrow SMQ analysis.

Table A34. Events for which Relative Risk was Associated with a P-value of Less Than 0.10 when All Severity Levels were Pooled in the Analysis: Narrow SMQ Criteria. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Analysis	Events with Relative Risk Having p<0.10	Risk*	p-value
20040132	Haemorrhages	0.38	0.028
20040132	Haemorrhage Terms (excl lab)	0.38	0.028
20040132	Hypertension	0.4	0.044
20040138	Toxic-septic shock conditions**	0 DEN 4 PLA	0.061
20040141	Hypertension	0.61	0.103
Any controlled PMO	Embolic and Thrombotic Events, Venous	0.64	0.040
Any controlled PMO	Haemorrhages	0.87	0.100
Any controlled PMO	Haemorrhage Terms (excl lab)	0.87	0.100
Any controlled PMO	Hypertension	0.86	0.002

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore, the number of subjects with the event are reported instead of RR.
DEN = Denosumab
PLA = Placebo

Reference ID: 3168397

Table A35 shows the events for which relative risk was associated with a p-value less than 0.10 when all severity levels were pooled using the sponsor's preferred term grouping in the analysis.

Table A35. Events for which Relative Risk was Associated with a P-value Less Than 0.10 when All Severity Levels were Pooled in Analysis: Sponsor's Preferred Term Grouping. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Analysis	Events with Relative Risk Having p<0.10	Risk*	p-value
20030216	Acute Coronary Syndromes: Cardiac Disorder**	0 DEN 5 PLA	0.031
20030216	Arrhythmia: Sinus Tachycardia**	0 DEN 5 PLA	0.031
20030216	Arrhythmia: Tachycardia	1.6	0.076
20030216	Other Vascular Disorder: Aortic Stenosis	2.6	0.096
20040138	Acute Coronary Syndromes: Angina Pectoris	2.1	0.073
20040138	Congestive Heart Failure: Pulmonary Oedema**	0 DEN 4 PLA	0.0612
20050141	Acute Coronary Syndromes: All PTs	0.49	0.093
20050141	Acute Coronary Syndromes: Chest Pain	0.2	0.021
Pool Large, pivotal	Acute Coronary Syndromes: Cardiac Disorder	0.17	0.070
Pool Large, pivotal	Arrhythmia: Sick Sinus Syndrome	3.2	0.026
Pool Large, pivotal	Arrhythmia: Sinus Tachycardia**	0 DEN 5 PLA	0.031
Pool Large, pivotal	Congestive Heart Failure: Cardiac Failure	1.4	0.073
Pool Large, pivotal	Congestive Heart Failure: Cardiomegaly	0.25	0.0648
Pool Large, pivotal	Congestive Heart Failure: Oedema	0.46	0.106
Pool Large, pivotal	Congestive Heart Failure: Oedema Peripheral	1.2	0.063
Pooled placebo controlled PMO	Acute Coronary Syndromes: Cardiac Disorder**	0 DEN 5 PLA	0.031
Pooled placebo controlled PMO	Arrhythmia: Tachycardia	1.6	0.063
Pooled placebo controlled PMO	Congestive Heart Failure: Rales	4.0	0.109
Pooled placebo controlled PMO	Other Vascular Disorders: Aortic Stenosis	2.6	0.096
Pooled Controlled PMO	Acute Coronary Syndromes: Cardiac Disorder**	0 DEN 5 PLA	0.019
Pooled Controlled PMO	Arrhythmia: Extrasystoles	0.6	0.073
Pooled Controlled PMO	Arrhythmia: Sinus Tachycardia	0.17	0.098
Pooled Controlled PMO	Congestive Heart Failure: Cardiac Failure Congestive	0.58	0.088
Pooled Controlled PMO	Congestive Heart Failure: Dyspnoea	0.79	0.089
Pooled Controlled PMO	Other Vascular Disorders: Vascular Pseudo-Aneurysm**	0 DEN 3 PLA	0.094

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore, the number of subjects with the event are reported instead of RR.
DEN = Denosumab
PLA = Placebo

Reference ID: 3168397

Table A36 shows the events for which relative risk was associated with a p-value less than 0.10 when Study 20030216 analyzed using a broad SMQ grouping of preferred terms.

Table A36. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Analyzed Using a Broad SMQ Grouping of Preferred Terms. Note that only events reported in Study 20030216 are shown in this table.

Events with Relative Risk Having p<0.10	Severity	RR*	p-value
Arrhythmia related investigations	Mild	1.3	0.05
	Fatal	0.3	0.057
Bradyarrhythmias	Moderate	3.5	0.031
	Serious	1.9	0.095
Cardiac Arrhythmias	Fatal	0.3	0.057
Cardiac Failure	Moderate	1.3	0.069
Cardiomyopathy	Fatal	0.36	0.076
Disorders of Sinus Node Function	Moderate	3.7	0.057
Embolic and Thrombotic Events	Severe	1.5	0.018
Embolic and Thrombotic Events, Arterial	Severe	1.7	0.032
Embolic and Thrombotic Events, Unspecified	Severe	1.8	0.071
	≥Severe	1.6	0.071
Gastrointestinal Haemorrhage	All pooled	1.4	0.082
	Moderate	2.1	0.018
Gastrointestinal Perforation, Ulceration, etc.	Moderate	1.4	0.061
	Serious	1.4	0.103
Ischaemic Heart Disease	Severe	2.0	0.0007
	≥Severe	1.7	0.002
	Serious	1.4	0.021
Myocardial Infarction	Severe	2.5	0.011
	≥Severe	1.5	0.097
Pulmonary Hypertension	≥Severe	2.0	0.103
Thrombophlebitis	Severe	2.6	0.096
	≥Severe	2.6	0.096
	Serious	2.3	0.074
Torsade de Pointes/QT Prolongation	Fatal	0.3	0.057

*Relative Risk estimates are reported.

Reference ID: 3168397

Table A37 shows the events for which relative risk was associated with a p-value less than 0.10 when studies analyzed separately analyzed using a broad SMQ grouping of preferred terms.

Table A37. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10 when Studies Analyzed Separately: Each Study Analyzed Using a Broad SMQ Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR. The events reported in Study 20030216 are reported in the previous table.

Study	Events with Relative Risk Having p<0.10	Severity	RR*	p-value
20040132	Haemorrhages	All pooled	0.36	0.018
		Mild	0.22	0.011
20040132	Haemorrhage Terms (excl lab)	All pooled	0.36	0.018
		Mild	0.22	0.011
20040132	Hypertension	All pooled	0.4	0.044
		Moderate	0.25	0.104
20040135	Hypertension	Moderate**	5 PLA 0 DEN	0.025
20040138	Cardiac Arrhythmias	Severe	2.0	0.056
20040138	Cardiac Failure	Mild	1.6	0.033
		Moderate	0.31	0.0003
		LT	0.17	0.069
20040138	Cardiomyopathy	Moderate	0.69	0.083
20040138	Gastrointestinal Perforation, ulceration, etc.	Mild	2.2	0.041
		Serious	0.47	0.054
20040138	Haemodynamic oedema, effusions, etc.	Mild	1.5	0.055
20040138	Pulmonary Hypertension	Serious	3.3	0.091
20040141	Gastrointestinal Haemorrhage	Mild**	4 ALE 0 DEN	0.061
20040141	Haemorrhages	Mild	1.9	0.085
20040141	Haemorrhage Terms (excl lab)	Mild	1.9	0.085
20040141	Hypertension	All pooled	0.61	0.103
20050234	Gastrointestinal Perforation, Ulceration, etc.	All pooled	0.22	0.035
		Moderate**	4 ALE 0 DEN	0.060
20050234	Haemorrhages	Moderate	0.16	0.067
20050234	Haemorrhage Terms (excl lab)	Moderate	0.16	0.067

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
ALE = Alendronate
DEN = Denosumab
LT = Life-threatening
PLA = Placebo

Reference ID: 3168397

Table A38 shows the events for which relative risk was associated with a p-value less than 0.10 when the pooled large, pivotal trial dataset was analyzed using a broad SMQ grouping of preferred terms.

Table A38. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Pooled Large, pivotal Trials Dataset Analyzed Using a Broad SMQ Grouping of Preferred Terms.

Events with Relative Risk Having p<0.10	Severity	RR*	p-value
Arrhythmia Related Investigations	Mild	1.25	0.090
Bradyarrhythmia	Moderate	2.3	0.061
	Severe	2.1	0.089
	≥Severe	2.1	0.073
	Serious	1.9	0.059
Cardiac Failure	LT	0.36	0.076
Conduction Defects	Severe	4.0	0.109
Disorders of Sinus Node Function	All	1.8	0.097
	Moderate	2.6	0.096
Embolic and Thrombotic Events	Severe	1.4	0.019
Embolic and Thrombotic Events, Arterial	Severe	1.7	0.017
	LT	0.5	0.054
Embolic and Thrombotic Events, Venous	Mild	0.5	0.100
Ischaemic Heart Disease	Severe	1.8	0.001
	≥Severe	1.4	0.030
Myocardial Infarction	Severe	2.5	0.003
Pulmonary Hypertension	≥Severe	1.7	0.106
	Serious	2.0	0.046
Thrombophlebitis	Serious	2.0	0.069

*Relative Risk estimates are reported.
All = All severity levels pooled
LT = Life Threatening

Reference ID: 3168397

Table A39 shows the events for which relative risk was associated with a p-value less than 0.10 when the pooled placebo-controled trials dataset was analyzed using a broad SMQ grouping of preferred terms.

Table A39. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Pooled Placebo-Controlled Trials Dataset Analyzed Using a Broad SMQ Grouping of Preferred Terms.

Events with Relative Risk Having p<0.10	Severity	RR*	p-value
Arrhythmia related investigations	Mild	1.3	0.033
	Fatal	0.3	0.057
Bradyarrhythmia	Moderate	3.5	0.031
	Serious	1.9	0.096
Cardiac arrhythmias	Fatal	0.3	0.057
Cardiomyopathy	Fatal	0.36	0.076
Disorders of Sinus Node Function	Moderate	3.7	0.057
Embolic and Thrombotic Events	Severe	1.5	0.024
Embolic and Thrombotic Events, Arterial	Severe	1.7	0.046
Embolic and Thrombotic Events, Unsp	Severe	1.8	0.071
	≥Severe	1.6	0.071
Gastrointestinal Haemorrhage	Moderate	1.9	0.024
Gastrointestinal Perforation, Ulceration, etc.	Moderate	1.4	0.033
	Serious	1.4	0.103
Ischaemic Heart Disease	Severe	1.8	0.002
	≥Severe	1.6	0.006
	Serious	1.4	0.027
Myocardial Infarction	Severe	2.3	0.020
Pulmonary Hypertension	≥Severe	2.0	0.103
Thrombophlebitis	Severe	2.6	0.096
	≥Severe	2.6	0.096
	Serious	2.3	0.074
Torsade de Pointes / QT Prolongation	Fatal	0.3	0.057

*Relative Risk estimates are reported.

Reference ID: 3168397

Table A40 shows the events for which relative risk was associated with a p-value less than 0.10 when the pooled placebo- or active- controlled trials dataset was analyzed using a broad SMQ grouping of preferred terms.

Table A40. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Pooled Placebo- or Active- Controlled PMO Trials Dataset Analyzed Using a Broad SMQ Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Arrhythmia related investigations	Fatal	0.33	0.061
Bradyarrhythmia	Moderate	2.9	0.058
Cardiac arrhythmias	Fatal	0.33	0.061
Cardiac arrhythmia terms	Mild	0.77	0.055
Cardiomyopathy	All	0.88	0.056
	Moderate	0.84	0.109
	Fatal	0.3	0.037
Disorders of Sinus Node Function	Moderate	3.1	0.105
Embolic and Thrombotic Events, Arterial	LT	0.33	0.061
Embolic and Thrombotic Events, Venous	All pooled	0.64	0.040
	Mild	0.42	0.050
	Moderate	0.53	0.058
Gastrointestinal Haemorrhage	Moderate	1.8	0.051
Haemorrhages	All pooled	0.86	0.073
	Mild	0.83	0.077
	Severe	0.62	0.077
Haemorrhage Terms (excl lab)	All pooled	0.87	0.089
	Mild	0.83	0.087
	Severe	0.62	0.077
Hypertension	All pooled	0.86	0.002
	Moderate	0.83	0.006
Ischaemic Heart Disease	Severe	1.6	0.029
	≥Severe	1.4	0.063
Myocardial Infarction	Mild**	0 DEN 3 PLA	0.094
	Severe	1.9	0.073
Pulmonary Hypertension	All pooled	0.81	0.086
	Moderate	0.68	0.033
Torsade de Pointes / QT Prolongation	Moderate	0.71	0.104
	Fatal	0.33	0.061

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening
PLA = Placebo

Reference ID: 3168397

Table A41 shows the events for which relative risk was associated with a p-value less than 0.10 when the individual studies were analyzed using a narrow SMQ grouping of preferred terms.

Table A41. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10 when Each Study Analyzed Separately: Analyzed Using a Narrow SMQ Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Dataset	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
20030216	Embolic and Thrombotic Events	Severe	1.5	0.071
20030216	Embolic and Thrombotic Events, Arterial	Severe	1.7	0.032
20030216	Ischaemic Heart Disease	Severe	2.0	0.0007
		≥Severe	1.7	0.002
		Serious	1.4	0.021
20030216	Myocardial Infarction	Severe	2.5	0.011
		≥Severe	1.5	0.097
20040132	Haemorrhages	All	0.38	0.028
		Mild	0.23	0.018
20040132	Haemorrhage Terms (excl lab)	All	0.38	0.028
		Mild	0.23	0.018
20040132	Hypertension	All	0.4	0.044
		Moderate	0.25	0.104
20040135	Hypertension	Moderate**	0 DEN 5 PLA	0.025
20040138	Cardiac Failure	Moderate	0.17	0.069
		LT	0.17	0.069
20040138	Embolic and thrombotic events	Moderate	2.1	0.059
20040138	Haemodynamic oedema, effusions, etc.	Mild	1.5	0.055
20040138	Toxic-septic shock conditions	All**	0 DEN 4 PLA	0.0612
		≥Severe**	0 DEN 4 PLA	0.0612
		Serious**	0 DEN 4 PLA	0.0612
20040141	Haemorrhages	Mild	1.9	0.085
20040141	Haemorrhage Terms (excl lab)	Mild	1.9	0.085
20040141	Hypertension	All	0.61	0.103
20050234	Haemorrhages	Moderate	0.16	0.067
20050234	Haemorrhage Terms (excl lab)	Moderate	0.16	0.067

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled
DEN = Denosumab
LT = Life-threatening
PLA = Placebo

Reference ID: 3168397

Table A42 shows the events for which relative risk was associated with a p-value less than 0.10 when pooled trial datasets were analyzed using a narrow SMQ grouping of preferred terms.

Table A42. Events with Relative Risk Estimates Associated with a P-value Less Than 0.10: Pooled Datasets Analyzed Using a Narrow SMQ Grouping of Preferred Terms. Note that in instances in which relative risk cannot be computed due to entries of zero, the number of subjects with the event are reported instead of RR.

Pooled Data	Events with Relative Risk Having p<0.10	Severity	Risk*	p-value
Large PTs	Cardiac Failure	LT	0.36	0.076
Large PTs	Embolic and Thrombotic Events	Severe	1.4	0.045
Large PTs	Embolic and Thrombotic Events, Arterial	Severe	1.7	0.017
		LT	0.5	0.054
Large PTs	Embolic and Thrombotic Events, Venous	Mild	0.5	0.100
Large PTs	Ischaemic Heart Disease	Severe	1.8	0.001
		≥Severe	1.4	0.030
Large PTs	Myocardial Infarction	Severe	2.5	0.003
Large PTs	Thrombophlebitis	Moderate	0.33	0.092
PC	Embolic and Thrombotic Events	Severe	1.4	0.092
PC	Embolic and Thrombotic Events, Arterial	Severe	1.7	0.046
PC	Ischaemic Heart Disease	Severe	1.8	0.002
		≥Severe	1.6	0.006
		Serious	1.4	0.027
PC	Myocardial Infarction	Severe	2.3	0.020
Any control	Embolic and Thrombotic Events, Arterial	LT	0.33	0.061
Any control	Embolic and Thrombotic Events, Venous	All	0.64	0.040
		Mild	0.42	0.050
		Moderate	0.53	0.058
Any control	Haemorrhages	All pooled	0.87	0.100
		Mild	0.84	0.101
		Severe	0.62	0.077
Any control	Haemorrhage Terms (excl lab)	All	0.87	0.100
		Mild	0.84	0.101
		Severe	0.62	0.077
Any control	Hypertension	All	0.86	0.002
		Moderate	0.83	0.006
Any control	Ischaemic Heart Disease	Severe	1.6	0.029
		≥Severe	1.4	0.063
Any control	Myocardial Infarction	Severe	1.9	0.073
Any control	Shock-associated circulatory or cardiac conditions	Moderate**	0 DEN 3 PLA	0.094

*Relative Risk estimates are reported, unless otherwise noted.
**Relative risk cannot be computed due to entries of zero, therefore the number of subjects with the event are reported instead of RR.
All = All severity levels pooled; DEN = Denosumab; LT = Life-threatening; PLA = Placebo; PC = Placebo-controlled; PTs = Pivotal trials

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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

BLA Number(s):	125-320, 125-331, 125-332, 125-333
Drug Name:	PROLIA (denosumab) 60mg/Q6M subcutaneous
Requested Indication(s):	(1) Treatment of postmenopausal osteoporosis (2) Prevention of postmenopausal osteoporosis (3) Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer (4) Treatment and prevention of bone loss associated with hormone ablation therapy with prostate cancer
Applicant:	Amgen, Inc.
Stamp Date:	12/19/08
PDUFA Date:	10/19/09
Review completed on:	8/10/09
Review Priority:	Standard
Biometrics Division:	Quantitative Safety and Pharmacopidemiology Group
Statistical Reviewer:	Anita Abraham, DrPH
Secondary Reviewers:	Paul Schuette, PhD; C. George Rochester, PhD, RAC
Medical Division(s):	Division of Reproductive and Urological Products (DRUP) and Division of Biologic Oncology Products (DBOP)
Clinical Team(s):	Suzanne Demko, PA-C (DBOP), Theresa Kehoe, MD (DRUP), Vaishali Popat, MD, MPH (DRUP) Adrienne Rothstein, PhD (DRUP)
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Keywords: Osteoporosis, Bone Loss, Osteonecrosis of the Jaw, Delayed Fracture Healing, Malignancies

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1 EXECUTIVE SUMMARY

This document represents a statistical safety review of Amgen Inc.'s application for the approval of their fully monoclonal antibody, denosumab (PROLIA) (BLA#'s: 125-320, 125-331, 125-332, 125-333), for use in the prevention and treatment of osteoporosis in post-menopausal (PMO) women, and for use in the prevention and treatment of bone loss in patients undergoing hormone ablation therapy (HALT), administered at the proposed dose of 60mg injected subcutaneously every 6 months. This review is a safety review, evaluating denosumab's impact on three adverse events of interest: (1) Osteonecrosis of the Jaw (ONJ), (2) Delayed Fracture Healing, and (3) Incidence of New Primary Malignancies.

Denosumab is a fully monoclonal antibody that binds to and inhibits the action of receptor activator of nuclear factor κB (RANK) ligand. The RANK ligand is a type I membrane protein that is directly involved in the activation of osteoclasts upon ligand binding. This ligand has also been found on the surface of T cells and transcriptionally regulates the transcription necrosis factor (TNF). The inhibition of osteoclast function by this antibody is believed to reduce the level of bone loss experienced in patients with postmenopausal osteoporosis and those undergoing hormone ablation therapy. However, drugs used in similar indications, bisphosphonates, have also been associated with adverse events relating to this disruption in the bone creation/resorption cycle. Two of the adverse events of concern due to this disruption are osteonecrosis of the jaw and delayed fracture healing. Also, as this biologic is known to inhibit a regulator of TNF, adverse events relating to the immunogenic response are of concern. A specific adverse event of concern due to this mechanism is a potential increase in the incidence of malignancies. This review will consider the incidence of these three adverse events, primarily focusing on four pivotal Phase 3 clinical studies and additionally considering five other Phase 2 and Phase 3 studies where a control arm was present. The studies that focused on PMO women were pooled for further analysis.

1.1 Conclusions and Recommendations

There does not appear to be a difference in risk of osteonecrosis of the jaw or delayed fracture healing between denosumab and placebo groups. The results for new primary malignancies are not as consistent. However, as all three of these adverse events may take time to develop, continued monitoring is advised.

For ONJ, though there were concerns that the ONJ adjudication committee selected by the sponsor used a narrow criterion (using MedDRA v.11.0) when ascertaining ONJ cases and no cases were identified, a broadening of the criterion in this analysis resulted in no significant difference between the denosumab and placebo groups. There was a significant difference in the severity gradient between the alendronate subjects and the placebo subjects in trials employing active controls, with alendronate subjects experiencing more severe adverse events. However, the denosumab and placebo groups tended to have similar distributions of events in all the analyses.

For delayed fracture healing, the nonclinical overview showed that the sponsor found issues in bony callus formation among genetically modified mice that were monitored after being subjected to closed femoral fractures. The bony callus appeared to be larger and had a different consistency compared to those in the placebo group. This issue may affect the mobility of the bone, but is not expected to affect its strength. Only the four pivotal trials (Study #'s 20030216, 20040132, 20040135 and 20040138) contained data that specifically considered fracture healing outcomes. Moreover, as the outcome of delayed fracture healing is one that can take up to five years to be fully determined, further long-term follow-up of this adverse event would be worthwhile. From the data provided, there appears to be a balanced distribution between groups for fracture healing outcomes.

For new primary maligancies, there generally appears to be a balanced distribution of adverse events with one notable exception. The only study that had significantly more events in the denosumab group was Study 20040138 whose population consisted of men with non-metastatic prostate cancer undergoing androgen deprivation therapy. The high level group term that drives the difference between groups in this study is "Metastases" and further investigation of this term shows that the increased number of adverse events in the denosumab group is mainly due to the preferred term "Metastases to bone". In all the other populations studied by the sponsor, this metastases issue does not arise and the difference between treatment and control groups is minimal. Again, as the appearance of new primary malignancies tends to be a long-term outcome, continued monitoring of this adverse event would be of use.

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1.2 Brief Overview of Clinical Studies

This review evaluates data provided by nine (9) studies. The studies that were chosen for the review included all blinded studies that contained a control arm (either alendronate and/or placebo). Four of these studies are considered to be pivotal by the sponsor (20030216, 20040132, 20040135 and 20040138). Of these nine trials, three were Phase 2 trials and six were Phase 3 trials. Seven of these studies (20010223, 20030216, 20040132, 20050141, 20050179, 20050234) evaluated the biologic in PMO women. Study 20040135 evaluated the biologic in a Phase 3 trial in women with breast cancer (HALT), and Study 20040138 evaluated the biologic in men with prostate cancer (HALT).

1.3 Statistical Issues and Findings

To quantitatively evaluate the three specific adverse events of interest in this review, categorical data analysis methods were used. First, after identifying subjects in the safety analysis set experiencing the adverse events of interest, differences between arms were quantified by risk differences and relative risks to determine if there was a significant difference between groups. If there were more than two groups in a study, Fisher's exact test was performed to determine if there was an overall difference between treatment arms, and this difference was then quantified using pairwise comparisons between the control arm and the arm of interest. A pooled analysis was performed, in which all subjects of the PMO studies of interest were pooled. In this analysis, for the denosumab arm, only subjects who received the 60mg Q6M dose of the investigational product were evaluated, as this is the dosage that is being evaluated for approval. In evaluating the pooled analyses, a Cochran-Mantel-Haenszel (CMH) chi-square was used to evaluate the difference between groups for severity gradients. Exact methods were employed when warranted by the number of events (fewer than 5 events in a category).

When evaluating ONJ related adverse events, there did not appear to be a significant difference between denosumab and the comparison arm in any of the studies. For the fracture healing outcome, fracture healing was evaluated only in the pivotal trials, so these four studies were evaluated separately. Only study 20030216 contained more than one subject per arm with a fracture healing complication, and while this may be due to a lack of events, the increased number in 20030216 may also be due to extra diligence as a radius healing substudy was a part of the protocol. For the evaluation of new primary malignancies, the only study that contained a statistically significant safety signal was study 20040138, as discussed previously. In all other studies evaluated, no major signals were observed.

2 INTRODUCTION

2.1 Overview

Denosumab is a fully monoclonal antibody that binds to and inhibits the action of receptor activator of nuclear factor κB (RANK) ligand. The RANK ligand is a type I membrane protein that is directly involved in the activation of osteoclasts upon ligand binding. This ligand has also been found on the surface of T cells and transcriptionally regulates the transcription necrosis factor (TNF). The inhibition of osteoclast function by this antibody is believed to reduce the level of bone loss experienced in patients with postmenopausal osteoporosis and those undergoing hormone ablation therapy. However, drugs used in similar indications, bisphosphonates, have also been associated with adverse events relating to this disruption in the bone creation/resorption cycle. Two of the adverse events of concern due to this disruption are osteonecrosis of the jaw and delayed fracture healing. Also, as this biologic is known to inhibit a regulator of TNF, adverse events relating to the immunogenic response are of concern. A specific adverse event of concern due to this mechanism is a potential increase in the incidence of malignancies. This review will consider the incidence of these three adverse events, primarily focusing on nine Phase 2 and Phase 3 studies and on a pooled analysis of the PMO trials.

2.2 Data Sources

Data from nine studies were used in the review. These studies were selected because they were double-blinded and had randomized treatment arms. In addition to these nine studies, other materials reviewed

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included the nonclinical study report and the summary review of Phase 1 and Phase 2 studies provided by the sponosor. Clinical study reports for each of the studies reviewed were also considered. For assessment of the "Delayed Fracture Healing" adverse event, fracture healing outcomes included in the fracture healing analysis dataset (AAEFX) were considered, when provided. (Note: While study 20010223 did include an AAEFX dataset, this dataset did not include any fracture healing outcome data).

Table 1 lists the studies included in this review and provides a brief description of the study population and length of study in each trial:

Table 1: List of all studies included in analysis

Study	Phase	Treatment Period	Follow-up Period	Approximate # of Subjects per Arm	Study Population
20010223	Phase 2	24 months	24 months	40	PMO Women
20030216*	Phase 3	36 months	——	3900	PMO Women
20040132*	Phase 3	24 months	24 months	165	PMO Women
20040135*	Phase 3	24 months	24 months	130	Women with Breast Cancer (HALT)
20040138*	Phase 3	36 months	24 months	730	Men with Prostate Cancer (HALT)
20050141	Phase 3	12 months	——	600	PMO Women
20050172	Phase 2	12 months	——	50	Japanese PMO Women
20050179	Phase 2	12 months	——	80	PMO Women
20050234	Phase 3	12 months	——	250	PMO Women

* trials considered pivotal by sponsor

As can be observed in Table 1, seven of the studies focused on PMO women and two studies considered subjects on hormone ablation therapy. Two of the Phase 2 studies included, 20010223 and 20050172, were dose-ranging studies that considered the osteoporosis indication. The third Phase 2 study, 20050179, compared denosumab to placebo and alendronate, where the primary objective was to assess the effect of denosumab on the cortical thickness of the distal radius at 12 months. Including study 20050179, three trials included an alendronate comparison arm: Studies 20010223, 20050179 and 20050234. Table 29, in the Appendix, summarizes the datasets considered in this analysis and where they are found in the CDER Electronic Document Room (EDR)

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3 OSTEONECROSIS OF THE JAW (ONJ)

3.1 Background

Osteonecrosis of the jaw (ONJ) is a rare condition that is usually identified by its unique clinical presentation of exposed bone in the oral cavity. Signs and symptoms of ONJ include localized pain, soft-tissue swelling and inflammation, loosening of previously stable teeth, drainage and exposed bone. The pathogenesis of this condition is not well understood, and it is likely that ONJ is a clinical entity with many possible etiologies. Recently, a link has been drawn between bisphosphonates and ONJ (Ruggiero et al. 2004). As both denosumab and bisphosphonates inhibit the action of osteoclasts, ONJ is an adverse event of interest for this biologic. Amgen assembled an external panel of independent experts to ensure that all potential cases of ONJ were reviewed and adjudicated based on standard definition criteria and events meeting these criteria were submitted for review by the independent ONJ Adjudication Committee, which was blinded to treatment assignments. There were no positively adjudicated cases of ONJ in any the studies under consideration, so this analysis will focus on possible symptoms of ONJ.

3.2 Analysis

To analyze the adverse event of ONJ, all the MedDRA version 11.0 preferred terms listed in the adverse events (AAE) dataset of the integrated summary of safety (ISS) were considered. The preferred terms that were determined to be possible signs, symptoms or precursors to ONJ were included in a list. After making this list, it was compared to the list of preferred terms used by the adjudication committee in selecting subjects to evaluate for this adverse event. The adjudication committee used 33 MedDRA preferred terms to select their subjects. An additional 35 preferred terms, which were considered to be related to ONJ, were included in the current evaluation. All of these terms and their occurence rates in the treatment groups compared to the control groups of the safety analysis datasets were tabulated and large differences in incidence.were considered; risk ratios, risk differences and related confidence intervals were calculated. If there were more than two groups in a study, Fisher's exact test was performed to determine if there was an overall difference between treatment arms, and this difference was then quantified using pairwise comparisons between the control arm and the arm of interest. Additional investigations include comparing serious vs. non-serious events and comparing the severity gradient for treatment in this class of events. A pooled analysis was performed, in which all subjects of the PMO studies analyzed were pooled. In this analysis, for the denosumab arm, only subjects who received the 60mg Q6M dose of the investigational product were evaluated, as this is the dosage that is being evaluated for approval. In evaluating the pooled analyses, a Cochran-Mantel-Haenszel chi-square was used to evaluate the difference between groups for severity gradients. Exact methods were employed when warranted by the number of events (fewer than 5 events in a category). Table 2 lists the terms used by the sponsor's ONJ adjudication committee and the additional terms used in this review:

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Table 2: MedDRA v.11.0 Terms used to identify ONJ-related Adverse Events

Terms used by ONJ Adjudication Committee:		Additional terms used in search:	
Abscess jaw	Oral cavity fistula	Gingival bleeding	Oral discomfort
Abscess oral	Oral surgery	Gingival cyst	Oral disorder
Alveolar osteitis	Oroantral fistula	Gingival disorder	Oral infection
Bone debridement	Osteitis	Gingival erythema	Oral pain
Bone erosion	Osteomyelitis	Gingival hypertrophy	Periodontal disease
Bone fistula	Osteomyelitis chronic	Gingival infection	Periodontitis
Bone infarction	Osteomyelitis drainage	Gingival operation	Tooth abscess
Dental fistula	Osteonecrosis	Gingival pain	Tooth avulsion
Dental necrosis	Pain in jaw	Gingival recession	Tooth deposit
Gingival abscess	Periodontal destruction	Gingival swelling	Tooth disorder
Gingival erosion	Periodontal infection	Gingivitis	Tooth extraction
Gingival ulceration	Periodontal operation	Jaw cyst	Tooth fracture
Jaw lesion excision	Primary sequestrum	Jaw disorder	Tooth infection
Jaw operation	Secondary sequestrum	Jaw fracture	Tooth injury
Loose tooth	Sequestrectomy	Mouth cyst	Tooth loss
Maxillofacial operation	Tertiary sequestrum	Mouth ulceration	Tooth repair
Necrosis		Oral bacterial infection	Toothache

3.2.1 Pre-clinical Findings

No pre-clinical studies were conducted to specifically consider this adverse event.

3.2.2 Phase 1 and 2 Trials

One case of periodontal infection was found in the phase 1 study 20030164. Additionally, one case of ONJ was reported in the Phase 2 study 20050134, which was not included in the nine studies under review, since it did not contain a control arm. Tabulations of relevant adverse events from trials where data was analyzed can be found in the Appendix, Section 8.1.1, Tables 30-33. A listing of all adverse events found in the Phase 2 studies and a quantification of relative risks and risk differences are provided below. Additionally, if the study contained more than 2 arms, a Fisher exact test was conducted to determine if there was a difference between any of the groups, and relative risks and risk differences were calculated using the placebo group as the reference.

Table 3 lists the number of subjects with adverse events and total subjects in the studies by arm, and Table 4 lists the results from the data analysis.

Table 3: Summary Table of Adverse Events for Phase 1 and 2 Trials for ONJ

Study	Subjects with Adverse Event			Total Subjects		
Number	Denosumab	Placebo	Alendronate	Denosumab	Placebo	Alendronate
20010223	34	6	6	314	46	46
20050172	14	2	—	158	54	—
20050179	3	10	2	83	83	81

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Table 4: Summary Table of Statistics for Phase 1 and 2 Trials for ONJ

Study		Fisher statistic	p-value
20010223	Difference between arms	0.5985	0.7414
20050179	Difference between arms	6.882	0.0314

Study	Placebo comparison group	Risk Diff.	95% CI	Rel. Risk	95% CI	p-value
20010223	Denosumab	-0.0222	(-0.152, 0.058)	0.8301	(0.391, 1.88)	0.6552
	Alendronate	0	(-0.146, 0.146)	1	(0.361, 2.77)	1
20050172*	Denosumab	0.0516	(-0.043, 0.115)	2.392	(0.626, 13.04)	0.2308
20050179*	Denosumab	-0.0843	(-0.180, -0.002)	0.3	(0.0651. 0.973)	0.0443
	Alendronate	-0.0958	(-0.190, -0.0177)	0.205	(0.0380, 0.808)	0.0191

*exact methods used

As can be observed from Table 4, there were no statistically significant differences in the number of adverse events in the treatment groups compared to placebo in any of trials. However, in Study 20050179, the placebo group had a significantly higher number of adverse events compared to the denosumab and alendronate groups.

3.2.3 Phase 3 Trials

All of the ONJ relevant adverse events in Phase 3 trials are tabulated below and differences between groups are quantified using relative risks and risk differences. A tabulation of all preferred terms used in the analysis are listed in the Appendix, Section 8.1.1, Tables 34-40.

Table 5 lists the number of subjects with adverse events and total subjects in the studies by arm, and Table 6 lists the risk differences and relative risks with their associated confidence intervals and p-values.

Table 5: Summary Table of Adverse Events for Phase 3 Trials for ONJ

Study	Subjects with Adverse Event			Total Subjects		
Number	Denosumab	Placebo	Alendronate	Denosumab	Placebo	Alendronate
20030216	158	155	—	3886	3876	—
20040132	20	16	—	164	165	—
20040135	3	1	—	129	120	—
20040138	19	24	—	731	725	—
20050141	30	—	25	593	—	586
20050234	6	—	11	253	—	249

Table 6: Summary Table of Statistics for Phase 3 Trials for ONJ

Study	Risk Diff.	95% CI	Rel. Risk	95% CI	p-value
20030216	0.00067	(-0.0081, 0.0095)	1.017	(0.8187, 1.263)	0.8809
20040132	0.025	(-0.438, 0.095)	1.258	(0.6825, 2.323)	0.468
20040135*	0.0149	(-0.0266, 0.0605)	2.791	(0.4092, 35.48)	0.5297
20040138	-0.0071	(-0.0254, 0.0107)	0.785	(0.4374, 1.409)	0.4229
20050141	0.0079	(-0.0166, 0.0328)	1.186	(0.7102, 1.981)	0.5187
20050234	-0.0205	(-0.0565, 0.0123)	0.537	(0.2084, 1.378)	0.2051

* exact methods used

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Table 6 indicates that there were no significant differences between groups for the number of adverse events in any of the trials.

3.2.4 Serious Adverse Events

Only five of the studies have any serious ONJ-related adverse events. Only studies 20030216 and 20040138 had any serious adverse events in the denosumab group. There did not appear to be a difference between groups in the number of serious adverse events in any of the studies. Tabulations of serious adverse events in all studies where there were SAEs are provided in the Appendix, Section 8.1.2, Tables 41-46.

3.2.5 Severity Gradient

There does not appear to be a difference between groups for the severity gradient of ONJ-related adverse events in any of the trials. Full tabulations of the severity gradient in all studies are provided in the Appendix, Section 8.1.3, Tables 47-56.

3.2.6 PMO Pooled Analysis

For the pooled analysis, all studies targeting post-menopausal women who were randomized to denosumab were pooled. This led to the pooling of 7 trials: 20010223, 20030216, 20040132 (36-month), 20050141, 20050172, 20050179, 20050234. For this analysis differences between treatments (alendronate, Denosumab 60mg Q6M and Placebo) in terms of PTs, HLGTs, Serious Events, Severity Gradient and Discontinuation of Drug for subjects experiencing ONJ-related adverse events.

Tables 7 and 8 list the number of subjects with ONJ-related preferred terms in order of most common occurrence for all subjects in the pooled studies.

Table 7: PMO Pooled Analysis - ONJ Preferred Terms (Part 1)

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Tooth infection	34 (0.67%)	44 (1.04%)	7 (0.73%)
Toothache	34 (0.67%)	35 (0.83%)	8 (0.83%)
Periodontitis	27 (0.53%)	19 (0.45%)	5 (0.52%)
Gingivitis	18 (0.35%)	11 (0.26%)	3 (0.31%)
Tooth fracture	15 (0.30%)	9 (0.21%)	7 (0.73%)
Pain in jaw	11 (0.22%)	6 (0.14%)	5 (0.52%)
Gingival infection	8 (0.16%)	11 (0.26%)	2 (0.21%)
Tooth disorder	8 (0.16%)	7 (0.17%)	3 (0.31%)
Mouth ulceration	9 (0.18%)	6 (0.14%)	2 (0.21%)
Gingival pain	7 (0.14%)	1 (0.02%)	3 (0.31%)
Tooth extraction	6 (0.12%)	5 (0.12%)	0 (0.00%)
Osteitis	5 (0.10%)	6 (0.14%)	0 (0.00%)
Gingival abscess	4 (0.08%)	4 (0.09%)	1 (0.10%)
Periodontal disease	4 (0.08%)	3 (0.07%)	0 (0.00%)
Oral pain	3 (0.06%)	3 (0.07%)	0 (0.00%)
Osteonecrosis	5 (0.10%)	1 (0.02%)	0 (0.00%)
Tooth injury	5 (0.10%)	1 (0.02%)	0 (0.00%)
Oral infection	3 (0.06%)	2 (0.05%)	0 (0.00%)
Gingival bleeding	4 (0.08%)	1 (0.02%)	0 (0.00%)
Loose tooth	0 (0.00%)	3 (0.07%)	2 (0.21%)

continuing

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Table 8: PMO Pooled Analysis - ONJ Preferred Terms (Part 2)

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Gingival swelling	0 (0.00%)	4 (0.09%)	0 (0.00%)
Abscess oral	1 (0.02%)	2 (0.05%)	0 (0.00%)
Gingival ulceration	0 (0.00%)	2 (0.05%)	0 (0.00%)
Osteomyelitis	2 (0.04%)	1 (0.02%)	0 (0.00%)
Periodontal infection	2 (0.04%)	0 (0.00%)	1 (0.10%)
Dental necrosis	1 (0.02%)	1 (0.02%)	0 (0.00%)
Gingival cyst	1 (0.02%)	1 (0.02%)	0 (0.00%)
Gingival disorder	1 (0.02%)	0 (0.00%)	1 (0.10%)
Oral bacterial infection	1 (0.02%)	1 (0.02%)	0 (0.00%)
Tooth loss	1 (0.02%)	0 (0.00%)	1 (0.10%)
Alveolar osteitis	0 (0.00%)	1 (0.02%)	0 (0.00%)
Bone erosion	0 (0.00%)	1 (0.02%)	0 (0.00%)
Bone fistula	0 (0.00%)	1 (0.02%)	0 (0.00%)
Bone infarction	0 (0.00%)	1 (0.02%)	0 (0.00%)
Gingival hypertrophy	1 (0.02%)	0 (0.00%)	0 (0.00%)
Gingival operation	0 (0.00%)	1 (0.02%)	0 (0.00%)
Jaw cyst	1 (0.02%)	0 (0.00%)	0 (0.00%)
Jaw disorder	1 (0.02%)	0 (0.00%)	0 (0.00%)
Mouth cyst	1 (0.02%)	0 (0.00%)	0 (0.00%)
Oral cavity fistula	1 (0.02%)	0 (0.00%)	0 (0.00%)
Oral disorder	0 (0.00%)	1 (0.02%)	0 (0.00%)
Tooth avulsion	0 (0.00%)	1 (0.02%)	0 (0.00%)
Tooth deposit	0 (0.00%)	1 (0.02%)	0 (0.00%)
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)

Table 9 lists the number of subjects with ONJ-related adverse events listed by high level group term.

Table 9: PMO Pooled Analysis - ONJ High Level Group Terms

High Level Group Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Dental and gingival conditions	100 (1.97%)	81 (1.91%)	24 (2.49%)
Infections - pathogen unspecified	51 (1.01%)	63 (1.49%)	8 (0.83%)
Bone disorder (excl. congenital and fractures)	23 (0.45%)	16 (0.38%)	5 (0.52%)
Injuries NEC	20 (0.39%)	11 (0.26%)	7 (0.73%)
Oral soft tissue conditions	12 (0.24%)	14 (0.33%)	2 (0.21%)
Head and neck therapeutic procedures	6 (0.12%)	6 (0.14%)	0 (0.00%)
Infections - pathogen class unspecified	3 (0.06%)	1 (0.02%)	3 (0.31%)
Bacterial infectious disorders	1 (0.02%)	1 (0.02%)	0 (0.00%)
Benign neoplasms gastrointestinal	1 (0.02%)	0 (0.00%)	0 (0.00%)
Gastrointestinal conditions NEC	1 (0.02%)	0 (0.00%)	0 (0.00%)
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)

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Table 10 lists the risk difference, relative risk and associated confidence intervals and statistics for the pooled analysis to evaluate a difference between groups.

Table 10: PMO Pooled Analysis - Overall ONJ Relative Risk and Risk Difference

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	0.000045	—	0.00192	0.1211	0.9444
RD 95% CI	(-0.0082, 0.0080)		(-0.01089, 0.0176)		
Relative Risk	0.9989	—	1.047		
RR 95% CI	(0.8195, 1.218)		(0.7505, 1.457)		

Table 11 lists the occurence of SAEs in the pooled analysis, and Table 12 evaluates the difference between treatment groups based on the frequency of SAEs by means of relative risk, risk difference and the Fisher exact test statistic.

Table 11: PMO Pooled Analysis - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
No SAE	204 (4.02%)	170 (4.02%)	39 (4.05%)
SAE present	3 (0.06%)	2 (0.05%)	3 (0.31%)
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)

Table 12: PMO Pooled Analysis - ONJ SAE Relative Risk and Risk Difference

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	0.00012	—	0.0026	5.45	0.0648
RD 95% CI	(-0.0012, 0.0013)		(.000353, 0.00867)		
Relative Risk	1.251	—	6.59		
RR 95% CI	(0.2502, 6.255)		(1.318, 32.92)		

Table 13 lists the ONJ associated adverse events in the pooled analysis by severity and evaluates the difference between groups using a Cochran-Mantel-Haenszel chi-square statistic.

Table 13: PMO Pooled Analysis - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	CMH Chi-square
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)	3.178
Mild	121 (2.38%)	94 (2.22%)	22 (2.28%)	
Moderate	91 (1.79%)	77 (1.82%)	18 (1.87%)	
Severe	4 (0.08%)	11 (0.26%)	4 (0.42%)	p-value
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)	0.2042

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Table 14 lists the subjects where the drug was discontinued among the pooled studies.

Table 14: PMO Pooled Analysis - ONJ Discontinuation of Drug

Drug Discontinued	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Drug discontinued	0 (0.00%)	0 (0.00%)	1 (0.10%)
Subjects with AE	206 (4.06%)	172 (4.06%)	41 (4.25%)

While there is no difference between any of the groups for ONJ-related adverse events (Table 10), there is a significant difference between the alendronate and placebo groups for serious adverse events (Table 12). There are significantly more serious adverse events for ONJ-related AEs in the alendronate group compared to the placebo group. This difference is not significant in the severity gradient or in the drug discontination tabulations (Tables 13 and 14). There are no differences in the number of events in any of the tables between the denosumab group and the placebo group.

3.3 Conclusions

From this analysis, there does not appear to be an increased risk of ONJ-related events in the denosumab group. There were some issues found with the sponsor's ONJ adjudication process, namely that the criterion provided by the sponsor for this adverse event may have been too narrow. However, using a larger number of ONJ-related dictionary-derived terms (or preferred terms, PTs) does not result in an imbalance between the denosumab and placebo groups in any of the trials. It could be argued that the larger list of adverse events used in this analysis may be too broad, but even considering events at the PT level, there does not appear to be a large difference between groups, and therefore it appears that denosumab does not increase the risk of ONJ-related adverse events.

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4 DELAYED FRACTURE HEALING

4.1 Background

Denosumab's inhibition of the function of osteoclasts in bone resorption leads to the issue of whether fracture healing would occur normally. Drugs that inhibit osteoclasts, bisphosphonates, were shown to inhibit fracture healing, and to cause a delay in the formation of a bony callus, which in turn delayed the healing of the fracture. The only human studies that took account of fracture healing outcomes were the four "pivotal" trials. All four of these trials included a separate dataset that accounted for patients with non-vertebral fractures. None of the other studies have any accounting of these outcomes.

4.2 Analysis

4.2.1 Methodology

Since fracture healing was only evaluated in the four pivotal trials, the other trials could not be evaluated for this outcome. All fracture occurences in the other trials were tabulated and are present in the appendix. In the pivotal Phase 3 trials, the fracture healing outcomes were tabulated. Because only Study 20030216 had more than one fracture healing event per group, it was the only study where risk ratios, risk differences and related confidence intervals were calculated for all fracture healing complications. Also, for all tabulations of fractures, only non-vertebral fractures were considered, as they are the adverse events of primary concern when dealing with delayed fracture healing issues. Only non-vertebral fractures were evaluated by the sponsor in the fracture healing datasets of the pivotal trials.

4.2.2 Pre-clinical Findings

In Study R2006458, performed by the sponsor, the effects of denosumab on fracture repair were assessed with cohorts of huRANKL knock-in mice that were treated for up to 6 weeks with either denosumab or alendronate beginning 2 days after being subjected to a closed femoral fracture. Fractures were evaluated 21 and 42 days post-fracture. Fractured bones from both denosumab and alendronate-treated mice had greater torsional stiffness and/or maximum torque relative to fractured bones from vehicle controls at both time points. Micro-computerized tomography (microCT) analysis on days 21 and 42 indicated that fracture calluses from denosumab-treated mice had significantly greater bone mineral content, bone area and bone volume. Overall callus size on day 42 was significantly greater in denosumab-treated mice versus control, this may be related to a greater level of unabsorbed cartilage, which was also observed with alendronate treatment.

Figure 1 shows the comparative microCT views of the fracture callus. (Amgen Nonclinical Overview p.11)

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Figure 1. Representative MicroCT Images of the Fracture Site in huRANKL Knock-In Mice Treated with Either Denosumab (AMG) or Alendronate (ALN)

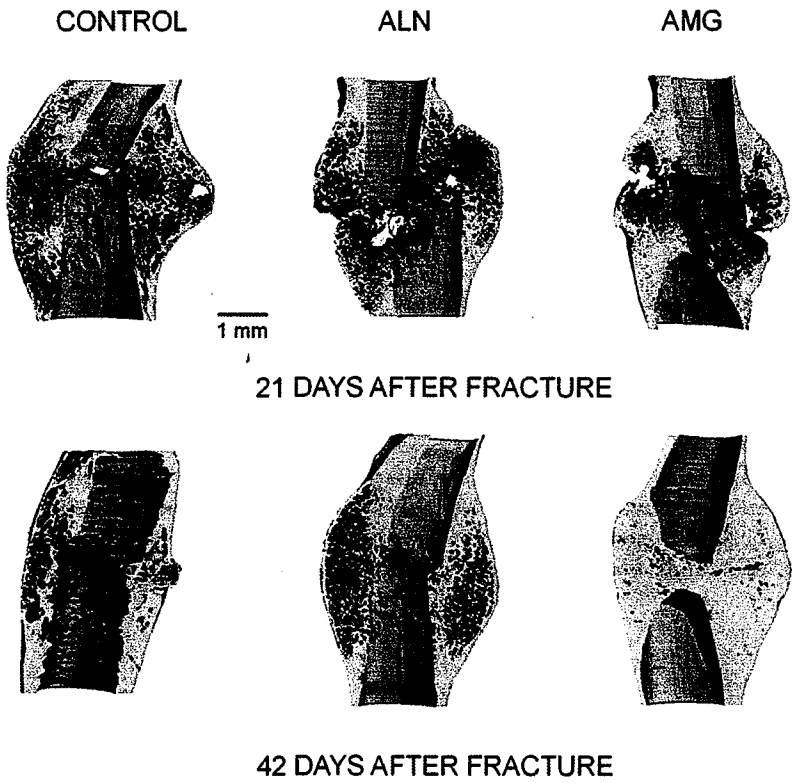

Figure 1: Amgen pre-clinical MicroCT findings comparing fracture healing outcomes in Control, Alendronate and Denosumab treated knock-in mice

Bone strength did not appear to be affected by the increased size of the callus, and the mechanical integrity of the fracture site was not decreased, however this large callus may pose an issue in patients that have fractures.

4.2.3 Phase 1 and 2 Trials

There were no Phase 1 or 2 studies that reported any abnormalities for fracture healing. However, since it does not appear that any evaluation of fracture healing outcomes were performed in the phase 1 and 2 trials, it may be that this is due to a lack of information. Considering the incidence rates of fractures in the Phase 2 studies evaluated, it appears that a maximum of 3% of all subjects experienced fractures during these studies, with foot and hand fractures being the most common. Tabulations of all fractures that occurred in the Phase 2 trials studied are listed in the Appendix, Section 8.2.1, Tables 57-60.

4.2.4 Phase 3 Trials

Tabulations of all fractures that occurred in the Phase 3 trials are listed in the Appendix, Section 8.2.1, Tables 61-66. The only Phase 3 studies that evaluated fracture healing outcomes were the pivotal trials. Of the four pivotal trials, the only study with significant data on fracture healing outcomes (more than 1 subject with a complication per group) was Study 20030216 which had a substudy that was focused on the

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healing of distal radius fractures. The tables of all fracture healing outcomes in the four pivotal trials are listed in the Appendix, Section 8.2.2, Tables 67-70.

Table 15 displays the relative risks and risk differences evaluated from Study 20030216.

Table 15: Study 20030216- Relative Risks and Risk Differences for Fracture Healing Complications

Complication	RR	95% RR CI	RD	95% RD CI
Any Complication	0.9924	(0.5548, 1.772)	-0.00048	(-0.0378, 0.0387)
Delayed Heal	1.201	(0.2127, 6.782)	0.0011	(-0.014, 0.0188)
Malunion	1.201	(0.2787, 5.176)	0.00166	(-0.015, 0.0213)
Chronic Pain	0.7645	(0.3089, 1.886)	-0.0071	(-0.033, 0.020)
Other	1.716	(0.6832, 4.315)	0.0138	(-0.011, 0.0425)

As can be observed from this table, none of the fracture healing complications are significantly different between groups in this study. However it should be noted that this study followed the subjects for only 36 months and fracture healing outcomes can take up to 5 years to develop.

4.3 Conclusions

None of the data provided by the studies with human subjects appears to show a difference between groups for fracture healing outcomes. However, the nonclinical findings of callus formation issues in mice do suggest that there may be some cause of concern. While the data in Study 20030216 shows an equal distribution between groups for fracture healing complications, longer-term studies conducted by the sponsor will be of interest.

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5 NEW PRIMARY MALIGNANCIES

5.1 Background

Tumor necrosis factor (TNF) plays an important role in host defense and tumor growth control. It is believed that anti-TNF antibody therapies may increase the risk of serious infections and malignancies. A meta-analysis in JAMA (Bongartz et al 2007) showed a statisticially significant increase in odds for malignancies in anti-TNF treated patients vs. placebo. Malignancies were significantly more common in patients treated with high-doses of anti-TNF antibodies.

5.2 Analysis

5.2.1 Methodology

To evaluate the occurence of new primary malignancies, the neoplasms system organ class (SOC) was the primary consideration. All adverse events in the neoplasm SOC that did not include the term "Benign" at the preferred term level or the high level group term level were tabulated, by high-level group term. The list of all preferred terms that appeared in the data using this criteria are tabulated in the appendix. All of these terms and their occurence rates in the treatment groups compared to the control groups of the safety analysis datasets were tabulated and large differences in incidence.were considered; risk ratios, risk differences and related confidence intervals were calculated. If there were more than two groups in a study, Fisher's exact test was performed to determine if there was an overall difference between treatment arms, and this difference was then quantified using pairwise comparisons between the control arm and the arm of interest. Additional investigations include comparing serious vs. non-serious events and comparing the severity gradient for treatment in this class of events. A pooled analysis was performed, in which all subjects of the PMO studies of interest were pooled. In this analysis, for the denosumab arm, only subjects who received the 60mg Q6M dose of the investigational product were evaluated, as this is the dosage that is being evaluated for approval. In evaluating the pooled analyses, a Cochran-Mantel-Haenszel chi-square was used to evaluate the difference between groups for severity gradients. Exact methods were employed when warranted by the number of events (fewer than 5 events in a category).

5.2.2 Pre-clinical Findings

No preclinical studies were conducted that considered this adverse event.

5.2.3 Phase 1 and 2 Studies

No Phase 1 and 2 malignancies were listed in the synopses of individual studies provided by the sponsor. The following tables outline the total number of events that occurred in the studies that were evaluated and evaluates the overall difference between groups in the studies with more than 2 arms (20010223 and 20050179) and quantifies the difference between groups using risk difference and relative risk. Tabulations of all events are provided in the Appendix, Section 8.3.1, Tables 71-74.

Table 16 lists the number of subjects with new primary malignancies and total subjects in the studies by arm, and Table 17 lists the results from the data analysis.

Table 16: Summary Table of Adverse Events for Phase 1 and 2 Trials for New Primary Malignancies

Study	Subjects with Adverse Event			Total Subjects		
Number	Denosumab	Placebo	Alendronate	Denosumab	Placebo	Alendronate
20010223	20	3	5	314	46	46
20050172	1	0	—	158	54	—
20050179	0	0	3	83	83	81

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Table 17: Summary Table of Statistics for Phase 1 and 2 Trials for New Primary Malignancies

Study		Fisher statistic	p-value
20010223	Difference between arms	1.5	0.5729
20050179	Difference between arms	4.188	0.0344

Study	Placebo comparison group	Risk Diff.	95% CI	Rel. Risk	95% CI	p-value
20010223*	Denosumab	-0.0015	(-0.113, 0.053)	0.9766	(0.330, 3.20)	0.9878
	Alendronate	0.0435	(-0.086, 0.185)	1.667	(0.4584, 7.58)	0.5309
20050172*	Denosumab	0.0063	(-0.063, 0.035)	undefined		0.7277
20050179*	Denosumab	0		1		1
	Alendronate	0.037	(-0.0878, 0.105)	undefined		0.0803

*exact methods used

Table 17 indicates that there is no significant difference for new primary malignancies between the denosumab group and the placebo group in any of the studies. In study 20050179, there is a significant difference between the alendronate group and the two other arms due to 3 subjects who experienced new primary malignancies in this group compared to none in the other two arms.

5.2.4 Phase 3 Trials

All of the Phase 3 trials with relevant events are tabulated below and differences between groups are quantified using relative risk and risk difference measures. A tabulation of all relevant adverse events are provided in the Appendix, Section 8.3.1, Tables 75-81.

Table 18: Summary Table of Adverse Events for Phase 3 Trials for New Primary Malignancies

Study	Subjects with Adverse Event			Total Subjects		
Number	Denosumab	Placebo	Alendronate	Denosumab	Placebo	Alendronate
20030216	187	167	——	3886	3876	——
20040132	7	4	——	164	165	——
20040135	9	8	——	129	120	——
20040138	105	79	——	731	725	——
20050141	7	——	8	593	——	586
20050234	3	——	3	253	——	249

Table 19: Summary Table of Statistics for Phase 3 Trials for New Primary Malignancies

Study	Risk Diff.	95% CI	Rel. Risk	95% CI	p-value
20030216	0.005	(-0.0043, 0.0144)	1.117	(0.9112, 1.369)	0.2877
20040132*	0.018	(-0.0243, 0.0655)	1.761	(0.5523, 7.392)	0.5294
20040135	0.0031	(-0.065, 0.0697)	1.047	(0.4295, 2.556)	0.9228
20040138	0.0347	(0.00054, 0.069)	1.318	(1.004, 1.732)	0.0465
20050141	-0.0018	(-0.0163, 0.0122)	0.8647	(0.3278, 2.28)	0.7772
20050234*	-0.00019	(-0.0248, 0.0242)	0.9842	(0.1841, 5.263)	1

*exact methods used

From Tables 18 and 19, it is observed that the only study with a significantly higher risk difference and relative risk of new malignancies in the denosumab arm is in Study 20040138. Upon further examination of

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this study, (Table 78 in the Appendix) the largest difference between groups is amongst those with the High Level Group Term (HLGT) "Metastases". To explore this issue further, we consider the Preferred Terms for subjects with this HLGT in Table 20:

Table 20: Study 20040138 - New Primary Malignancies - Preferred Terms where HLGT = "Metastases"

HLGT= Metastases	Denosumab	Placebo
Dictionary-Derived Term	60mg Q6M	
Subjects in Arm	731 (100.00%)	725 (100.00%)
Metastases to bone	34 (4.65%)	25 (3.53%)
Metastases to liver	4 (0.55%)	3 (0.41%)
Metastases to spine	4 (0.55%)	1 (0.14%)
Metastases to lymph nodes	1 (0.14%)	2 (0.27%)
Metastasis	3 (0.47%)	0 (0.00%)
Metastases to pleura	1 (0.14%)	1 (0.14%)
Metastases to lung	1 (0.14%)	0 (0.00%)
Metastases to abdominal cavity	1 (0.14%)	0 (0.00%)
Subjects with HLGT Metastases	48 (6.57%)	31 (4.28%)

The difference in subjects with this HLGT appears to be driven by a difference in patients experiencing bone metastasis when undergoing treatment with denosumab. However, this difference is not statistically significant ($p = 0.2445$).

5.2.5 Serious Adverse Events

Tabulations of serious adverse events for each study appear in the Appendix, Section 8.3.2, Tables 81-90. There does not appear to be a significant difference between groups with regards to serious adverse events in any of the studies, except for Study 20010223 (Tables 81, 82). In this study, the 4 subjects in the high dose denosumab group (100mg Q6M) who experienced an incidence of a new primary malignancy, all experienced serious adverse events Further investigation finds that 3 of these 4 subjects died due to cancer. When comparing this group to the placebo group, the risk difference is not statistically significant at the 0.05 level (p-value=0.0633), as shown in Table 104 in Appendix 5, Section 8.5. While the incidence of fatal events in this groups appears to be higher than in the alendronate and placebo groups (which had 2 SAEs in each group), it is not possible to determine if this is due to chance. Since the higher dose denosumab group in this same study (210mg Q6M) had fewer subjects with SAEs, 2, and did not have fatalities due to malignancies, it does not appear to be a dose-response relationship. The sponsor has stated that the three subjects that experienced fatalities all had issues that predisposed the patients to cancer (family history, previous neoplasm, smoking status) Differences in the number of SAEs between this group and the placebo, and between all denosumab groups and the placebo are not statistically significant.

5.2.6 Severity Gradient

Other than the fatal events described in the previous section that occured in Study 20010223, there does not appear to be a difference between groups with respect to a severity gradient. All studies appeared to have an equal distribution in terms of severity for the different treatment arms. All tabulations of the severity gradient are provided in the Appendix, Section 8.3.3, Tables 91-100.

5.2.7 PMO Pooled Analysis

For the pooled analysis, all studies targeting post-menopausal women that were randomized on denosumab were pooled. This lead to the pooling of 7 trials: 20010223, 20030216, 20040132 (36-month), 20050141, 20050172, 20050179, 20050234. For this analysis, the reviewer evaluated the differences between treatments

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(alendronate, denosumab 60mg Q6M, and placebo) in terms of HLGTs, SOC, Serious Events, Severity Gradient and Discontinuation of Drug for subjects experiencing new primary malignancies.

Table 21 lists the occurrence of new primary malignancies by HLGT for each arm in descending order of total subject frequency.

Table 21: PMO Pooled Analysis - New Primary Malignancies - High Level Group Term

High Level Group Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
Skin neoplasms	51 (1.00%)	49 (1.16%)	5 (0.52%)
Breast neoplasms	38 (0.75%)	30 (0.71%)	5 (0.52%)
GI neoplasms	37 (0.73%)	25 (0.59%)	1 (0.10%)
Respiratory and mediastinal neoplasms	15 (0.30%)	25 (0.59%)	2 (0.21%)
Reproductive neoplasms female	21 (0.41%)	9 (0.21%)	3 (0.32%)
Metastases	10 (0.20%)	9 (0.21%)	0 (0.00%)
Miscellaneious and site unspecified neoplasms	9 (0.18%)	5 (0.12%)	1 (0.10%)
Renal and urinary tract neoplasms	6 (0.12%)	8 (0.19%)	0 (0.00%)
Nervous system neoplasms	6 (0.12%)	7 (0.16%)	0 (0.00%)
Plasma cell neoplasms	6 (0.12%)	4 (0.09%)	0 (0.00%)
Endocrine neoplasms	7 (0.14%)	2 (0.05%)	0 (0.00%)
Lymphomas non-Hodgkin's B-cell	2 (0.04%)	4 (0.09%)	0 (0.00%)
Hepatobiliary neoplasms	1 (0.02%)	3 (0.07%)	0 (0.00%)
Leukaemias	2 (0.04%)	2 (0.05%)	0 (0.00%)
Lymphomas NEC	2 (0.04%)	2 (0.05%)	0 (0.00%)
Haematopoietic neoplasms	3 (0.06%)	0 (0.00%)	0 (0.00%)
Lymphomas non-Hodgkin's unspecified histology	1 (0.02%)	1 (0.02%)	1 (0.10%)
Cancer-related morbidities	2 (0.04%)	0 (0.00%)	0 (0.00%)
Lymphomas non-Hodgkin's T-cell	2 (0.04%)	0 (0.00%)	0 (0.00%)
Skeletal neoplasms malignant and unspecified	1 (0.02%)	1 (0.02%)	0 (0.00%)
Mesotheliomas	1 (0.02%)	0 (0.00%)	0 (0.00%)
Ocular neoplasms	0 (0.00%)	1 (0.02%)	0 (0.00%)
Soft tissue sarcomas	0 (0.00%)	1 (0.02%)	0 (0.00%)
Subjects with AE	206 (4.06%)	175 (4.14%)	18 (1.87%)

Table 22 lists the occurrence of adverse events by system organ class for the pooled analysis.

Table 22: PMO Pooled Analysis - New Primary Malignancies - System Organ Class

System Organ Class (SOC)	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Neoplasms	206 (4.06%)	175 (4.14%)	18 (1.87%)
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)

Table 23 lists the risk difference, relative risk, and associated p-value for the difference between groups by SOC in the pooled analysis.

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Table 23: PMO Pooled Analysis - New Primary Malignancies - Relative Risks and Risk Differences of SOC compared to Placebo

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	-0.00075	—	-0.0227	13.41	0.001
RD 95% CI	(-0.0090, 0.0073)		(-0.0322, -0.0108)		
Relative risk	0.9818	—	0.4519		
RR 95% CI	(0.8063, 1.196)		(0.2805, 0.7256)		

Table 24 lists the number of subjects with serious adverse events in the pooled analysis.

Table 24: PMO Pooled Analysis - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
No SAE	54 (1.06%)	50 (1.18%)	6 (0.62%)
SAE present	160 (3.15%)	129 (3.05%)	12 (1.25%)
Subjects with AE	206 (4.06%)	175 (4.14%)	18 (1.87%)

Table 25 lists the risk difference, relative risk, and associated p-value for the difference between groups by SAE occurrence in the pooled analysis.

Table 25: PMO Pooled Analysis - New Primary Malignancies - Relative Risks and Risk Differences of SAE compared to Placebo

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	0.001	—	-0.018	12.56	0.002
RD 95% CI	(-0.006, 0.008)		(-0.026, -0.0078)		
Relative Risk	1.034	—	0.4087		
RR 95% CI	(0.8238, 1.299)		(0.2287, 0.7279)		

Table 26 lists the number of subjects by severity grade and the associated p-value in the pooled analysis.

Table 26: PMO Pooled Analysis - New Primary Malignancies - Severity Gradeient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	CMH Chi-square
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)	2.526
Mild	36 (0.71%)	27 (0.64%)	6 (0.62%)	
Moderate	58 (1.14%)	55 (1.30%)	3 (0.31%)	p-value
Severe	92 (1.81%)	64 (1.51%)	7 (0.62%)	0.2827
Life Threatening	14 (0.26%)	17 (0.40%)	2 (0.21%)	
Fatal	20 (0.39%)	26 (0.61%)	1 (0.10%)	
Subjects with AE	206 (4.06%)	175 (4.14%)	18 (1.87%)	

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Table 27 lists the number of subjects that discontinued their treatment in the pooled analysis.

Table 27: PMO Pooled Analysis - New Primary Malignancies - Discontinuation of Drug

Drug Discontinued	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects	5073 (100.00%)	4231 (100.00%)	963 (100.00%)
No	150 (2.96%)	137 (3.24%)	13 (1.65%)
Yes	63 (1.24%)	42 (0.99%)	5 (0.52%)
Subjects with AE	206 (4.06%)	175 (4.14%)	18 (1.87%)

Table 28 lists the risk difference, relative risk, and associated p-value for the difference between groups by drug discontinuation in the pooled analysis.

Table 28: PMO Pooled Analysis - New Primary Malignancies - Relative Risks and Risk Differences of drug discontinuation compared to Placebo

Reference Group= Placebo	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW	Fisher statistic value	p-value
Risk difference	0.012	—	-0.0047	4.387	0.1111
RD asy 95% CI	(-0.0019, 0.0068)		(-0.0094, 0.0025)		
Relative Risk	1.251	—	0.523		
RR asy 95% CI	(0.8506, 1.84)		(0.2136, 1.277)		

As can be observed from Tables 23, 25 and 28, there is no significant difference between denosumab and placebo in any of the analyses. There is a significant difference between placebo and alendronate in terms of the incidence of primary malignancies and serious events, but this difference may be due to the fact that malignancies are more likely to be captured in studies of longer duration, and the alendronate groups in the studies that are pooled have shorter follow up times compared to some of the denosumab and placebo groups. In Table 21, we observe that there is little difference between groups in the distribution of neoplasms by type, and in Table 22, we observe that the incidence of new malignancies by system organ class is nearly identical between denosumab and placebo.

5.3 Conclusions

In most of the studies, the incidence of new malignancies were balanced between the treatment and placebo groups, however, there were two populations for which a potential safety signal exists. First, in the population of men with prostate cancer undergoing HALT therapy (study 20040138), there did appear to be a higher rate of new malignancies in the denosumab arm, and this difference was driven primarily by metastases. Further investigation showed that this was primarily due to metastasis to the bone.

Another area of concern was in the patients in Study 20010223 that were in the high dose group (100mg Q6M). Of the four deaths in this study, three of the subjects belonged to this arm and experienced death due to a new primary malignancy. This issue was not observed in the higher dose arm of this study, and was not repeated in any of the other studies, but it is still notable.

Since malignancies develop over a longer term, this is still a potential area of concern which may need to be monitored for a longer duration.

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6 DISCUSSION AND CONCLUSIONS

Subjects treated with denosumab had similar risk for osteonecrosis of the jaw and delayed fracture healing compared to placebo subjects. The results for new primary malignancies are not as consistent. However, as all three of these adverse events of interest can develop over long-term use of the drug, they still need to be monitored.

For ONJ, though there were concerns that the ONJ adjudication committee selected by the sponsor used a narrow criterion (using MedDRA v.11.0) when ascertaining ONJ cases and no cases were identified, a broadening of the criterion in this analysis resulted in no significant difference between the denosumab and placebo groups. There was a significant difference in the severity gradient between the alendronate subjects and the placebo subjects, in trials employing active controls, with alendronate subjects experiencing more severe adverse events. However, the denosumab and placebo groups tended to have similar distributions of events in all the analyses.

For delayed fracture healing, the nonclinical overview showed that the sponsor found issues in bony callus formation among genetically modified mice that were monitored after being subjected to closed femoral fractures. The bony callus appeared to be larger and had a different consistency compared to those in the placebo group. This issue may affect the mobility of the bone, but is not expected to affect its strength. Only the four pivotal trials (Study'#'s 20030216, 20040132, 20040135 and 20040138) contained data that specifically considered fracture healing outcomes. Moreover, as the outcome of delayed fracture healing is one that can take up to five years to be fully determined, further long-term follow-up of this adverse event would be worthwhile. From the data provided, there appears to be a balanced distribution between groups for fracture healing outcomes.

For new primary maligancies, there generally appears to be a balanced distribution of adverse events with one notable exception. The only study that had significantly more events in the denosumab group was Study 20040138 whose population consisted of men with non-metastatic prostate cancer undergoing androgen deprivation therapy. The high level group term that drives the difference between groups in this study is "Metastases" and further investigation of this term shows that the increased number of adverse events in the denosumab group is mainly due to the preferred term "Metastases to bone". In all the other populations studied by the sponsor, this metastases issue does not arise and the difference between treatment and control groups is minimal. Again, as the appearance of new primary malignancies tends to be a long-term outcome, continued monitoring of this adverse event may be of use.

7 REFERENCES

References

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Ruggiero SL, Rosenberg TJ, Engroff SL.(2004) "Osteonecrosis of the Jaws Associated with the Use of Bisphosphonates: A review of 63 cases." JOMS 62: 527-534

Reference ID: 3168397

8 APPENDICES

Table 29: Listing and location of all datasets used in review

Study	Phase	Location	Datasets
20010223	Phase 2	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20010223\analysis	AAE, ASLINFO, AEX
20030216	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20030216\analysis	AAE, ASLINFO, AEX, AAEFX
20040132	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20040132-36-Month\analysis	AAE, ASLINFO, AEX, AAEFX
20040135	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20040135\analysis	AAE, ASLINFO, AEX, AAEFX
20040138	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20040138\analysis	AAE, ASLINFO, AEX, AAEFX
20050141	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20050141\analysis	AAE, ASLINFO, AEX
20050172	Phase 2	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20050172\analysis	AAE, ASLINFO, AEX
20050179	Phase 2	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20050179\analysis	AAE, ASLINFO, AEX
20050234	Phase 3	\\cbsap58\M\eCTD_Submissions\STN125320\0000\m5\datasets\20050234\analysis	AAE, ASLINFO, AEX

8.1 Osteonecrosis of the Jaw (ONJ) Analysis Tables

8.1.1 Tables of Preferred Term by Treatment Group for ONJ Risk Factors

Table 30: Study 20010223 - ONJ Preferred Terms (Part 1)

Dictionary-Derived Term	Denosumab				
	6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
Toothache	3	1	0	1	2
Tooth infection	3	3	0	1	2
Tooth fracture	1	0	1	2	0
Gingival infection	0	0	0	0	1
Pain in jaw	0	0	0	1	0
Oral infection	0	0	0	1	0
Mouth ulceration	0	0	0	0	1
Gingivitis	1	0	0	0	0
Gingival pain	1	0	0	0	0
Gingival ulceration	0	1	0	0	0
Periodontal disease	0	0	0	0	0
Oral discomfort	0	0	0	0	0
Gingival disorder	0	0	0	0	0
Tooth disorder	0	1	0	0	0
Subjects with AE	5	5	1	6	5

Reference ID: 3168397

Table 31: Study 20010223 - ONJ Preferred Terms (Part 2)

Dictionary-Derived Term	Denosumab 100mg Q6M	Denosumab 210mg Q6M	Alendronate	Placebo
Subjects in Arm	41	46	46	46
Toothache	0	3	2	1
Tooth infection	0	0	2	0
Tooth fracture	1	1	1	0
Gingival infection	0	1	1	1
Pain in jaw	0	0	1	1
Oral infection	1	1	0	0
Mouth ulceration	2	0	0	0
Gingivitis	1	1	0	0
Gingival pain	0	1	0	0
Gingival ulceration	0	0	0	1
Periodontal disease	0	0	0	2
Oral discomfort	0	0	0	1
Gingival disorder	0	0	1	0
Tooth disorder	0	0	0	0
Subjects with AE	5	7	6	6

Table 32: Study 20050172 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 14mg Q6M	Denosumab 60mg Q6M	Denosumab 100mg Q6M	Placebo
Subjects in Arm	53	54	51	54
Gingivitis	1	3	1	1
Periodontitis	0	2	3	1
Tooth fracture	0	0	1	0
Toothache	0	0	1	0
Tooth extraction	1	0	0	0
Gingival bleeding	0	1	0	0
Gingival swelling	0	0	1	0
Subjects with AE	2	6	6	2

Table 33: Study 20050179 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	83	83	81
Periodontitis	2	1	1
Tooth infection	1	1	0
Tooth abscess	0	1	1
Abscess jaw	0	1	0
Gingival infection	0	1	0
Loose tooth	0	1	0
Mouth ulceration	0	1	0
Oral discomfort	0	1	0
Oral infection	0	1	0
Pain in jaw	0	1	0
Toothache	0	1	0
Subjects with AE	3	10	2

Reference ID: 3168397

Table 34: Study 20030216 - ONJ Preferred Terms (Part 1)

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
Tooth infection	26	41
Toothache	22	31
Periodontitis	20	17
Tooth abscess	19	12
Gingivitis	12	10
Tooth fracture	6	7
Tooth disorder	6	7
Gingival infection	7	6
Osteitis	5	6
Mouth ulceration	7	4
Pain in jaw	5	3
Tooth extraction	5	3
Tooth injury	5	1
Gingival abscess	2	4
Oral pain	2	3
Osteonecrosis	4	1
Gingival pain	3	1
Oral infection	3	1
Gingival bleeding	3	1
Periodontal disease	3	1

Table 35: Study 20030216 - ONJ Preferred Terms (Part 2)

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
Abscess oral	1	2
Gingival swelling	0	3
Periodontal infection	2	0
Osteomyelitis	1	1
Loose tooth	0	2
Oral bacterial infection	1	1
Mouth cyst	1	0
Jaw cyst	1	0
Gingival hypertrophy	1	0
Gingival disorder	1	0
Oral cavity fistula	1	0
Bone erosion	0	1
Bone fistula	0	1
Bone infarction	0	1
Gingival operation	0	1
Dental necrosis	1	0
Gingival ulceration	0	1
Gingival cyst	1	0
Oral disorder	0	1
Tooth avulsion	0	1
Tooth disorder	0	1
Subjects with AE	158	155

Reference ID: 3168397

Table 36: Study 20040132 - 36 months - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	164	165
Toothache	4	2
Tooth abscess	4	2
Tooth infection	3	2
Pain in jaw	3	1
Tooth fracture	2	2
Tooth extraction	1	2
Gingival infection	0	3
Oral discomfort	1	0
Gingival abscess	1	0
Gingivitis	1	0
Gingival pain	1	0
Alveolar osteitis	0	1
Dental necrosis	0	1
Gingival cyst	0	1
Periodontal disease	1	0
Gingival swelling	0	1
Mouth ulceration	0	1
Subjects with AE	20	16

Table 37: Study 20040135 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
Tooth infection	1	1
Tooth abscess	1	0
Pain in jaw	1	1
Subjects with AE	3	1

Reference ID: 3168397

Table 38: Study 20040138 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Tooth infection	7	3
Toothache	1	6
Tooth abscess	2	3
Gingivitis	3	0
Bone erosion	0	3
Pain in jaw	1	1
Osteomyelitis	1	1
Oral pain	1	1
Tooth fracture	1	1
Tooth disorder	0	2
Gingival infection	1	0
Periodontal disease	1	0
Mouth ulceration	1	0
Gingival pain	1	0
Gingival recession	0	1
Jaw cyst	0	1
Oral disorder	0	1
Osteonecrosis	0	1
Tooth extraction	1	0
Tooth repair	0	1
Subjects with AE	19	24

Table 39: Study 20050141 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Toothache	6	5
Tooth fracture	6	2
Tooth abscess	7	1
Tooth infection	2	4
Tooth disorder	2	3
Gingivitis	2	3
Gingival pain	2	3
Periodontitis	2	2
Mouth ulceration	1	2
Pain in jaw	2	1
Gingival abscess	1	1
Osteomyelitis	1	0
Oral pain	1	0
Loose tooth	0	1
Oral discomfort	0	1
Tooth loss	0	1
Osteonecrosis	1	0
Subjects with AE	30	25

Reference ID: 3168397

Table 40: Study 20050234 - ONJ Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
Tooth fracture	1	4
Pain in jaw	1	3
Periodontitis	1	2
Periodontal infection	0	1
Loose tooth	0	1
Tooth abscess	0	1
Gingival infection	0	1
Tooth infection	0	1
Toothache	0	1
Gingival pain	1	0
Jaw disorder	1	0
Tooth loss	1	0
Subjects with AE	6	11

8.1.2 Tables of Serious Adverse Events (SAEs) by Treatment Group for ONJ Risk Factors

Table 41: Study 20010223 - ONJ Serious Adverse Events (Part 1)

Serious Adverse Event	Denosumab 6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
No SAE	5	5	1	6	5
SAE present	0	0	0	0	0
Subjects with AE	5	5	1	6	5

Table 42: Study 20010223 - ONJ Serious Adverse Events (Part 2)

Serious Adverse Event	Denosumab 100mg Q6M	210mg Q6M	Alendronate	Placebo
Subjects in Arm	41	46	46	46
No SAE	5	7	6	5
SAE present	0	0	0	1
Subjects with AE	5	7	6	6

Reference ID: 3168397

Table 43: Study 20050141 - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
No SAE	30	25
SAE present	0	1
Subjects with AE	30	25

Table 44: Study 20050234 - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
No SAE	6	9
SAE present	0	2
Subjects with AE	6	11

Table 45: Study 20030216 - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
No SAE	156	154
SAE present	3	1
Subjects with AE	158	155

Table 46: Study 20040138 - ONJ Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
No SAE	18	23
SAE present	1	1
Subjects with AE	19	24

8.1.3 Tables of Severity Gradient by Treatment Group for ONJ Risk Factors

Table 47: Study 20010223 - ONJ Severity Gradient (part 1)

Adverse Event	Denosumab				
Severity Grade	6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
Mild	1	3	0	3	3
Moderate	4	3	1	2	2
Severe	1	0	0	0	0
Subjects with AE	5	5	1	6	5

Reference ID: 3168397

Table 48: Study 20010223 - ONJ Severity Gradient (part 2)

Adverse Event	Denosumab		Alendronate	Placebo
Severity Grade	100mg Q6M	210mg Q6M		
Subjects in Arm	41	46	46	46
Mild	0	3	2	4
Moderate	4	4	4	1
Severe	1	0	0	2
Subjects with AE	5	7	6	6

Table 49: Study 20050172 - ONJ Severity Gradient

Adverse Event		Denosumab		Placebo
Severity Grade	14mg Q6M	60mg Q6M	100mg Q6M	
Subjects in Arm	53	54	51	54
Mild	2	6	6	2
Moderate	0	0	0	0
Severe	0	0	0	0
Subjects with AE	2	6	6	2

Table 50: Study 20050179 - ONJ Severity Gradient

Adverse Event	Denosumab	Placebo	Alendronate
Severity Grade	60mg Q6M		70mg QW
Subjects in Arm	83	83	81
Mild	2	10	1
Moderate	1	0	1
Severe	0	0	0
Subjects with AE	3	10	2

Table 51: Study 20030216 - ONJ Severity Gradient

Adverse Event	Denosumab	Placebo
Severity Grade	60mg Q6M	
Subjects in Arm	3886	3876
Mild	82	78
Moderate	83	78
Severe	2	8
Subjects with AE	158	155

Table 52: Study 20040132 - 36 months - ONJ Severity Gradient

Adverse Event	Denosumab	Placebo
Severity Grade	60mg Q6M	
Subjects in Arm	164	165
Mild	10	6
Moderate	11	10
Severe	0	1
Subjects with AE	20	16

Reference ID: 3168397

Table 53: Study 20040135 - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
Mild	1	1
Moderate	2	0
Severe	0	0
Subjects with AE	3	1

Table 54: Study 20040138 - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Mild	11	14
Moderate	8	10
Severe	1	2
Subjects with AE	19	24

Table 55: Study 20050141 - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Mild	24	17
Moderate	7	10
Severe	2	1
Subjects with AE	30	25

Table 56: Study 20050234 - ONJ Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects	253	249
Mild	6	3
Moderate	1	5
Severe	0	3
Subjects with AE	6	11

Reference ID: 3168397

8.2 Delayed Fracture Healing Analysis Tables

8.2.1 Tables of All Non-vertebral Fractures by Treatment Group

Table 57: Study 20010223 - Fracture Preferred Terms (part 1)

Dictionary-Derived Term	6mg Q3M	14mg Q6M	Denosumab 14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
Foot fracture	0	2	2	2	4
Rib fracture	0	0	3	0	1
Fibula fracture	0	0	1	1	0
Humerus fracture	0	1	1	0	1
Hand fracture	0	1	0	0	1
Tibia fracture	0	0	1	1	0
Radius fracture	0	1	1	0	0
Sternal fracture	1	0	0	0	0
Ulna fracture	0	1	0	0	0
Fractured sacrum	0	0	0	0	1
Lumbar vertebral fracture	0	0	0	0	0
Femur fracture	0	0	0	0	0
Ilium fracture	0	0	0	0	0
Facial bones fracture	0	0	0	0	1
Subjects with AE	1	4	7	3	7

Table 58: Study 20010223 - Fracture Preferred Terms (part 2)

Dictionary-Derived Term	Denosumab 100mg Q6M	Denosumab 210mg Q6M	Alendronate	Placebo
Subjects in Arm	41	46	46	46
Foot fracture	1	4	1	3
Rib fracture	1	1	0	0
Fibula fracture	1	1	0	1
Humerus fracture	1	0	0	1
Hand fracture	0	1	1	0
Tibia fracture	1	0	0	0
Radius fracture	1	0	0	0
Sternal fracture	1	0	0	0
Ulna fracture	1	0	0	0
Fractured sacrum	0	1	0	0
Lumbar vertebral fracture	1	0	0	0
Femur fracture	0	0	1	0
Ilium fracture	0	1	0	0
Facial bones fracture	0	0	0	0
Subjects with AE	4	7	3	5

Reference ID: 3168397

Table 59: Study 20050172 - Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 14mg Q6M	Denosumab 60mg Q6M	Denosumab 100mg Q6M	Placebo
Subjects in Arm	53	54	51	54
Fibula fracture	0	0	0	1
Foot fracture	0	1	0	0
Radius fracture	0	0	0	1
Subjects with AE	0	1	0	2

Table 60: Study 20050179 - Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	83	83	81
Hand fracture	0	0	1
Subjects with AE	0	0	1

Table 61: Study 20030216 - Non- Vertebral Fracture Preferred Terms

Dictionary-Derived Term	Denosumab	Placebo
Subjects in Arm	3886	3876
Radius fracture	104	116
Humerus fracture	42	50
Ulna fracture	37	39
Foot fracture	34	40
Rib fracture	40	33
Hand fracture	21	31
Fibula fracture	19	32
Femur fracture	15	28
Femoral neck fracture	16	20
Tibia fracture	9	15
Wrist fracture	8	10
Pelvic fracture	8	10
Clavicle fracture	8	6
Patella fracture	9	5
Facial bones fracture	3	8
Fractured ischium	2	3
Sternal fracture	2	3
Fractured sacrum	1	3
Scapula fracture	1	2
Fracture	1	2
Acetabulum fracture	2	0
Upper limb fracture	1	1
Skull fracture	1	1
Lower limb fracture	1	0
Fractured coccyx	1	0
Ilium fracture	0	1
Pubic rami fracture	0	1
Subjects with AE	306	367

Reference ID: 3168397

Table 62: Study 20040132 - 36 months - Non- Vertebral Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	160	161
Ankle fracture	0	2
Clavicle fracture	1	0
Fibula fracture	2	2
Foot fracture	6	7
Hand fracture	0	1
Humerus fracture	1	3
Patella fracture	2	1
Radius fracture	1	1
Tibia fracture	0	2
Subjects with AE	13	15

Table 63: Study 20040135 - Non- Vertebral Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Sutbjects in Arm	117	108
Femoral neck fracture	1	1
Fibula fracture	2	0
Foot fracture	3	2
Fracture	1	0
Patella fracture	0	1
Radius fracture	1	2
Rib fracture	2	1
Tibia fracture	1	1
Wrist fracture	0	1
Subjects with AE	10	9

Reference ID: 3168397

Table 64: Study 20040138 - Non- Vertebral Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Acetabulum fracture	2	0
Clavicle fracture	1	3
Facial bones fracture	1	1
Femoral neck fracture	3	2
Femur fracture	4	3
Fibula fracture	0	4
Foot fracture	6	0
Forearm fracture	1	0
Fracture	0	1
Fractured ischium	1	0
Fractured sacrum	0	1
Hand fracture	2	3
Humerus fracture	3	6
Ilium fracture	0	1
Patella fracture	1	0
Pelvic fracture	1	0
Radius fracture	2	12
Rib fracture	16	14
Scapula fracture	3	0
Skull fracture	1	0
Tibia fracture	1	4
Ulna fracture	2	6
Subjects with AE	45	44

Table 65: Study 20050141 - Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Foot fracture	3	5
Radius fracture	2	5
Rib fracture	1	5
Humerus fracture	4	1
Hand fracture	3	1
Ulna fracture	1	3
Tibia fracture	2	1
Fibula fracture	1	2
Lumbar vertebral fracture	2	0
Thoracic vertebral fracture	1	1
Clavicle fracture	0	2
Facial bones fracture	1	1
Wrist fracture	1	0
Patella fracture	1	0
Femur fracture	0	1
Pelvic fracture	1	0
Subjects with AE	19	24

Reference ID: 3168397

Table 66: Study 20050234 - Fracture Preferred Terms

Dictionary-Derived Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	249	253
Wrist fracture	2	1
Foot fracture	2	1
Radius fracture	1	1
Fractured sacrum	0	1
Fibula fracture	1	0
Humerus fracture	1	0
Pelvic fracture	1	0
Rib fracture	1	0
Subjects with AE	8	4

Reference ID: 3168397

8.2.2 Tables of Fracture Healing Outcomes from Four Pivotal Trials

Table 67: Study 20030216 - Fracture Healing Outcomes

Fracture Healing Complications	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
Any Complication	19	23
Delayed Heal	2	2
Malunion	3	3
Nonunion	0	1
Chronic Pain	7	11
Other	10	7
Subjects with non-vertebral fracture	303	364

Table 68: Study 20040132 - 36 months - Fracture Healing Outcomes

Fracture Healing Complications	Denosumab 60mg Q6M	Placebo
Subjects in Arm	164	165
Any Complication	1	0
Delayed Heal	1	0
Subjects with non-vertebral fracture	13	15

Table 69: Study 20040135 - Fracture Healing Outcomes

Fracture Healing Complications	Denosumab 60mg Q6M	Placebo
Sutbjects in Arm	129	120
Any Complication	0	1
Delayed Heal	0	1
Subjects with non-vertebral fracture	10	9

Table 70: Study 20040138 - Fracture Healing Outcomes

Fracture Healing Complications	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Any Complication	1	1
Chronic Pain	1	0
Other	0	1
Subjects with non-vertebral fracture	44	44

Reference ID: 3168397

8.3 New Primary Malignancies

8.3.1 Tables of High Level Group Terms by Treatment Group for Primary Malignancies

Table 71: Study 20010223 - New Primary Malignancies High Level Group Terms (Part 1)

High Level Group Term	6mg Q3M	14mg Q6M	Denosumab 14mg Q3M	30mg Q3M	60mg Q6M
Total Subjects	43	53	44	40	47
GI neoplasms	1	0	1	1	0
Breast neoplasms	0	0	2	1	0
Skin neoplasms	0	0	0	0	1
Miscellaneouse and site unspecified neoplasms	0	2	0	0	0
Lymphomas non-Hodgkin's B-cell	1	0	0	0	0
Respiratory and mediastinal neoplasms	0	2	0	0	0
Nervous system neoplasms	0	0	1	0	0
Reproductive neoplasms female	0	0	1	0	0
Skeletal neoplasms	0	0	0	0	0
Lymphomas non-Hodgkin's unspecified histology	0	0	0	0	0
Subjects with AE	2	4	5	2	1

Table 72: Study 20010223 - New Primary Malignancies High Level Group Terms (Part 2)

High Level Group Term	Denosumab 100mg Q6M	Denosumab 210mg Q6M	Placebo	Alendronate
Subjects in Arm	41	46	46	46
GI neoplasms	2	1	1	1
Breast neoplasms	0	1	0	0
Skin neoplasms	0	0	0	3
Miscellaneouse and site unspecified neoplasms	1	0	0	0
Lymphomas non-Hodgkin's B-cell	0	0	1	0
Respiratory and mediastinal neoplasms	0	0	0	0
Nervous system neoplasms	1	0	0	0
Reproductive neoplasms female	0	0	0	0
Skeletal neoplasms	0	0	1	0
Lymphomas non-Hodgkin's unspecified histology	0	0	0	1
Subjects with AE	4	2	3	5

Table 73: Study 20050172 - New Primary Malignancies High Level Group Terms

High Level Group Term	Denosumab 14mg Q6M	Denosumab 60mg Q6M	Denosumab 100mg Q6M	Placebo
Subjects in Arm	53	54	51	54
Breast neoplasms	0	1	0	0
Subjects with AE	0	1	0	0

Reference ID: 3168397

Table 74: Study 20050179 - New Primary Malignancies High Level Group Terms

High Level Group Term	Denosumab 60mg Q6M	Placebo	Alendronate 70mg QW
Subjects in Arm	83	83	81
Breast neoplasms	0	0	2
Reproductive neoplasms female	0	0	1
Subjects with AE	0	0	3

Table 75: Study 20030216 - New Primary Malignancies High Level Group Terms

Adverse Event High Level Group Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	3886	3876
Skin neoplasms	46	49
Breast neoplasms	34	30
GI neoplasms	35	24
Respiratory and mediastinal neoplasms	15	25
Reproductive neoplasms female	19	9
Metstases	9	9
Renal and urinary tract neoplasms	5	8
Nervous system neoplasms	5	7
Plasma cell neoplasms	6	4
Miscellaneous and site unspecified neoplasms	7	3
Endocrine neoplasms	7	2
Leukaemias	2	2
Lymphomas non-Hodgkin's B-cell	2	2
Lymphomas NEC	2	2
Hepatobiliary neoplasms	1	3
Haematopoietic neoplasms	3	0
Ocular neoplasms	1	1
Lymphomas non-Hodgkin's unspecified histology	1	1
Cancer-related morbidities	2	0
Mesotheliomas	1	0
Soft tissue sarcomas	0	1
Skeletal neoplasms	1	0
Subjects with AE	187	167

Table 76: Study 20040132 - 36 months - New Primary Malignancies High Level Group Terms

Adverse Event High Level Group Term	Denosumab 60mg Q6M	Placebo
Total Subjects	164	165
Miscellaneous and site unspecified	1	2
Reproductive neoplasms female	2	0
Breast neoplasms	1	1
Nervous system neoplasms	1	0
Skin neoplasms	1	0
Lymphomas non-Hodgkin's B-cell	0	1
Lymphomas non-Hodgkin's T-cell	1	0
Subjects	7	4

Reference ID: 3168397

Table 77: Study 20040135 - New Primary Malignancies High Level Group Terms

Adverse Event High Level Group Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
Metastases	3	3
Skin neoplasms	2	3
Breast neoplasms	3	1
Miscellaneous and site unspecified neoplasms	1	1
Endocrine neoplasms	1	0
Respiratory and mediastinal neoplasms	1	0
Cancer-related morbidities	1	0
Gastrointestinal neoplasms	0	1
Hepatobiliary neoplasms	1	0
Subjects with AE	9	8

Table 78: Study 20040138 - New Primary Malignancies High Level Group Terms

Adverse Event High Level Group Term	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Metastases	48	31
Skin neoplasms	19	15
Gastrointestinal neoplasms	12	10
Reproductive neoplasms male	12	8
Renal and urinary tract neoplasms	7	6
Respiratory and mediastinal neoplasms	7	3
Miscellaneous and site unspecified neoplasms	6	1
Nervous system neoplasms	1	2
Leukaemias	1	1
Lymphomas non-Hodgkin's B-cell	1	1
Cancer related morbidities	1	0
Lymphomas NEC	1	0
Breast neoplasms	0	1
Endocrine neoplasms	0	1
Hepatobiliary neoplasms	0	1
Lymphomas non-Hodgkin's unspecified histology	0	1
Skeletal neoplasms	0	1
Subjects with AE	105	79

Reference ID: 3168397

Table 79: Study 20050141 - New Primary Malignancies High Level Group Terms

High Level Group Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Breast neoplasms	1	2
Skin neoplasms	1	2
Respiratory and mediastinal neoplasms	2	0
Miscellaneous and site unspecified neoplasms	1	1
Reproductive neoplasms female	2	0
Lymphomas non-Hodgkin's T-cell	0	1
Metastases	0	1
Renal and urinary tract neoplasms	0	1
Gastrointestinal neoplasms	0	1
Subjects with AE	7	8

Table 80: Study 20050234 - New Primary Malignancies High Level Group Terms

High Level Group Term	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
Skin neoplasms	1	1
Breast neoplasms	0	2
Respiratory and mediastinal neoplasms	1	0
Gastrointestinal neoplasms	1	0
Subjects with AE	3	3

Reference ID: 3168397

8.3.2 Tables of Serious Adverse Events by Treatment Group for Primary Malignancies

Table 81: Study 20010223 - New Primary Malignancies - Serious Adverse Events (part 1)

Serious			Denosumab		
Adverse Event	6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects	43	53	44	40	47
No SAE	0	4	1	1	1
SAE present	2	0	4	1	1
Subjects with AE	2	4	5	2	1

Table 82: Study 20010223 - New Primary Malignancies - Serious Adverse Events (part 2)

Serious	Denosumab		Placebo	Alendronate
Adverse Event	100mg Q6M	210mg Q6M		
Subjects in Arm	41	46	46	46
No SAE	0	0	1	3
SAE present	4	2	2	2
Subjects with AE	4	2	3	5

Table 83: Study 20050172 - New Primary Malignancies - Serious Adverse Events

Serious		Denosumab		Placebo
Adverse Event	100mg Q6M	14mg Q6M	60mg Q6M	
Subjects	53	54	51	54
No SAE	0	0	0	0
SAE present	0	0	1	0
Subjects with AE	0	0	1	0

Table 84: Study 20050179 - New Primary Malignancies - Serious Adverse Events

Serious	Denosumab	Placebo	Alendronate
Adverse Event	60mg Q6M		70mg QW
Subjects in Arm	83	83	81
No SAE	0	0	0
SAE present	0	0	3
Subjects with AE	0	0	3

Table 85: Study 20030216 - New Primary Malignancies - Serious Adverse Events

Serious	Denosumab	
Adverse Event	60mg Q6M	Placebo
Subjects in Arm	3886	3876
No SAE	50	46
SAE present	144	125
Subjects with AE	187	167

Reference ID: 3168397

Table 86: Study 20040132 - 36 months - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects in Arm	164	165
No SAE	1	2
SAE present	6	2
Subjects with AE	7	4

Table 87: Study 20040135 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
No SAE	7	7
SAE present	2	1
Subjects with AE	9	8

Table 88: Study 20040138 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Placebo
Subjects	731	725
No SAE	73	43
SAE present	36	41
Subjects with AE	105	79

Table 89: Study 20050141 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
No SAE	2	2
SAE present	6	5
Subjects with AE	7	8

Table 90: Study 20050234 - New Primary Malignancies - Serious Adverse Events

Serious Adverse Event	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
No SAE	1	1
SAE present	2	2
Subjects with AE	3	3

Reference ID: 3168397

8.3.3 Tables of Severity Gradient by Treatment Group for Primary Malignancies

Table 91: Study 20010223 - New Primary Malignancies - Severity Gradient (part 1)

Adverse Event			Denosumab		
Severity Grade	6mg Q3M	14mg Q6M	14mg Q3M	30mg Q3M	60mg Q6M
Subjects in Arm	43	53	44	40	47
Mild	1	3	0	0	1
Moderate	0	1	1	1	1
Severe	0	0	4	1	0
Life Threatening	1	0	0	0	0
Fatal	0	0	0	0	0
Subjects with AE	2	4	5	2	1

Table 92: Study 20010223 - New Primary Malignancies - Severity Gradient (part 2)

Adverse Event	Denosumab		Placebo	Alendronate
Severity Grade	100mg Q6M	210mg Q6M		
Subjects in Arm	41	46	46	46
Mild	0	0	0	3
Moderate	0	1	1	1
Severe	1	1	2	0
Life Threatening	0	0	0	1
Fatal	3	0	0	0
Subjects with AE	4	2	3	5

Table 93: Study 20050172 - New Primary Malignancies - Severity Gradient

Adverse Event		Denosumab		Placebo
Severity Grade	14mg Q6M	60mg Q6M	100mg Q6M	
Subjects in Arm	53	54	51	54
Mild	0	0	0	0
Moderate	0	0	0	0
Severe	0	1	0	0
Subjects with AE	0	1	0	0

Table 94: Study 20050179 - New Primary Malignancies - Severity Gradient

Adverse Event	Denosumab	Placebo	Alendronate
Severity Grade	60mg Q6M		70mg QW
Subjects in Arm	83	83	81
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	3
Subjects with AE	0	0	3

Reference ID: 3168397

Table 95: Study 20030216 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects	3886	3876
Mild	31	26
Moderate	52	51
Severe	83	61
Life Threatening	14	17
Fatal	20	26
Subjects with AE	187	167

Table 96: Study 20040132 - 36 months - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	164	165
Mild	2	1
Moderate	1	2
Severe	4	1
Subjects with AE	7	4

Table 97: Study 20040135 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	129	120
Mild	2	2
Moderate	5	1
Severe	4	4
Life Threatening	0	1
Fatal	1	1
Subjects with AE	9	8

Table 98: Study 20040138 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Placebo
Subjects in Arm	731	725
Mild	13	13
Moderate	46	23
Severe	42	34
Life Threatening	7	7
Fatal	6	9
Subjects with AE	105	79

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Table 99: Study 20050141 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	593	586
Mild	1	1
Moderate	4	2
Severe	3	2
Life Threatening	0	1
Fatal	0	1
Subjects with AE	8	7

Table 100: Study 20050234 - New Primary Malignancies - Severity Gradient

Adverse Event Severity Grade	Denosumab 60mg Q6M	Alendronate 70mg QW
Subjects in Arm	253	249
Mild	1	2
Moderate	1	0
Severe	1	1
Subjects with AE	3	3

Reference ID: 3168397

8.4 Preferred Terms found in Malignancies Search Using Specified Criteria

Table 101: MedDRA 11.0 Preferred Terms used in Malignancies Search (Part 1)

Abdominal neoplasm	Colon cancer	Lung neoplasm malignant
Acral lentiginous melanoma stage unspecified	Colon cancer metastatic	Lung squamous cell carcinoma stage unspecified
Acute myeloid leukaemia	Colon neoplasm	Lymph node cancer metastatic
Adenocarcinoma	Colorectal cancer	Lymphoma
Adenocarcinoma of the cervix	Diffuse large B-cell lymphoma	Lymphoproliferative disorder
Adenocarcinoma pancreas	Diffuse large B-cell lymphoma recurrent	Malignant ascites
Adrenal neoplasm	Dysplastic naevus syndrome	Malignant glioma
Basal cell carcinoma	Endometrial cancer	Malignant lymphoid neoplasm
B-cell lymphoma	Essential thrombocythaemia	Malignant melanoma
Bladder cancer	Follicle centre lymphoma, follicular grade I, II, III stage III	Malignant melanoma in situ
Bladder transitional cell carcinoma	Gallbladder cancer	Malignant neoplasm progression
Bone neoplasm malignant	Gallbladder cancer metastatic	Malignant pleural effusion
Bowen's disease	Gammopathy	Mantle cell lymphoma
Brain cancer metastatic	Gastric cancer	Maxillofacial sinus neoplasm
Brain neoplasm	Gastrointestinal carcinoma	Meningeal neoplasm
Brain neoplasm malignant	Giant cell tumour of tendon sheath	Meningioma
Breast cancer	Glioblastoma	Mesothelioma malignant
Breast cancer in situ	Glioblastoma multiforme	Metastases to abdominal cavity
Breast cancer metastatic	Head and neck cancer	Metastases to adrenals
Breast neoplasm	Hepatic neoplasm	Metastases to bone
Bronchial carcinoma	Hepatic neoplasm malignant	Metastases to bone marrow
Cancer pain	Infected neoplasm	Metastases to central nervous system
Carcinoid tumour of the stomach	Intestinal adenocarcinoma	Metastases to chest wall
Cerebellar tumour	Lentigo maligna stage unspecified	Metastases to fallopian tube
Cervix carcinoma	Lip and/or oral cavity cancer	Metastases to large intestine
Cervix carcinoma stage 0	Lung adenocarcinoma	Metastases to liver
Chondrosarcoma	Lung adenocarcinoma metastatic	Metastases to lung
Choroidal naevus	Lung cancer metastatic	Metastases to lymph nodes
Chronic lymphocytic leukaemia	Lung neoplasm	Metastases to meninges

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Table 102: MedDRA 11.0 Preferred Terms used in Malignancies Search (Part 2)

Metastases to pleura	Oesophageal squamous cell carcinoma	Recurrent cancer
Metastases to skin	Ovarian cancer	Renal cancer
Metastases to spine	Ovarian cancer metastatic	Salivary gland cancer
Metastasis	Ovarian cancer recurrent	Skin cancer
Metastatic bronchial carcinoma	Ovarian epithelial cancer	Small cell lung cancer metastatic
Metastatic malignant melanoma	Ovarian neoplasm	Small cell lung cancer stage unspecified
Metastatic neoplasm	Pancreatic carcinoma	Small intestine carcinoma
Metastatic renal cell carcinoma	Pancreatic carcinoma metastatic	Squamous cell carcinoma
Multiple myeloma	Papillary thyroid cancer	Squamous cell carcinoma of skin
Mycosis fungoides	Paranasal sinus neoplasm	Teratoma
Myelodysplastic syndrome	Paraproteinaemia	Throat cancer
Nasal cavity cancer	Pharyngeal cancer stage unspecified	Thyroid cancer
Neoplasm	Plasmacytoma	Thyroid neoplasm
Neoplasm malignant	Prostate cancer	Tongue neoplasm malignant stage unspecified
Neoplasm prostate	Prostate cancer metastatic	Urethral cancer recurrent
Neurilemmoma	Prostate cancer recurrent	Uterine cancer
Neuroendocrine carcinoma of the skin	Pseudolymphoma	Uterine leiomyosarcoma
Non-Hodgkin's lymphoma	Rectal cancer	Vaginal cancer
Non-small cell lung cancer	Rectal cancer metastatic	Vaginal cancer metastatic
Non-small cell lung cancer metastatic	Rectal cancer stage III	Vulval cancer
Oesophageal carcinoma	Rectal neoplasm	Waldenstrom's macroglobulinaemia

8.5 Analysis of Malignancy Fatalities in Study 20010223

Table 103: Analysis of Malignancy Fatalities in Study 20010223

Comparison	Risk Difference	95% Exact CI	p-value
# of Deaths in 100mg Q6M Denosumab group compared to Placebo	0.0732	(-0.00784, 0.208)	0.0633
# of Deaths in all Denosumab groups compared to Placebo	.00096	(-0.0683, 0.0278)	0.682
# of SAEs in 100mg Q6M Denosumab group compared to Placebo	0.0541	(-0.0647, 0.193)	0.364
# of SAEs in all Denosumab groups compared to Placebo	-0.00526	(-0.111, 0.0372)	0.946

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9 SIGNATURES

Primary Statistical Reviewer:
Date: August 10, 2009

Anita Abraham, DrPH
Mathematical Statistician, Division of Biometrics VI

Secondary Reviewer(s):

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Reference ID: 3168397

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

STATISTICAL REVIEW AND EVALUATION

BLA Number	125331, 125320, 125332, and 125333
Drug Name:	denosumab (PROLIA)
Indication(s):	- Prevention of osteoporosis in postmenopausal women - Treatment of osteoporosis in postmenopausal women - Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer - Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer
Applicant:	Amgen Inc.
Date submitted:	January 5, 2009
PDUFA Date:	October 19, 2009
Date review completed	July 8, 2009
Review Priority:	Standard
Biometrics Division:	Quantitative Safety and Pharmacoepidemiology Division
Statistical Reviewer:	Mandi Yu, Ph.D., Mathematical Statistician
Secondary Reviewers:	Paul Schuette, Ph.D., Mathematical Statistician George Rochester, Ph.D., Acting Director
Medical Division:	Division of Reproductive and Urologic Products, and Division of Biologic Oncology Products
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Project Manager:	Celia Peacock, MPH, RD, Division of Reproductive and Urologic Products Melanie Pierce, B.S., Division of Biologic Oncology Products

Keywords: serum calcium low, hypocalcemia, renal function, vitamin D, osteoporosis, bone loss, breast cancer, prostate cancer

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1. Executive Summary

Denosumab is a fully human monoclonal antibody that binds to RANKL with high affinity and specificity. Denosumab is intended to prevent and treat postmenopausal osteoporosis (PMO), and to prevent and treat bone loss associated with hormone-ablative therapy (HALT) with breast cancer or with prostate cancer. The proposed dose for denosumab is 60 mg of subcutaneous administration once every six months.

Hypocalcemia was one of the pre-identified composite adverse events during clinical drug development phase for safety surveillance. This review evaluated the effect of denosumab on the incidence and severity of hypocalcemia using data on adverse events (AE) and laboratory serum calcium. The evaluations were also conducted within subgroups of subjects by their baseline vitamin D levels, baseline creatinine clearance levels, and proton pump inhibitors (PPI) medication exposure status. Based on serum calcium data, evaluations on the maximum difference across the entire study period and the time to the first hypocalcemia event were conducted. The incidence of hypocalcemia during the extended off-treatment phases was also evaluated.

1.1. Conclusions and Recommendations

Based on AE data, denosumab was not associated with hypocalcemia in terms of incidence and severity for all subjects or subgroups of subjects with different baseline vitamin D levels, creatinine clearance levels, and proton pump inhibitors medication exposure status.

However, based on serum calcium data, a higher risk of mild hypocalcemia (i.e. Grade 1 hypocalcemia) was observed among denosumab subjects than placebo subjects for the pooled PMO pivotal studies (20040132 and 20030216) and HALT study 20040138. The relative risks of hypocalcemia for subjects treated with denosumab compared to subjects treated with placebo were 3.59 (95% CI 2.19-5.88) in the pooled PMO pivotal studies and 5.36 (95% CI 2.15-13.41) in study 20040138. If denosumab is approved, it is recommended that the sponsor consider labeling mild hypocalcemia as a potential adverse drug effect.

1.2. Statistical Issues and Findings

Because hypocalcemia adverse events are rare, trials were pooled where appropriate to assess the effect of denosumab on hypocalcemia. A wide range of pooling schemes was considered in this review. Among the four indications for which the sponsor was seeking approval, the first two concerns with the population of postmenopausal women (PMO), therefore, the phase-III pivotal trials (20040132 and 20030216) designed for these two indications were pooled together as well as analyzed separately. The pivotal trials for the two HALT indications were analyzed separately because each study focused on a single gender, men in 20040138 and women in 20040135. In addition, five phase-II or phase-III, non-pivotal, randomized, controlled trials with at least one denosumab arm were evaluated: 20010223, 20050141, 20050172, 20050179 and 20050234.

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Based on AE data, the reported incidence of hypocalcemia is low, and denosumab was not associated with hypocalcemia, in terms of either incidence or severity, in all subjects and subgroups with differential baseline renal functions, baseline vitamin D levels, and concomitant PPI exposure status. However, it was observed that subjects exposed to PPI were associated with a higher rate of hypocalcemia than those with no PPI exposure regardless of their treatment assignments. For the pooled PMO studies, the rate of hypocalcemia is approximately 2.7% for both treatment groups. For HALT study 20040135, the rates are 6.2% for the denosumab group and 3.3% for the placebo group. For HALT study 20040138, the rates are 3.0% for the denosumab group and 2.2% for the placebo group. Most hypocalcemia events were symptomatic and mild to modest in severity.

Analysis of laboratory serum calcium data focused on subjects enrolled in pivotal studies. A lower normal cutoff value of 8.5mg/dl was used to identify hypocalcemia events. Denosumab subjects were 3.59 times (95% C.I.: 2.19-5.88) as likely to develop hypocalcemia than subjects in the placebo group in the pooled PMO studies. No difference was observed on HALT study 20040135. In HALT study 20040138, the risk ratio of hypocalcemia was 5.36 (95% C.I.: 2.15-13.41) for denosumab subjects compared to placebo subjects. However, when a cutoff value of 7.5md/gl was used, as suggested in (b) (4), denosumab is not associated with hypocalcemia in any of the studies. The maximum differences in serum calcium values across all visits were small and comparable between treatment groups.

Approximately 58% of denosumab treated subjects had their first hypocalcemia event at their month-1 visit compared with only 18.5% of placebo treated subjects. The incidence of hypocalcemia was comparable between treatment groups for the remaining eight visits. A Kaplan-Meier survival analysis shows a statistically significant difference (p-value <0.0001) between the survival curves for the denosumab and the placebo groups. Denosumab subjects showed a higher risk of hypocalcemia than placebo subjects during the early stages of the study. At later stages, the survival curves were similar between the two treatment groups.

Finally, no statistically significant difference was observed for the incidence of hypocalcemia in the off-treatment AE data. Laboratory serum calcium data were not available for off-treatment assessments.

2. Introduction

Hypocalcemia is a condition in which there is a lower than normal level of calcium in the circulating blood. The concentration of calcium in the serum is regulated by the action of parathyroid hormone and vitamin D on the kidneys, bones, and gastrointestinal tract. Because denosumab may reduce the blood calcium levels, as do most antiresorpatives agents, hypocalcemia has been identified as a potential safety concern in patients who are administered denosumab.

The objectives for this safety analysis are to: 1) ascertain the frequency of hypocalcemia; 2) evaluate the risk of hypocalcemia for the denosumab treated group relative to the

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placebo group; 3) ascertain the severity of the hypocalcemia adverse events; 4) evaluate the impact of denosumab on the time to hypocalcemia adverse events; 5) compare the incidences of hypocalcemia between the denosumab group and the placebo group within subgroups defined by baseline vitamin D level and baseline renal function status, and 6) evaluate the possible impact of proton pump inhibitors (PPI) on hypocalcemia.

3. Data Resources

This review focused on the safety population in all randomized, controlled clinical trials. The safety population, as defined by the sponsor, was comprised of all randomized subjects who received at least one dose of investigational drug. The primary focus was four phase-III, placebo-controlled, multi-national pivotal studies: PMO study 20030216, PMO study 20040132, HALT study 20040135 and HALT study 20040138.

Additional analyses on non-pivotal studies, which were also controlled, randomized trials with at least one denosumab treatment group, were also conducted. These selected non-pivotal studies are study 20010223, study 20050141, study 20050172, study 20050179, and study 20050234.

For the off-treatment evaluation of the risk of hypocalcemia, the following clinical trials were included: PMO study 20040132 24-48month, HALT study 20040135 and HALT study 20040138, the open-label PMO study 20060289 (extension study for study 20030216).

4. Methodology

4.1. Definition of hypocalcemia based on MedDRA (v11.0) terms

A hypocalcemia adverse event is defined as any MedDRA Preferred Term, which is potentially indicative of serum calcium level decreases, as listed in Table 1. A subject is classified as having hypocalcemia if the subject was associated with at least one hypocalcemia adverse event.

Table 1 lists the preferred terms used to define a hypocalcemia event in this review as well as those listed in the Sponsor's safety report. The first nine preferred terms used for this review are identical to those identified by the sponsor. Medical officers from the Division of Reproductive and Urologic Products provided the following terms to be added to the search: "Hypoparathyroidism," "Blood parathyroid hormone decreased," "Hypomagnesemia," "Magnesium deficiency," "Blood magnesium decreased," "Hyperphosphatemia," "Calcium phosphate product increased," "Blood phosphorus increased," "Vitamin D decreased," and "Vitamin D deficiency."

Only treatment-emergent adverse events, defined as events occurring after the first dose of the investigational drug, were considered for this analysis. To evaluate the sensitivity of our analyses to the selection of cutoff date for including an adverse event in the analysis dataset, two sets of analyses were conducted on adverse events that 1) occurred

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up to 30 days after the last dose of investigational drug, and 2) occurred prior to the last visit regardless it was scheduled or unscheduled.

Table 1: Preferred terms for defining a possible hypocalcemia event (MedDRA v11.0)

Index	Preferred Terms	This review	The sponsor
1	Hypocalcaemia	√	√
2	Blood calcium decreased	√	√
3	Calcium ionised decreased	√	√
4	Calcium deficiency	√	√
5	Paraesthesia	√	√
6	Paraesthesia oral	√	√
7	Hypoaesthesia	√	√
8	Hypoaesthesia oral	√	√
9	Tetany	√	√
10	Hypoparathyroidism	√	
11	Blood parathyroid hormone decreased	√	
12	Hypomagnesemia	√	
13	Magnesium deficiency	√	
14	Blood magnesium decreased	√	
15	Hyperphosphatemia	√	
16	Calcium phosphate product increased	√	
17	Blood phosphorus increased	√	
18	Vitamin D decreased	√	
19	Vitamin D deficiency	√	

4.2. Definition of hypocalcemia based on laboratory calcium data

To fully capture hypocalcemia events, laboratory data on serum calcium were used as supplemental sources. Although the most definitive method to identify clinically relevant alterations in serum calcium is based on ionized calcium values, the sponsor did not provide the data due to data collection issues. The sponsor provided three serum calcium measures: calcium values, calcium values corrected for albumin if albumin is less than 4g/dL, and calcium values corrected for albumin regardless of albumin values. According to the NCI/CTCAE v3.0 guidance, hypocalcemia is confirmed if the calcium value corrected for albumin when serum albumin is less than 4.0g/dl, computed as total calcium (mg/dl)-0.8[albumin(g/dl)-4], is below an institution's lower limit of normal (LLN) range. Following this guidance, the measurements of albumin-adjusted calcium were used in this review to evaluate hypocalcemia.

According to the sponsor, all laboratory serum calcium values were assessed at a central laboratory and a uniform LLN value of 8.5mg/dl applied to the albumin-adjusted calcium measurements collected in the two pivotal PMO studies (20040132 and 20030216) and a uniform LLN value of 8.4mg/dl applied to the calcium measurements in the two pivotal HALT studies (20040135 and 20040138). These two LLN values were used as the criteria for confirming potential hypocalcemia adverse events in the corresponding pivotal studies in this review.

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4.3. Stratification factors

4.3.1. 25-hydroxy vitamin D levels

Vitamin D is important in the absorption, metabolism, and function of calcium. Vitamin D deficiency can lead to low blood calcium. Although all study subjects should have a baseline serum 25-hydorxy vitamin D value greater than 20 ng/ml to be eligible (subjects with vitamin D values less than 20 ng/ml but greater than 12ng/ml at baseline were supplemented with 800-1000 IU vitamin D daily before being re-screened for eligibility), and were instructed to take at least 400 IU vitamin D daily during the treatment phase, subjects may still be at risk of low vitamin D for some study periods. Therefore, the impact of denosumab on hypocalcemia for subjects with various degrees of vitamin D levels was considered. 25-hydroxy vitamin D is considered the most accurate measure of the amount of vitamin D in a human body. The baseline values of this measure were used to classify subjects into four groups based on vitamin D levels. The normal 25-hydroxy vitamin D ranges provided by the sponsor varied by studies as shown in Table 2. Since the variations were relatively small, uniform cutoff values were used to obtain the vitamin D groups. According to guidance from the medical officer from FDA, the vitamin D subgroups were defined to be: less than 12ng/ml, no less than 12ng/ml to 20ng/ml, no less than 20ng/ml to 32ng/ml and greater than 32ng/ml.

Table 2: Normal ranges of 25-hydroxy vitamin D (ng/ml)

Study ID	Lower Limit of Normal Range (LLN)	Upper Limit of Normal Range (ULN)
20030216	9.5	52
20040132	9.5	52
20040135	10 or 15	68 or 80
20040138	9	37.6

4.3.2. Renal function

Low serum calcium levels are often seen in patients with kidney diseases. The impact of denosumab on hypocalcemia may vary by renal function. Because creatinine clearance provides more definitive information about the status of renal function than does creatinine, this measure was used in this review to evaluate a subject's baseline renal function.

The sponsor estimated the baseline values of creatinine clearance for all subjects in the four pivotal studies. The estimation equation adopted by the sponsor was Cockcroft and Gault equation as below:

$$\text{Creatinine Clearance}=\frac{(104-\text{age in years})\times\text{weight in kg}\times(0.85\text{ if female})}{72\times\text{serum creatinine in mg/dL}}$$. However, the sponsor did not provide the corresponding normal reference ranges for the estimated creatinine clearance values. After consulting a medical officer, uniform cutoffs were used to classify subjects into four renal function groups based on the estimated baseline creatinine clearance values. The creatinine clearance ranges of each group were less than

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30 ml/min, no less than 30 ml/min to 60 ml/min, no less than 60 ml/min to 90ml/min, and greater than or equal to 90ml/min.

4.4. Proton pump inhibitor (PPI) exposure

Hypocalcemia events can be influenced by concomitant use of PPI medications. In this review, PPI exposure was defined as whether one subject had received any PPI medications according to the World Health Organization ATC classification system and DDD assignment 2009 (http://www.whocc.no/atcddd/) across the entire study period. Table 3 shows the list of generic names for approved PPI medications by ATC/DDD index 2009.

Table 3: ATC codes and names of approved PPI (ATC code: A02BC) medications

ATC code	Name	DDD (mg)	Administration Route: Oral	Parenteral
A02BC01	omeprazole	20	√	√
A02BC02	pantoprazole	40	√	√
A02BC03	lansoprazole	30	√	
A02BC04	rabeprazole	20	√	
A02BC05	esomeprazole	30	√	√

4.5. Safety endpoints

Fifteen variables were derived and used to capture the frequency and the severity of hypocalcemia as summarized in Table 4. The first 14 variables are binary while the last is continuous. As noted earlier, the primary variable of interest, indicator variable 1, captured whether a subject had at least one hypocalcemia adverse event. This variable allows one to evaluate the incidence of hypocalcemia. Indicator variables 2-9 were derived based on the severity levels and toxicity grades of hypocalcemia adverse events assigned by the investigators, and were created to aid examine the severity of hypocalcemia.

Indicator variable 10 was used to determine whether one subject had any laboratory calcium value across the entire study period that fell below the pre-specified lower limit of normal range. In other words, this variable captured whether there was any confirmed hypocalcemia adverse event based on laboratory calcium measurements. Variables 11-14 are subject level variables based on laboratory calcium values. They show whether the lowest calcium value for one subject met the criterion for one of the non-death four toxicity grades according to NCI/CTCAE v3.0.

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Table 4: Variables of interest for the evaluation of hypocalcemia

	Variable Name	Description
1	Hypocalcemia AE (Primary)	Any adverse event with any of the MedDRA preferred terms as listed in Table 1.
2	Hypocalcemia Serious AE	Any adverse event classified as Serious.
3	Severe hypocalcemia AE	Any most severe adverse event categorized as Severe.
4	Modest hypocalcemia AE	Any most severe adverse event categorized as Modest.
5	Mild hypocalcemia AE	Any most severe adverse event categorized as Mild.
6	Grade 1 toxicity hypocalcemia AE	Any most toxic adverse event classified as Grade 1.
7	Grade 2 toxicity hypocalcemia AE	Any most toxic adverse event classified as Grade 2.
8	Grade 3 toxicity hypocalcemia AE	Any most toxic adverse event classified as Grade 3.
9	Grade 4 Toxicity hypocalcemia AE	Any most toxic adverse event classified as Grade 4.
10	Calcium corrected<8.5mg/dl	Any study period Corrected Calcium value that falls below 8.5mg/dl.
11	Grade 1 toxicity calcium value	Any lowest Corrected Calcium value across all study period <8.5mg/dl and ≥8.0mg/dl.
12	Grade 2 toxicity calcium value	Any lowest Corrected Calcium value across all study period <8.0mg/dl and ≥7.0mg/dl.
13	Grade 3 toxicity calcium value	Any lowest Corrected Calcium value across all study period <7.0mg/dl and ≥6.0mg/dl.
14	Grade 4 toxicity calcium value	Any lowest Corrected Calcium value across all study period <6.0mg/dl.
15	Max calcium difference	Maximum changes in Corrected Calcium values during any study period and calculated as: Min. Calcium value-Max. Calcium value.

According to the sponsor's protocols, abnormal lab findings without clinical significance were not recorded as AE, but lab values changes requiring therapy or adjustment in prior therapy were considered as AE. Therefore, the proportion of hypocalcemia adverse event determined based on albumin-adjusted calcium laboratory data is expected to be higher than those obtained based on adverse event data.

The last variable of interest is a continuous variable, which captures the maximum changes in albumin-adjusted calcium values. Large negative values mean serum calcium declines, which may suggest the occurrences of hypocalcemia.

4.6. Analysis methods

This analysis focuses on the safety population in all randomized, controlled clinical trials. The safety population, as defined by the sponsor, was comprised of all randomized subjects who received at least one dose of study treatment. The initial analysis was conducted on the four pivotal studies that were phase III, placebo-controlled clinical trials. The study IDs for the pivotal studies are 20030216, 20040132, 20040135 and 20040138. Additional analyses on non-pivotal studies which were also controlled, randomized trials with at least one denosumab arm were also conducted. The study IDs for these selected non-pivotal studies are 20010223, 20050141, 20050172, 20050179 and

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20050234. Denosumab dosing regimens tested in these studies include 100mg every 6 months (Q6M), 14mg every 3 months (Q3M), 14mg Q6M, 210mg Q6M, 30mg Q3M, 6mg Q3M, and 60mg Q6M. The route of administration for denosumab and placebo is subcutaneous (SC). An active control treatment, alendronate, was self-administered 70mg oral tablets weekly (QW). Table 5 and Table 6 show the intent to treat population sizes and the safety population sizes by treatment groups for all clinical studies involved in this analysis respectively.

Table 5: Sample sizes for the intent to treat population by studies and by treatments

Treatment Groups	Pivotal Studies (last 3 digits)				Non-pivotal Studies (last 3 digits)				
	216	132	135	138	223	141	179	234	172
alendronate 70mg QW	-	-	-	-	47	595	81	251	-
denosumab 100mg Q6M	-	-	-	-	42	-	-	-	57
denosumab 14mg Q3M	-	-	-	-	44	-	-	-	-
denosumab 14mg Q6M	-	-	-	-	54	-	-	-	57
denosumab 210mg Q6M	-	-	-	-	47	-	-	-	-
denosumab 30mg Q3M	-	-	-	-	41	-	-	-	-
denosumab 6mg Q3M	-	-	-	-	44	-	-	-	-
denosumab 60mg Q6M	3940	166	131	739	47	594	83	253	56
placebo	3928	166	121	729	46	-	83	-	56
Total subjects	7868	332	252	1468	412	1189	247	504	226

Table 6: Sample sizes for the safety population by studies and by treatments

Treatment Groups	Pivotal Studies (last 3 digits)				Non-pivotal Studies (last 3 digits)				
	216	132	135	138	223	141	179	234	172
alendronate 70mg QW	-	-	-	-	46	586	81	249	-
denosumab 100mg Q6M	-	-	-	-	41	-	-	-	51
denosumab 14mg Q3M	-	-	-	-	44	-	-	-	-
denosumab 14mg Q6M	-	-	-	-	53	-	-	-	53
denosumab 210mg Q6M	-	-	-	-	46	-	-	-	-
denosumab 30mg Q3M	-	-	-	-	40	-	-	-	-
denosumab 6mg Q3M	-	-	-	-	43	-	-	-	-
denosumab 60mg Q6M	3886	164	129	731	47	593	83	253	54
placebo	3876	165	120	725	46	-	83	-	54
Total subjects	7762	329	249	1456	406	1179	247	502	212

Data from off-treatment studies were used to determine the risk of hypocalcemia for subjects who no longer received denosumab for extended periods. The clinical trials for which the off-treatment assessments were conducted include PMO study 20040132 24-48month, HALT study 20040135, and HALT study 20040138. An open label PMO study 20060289 (extension study for study 20030216) was also evaluated. Separate analyses on the incidences of hypocalcemia based on adverse event data sets were carried out for each of the four trials separately. Additionally, the incidence of hypocalcemia on the laboratory calcium data was also evaluated for study 20040132. Laboratory data for the remaining three studies were not evaluated because they were not available. The sample sizes for the extension phase population are shown in Table 7.

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Table 7: Sample Sizes for the off-treatment studies

	Study ID			
	20060289	20040132	20040135	20040138
Safety Population	7762*	329	249	1456
denosumab 60mg Q6M	3886*	164	129	731
placebo	3876*	165	120	725
Extension Phase Population	4549	256	185	778
denosumab 60mg Q6M†	2346	128	96	406
placebo†	2203	128	89	372

Notes: *: Sample sizes are based on the safety population of study 20030216
†: For the open-label, single-arm extension study 20060289, the treatment groups are the original assignments in study 20030216.

To evaluate the effect of denosumab on the incidence of hypocalcemia, both parametric and nonparametric tests were performed. The statistical tests include Pearson Chi-Square Test, Fisher's Exact Test, Risk Difference with 95% asymptotic confidence intervals and 95% exact confidence intervals, and Risk Ratio with 95% asymptotic confidence intervals and 95% exact confidence intervals.

5. Findings

5.1. On-treatment evaluations

5.1.1. Hypocalcemia based on adverse events data

5.1.1.1. Distribution of hypocalcemia adverse events

Among a total of 12342 safety subjects across all nine trials, 11184 had at least one adverse event of any kind and 352 had at least one hypocalcemia adverse event as defined in Table 1. The number and proportion of subjects with various number of hypocalcemia adverse events across all four pivotal studies and the selected non-pivotal studies are shown in Table 8 and Table 9 respectively. 142 (2.89%) subjects in the denosumab 60mg Q6M group and 130 (2.66%) subjects in the placebo group across all pivotal studies had at least one hypocalcemia adverse event. For both groups, most subjects had only one occurrence of hypocalcemia.

Table 8: Number of hypocalcemia adverse events per subject across all pivotal studies

Treatment Group	Number of hypocalcemia adverse events n (%)					
	0	1	2	3	4	6
denosumab 60mg Q6M (N=4910)	4768 (97.11)	119 (2.42)	18 (0.37)	4 (0.08)	1 (0.02)	0 (0.00)
placebo (N=4886)	4756 (97.34)	113 (2.31)	15 (0.31)	0 (0.00)	1 (0.02)	1 (0.02)

406 subjects in Study 20010223 had missing values for the variable TRTA (actual treatment received). For these subjects, the values on variable ARM (planned treatment) were used instead. Most subjects with hypocalcemia adverse event had only one event.

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It is worth noting that one subject who received denosumab 60mg Q6M experienced four hypocalcemia episodes.

Table 9: Number of subjects with various number of hypocalcemia adverse events across all non-pivotal studies

Treatment Group	Number of hypocalcemia adverse events n (%)			
	0	1	2	4
alendronate 70mg QW (N=962)	943 (98.02)	18 (1.87)	1 (0.10)	0 (0.00)
denosumab 100mg Q6M (N=92)	84 (91.3)	7 (7.61)	1 (1.09)	0 (0.00)
denosumab 14mg Q3M (N=44)	37 (84.09)	4 (9.09)	3 (6.82)	0 (0.00)
denosumab 14mg Q6M (N=106)	102 (96.23)	3 (2.83)	1 (0.94)	0 (0.00)
denosumab 210mg Q6M (N=46)	44 (95.65)	2 (4.35)	0 (0.00)	0 (0.00)
denosumab 30mg Q3M (N=40)	38 (95.00)	2 (5.00)	0 (0.00)	0 (0.00)
denosumab 6mg Q3M (N=43)	42 (97.67)	0 (0.00)	1 (2.33)	0 (0.00)
denosumab 60mg Q6M (N=1030)	1003(97.38)	24 (2.33)	2 (0.19)	1 (0.10)
placebo (N=183)	173 (94.54)	10 (5.46)	0 (0.00)	0 (0.00)

5.1.1.2. Incidence of serious hypocalcemia adverse events

There were no deaths that can be attributed to hypocalcemia. Among the subjects in all four pivotal studies, four subjects had five serious hypocalcemia adverse events.

One subject (Unique Subject Id: 20030216-(b) (6) reported to have a serious hypocalcemia adverse event was an 80-year old, white woman from the United Kingdom. She was enrolled in the PMO study 20030216, received placebo drug, and completed the study. She experienced an event reported as "Hypocalcemia" and was hospitalized after this event. The event end date was not provided, so the duration of this adverse event is not known.

The remaining three subjects were all enrolled in HALT study 20040138. Subject 20040138(b) (6) was a 75-year old white man from the United States who received denosumab 60mg Q6M treatment. He had two episodes of serious hypocalcemia events. Both events occurred on the same day and lasted for three days. One episode was reported to be "numbness in left arm" and the other was reported to be "numbness in right hand." Both events were coded at the MedDRA Preferred Term level as "Hypoaesthesia." He was also hospitalized after these events.

The third subject who had a serious hypocalcemia adverse event was subject 20040138-(b) (6). He was an 83-year old white man recruited from Canada who received the placebo treatment. This adverse event was reported as "numbness right and left hands." After this event, this patient was hospitalized and removed from this study.

The fourth subject with serious hypocalcemia adverse event was assigned to the denosumab 60mg Q6M treatment group in the HALT study 20040138. This patient was an 83-year old white man from the United States. His unique subject id was 20040138-(b) (6). The serious event was reported as "Hypocalcemia" and it occurred 12 days after the patient received the most recent dose of denosumab and lasted for 9 days. After this

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event, this patient received medication, no longer received denosumab, was hospitalized and removed from this study.

5.1.1.3. Incidence of hypocalcemia

The primary objective is to compare the incidence of hypocalcemia between denosumab and placebo groups. The secondary focus is to evaluate whether subjects who received denosumab of proposed marketing dose were at higher risks of hypocalcemia compared with subjects who received the active comparator drug (i.e. alendronate 70mg QW).

The outline of this section is as follows. Section 5.1.1.3.1 presents the results of the pooled analysis based on four pivotal studies and five non-pivotal randomized controlled studies. Section 5.1.1.3.2 and Section 5.1.1.3.3 show the results on pivotal studies for PMO indications and HALT indications respectively.

5.1.1.3.1. Pooled analysis on pivotal and selected non-pivotal studies

Because of the low incidence of hypocalcemia, individual studies were pooled together, when appropriate, to support analysis. As defined earlier, an adverse event was defined as hypocalcemia if it was related to any pre-identified potential MedDRA preferred terms listed in Table 1. Table 10 presents the incidence of hypocalcemia by treatment groups based on all pivotal and all five non-pivotal randomized, controlled studies with at least one denosumab arm. Table 11 compares the incidences of hypocalcemia between proposed denosumab marketing dose group and placebo group on all pivotal studies and three selected placebo-controlled non-pivotal studies. Table 12 compares the incidences between the denosumab and the placebo groups on pivotal studies. Finally, Table 13 compares the incidences between the treatment groups on all non-pivotal studies. In all of the above tables, the placebo group was used as the reference in computing the inferential statistics for all denosumab groups. For alendronate group, the reference group was the proposed denosumab marketing dose treatment group. Because these analyses are exploratory, multiplicity correction issues are not considered.

The incidence of hypocalcemia was comparable between the denosumab group and the placebo group except for two non-marketing dose groups (denosumab 14mg Q3M and denosumab 100mg Q6M) on pooled pivotal and non-pivotal studies. Consistent results were observed across other sets of analysis.

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Table 10: Incidence of hypocalcemia of any potential Preferred Term on pivotal (20040132, 20030216, 20040135, and 20040318) and selected non-pivotal studies (20010223, 20050141, 20050172, 20050179, and 20050234)

Treatment Group	Incidence n (%)	P-values		Estimates (asymptotic 95% CI)	
		Chisq	Fisher	RD (%)	RR
denosumab Any Dose (N=6311)	193 (3.06)	0.3513	0.3708	0.30 (-0.32, 0.92)	1.11 (0.89, 1.37)
denosumab 6mg Q3M (N=43)	1 (2.33)	0.8619	1.0000	-0.44 (-4.96, 4.96)	0.84 (0.12, 5.88)
denosumab 14mg Q6M (N=106)	4 (3.77)	0.5308	0.5406	1.01 (-2.64, 4.67)	1.37 (0.52, 3.62)
denosumab 14mg Q3M (N=44)	7 (15.91)	<0.0001	<0.0001	13.15 (2.33, 23.96)	5.76 (2.86, 11.58)
denosumab 30mg Q3M (N=40)	2 (5.00)	0.7357	0.3060	2.24 (-4.53, 9.01)	1.81 (0.46, 7.06)
denosumab 60mg Q6M (N=5940)	169 (2.85)	0.7921	0.8170	0.08 (-0.54, 0.70)	1.03 (0.83, 1.28)
denosumab 100mg Q6M (N=92)	8 (8.70)	*0.0007*	*0.0046*	5.93 (0.16, 11.71)	3.15 (1.59, 6.23)
denosumab 210mg Q6M (N=46)	2 (4.35)	0.5145	0.3668	1.59 (-4.32, 7.50)	1.57 (0.40, 6.17)
alendronate 70mg QW * (N=962)	19 (1.98)	0.1241	0.1352	-0.87 (-1.85, 0.11)	0.69 (0.43, 1.11)
placebo (N=5069)	140 (2.76)	NA	NA	NA	NA

Note: * denosumab 60mg Q6M was treated as the reference group

Table 11: Incidence of hypocalcemia of any potential Preferred Term on pivotal PMO studies (20040132 and 20030216) and selected non-pivotal PMO studies with placebo arm (20010223, 20050172, and 20050179)

Treatment Group	Incidence n (%)	P-values		Estimates (asymptotic 95% CI)	
		Chisq	Fisher	RD (%)	RR
denosumab 60mg Q6M (N=4234)	121 (2.86)	0.9627	1.0000	0.02 (-0.69, 0.73)	1.01 (0.78, 1.29)
placebo (N=4224)	120 (2.84)	NA	NA	NA	NA

Table 12: Incidence of hypocalcemia of any potential Preferred Term on pivotal studies only (20040132, 20030216, 20040135, and 20040318)

Treatment Group	Incidence n (%)	P-values		Estimates (asymptotic 95% CI)	
		Chisq	Fisher	RD (%)	RR
denosumab 60mg Q6M (N=4910)	142 (2.89)	0.4858	0.4992	0.23 (-0.42, 0.88)	1.09 (0.86, 1.37)
placebo (N=4886)	130 (2.66)	NA	NA	NA	NA

Reference ID: 3168397

Table 13: Incidence of hypocalcemia of any potential Preferred Term on non-pivotal studies only (20010223, 20050141, 20050172, 20050179, and 20050234)

Treatment Group	Incidence n (%)	P-values		Estimates (asymptotic 95% CI)	
		Chisq	Fisher	RD (%)	RR
denosumab 6mg Q3M (N=43)	1 (2.33)	0.3894	0.6948	-3.14 (-8.72, 2.44)	0.43 (0.06, 3.24)
denosumab 14mg Q6M (N=106)	4 (3.77)	0.5188	0.5842	-1.69 (-6.59, 3.21)	0.69 (0.22, 2.15)
denosumab 14mg Q3M (N=44)	7 (15.91)	0.0181	0.0268	10.44 (-0.85, 21.74)	2.91 (1.17, 7.22)
denosumab 30mg Q3M (N=40)	2 (5.00)	0.9061	1.0000	-0.46 (-7.98, 7.05)	0.92 (0.21, 4.02)
denosumab 60mg Q6M (N=1030)	27 (2.62)	0.0393	0.0575	-2.84 (-6.28, 0.59)	0.48 (0.24, 0.97)
denosumab 100mg Q6M (N=92)	8 (8.70)	0.3067	0.3118	3.23 (-3.40, 9.86)	1.59 (0.65, 3.90)
denosumab 210mg Q6M (N=46)	2 (4.35)	0.7613	1.0000	-1.12 (-7.87, 5.63)	0.80 (0.18, 3.51)
alendronate 70mg QW * (N=962)	19 (1.98)	0.3372	0.3725	-0.65 (-1.96, 0.67)	0.75 (0.42, 1.35)
placebo (N=183)	10 (5.46)	NA	NA	NA	NA

Note: * denosumab 60mg Q6M was treated as the reference group

5.1.1.3.2. PMO indications

Table 14 shows the frequencies and incidences of potential hypocalcemia on the pooled PMO pivotal studies (i.e. 20040132 and 20030216). In total, 4050 subjects received denosumab 60mg Q6M and 4041 subjects received placebo.

No subject in the denosumab group was recorded to have an adverse effect that could be specifically named as "Hypocalcemia." Two subjects in the placebo groups were reported to have at least one specific hypocalcemia adverse event.

The counts and proportions of subjects who experienced any potential hypocalcemia event were similar for both treatment groups (112 (2.77%) for denosumab 60mg Q6M group and 110 (2.72%) for the placebo group). Statistical tests, e.g. Chi-square test, Fisher's exact test, as well as risk differences and risk ratios, for comparing the incidences of events between the two treatment groups were not statistically significant. Comparisons of incidences of hypocalcemia between the two treatment groups were also conducted at the MedDRA grouping levels of System Organ Class, High Level Group Term, High Level Term and Preferred Term respectively. The majority of hypocalcemic events were captured via the preferred terms of *Paresthesia* and *Hypoesthesia*. Both terms fell under *Nervous system disorders* System Organ Class, *Neurological disorders NEC* High Level Group Term. In terms of High Level Term, *Paresthesia* fell under *Paraesthesias and dysaesthesias* and *Hypoesthesia* fell under *Sensory abnormalities NEC*. At all of the above MedDRA levels, the difference of incidences between the denosumab and the placebo groups were not statistically significant.

Reference ID: 3168397

Reference ID: 3168397

Table 14: Frequency and incidence of hypocalcemia on the pooled PMO safety population by MedDRA (v11.0) Preferred Term, System Organ Class, High Level Group Term and High Level Term

MedDRA Grouping Level	MedDRA Terms	Treatment Group		P-values		Estimates (asymptotic 95% CI)	
		denosumab 60mg Q6M N=4050 n (%)	placebo N=4041 n (%)	Chisq	Fisher	RD (%)	RR
Any PT	Any Preferred Term related to hypocalcemia	112 (2.77)	110 (2.72)	0.9050	0.9458	0.04 (-0.67, 0.76)	1.02 (0.78, 1.32)
System Organ Class	Endocrine disorders	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Gastrointestinal disorders	2 (0.05)	3 (0.07)	0.6528	0.6871	-0.02 (-0.17, 0.11)	0.67 (0.13, 3.33)
	Investigations	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Metabolism and nutrition disorders	1 (0.02)	3 (0.07)	0.3161	0.3744	-0.05 (-0.20, 0.07)	0.33 (0.05, 2.32)
	Nervous system disorders	104 (2.57)	100 (2.47)	0.7890	0.8316	0.09 (-0.59, 0.78)	1.04 (0.79, 1.36)
High Level Group Term	Bone, calcium, magnesium and phosphorus metabolism disorders	0 (0.00)	2 (0.05)	0.1568	0.2494	-0.05 (-0.18, 0.05)	0.00 (0.00, 1.92)
	Neurological disorders NEC	104 (2.57)	100 (2.47)	0.7890	0.8316	0.09 (-0.59, 0.78)	1.04 (0.79, 1.36)
	Oral soft tissue conditions	2 (0.05)	3 (0.07)	0.6528	0.6871	-0.02 (-0.17, 0.11)	0.67 (0.13, 3.33)
	Parathyroid gland disorders	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Vitamin related disorders	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.10, 9.56)
	Water, electrolyte and mineral investigations	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
High Level Term	Calcium metabolism disorders	0 (0.00)	2 (0.05)	0.1568	0.2494	-0.05 (-0.18, 0.05)	0.00 (0.00, 1.92)
	Fat soluble vitamin deficiencies and disorders	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.10, 9.56)
	Hypoparathyroid disorders	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Mineral and electrolyte analyses	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
	Oral soft tissue pain and paraesthesia	1 (0.02)	2 (0.05)	0.5623	0.6245	-0.02 (-0.16, 0.09)	0.50 (0.07, 3.81)
	Oral soft tissue signs and symptoms	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.10, 9.56)
	Paraesthesias and dysaesthesias	65 (1.60)	60 (1.48)	0.6613	0.7186	0.12 (-0.42, 0.67)	1.08 (0.76, 1.53)
	Sensory abnormalities NEC	42 (1.04)	42 (1.04)	0.9918	1.0000	0.00 (-0.45, 0.45)	1.00 (0.65, 1.52)
Preferred Term	Hypocalcaemia	0 (0.00)	2 (0.05)	0.1568	0.2494	-0.05 (-0.18, 0.05)	0.00 (0.00, 1.92)
	Paraesthesia	65 (1.60)	60 (1.48)	0.6613	0.7186	0.12 (-0.42, 0.67)	1.08 (0.76, 1.53)

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Paraesthesia oral	1 (0.02)	2 (0.05)	0.5623	0.6245	-0.02 (-0.16, 0.09)	0.50 (0.07, 3.81)
Hypoaesthesia	42 (1.04)	42 (1.04)	0.9918	1.0000	0.00 (-0.45, 0.45)	1.00 (0.65, 1.52)
Hypoaesthesia oral	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.10, 9.56)
Hypoparathyroidism	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
Blood magnesium decreased	1 (0.02)	0 (0.00)	0.3178	1.0000	0.02 (-0.07, 0.14)	NA
Vitamin D deficiency	1 (0.02)	1 (0.02)	0.9987	1.0000	0.00 (-0.12, 0.12)	1.00 (0.61, 5.71)

5.1.1.3.3. HALT indications

Table 15 and Table 16 present the frequencies and incidences of hypocalcemia for study 20040135 and study 20040138 respectively. For 20040135, no subject was identified to have specific Hypocalcemia adverse event in either treatment groups. The incidences of hypocalcemia at all MedDRA grouping levels were comparable between the two treatment groups.

Table 15: Frequency and incidence of hypocalcemia on the safety population of 20040135 by MedDRA (v9.0) Preferred Term, System Organ Class, High Level Group Term and High Level Term

MedDRA Grouping Level	MedDRA Terms	Treatment Group		P-values		Estimates (Exact 95% CI)	
		denosumab 60mg G6M N=129 n (%)	placebo N=120 n (%)	Chisq	Fisher	RD (%)	RR
Any PT	Any Preferred Term related to hypocalcemia	8 (6.20)	4 (3.33)	0.2910	0.3797	2.87 (-3.28, 8.98)	1.86 (0.61, 7.15)
SOC	Gastrointestinal disorders	1 (0.78)	0 (0.00)	0.3338	1.0000	0.78 (-2.60, 4.68)	NA
	Nervous system disorders	7 (5.43)	4 (3.33)	0.4219	0.5426	2.09 (-3.87, 8.25)	1.63 (0.51, 6.89)
HLGT	Neurological disorders NEC	7 (5.43)	4 (3.33)	0.4219	0.5426	2.09 (-3.87, 8.25)	1.63 (0.51, 6.89)
	Oral soft tissue conditions	1 (0.78)	0 (0.00)	0.3338	1.0000	0.78 (-2.60, 4.68)	NA
HLT	Oral soft tissue pain and paraesthesia	1 (0.78)	0 (0.00)	0.3338	1.0000	0.78 (-2.60, 4.68)	NA
	Paraesthesias and dysaesthesias	2 (1.55)	2 (1.67)	0.9419	1.0000	-0.12 (-4.58, 4.19)	0.93 (0.12, 7.19)
	Sensory abnormalities NEC	6 (4.65)	4 (3.33)	0.5966	0.7505	1.32 (-4.48, 7.09)	1.40 (0.43, 6.41)
PT	Paraesthesia	2 (1.55)	2 (1.67)	0.9419	1.0000	-0.12 (-4.58, 4.19)	0.93 (0.12, 7.19)
	Paraesthesia oral	1 (0.78)	0 (0.00)	0.3338	1.0000	0.78 (-2.60, 4.68)	NA
	Hypoaesthesia	6 (4.65)	4 (3.33)	0.5966	0.7505	1.32 (-4.48, 7.09)	1.40 (0.43, 6.41)

Reference ID: 3168397

For 20040138, one subject who received denosumab was identified to have specific hypocalcemia events and no subject in the placebo group had any specific hypocalcemia events. The incidences of hypocalcemia were comparable between the treatment groups at all MedDRA grouping levels. This finding is consistent with the those from the pooled PMO analysis and 20040135 analysis.

Table 16: Frequency and incidence of hypocalcemia on the safety population of 20040138 by MedDRA (v9.0) Preferred Term, System Organ Class, High Level Group Term and High Level Term

MedDRA Grouping Level	MedDRA Terms	Treatment Group		P-values		Estimates (Exact 95% CI)	
		Denosumab 60mg Q6M N=731 n (%)	placebo N=725 n (%)	Chisq	Fisher	RD (%)	RR
Any PT	Any Preferred Term related to hypocalcemia	22 (3.01)	16 (2.21)	0.3368	0.4116	0.80 (-0.93, 2.55)	1.36 (0.72, 2.56)
SOC	Metabolism and nutrition disorders	1 (0.14)	0 (0.00)	0.9953	1.0000	0.00 (-0.72, 0.72)	0.99 (0.06, 16.65)
	Nervous system disorders	21 (2.87)	15 (2.07)	0.3234	0.3993	0.80 (-0.87, 2.52)	1.39 (0.72, 2.65)
HLGT	Bone, calcium, magnesium and phosphorus metabolism disorders	1 (0.14)	0 (0.00)	0.3191	1.0000	0.14 (-0.42, 0.82)	NA
	Neurological disorders NEC	21 (2.87)	15 (2.07)	0.3234	0.3993	0.80 (-0.87, 2.52)	1.39 (0.72, 2.65)
	Vitamin related disorders	0 (0.00)	1 (0.14)	0.3152	0.4979	-0.14 (-0.83, 0.41)	0.00 (0.00, 7.94)
HLT	Calcium metabolism disorders	1 (0.14)	0 (0.00)	0.3191	1.0000	0.14 (-0.42, 0.82)	NA
	Fat soluble vitamin deficiencies and disorders	0 (0.00)	1 (0.14)	0.3152	0.4979	-0.14 (-0.83, 0.41)	0.00 (0.00, 7.94)
	Paraesthesias and dysaesthesias	6 (0.82)	6 (0.83)	0.9886	1.0000	-0.01 (-1.11, 1.08)	0.99 (0.34, 2.90)
	Sensory abnormalities NEC	16 (2.19)	9 (1.24)	0.1641	0.2256	0.95 (-0.43, 2.44)	1.76 (0.80, 3.94)
PT	Hypocalcaemia	1 (0.14)	0 (0.00)	0.3191	1.0000	0.14 (-0.42, 0.82)	NA
	Paraesthesia	6 (0.82)	6 (0.83)	0.9886	1.0000	-0.01 (-1.11, 1.08)	0.99 (0.34, 2.90)
	Hypoaesthesia	16 (2.19)	9 (1.24)	0.1641	0.2256	0.95 (-0.43, 2.44)	1.76 (0.80, 3.94)
	Vitamin D deficiency	0 (0.00)	1 (0.14)	0.3152	0.4979	-0.14 (-0.83, 0.41)	0.00 (0.00, 7.94)

5.1.1.4. Subgroup analysis on the incidence of hypocalcemia

5.1.1.4.1. Incidence of hypocalcemia by baseline vitamin D levels

Baseline vitamin D values were missing for two subjects in each of the four pivotal studies. The unique subject identification numbers were 2030216-(b) (6), 20030216-(b) (6), 20040132-(b) (6) 20040132-(b) (6), 20040135(b) (6), 20040135-(b) (6) 20040138-(b) (6) and 20040138(b) (6). Six of them were from North America, one from Western Europe and one from Latin America. Five were assigned to the placebo treatment and the rest were assigned to the Denosumab 60mg Q6M treatment. Six of them completed the study, one failed to comply due to a vacation occurred before month-18-visit, and the other subject did not complete because of "disease progression due to bone loss." None of them were identified as hypocalcemia patients based on adverse events data.

Table 17, Table 18 and Table 19 summarize the incidences of hypocalcemia of any potential preferred term and of each preferred term by baseline vitamin D values on the pooled pivotal PMO studies, the pivotal study 20040135 and the pivotal study 20040138 respectively. For the pooled PMO studies, the incidences of hypocalcemia with any potential PT and with each PT were comparable between the treatment groups. For study 20040135, among subjects whose baseline vitamin D were between 12ng/ml and 20ng/ml, the incidence of hypocalcemia with any potential PT was 6 (9.68%) for the denosumab group and zero for the placebo group. For study 20040138, the incidences of hypocalcemia were similar across the two treatment groups in all vitamin D groups.

5.1.1.4.2. Incidence of hypocalcemia by baseline renal function

A total of seven subjects had missing values on baseline creatinine clearance. Subject 20030216-(b) (6) also had a missing value on creatinine. This subject was a white woman from Czech Republic who was 70-year old at the time of assignment to denosumab treatment. Her other baseline lab test results were within normal ranges. It appears that the other six subjects had missing values for creatinine clearance because their baseline weights were missing. These subjects were excluded from this stratified analysis.

Table 20, Table 21 and Table 22 present the subgroup analysis on the incidences of hypocalcemia by baseline creatinine clearance levels for the pooled pivotal PMO studies, the pivotal study 20040135 and the pivotal study 20040138 respectively. In an analysis similar to the subgroup analysis by baseline vitamin D levels, incidences of hypocalcemia was evaluated for adverse events defined by any potential PT and adverse events defined by each PT. For all three sets of analyses, the incidences of hypocalcemia were similar between the denosumab group and the placebo group.

Reference ID: 3168397

Reference ID: 3168397

Table 17: Incidence of hypocalcemia by baseline vitamin D levels for the pooled safety population of PMO studies (study 20040132-24 month and study 20030216)

MedDRA Preferred Terms	Vitamin D <12 (ng/ml) Treatment Group		12≤Vitamin D<20 (ng/ml) Treatment Group		20≤Vitamin D<32 (ng/ml) Treatment Group		Vitamin D≥32 (ng/ml) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	10	9	2028	2016	1380	1410	630	604
Any potential Preferred Term	0	0	58 (2.86)	52 (2.58)	36 (2.61)	37 (2.62)	18 (2.86)	21 (3.48)
Paraesthesia	0	0	30 (1.48)	27 (1.34)	25 (1.81)	20 (1.42)	10 (1.59)	13 (2.15)
Hypoaesthesia	0	0	26 (1.28)	18 (0.89)	9 (0.65)	14 (0.99)	7 (1.11)	10 (1.66)
Hypoparathyroidism	0	0	1 (0.05)	0	0	0	0	0
Blood magnesium decreased	0	0	1 (0.05)	0	0	0	0	0
Vitamin D deficiency	0	0	1 (0.05)	0	0	0	0	0

Table 18: Incidence of hypocalcemia by baseline vitamin D levels for the safety population of study 20040135

MedDRA Preferred Terms	Vitamin D <12 (ng/ml) Treatment Group		12≤Vitamin D<20 (ng/ml) Treatment Group		20≤Vitamin D<32 (ng/ml) Treatment Group		Vitamin D≥32 (ng/ml) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	16	26	62	47	50	46	0	0
Any potential Preferred Term	0	1 (3.85)	6 (9.68) **	0	2 (4.00)	3 (6.52)	0	0
Paraesthesia	0	1 (3.85)	1 (1.61)	0	1 (2.00)	1 (2.17)	0	0
Paraesthesia oral	0	0	1 (1.61)	0	0	0	0	0
Hypoaesthesia	0	1 (3.85)	4 (6.45)	0	2 (4.00)	3 (6.52)	0	0

Note: ** Fisher's exact test P-value=0.03565

Reference ID: 3168397

Table 19: Incidence of hypocalcemia by baseline vitamin D levels for the safety population of 20040138 study

MedDRA Preferred Terms	Vitamin D <12 (ng/ml) Treatment Group		12≤Vitamin D<20 (ng/ml) Treatment Group		20≤Vitamin D<32 (ng/ml) Treatment Group		Vitamin D≥32 (ng/ml) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	4	4	194	191	381	377	152	151
Any potential Preferred Term	0	0	3 (1.55)	4 (2.09)	15 (3.94)	9 (2.39)	4 (2.63)	3 (1.99)
Hypocalcaemia	0	0	0	0	0	0	1 (0.66)	0
Paraesthesia	0	0	0	1 (0.52)	6 (1.57)	5 (1.33)	0	0
Hypoaesthesia	0	0	3 (1.55)	3 (1.57)	10 (2.62)*	3 (0.80)	3 (1.97)	3 (1.99)
Vitamin D deficiency	0	0	0	0	0	1 (0.27)	0	0

Note: * Fisher's exact test P-value=0.0896

Table 20: Incidence of hypocalcemia by baseline creatinine clearance levels for the pooled safety population of PMO studies (study 20040132-24 month and study 20030216)

MedDRA Preferred Terms	Cr.Clearance<30 (ml/min) Treatment Group		30≤Cr.Clearance<60 (ml/min) Treatment Group		60≤Cr.Clearance<90 (ml/min) Treatment Group		Cr.Clearance≥90 (ml/min) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	36	37	1425	1408	2089	2124	498	469
Any potential Preferred Term	0	1 (2.70)	36 (2.53)	37 (2.63)	66 (3.16)	62 (2.92)	10 (2.01)	9 (1.92)
Hypocalcaemia	0	1 (2.70)	0	0	0	1 (0.05)	0	0
Paraesthesia	0	0	18 (1.26)	23 (1.63)	45 (2.15)	32 (1.51)	2 (0.40)	5 (1.07)
Paraesthesia oral	0	0	1 (0.07)	0	0	2 (0.09)	0	0
Hypoaesthesia	0	0	17 (1.19)	12 (0.85)	18 (0.86)	24 (1.13)	7 (1.41)	5 (1.07)
Hypoaesthesia oral	0	0	1 (0.07)	0	0	0	0	1 (0.21)
Hypoparathyroidism	0	0	0	0	1 (0.05)	0	0	0
Blood magnesium decreased	0	0	0	0	1 (0.05)	0	0	0
Vitamin D deficiency	0	0	0	1 (0.07)	1 (0.05)	0	0	0

Reference ID: 3168397

Table 21: Incidence of hypocalcemia by baseline creatinine clearance levels for the safety population of study 20040135

MedDRA Preferred Terms	Cr.Clearance<30 (ml/min) Treatment Group		30≤Cr.Clearance<60 (ml/min) Treatment Group		60≤Cr.Clearance<90 (ml/min) Treatment Group		Cr.Clearance≥90 (ml/min) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	12	11	58	57	59	51	0	0
Any potential Preferred Term	0	0	3 (5.17)	1 (1.75)	5 (8.47)	3 (5.88)	0	0
Paraesthesia	0	0	0	0	2 (3.39)	2 (3.92)	0	0
Paraesthesia oral	0	0	0	0	1 (1.69)	0	0	0
Hypoaesthesia	0	0	3 (5.17)	1 (1.75)	3 (5.08)	3 (5.88)	0	0

Table 22: Incidence of hypocalcemia by baseline creatinine clearance levels for the safety population of study 20040138

MedDRA Preferred Terms	Cr.Clearance<30 (ml/min) Treatment Group		30≤Cr.Clearance<60 (ml/min) Treatment Group		60≤Cr.Clearance<90 (ml/min) Treatment Group		Cr.Clearance≥90 (ml/min) Treatment Group	
	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)	Dmab n (%)	Placebo n (%)
Number of subjects	4	2	173	183	350	341	203	199
Any potential Preferred Term	1 (25.00)	0	2 (1.16)	2 (1.09)	13 (3.71)	9 (2.64)	6 (2.96)	5 (2.51)
Hypocalcaemia	1 (25.00)	0	0	0	0	0	0	0
Paraesthesia	0	0	1 (0.58)	1 (0.55)	3 (0.86)	1 (0.29)	2 (0.99)	4 (2.01)
Hypoaesthesia	0	0	1 (0.58)	1 (0.55)	11 (3.14)	7 (2.05)	4 (1.97)	1 (0.50)
Vitamin D deficiency	0	0	0	0	0	1 (0.29)	0	0

5.1.1.5. PPI exposure on hypocalcemia

Table 23 shows the frequency and percentage of subjects with different number of PPI medications. Approximately 15% to 18% subjects had at least one PPI medication across all four pivotal studies. The majority of PPI exposed subjects had only one PPI medication. The maximum number of PPI medications per subject was around 3 to 4 for study 20040132, study 20040135, and study 20040138. For study 20030216, the maximum number of PPI medication one received is 10 and this occurred on only one subject.

Table 23: Frequency and percentage of subjects with different number of PPI medications by study

Study ID	No. of PPI Medications	No. of subjects	Percentage
20030216	0	6463	82.2
	1	997	12.7
	2	267	3.4
	3	94	1.2
	4	27	0.3
	5	9	0.1
	6	4	0.1
	10	1	0.0
20040132	0	285	85.8
	1	34	10.2
	2	10	3.0
	3	3	0.9
20040135	0	209	82.9
	1	31	12.3
	2	11	4.4
	4	1	0.4
20040138	0	1248	85.0
	1	180	12.3
	2	29	2.0
	3	7	0.5
	4	4	0.3

Table 24 presents the incidence of hypocalcemia for both treatment groups by PPI exposure status and by study. Within both PPI exposure groups, the incidence of hypocalcemia is similar between the two treatment groups for the pooled PMO studies (20040132 and 20030216), study 20040135, and study 20040138. For example, for the pooled PMO studies, the incidence of hypocalcemia is approximately 3.2% for both treatment groups among subjects with PPI exposure, and the incidence is around 2.6% for both treatment groups among subject without PPI exposure. However, based on additional logistic regression analysis of PPI exposure and treatments on the incidence of hypocalcemia (results not shown in the review), PPI exposure is associated with hypocalcemia for study 20040135 and study 20040138 regardless of treatment groups. In other words, subjects with PPI exposure were more likely to experience hypocalcemia than those with no PPI exposure for study 20040135 and study 20040138.

Reference ID: 3168397

Table 24: Incidence of hypocalcemia within PPI exposed group and PPI not-exposed group by study

Study		PPI Exposed		PPI Not-exposed	
		denosumab 60mg Q6M	placebo	denosumab 60mg Q6M	placebo
Pooled PMO	No. of subjects	726	716	3324	3325
	No. (%) of cases	23 (3.2)	23 (3.2)	89 (2.7)	87 (2.6)
20040135	No. of subjects	16	27	615	621
	No. (%) of cases	2 (18.8)	2 (7.4)	5 (4.4)	2 (2.2)
20040138	No. of subjects	116	104	615	621
	No. (%) of cases	8 (6.9)	4 (3.8)	14 (2.3)	12 (1.9)

5.1.1.6. Severity/toxicity of hypocalcemia

5.1.1.6.1. Severity of hypocalcemia for PMO indications

The incidence of hypocalcemia of any potential PT and by each PT by severity levels on the pooled pivotal PMO studies (i.e. 20040132 and 20030216) are shown in Table 25. Most events were mild or moderate. Two denosumab treated subjects had at least one severe event. Both subjects were identified via potential symptoms of hypocalcemia. One subject was identified as having severe Paraesthesia and the other subject was identified as having severe Hypoaesthesia. In comparison, a total of six subjects who received the placebo drug had severe events. One subject experienced a severe Hypocalcemia episode, one subject had severe Paraesthesia and four subjects had severe Hypoaesthesia. To summarize the results, the incidences of hypocalcemia at each severity level were similar between the denosumab group and the placebo group.

Reference ID: 3168397

Table 25: Incidence of hypocalcemia of any potential Preferred Term and by Preferred Term with differential severity levels on pooled PMO studies (20040132 and 20030216)

MedDRA Preferred Terms	Severity Level	Treatment Group	
		denosumab 60mg G6M n (%)	Placebo n (%)
Number of subjects		N=4050	N=4041
Any potential Preferred Term	Mild	79 (1.95)	77 (1.91)
	Moderate	29 (0.72)	26 (0.64)
	Severe	2 (0.05)	6 (0.15)
Hypocalcaemia	Moderate	0 (0.00)	1 (0.02)
	Severe	0 (0.00)	1 (0.02)
Paraesthesia	Mild	51 (1.26)	42 (104)
	Moderate	13 (0.32)	17 (0.42)
	Severe	1 (0.02)	1 (0.02)
Paraesthesia oral	Mild	0 (0.00)	1 (0.02)
	Moderate	1 (0.02)	1 (0.02)
Hypoaesthesia	Mild	27 (0.67)	30 (0.74)
	Moderate	14 (0.35)	8 (0.20)
	Severe	1 (0.02)	4 (0.10)
Hypoaesthesia oral	Mild	1 (0.02)	1 (0.02)
Hypoparathyroidism	Moderate	1 (0.02)	0 (0.00)
Blood magnesium decreased	Moderate	1 (0.02)	0 (0.00)
Vitamin D deficiency	Mild	0 (0.00)	1 (0.02)
	Moderate	1 (0.02)	0 (0.00)

5.1.1.6.2. Toxicity of hypocalcemia for HALT indications

Table 26 shows the incidences of hypocalcemia of any potential PT and by each PT at different toxicity grades by treatment groups. Most events were graded at toxicity level 1 or 2. For study 20040138, two subjects in denosumab group had toxicity grade 3 adverse events. One of the two subjects had toxicity grade 3 Hypocalcaemia and the other subject had toxicity grade 3 Hypoaesthesia. Except for this observation, the incidences were comparable across the two treatment groups at all toxicity grades.

Reference ID: 3168397

Table 26: Incidence of hypocalcemia of any potential Preferred Term and by Preferred Term with differential toxicity grades on study 20040135 and study 20040138 separately

Study ID	MedDRA Preferred Term	Toxicity Grade	Treatment Group	
			denosumab 60mg G6M n (%)	placebo n (%)
Study 20040135	Number of subjects		N=129	N=120
	Any potential Preferred Term	Grade 1	7 (5.43)	3 (2.50)
		Grade 2	1 (0.78)	1 (0.83)
	Paraesthesia	Grade 1	1 (0.78)	2 (1.67)
		Grade 2	1 (0.78)	0 (0.00)
	Paraesthesia oral	Grade 1	1 (0.78)	0 (0.00)
	Hypoaesthesia	Grade 1	7 (5.43)	3 (2.50)
		Grade 2	0 (0.00)	1 (0.83)
Study 20040138	Number of subjects		N=731	N=725
	Any potential Preferred Term	Grade 1	14 (1.92)	10 (1.38)
		Grade 2	6 (0.82)	5 (0.69)
		Grade 3	2 (0.27)	0 (0.00)
	Hypocalcaemia	Grade 3	1 (0.14)	0 (0.00)
	Paraesthesia	Grade 1	4 (0.55)	5 (0.69)
		Grade 2	2 (0.27)	1 (0.14)
	Hypoaesthesia	Grade 1	11 (1.50)	5 (0.69)
		Grade 2	4 (0.55)	4 (0.55)
		Grade 3	1 (0.14)	0 (0.00)
	Vitamin D deficiency	Grade 1	0 (0.00)	1 (0.14)

5.1.2. Hypocalcemia based on laboratory data

5.1.2.1. Incidence and toxicity of hypocalcemia

A hypocalcemia event based on laboratory findings was confirmed if the lowest albumin-adjusted calcium value across the entire study fell below 8.5mg/dl. The toxicity level for such a hypocalcemia adverse event was also determined following NCI/CTCAT v3.0 guidance. Table 27 shows the incidences of hypocalcemia based on the laboratory data for the pooled PMO studies, Study 20040135 and Study 20040138 separately.

Reference ID: 3168397

Table 27: Incidence of hypocalcemia defined as albumin-adjusted calcium<8.5mg/dl*

Study ID	denosumab 60mg Q6M		placebo		P-values		Estimates (asymptotic 95% CI)	
	n (%)	No. of subj.	n (%)	No. of subj.	Chisq	Fisher	RD (%)	RR
Pooled PMO	72 (1.78)	4050	20 (0.49)	4041	<.0001	<.0001	1.28 (0.82, 1.74)	3.59 (2.19, 5.88)
20040135	2 (1.55)	129	2 (1.67)	120	0.9419	1.000	-0.12 (-3.25, 3.01)	0.93 (0.13, 6.50)
20040138	27 (3.69)	731	5 (0.69)	725	<.0001	<.0001	3.00 (1.51, 4.50)	5.36 (2.07, 13.8341)

Note: * A LLN value of 8.4mg/dl is used for Study 20040135 and Study 20040138.

For the pooled PMO analysis (study 20040132 and study 20030216), 72 (1.78%) subjects who received denosumab had at least one albumin-adjusted calcium value less than 8.5mg/dl, and in comparison, 20 (0.49%) placebo treated subjects had at least one calcium value that falls below 8.5mg/dl. The relative risk of experiencing hypocalcemia was 3.59 for denosumab relative to placebo, and the Fisher's exact test for this incidence discrepancy was significant at .0001 level. For study 20040135, the incidences were comparable between the two treatment groups. For study 20040138, the relative risk of having hypocalcemia was 5.36 for denosumab treated subjects compared to placebo treated subjects, which was also statistically significant. The sensitivity of this analysis to the use of different calcium measures was evaluated. The findings on the total serum calcium values and the albumin-adjusted calcium values regardless of subjects' albumin levels are consistent with the results presented in Table 27.

Table 28 shows that most laboratory-confirmed hypocalcemia adverse events were toxicity-grade-1 events. Denosumab was found to be associated with higher risks of toxicity grade 1 hypocalcemia events for the pooled PMO studies (study 20040132 and study 20030216) and the HALT study 20040138. The incidence of toxicity grade 2 hypocalcemia was comparable between the denosumab and the placebo groups for all pivotal studies.

Table 28: Toxicity grades of hypocalcemia on laboratory albumin-adjusted calcium levels

Study ID	Toxicity Grade	denosumab 60mg Q6M		placebo		P-values		Estimates (asymptotic 95% CI)	
		n (%)	No.of subj.	n (%)	No.of subj.	Chisq	Fisher	RD (%)	RR
Pooled PMO	1	65 (1.60)	4050	15 (0.37)	4041	<.0001	<.0001	1.22 (0.80, 1.65)	4.32 (2.47, 7.57)
Pooled PMO	2	7 (0.17)	4050	4 (0.10)	4041	0.3675	0.5486	0.07 (-0.09, 0.23)	1.75 (0.51, 5.96)
Pooled PMO	3	0 (0.00)	4050	1 (0.02)	4041	0.3167	0.4994	-0.02 (-0.07, 0.02)	0.33 (0.01, 8.16)
20040135	1	2 (1.55)	129	2(1.67)	120	0.9419	1.000	-0.12 (-3.25, 3.01)	0.93 (0.13, 6.50)
20040138	1	24 (3.28)	731	4 (0.55)	725	0.0001	0.0002	2.73 (1.33, 4.13)	5.95 (2.08, 17.06)
20040138	2	3 (0.41)	731	1 (0.14)	725	0.3206	0.6245	0.27 (-0.26, 0.81)	2.98 (0.31, 28.54)

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[redacted] (b) (4) a cutoff value of 7.5mg/dl was adopted to evaluate the incidences of laboratory serum calcium declines. A sensitivity analysis based on this labeling criterion was carried out and the results for the incidence of hypocalcemia are shown in Table 29. Based on the cutoff value of 7.5mg/dl, the incidence of hypocalcemia was comparable between the denosumab treated subjects and placebo treated subjects on the pooled PMO studies. For the two HALT studies, no subject was identified to have hypocalcemia based on the cutoff value of 7.5mg/dl.

Table 29: Incidence of hypocalcemia defined as albumin-adjusted calcium<7.5mg/dl

Study ID	denosumab 60mg Q6M		placebo		P-values		Estimates (asymptotic 95% CI)	
	n (%)	No.of subj.	n (%)	No.of subj.	Chisq	Fisher	RD (%)	RR
Pooled PMO	2 (0.05)	4050	2 (0.05)	4041	0.9982	1.0000	-0.00 (-0.10, 0.10)	1.00 (0.14, 7.08)
20040135	0	129	0	120	NA	NA	NA	NA
20040138	0	731	0	725	NA	NA	NA	NA

5.1.2.2. Declines in albumin-adjusted calcium levels

Table 30 shows the means of the maximum differences in albumin-adjusted calcium values across the entire study for the pooled PMO studies, 20040135 and 20040138 respectively. The mean maximum difference was approximately 1 mg/dl in all studies. The maximum difference in calcium values was slightly greater for the denosumab group compared with the placebo groups. Although the differences between treatment groups were statistically significant, given the width of normal calcium range, of approximately 2.7mg/dl, these results alone do not provide authoritative evidence that denosumab is potentially associated with higher risks of serum calcium reduction.

Table 30: Mean maximum differences in albumin-adjusted calcium levels

Study ID	Treatment Group		Mean Diff. (denosumab-placebo) (mg/dl)	S.E (Mean Diff.)
	denosumab 60mg Q6M (mg/dl)	placebo (mg/dl)		
Pooled PMO	-0.97	-0.91	-0.06	0.01***
20040135	-0.96	-0.78	-0.18	0.04***
20040138	-1.01	-0.81	-0.20	0.02***

Note: *** denotes the mean difference is statistically significant at 0.001 level based on the two-sample t-test.

Because using the mean to summarize a distribution can be misleading when outliers are present, an alternative approach was used. Table 31 presents the minimum, 5th percentile, 25th percentile, 50th percentile, 75th percentile and maximum to further describe the distributions of the maximum calcium reduction within each treatment groups. For the pooled PMO analysis, the largest calcium differences were 3.2mg/dl and 3.9mg/dl for the denosumab and the placebo groups respectively. Although the magnitudes of the maximum difference for both groups were large, the differences were comparable. The remaining statistics were also comparable across the two treatment groups.
Similar patterns were observed for study 20040135 and study 20040138. Boxplots for comparing the distributions of maximum calcium changes between denosumab and

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placebo groups are displayed in Figure 1. From this figure, the maximum calcium changes across the entire study period were distributed similarly in the denosumab group and the placebo groups for all pivotal studies (pooled studies for PMO indications), although the magnitude of the difference is slightly larger for denosumab than placebo.

Table 31: Percentiles of the maximum declines in albumin-adjusted calcium levels

Study ID	Statistics	Treatment Group		Percentile Difference (denosumab-placebo)
		denosumab 60mg Q6M (mg/dl)	placebo (mg/dl)	
Pooled PMO	Number of subjects	4050	4041	
	Minimum	-3.2	-3.9	0.7
	5th Percentile	-1.6	-1.5	-0.1
	25th Percentile	-1.2	-1.1	-0.1
	50th Percentile	-0.9	-0.9	0
	75th Percentile	-0.8	-0.7	-0.1
	Maximum	0	0	0
Study 20040135	Number of subjects	129	120	
	Minimum	-2.5	-2.1	-0.4
	5th Percentile	-1.5	-1.35	-0.15
	25th Percentile	-1.2	-0.9	-0.3
	50th Percentile	-0.9	-0.8	-0.1
	75th Percentile	-0.7	-0.6	-0.1
	Maximum	-0.1	-0.3	0.2
Study 20040138	Number of subjects	731	725	
	Minimum	-2.4	-2	-0.4
	5th Percentile	-1.7	-1.4	-0.3
	25th Percentile	-1.2	-1	-0.2
	50th Percentile	-1	-0.8	-0.2
	75th Percentile	-0.8	-0.6	-0.2
	Maximum	-0.1	0	-0.1

Reference ID: 3168397

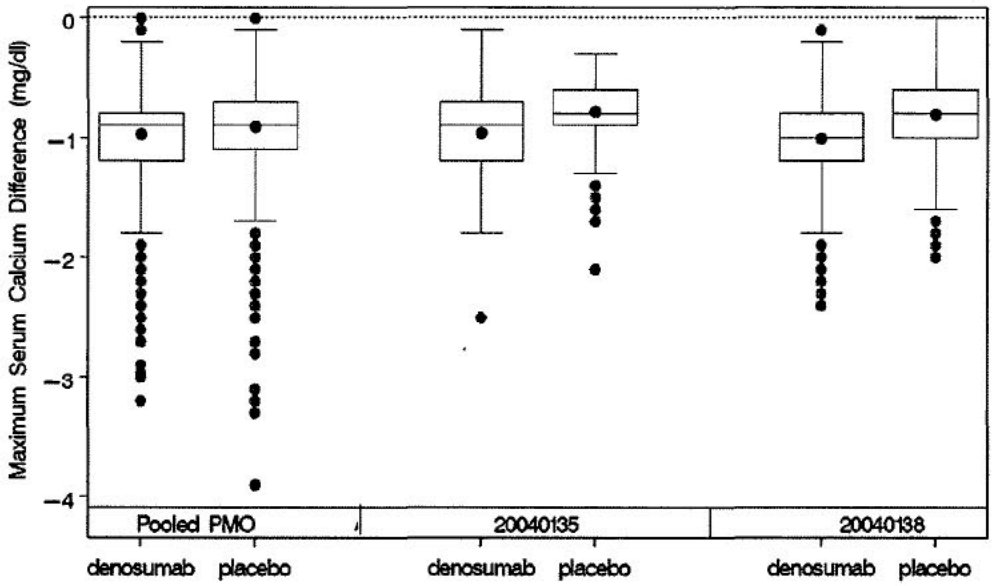

Figure 1: Boxplots for maximum serum calcium differences in denosumab and placebo groups for the pooled PMO studies (20040132 and 20030216), study 20040135, and study 20040138.

5.1.2.3. Time to hypocalcemia event

Consistent with the definition in Section 4.1.2.1, a hypocalcemia adverse event is confirmed if an albumin-adjusted calcium value fell below 8.5mg/dl. Because hypocalcemia events are rare, evaluations of the time to hypocalcemia were based on the pooled data from all four pivotal studies (20040132, 20030216, 20040135, and 20040138).

A total of 128 subjects across all pivotal studies had abnormal lab calcium values throughout the entire study period. Among these subjects, three had two abnormal calcium tests and the rest of 125 subjects had only once abnormal test results. The unique subject identification numbers for these three subjects are 20030216 (b) (6) 20030216 (b) (6) and 20040138 (b) (6). Table 32 lists the abnormally low albumin-adjusted calcium laboratory values and the time to these abnormal values for subjects with more than once abnormal tests throughout the entire study period. For these subjects, the time to hypocalcemia was defined as the time to the first abnormal calcium test. For the remaining 125 subjects with only one abnormal test, the time to hypocalcemia was the time to their abnormal calcium test.

Table 32: Days to abnormal albumin-adjusted calcium tests for subjects with more than one abnormal calcium values

Subject ID	Visit	Days to Abnormal Lab Tests	Lab Results	Normal Low Limit
20030216-(b) (6)	Month 1	34	8.4	8.5
	Month 36	1079	8.4	8.5
20030216-	Month 24	734	8.4	8.5
	Month 36	1098	8.4	8.5
20040138-	Day 1	1	8.2	8.4
	Month 30	911	8.2	8.4

Figure 2 shows the histogram of time to hypocalcemia for the 128 subjects with at least one hypocalcemia adverse events on laboratory calcium values in all pivotal studies by study visits and by treatment assignments. From this figure, most laboratory hypocalcemia adverse events occurred at the beginning of the study, i.e. day-1 visit or month-1 visit. A modest proportion of hypocalcemia adverse events occurred at month-12 visit when subjects received the second dose of the investigational drug. More hypocalcemia events were observed to occur at month 1 for subjects who received denosumab than those who received placebo. Table 33 presents the frequency and percentage of subjects who had their first hypocalcemia event at each visit by treatment groups across all pivotal studies. Approximately 58% of denosumab treated subjects had their first hypocalcemia event at month-1 visit compared with only 18.5% of placebo treated subjects did. The incidence of hypocalcemia is comparable between the two treatment groups at the remaining eight visits.

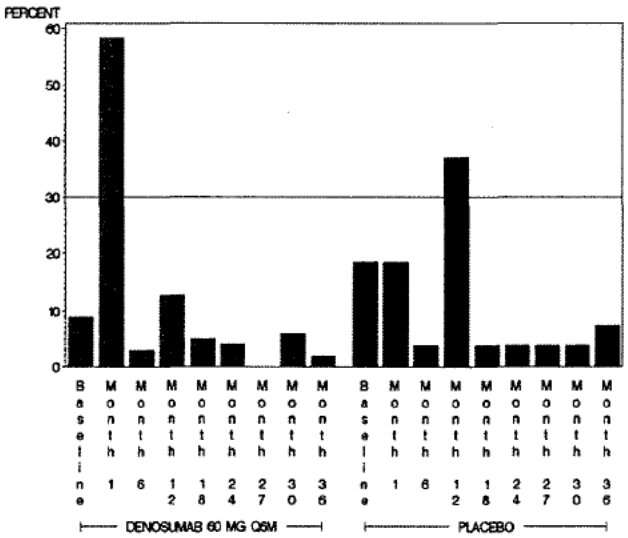

Figure 2: Histogram of the time to hypocalcemia for subjects with at least one hypocalcemia adverse events on laboratory calcium values in all pivotal studies by visit names and by treatment assignments.

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Table 33: Frequency and percentage of subjects who had their first hypocalcemia event at each visit by treatment groups across all pivotal studies

Visit	denosumab 60mg Q6M (No. of subjects: 4910)		placebo (No. of subjects: 4886)	
	Frequency	Percentage	Frequency	Percentage
Baseline	9	8.9	5	18.5
Month 1	59	58.4	5	18.5
Month 6	3	3.0	1	3.7
Month 12	13	12.9	10	37.0
Month 18	5	5.0	1	3.7
Month 24	4	4.0	1	3.7
Month 27	0	0.0	1	3.7
Month 30	6	5.9	1	3.7
Month 36	2	2.0	2	7.4
Total	101	100.0	27	100.0

To further explore the effect of denosumab on the time to hypocalcemia, Kaplan-Meier survival analysis was performed to estimate the rate of hypocalcemia. Figure 3 shows the Kaplan-Meier curves for the two treatment groups.

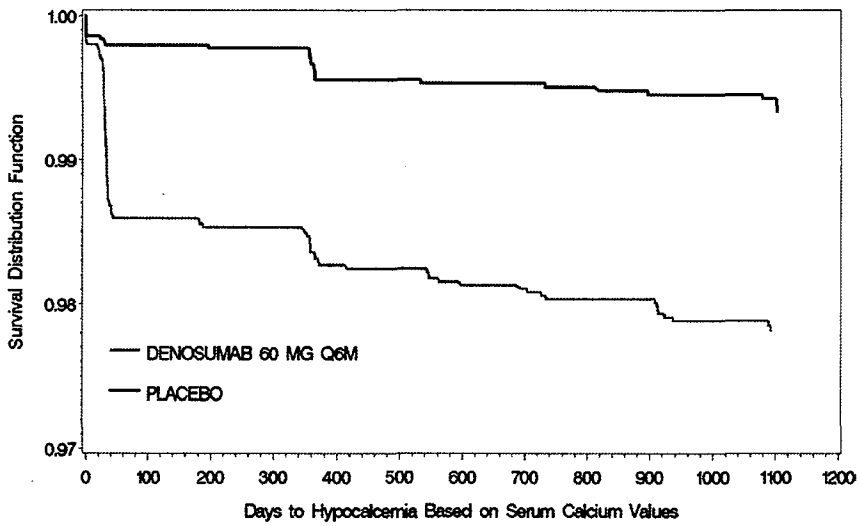

Figure 3: Kaplan-Meier survival curve of days to hypocalcemia event on serum calcium values for all pivotal studies

The difference between the survival curves for the denosumab group and the placebo group was statistically significant according to the logrank test (chi-square=42.453; p <.0001.) The denosumab subjects appear to be associated with a higher risk of hypocalcemia than the placebo subjects are during earlier stage of the study. At later stages of study, the survival curves are similar between the two treatment groups.

This survival analysis is based on hypocalcemia data derived from the laboratory calcium values collected at each scheduled clinical visit. Note that these nine scheduled visits are not equally spaced. Month-1 visit is the only visit scheduled at one month after a subject

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receives a dose of treatment. From Figure 3, the main contributor for the difference in survival curves between the two treatments seems to be the rapid decline in the survival function occurred after about 30 days for the denosumab group. Because laboratory calcium data are not available for one month after each dose administration, whether a decline in survival curve will occur for denosumab subjects one month after each successive dose administration cannot be determined.

5.2. Off-treatment evaluations

As shown in Table 34, the incidence of hypocalcemia is small for the 2-year off-treatment phase of study 20040132. There is zero incidence of hypocalcemia during the off-treatment phase for both study 20040135 and 20040138. For the open-label, single arm study 20060289, the incidence of hypocalcemia is small and comparable between the original treatment groups as in study 20030216.

Table 34: The number of hypocalcemia adverse events

Study ID	Treatment Group	Number of adverse events n (%)		
		0	1	2
20060289	denosumab 60mg Q6M (N=2346)	2295 (97.83)	45 (1.92)	6 (0.26)
	placebo (N=2203)	2156 (97.87)	43 (1.95)	4 (0.18)
20040132	denosumab 60mg Q6M (N=128)	125 (97.66)	3 (2.34)	-
	placebo (N=128)	126 (98.44)	2 (1.56)	-
20040135	denosumab 60mg Q6M (N=96)	96 (100.0)	-	-
	placebo (N=89)	89 (100.0)	-	-
20040138	denosumab 60mg Q6M (N=406)	406 (100.0)	-	-
	placebo (N=372)	372 (100.0)	-	-

6. Discussion

Based on adverse event data, there were no statistically significant differences in terms of incidence and severity of hypocalcemia between denosumab 60mg Q6M and placebo for all pivotal studies. The hypocalcemia events identified in the adverse event data were mainly associated with the symptoms of hypocalcemia. Two MedDRA Preferred Terms were responsible for around 90% of all hypocalcemia events, and they were: Hypoaesthesia and Paraesthesia.

However, based on the laboratory data, statistically significant higher risk of hypocalcemia was observed among subjects who received denosumab 60mg Q6M than subjects who received placebo drug for the pooled PMO pivotal studies (study 20040132 and study 20030216) and study 20040138. The relative risk for hypocalcemia can be as high as 5.36, which was observed for study 20040138. These analyses were conducted based on the lower limit of the reference range of albumin-adjusted calcium (i.e. 8.5mg/dl) provided by the sponsor. Although the analyses presented in this report are exploratory, the magnitudes of these two relative risks suggest a potential safety signal.

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Larger incidences of hypocalcemia based on laboratory data were observed (denosumab 60mg Q6M: 129 (2.63%) vs. placebo: 30 (0.61%)) than the incidence of hypocalcemia based on adverse events data (denosumab 60mg Q6M: 1 (0.02%) vs. placebo: 2 (0.04%)). These observed discrepancies may be due to the way the adverse events data were collected as described in the sponsor's protocols: "abnormal lab findings without clinical significance should not be recorded as AE, however, lab values changes requiring therapy or adjustment in prior therapy are considered AE". It is worth noting that in the (b) (4), a cutoff value of 7.5mg/dl was used to evaluate laboratory serum calcium declines. Under this criterion, no difference in terms of hypocalcemia incidence was observed for any of the pivotal studies.

The average of the maximum differences in calcium across all visits was no more than 1 mg/dl. Slightly larger differences were observed in the denosumab group than the placebo group. Given the width of calcium normal range, 2.7mg/dl, it was difficult to determine whether this difference was clinically meaningful. There were no statistically significant differences in the incidences of hypocalcemia between the denosumab 60mg Q6M group and placebo group by baseline renal function, by baseline vitamin D levels, or by PPI exposure status.

Among subjects who had at least one hypocalcemia event based on serum calcium values, a higher proportion of denosumab treated subjects, 59 (58.4%), had their first hypocalcemia event at month-1 visit than did the placebo treated subjects, 5 (18.5%). For the remaining visits, the proportion of subjects with hypocalcemia was comparable between the denosumab and the placebo groups. In addition, the Kaplan-Meier survival analysis on the time to hypocalcemia suggests that denosumab subjects were associated with a higher risk of hypocalcemia than the placebo subjects during earlier stage of the study. According to the logrank test, the difference between the survival curves for the denosumab group and the placebo group was statistically significant.

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Reference ID: 3168397

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

BLA Numbers	125331, 125320, 125332 and 125333
Drug Name	Denosumab (PROLIA)
Indications	(1) Treatment of osteoporosis in postmenopausal women (2) Prevention of osteoporosis in postmenopausal women (3) Treatment and prevention of bone loss associated with hormone-ablative therapy for breast cancer (4) Treatment and prevention of bone loss associated with hormone-ablative therapy for prostate cancer
Applicant	Amgen, Inc.
PDUFA Date	October 19, 2009
Date Submitted	July 10, 2009
Review Priority	Standard
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Secondary Reviewers	Paul Schuette, PhD, Mathematical Statistician
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1 Executive Summary

This is a statistical safety review of the hypersensitivity and immunogenicity of denosumab as submitted by Amgen. The main objective of this safety review is to provide a quantitative assessment of the hypersensitivity and immunogenicity of denosumab using data from phase 2 and 3 clinical trial studies as part of BLA package 125-320. The sponsor requested approval for four indications: (1) treatment for postmenopausal osteoporosis (PMO) in women (2) prevention of PMO in women (3) treatment and prevention of bone loss in patients undergoing aromatase inhibitor therapy (AIT) for non-metastatic breast cancer (BC) and (4) treatment and prevention of bone loss in patients undergoing androgen deprivation therapy (ADT) for prostate cancer (PC). Data used in this review were from phase 3 pivotal trials (20030216, 20040132, 20040135 and 20040138) and other phase 2 and 3 trials (20010223, 20040245, 20050141, 20050172, 20050179, 20050141, 20050233, 20050234 and 20050237).

The pre-specified safety outcomes were incidence of hypersensitivity and immunogenicity. Exploratory analyses of outcomes for hypersensitivity were also done at all levels of the MedDRA hierarchy, by demographics and baseline characteristics, and severity or NCI toxicity grade, where applicable.

Hypersensitivity was defined in this review using a narrow list of preferred terms (see Appendix A) that were considered by the sponsor in their analysis and other preferred terms that were determined by the reviewer to be directly related to hypersensitivity. Additional terms that were determined by the medical officer in the Quantitative Safety and Pharmacoepidemiology Group were also included (see Appendix B) to allow for a broader analysis.

The pivotal PMO studies 20030216 and 20040132 (pooled or not pooled) yielded statistically significant findings. Study 200301216 was the largest among the four pivotal studies with almost 80% of the total subjects in the safety population. The MedDRA high level

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terms (HLTs) Dermatitis and eczema (Eczema, Dermatitis, Dermatitis allergic, Dermatitis atopic and Dermatitis contact) and Rashes, eruptions and exanthems NEC (Rash, Rash generalised, Rash macular, Rash maculo-papular and Rash vesicular) were significantly different between treatment arms. The number of events (incidence) for denosumab vs placebo were 124 (3.1%) vs 69 (1.7%) for the Dermatitis and eczema HLT, and 117 (2.9%) vs 83 (2.1%) for the Rashes, eruptions and exanthems NEC HLT. Eczema was significantly different between treatment arms (relative risk 1.959 [95% CI: (1.235,3.107)] and risk difference of 0.006 [95% CI: (0.002,0.011)]) with crude incidences of 1.3% (denosumab) vs 0.7% (placebo). Rash was the most common event in the Rashes, eruptions and exanthems NEC HLT and was also significantly different between treatment arms (p-value = 0.026, relative risk 1.387 [95% CI (1.038,1.852)] and risk difference of 0.007 [95% CI (0.001,0.014)]) with crude incidences of 2.6% (denosumab) vs 1.9% (placebo).

Eczema and Rash were each reported as the first adverse event most of the time within the Skin and subcutaneous tissue disorders SOC (Skin SOC) in the adverse event database prior to reports of subsequent Skin SOC events. In terms of severity of Eczema, there were many more moderate cases in the denosumab arm compared to placebo. The onset times of Eczema were generally early for denosumab and late for placebo. It was difficult to assess duration because of many continuing cases in both arms. At least 94% of all subjects in both arms either continued treatment or completed the study. Nine Eczema subjects in denosumab and one in placebo had Eczema reported prior to the study. Excluding these subjects from the analysis did not affect the results. For the onset times of Rash, there were more events early on for denosumab than placebo but the two arms were similar thereafter.

No significant findings were found in HALT studies 20040135 and 20040138, pooled or not pooled.

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Events for SMQs, baseline and demographic characteristics, and events considered serious were largely balanced between treatment arms for all four pivotal studies. However, the following events were reported only in the denosumab arm and not in placebo: one life-threatening and one fatal case of Shock, one case of Circulatory collapse, four cases of Dermatitis atopic, and four cases of Toxic skin eruption (one of which was considered serious).

The hypersensitivity events found in the adverse event database for the four pivotal studies were very similar to those reported in other phase 2 and 3 studies. They were also approximately similar in terms of crude incidence rates. There were no indications of hypersensitivity associated with varying doses and the adverse events for denosumab were not different from active-control.

For immunogenicity, positive tests for binding antibodies were found in 6 of 12 studies but the subject incidence was only at most 1.6% in any of the studies. There was no evidence of any correlation between subjects with positive binding antibody tests and their respective adverse event profiles. No neutralizing antibodies were found in any of the studies with antibody tests.

In conclusion, denosumab does not appear to be immunogenic. However, hypersensitivity seems to be a concern particularly in the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs within the Skin SOC. This review provided exploratory statistical results that show higher incidences and significant differences of denosumab over placebo of potential hypersensitivity events within these MedDRA grouping levels. Eczema (specially moderate to severe cases) and Rash, in particular, were found to be of major concern. Cautions regarding these two events, including other events within the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs, may warrant inclusion in the label and that post-market monitoring could also be considered.

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2 Introduction

As a monoclonal antibody, denosumab has the potential of immunogenicity or eliciting an immune response. The main concerns are (1) drug allergenicity or hypersensitivity and (2) the alteration of the pharmacokinetics, pharmacodynamics or toxicities ([4],[6]-[8]). Hypersensitivity is a condition where a stimulus causes symptoms that are said to be objectively reproducible and that occur at a dose that is within tolerance levels of normal subjects ([1]). It may be allergic (immune-mediated) or non-allergic (not immune-mediated).

The objectives of this statistical safety review are the following:

- Review the immunogenicity of denosumab based on antibody tests (both pre-existing and developing).
- For patients with positive antibody test results, characterize antibody responses and investigate potential correlation with any adverse events or hypersensitivity reactions.
- Evaluate the risks of hypersensitivity of denosumab relative to placebo at various Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 grouping levels: Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT) and primary System Organ Class (SOC).
- Summarize the baseline and demographic characteristics of subjects with hypersensitivity and determine which groups are potentially at risk.
- Determine the incidence, timing and accounting for severity/toxicity grade of hypersensitivity outcomes.
- Compare denosumab with the active-control in terms of hypersensitivity outcomes.

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3 Statistical Methods

3.1 Endpoints

The following list of MedDRA preferred terms was used to define hypersensitivity:

I. Hypersensitivity and Drug hypersensitivity

II. Application site hypersensitivity, Documented hypersensitivity to administered drug, Human seminal plasma hypersensitivity, Implant site hypersensitivity, Infusion site hypersensitivity, Injection site hypersensitivity, Type I hypersensitivity, Type II hypersensitivity and Type IV hypersensitivity

III. PTs based on the following Standardised MedDRA Queries (SMQs) : (a) Angioedema (b) Anaphylactic reaction (b) Severe cutaneous adverse reaction

IV. Dermatitis, Dermatitis allergic, Dermatitis atopic, Dermatitis contact and Eczema

This list is called the primary set (or set P). A subject with at least one adverse event in set P is said to have a hypersensitivity reaction. Items I, III and IV were considered by the sponsor in their analysis. Events in II are in the same MedDRA high level term (HLT) as the Hypersensitivity PT. A complete listing of events for the SMQs is given in Appendix A.

A sensitivity analysis was also carried out by analyzing a broader set consisting of PTs from set P plus additional PTs given in Appendix B. The PTs in Appendix B were reviewed by the medical officer in the Quantitative Safety and Pharmacoepidemiology Group (QSPG) and were classified as possible causes of allergic reactions. This broader set of PTs is called the sensitivity set (or set S). Note that set S has more sensitivity but may have less specificity than set P when comparing treatment arms at various MedDRA levels. However, it is of interest to evaluate the analysis based on set S and compare it with the analysis of set P.

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The following primary SOCs were also reviewed for potential hypersensitivity PTs: (1) Skin and subcutaneous tissue disorders (2) Immune system disorders (3) General disorders and administration site conditions.

3.2 Statistical Tools

In order to detect and assess associations between treatment arms (denosumab vs placebo), p-values obtained from the Pearson Chi-square and Fisher's Exact tests were reported. The Chi-square test is appropriate when expected counts in a cross-table are relatively large ($\geq$ 5) whereas the Fisher's Exact test is appropriate when the expected counts are low ($<$ 5). To estimate the magnitude of associations that are found to be significant, the odds ratios, relative risk and risk difference, with corresponding 95% confidence intervals, were also reported. The confidence interval for the odds ratio is exact whereas those for relative risk and risk difference are asymptotic. All calculations were done in SAS 9.1.

3.3 Data

The main analysis for hypersensitivity was carried out on the pivotal studies which included phase 3 randomized, multi-center, double-blind and placebo-controlled studies for postmenopausal osteoporosis (PMO; studies 20030216 and 20040132) and hormone-ablative therapy (HALT; studies 20040135 and 20040138). See Table 1 for a short summary of these studies. Other phase 2 (20010223, 20050172, and 20050179) and phase 3 (20050141 and 20050234) studies were also reviewed for crude incidence rates and potentially dose-related hypersensitivity events. These five studies all involved PMO subjects.

For immunogenicity, the following studies with available data for antibody tests were reviewed: 20010223, 20030216, 20030245, 20040132, 20040135, 20040138, 20050141, 20050172,

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Table 1: Summary of Pivotal Studies.

	Study	Treatment Arm Size Denosumab	Placebo	Total	Population	Study Duration
PMO	20030216	3886	3876	7762	women with low BMD	36 months
	20040132	164	165	329	women with low BMD; $\leq$ 90 yr non-mBC with AIT	24 months plus 24 months safety follow-up
HALT	20040135	129	120	249	women with low BMD; $\geq$ 18 yr; non-mBC with AIT	24 months plus 24 months safety follow-up
	20040138	731	725	1456	men with low BMD; non-mPC with ADT	36 months plus 24 months safety follow-up

BMD = bone mineral density; AIT = aromatase inhibitor therapy; ADT = androgen deprivation therapy; mBC = metastatic breast cancer; mPC = metastatic prostate cancer

20050179, 20050233, 20050234 and 20050237.

The primary data sources for this review were the following analysis data model (ADaM) files:

- Subject Level Information Analysis Data (ASLINFO)
- Adverse Events Analysis Data (AAE)
- Antibody Analysis Data (AAB)
- Investigational Product Administration Analysis Data (AEX; Exposure Data)
- General Medical and Surgical History Analysis Data (AMHGENL)

Only events that occurred during the treatment period for all subjects in the safety population were considered in the analysis. Unless stated otherwise, the treatment period was

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defined as the time from the first dose date up to 213 days over the last dose date (approximately 6 months plus 30 days). Six months was the window between dose administration of the pivotal studies.

4 Hypersensitivity

4.1 Pivotal Studies

In this section, the four pivotal studies [20030216 and 20040132 (PMO); 20040135 and 20040138 (HALT)] were reviewed. For brevity, PMO in this section refers to studies 20030216 and 20040132 and HALT refers to studies 20040135 and 20040138.

4.1.1 Various MedDRA Levels Analyses

Table 2: Number of Groups Per MedDRA Level

	Set P		Set S	
MedDRA Level	PMO	HALT	PMO	HALT
PT	28	14	38	19
HLT	19	11	24	14
HLGT	10	7	12	8
SOC	7	5	8	6

Table 2 provides a summary of the number of PTs, HLTs, HLGTs, and SOCs, within the treatment periods, that were found in the adverse event database using sets P and S. For example, there 28 PTs found in the adverse event dataset for the PMO studies using set P. These PTs were mapped to 19 HLTs, 10 HLGTs and 7 primary SOCs. Only primary SOC mappings were considered in the analysis.

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To assess possible associations between a MedDRA grouping level and treatment arms, all identified groups from each level were analyzed using a SAS macro that calculates p-values from the Pearson Chi-square and Fisher's Exact tests, and also odds ratios, relative risks and risk differences, with corresponding confidence intervals. P-values at the 0.05 level where considered significant. As an example, when all 38 set S PTs from the PMO studies were run using the SAS macro, the Eczema was found to be significant. Tables 3 and 4 show the results for the PMO studies including other MedDRA levels.

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Table 3: MedDRA Level Analysis (Set P, Denosumab vs Placebo, PMO)

MedDRA Level	Name	No. of PTs		Pearson's Chi-square p-value	Fisher's Exact p-value	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
		Denosumab	Placebo					
PT	Eczema	53	27	0.004	0.005	1.971 (1.215,3.266)	1.959 (1.235,3.107)	0.006 (0.002,0.011)
HLT	Dermatitis and eczema	124	69	< 0.001	< 0.001	1.817 (1.338,2.484)	1.792 (1.340,2.398)	0.014 (0.007,0.020)
HLGT	Epidermal and dermal conditions	132	74	< 0.001	< 0.001	1.805 (1.343,2.441)	1.779 (1.342,2.356)	0.0143 (0.007,0.0211)
SOC	Skin and subcutaneous tissue disorders	161	106	0.001	0.001	1.536 (1.190,1.990)	1.515 (1.190,1.928)	0.0135 (0.006,0.021)

Table 3 shows that, aside from the Eczema PT, the Dermatitis and eczema HLT, Epidermal and dermal conditions HLGT and Skin and subcutaneous tissue disorders SOC were all significantly different between treatment arms when considering set P. The relative risk for denosumab over placebo ranged from 1.5 to almost 2 from the top to bottom in the MedDRA hierarchy. When each study was analyzed separately, only 20030216 was found to be significant, with very similar results as the pooled analysis. This means that the pooled PMO results were being driven by 20030216 which has the largest number of subjects enrolled (see Table 1). Table 5 shows events in the Skin and subcutaneous tissue disorders SOC based on set S. Eczema has a higher crude incidence rate in the denosumab arm than placebo (1.3% vs 0.6%) for study 20030216. In general, events in set P under the Dermatitis and eczema HLT have higher crude incidences (3.1% vs 1.7%) in the denosumab arm over placebo.

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Table 4: MedDRA Level Analysis (Set S, Denosumab vs Placebo, PMO)

MedDRA Level	Name	No. of PTs		Pearson's Chi-square p-value	Fisher's Exact p-value	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
		Denosumab	Placebo					
PT	Eczema	53	27	0.004	0.005	1.971 (1.215,3.266)	1.959 (1.235,3.107)	0.006 (0.002,0.011)
	Rash	107	77	0.026	0.030	1.397 (1.029,1.904)	1.387 (1.038,1.852)	0.007 (0.001,0.014)
HLT	Dermatitis and eczema	124	69	< 0.001	< 0.001	1.817 (1.338,2.484)	1.792 (1.340,2.398)	0.014 (0.007,0.020)
	Rashes, eruptions and exanthems NEC	117	83	0.016	0.018	1.418 (1.057,1.908)	1.405 (1.064,1.856)	0.008 (0.002,0.015)
HLGT	Epidermal and dermal conditions	253	161	< 0.001	< 0.001	1.602 (1.303,1.974)	1.564 (1.290,1.897)	0.022 (0.013,0.032)
SOC	Skin and subcutaneous tissue disorders	282	193	< 0.001	< 0.001	1.489 (1.228,1.807)	1.455 (1.218,1.738)	0.022 (0.011,0.032)

Table 4 shows the results when using the set S PTs for the pooled PMO studies. The Dermal and epidermal conditions HLGT and the Skin and subcutaneous tissue disorders SOC (Skin SOC) were both found to be significantly different between treatment arms. Within the Dermal and epidermal conditions HLGT, the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs were significantly different between treatment arms. Within the Dermatitis and eczema HLT, Eczema was significantly different between treatment arms and within the Rashes, eruptions and exanthems NEC HLT, Rash was significantly different between treatment arms. Thus, significant differences between arms were found in the following two mappings: (1) Eczema PT, Dermatitis and eczema HLT, Epidermal and dermal conditions HLGT, and Skin and subcutaneous tissue disorders SOC and (2) Rash PT, Rashes, eruptions and exanthems NEC HLT, Epidermal and dermal conditions HLGT, and Skin and subcutaneous tissue disorders SOC. For (1), similar results were obtained (i.e. all levels were significant) when 20030216 was analyzed alone instead of the pooled PMO. When 20040132 was analyzed alone, there were no significant results at any level. For (2), Rash was significant only in study 20040132 when the studies were analyzed individually. The Rashes, eruptions and exanthems NEC HLT was significant for the pooled PMO studies but not for either of the studies analyzed individually. For the Rashes, eruptions and exanthems NEC HLT, there were 117 (2.9%) vs 83 (2.1%) events in the denosumab vs placebo arms, most of which were Rash.

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Table 5: Skin and subcutaneous tissue disorders SOC (Set S)

	PMO				HALT				TOTAL	
	20030216		20040132		20040135		20040138			
HLGT, HLT, and PT	D	P	D	P	D	P	D	P	D	P
Safety Population	3886 (%)	3876 (%)	164 (%)	165 (%)	129 (%)	120 (%)	731 (%)	725 (%)	4910 (%)	4886 (%)
Epidermal and dermal conditions	234 (6.0)	150 (3.9)	19 (11.6)	11 (6.7)	13 (10.1)	12 (10.0)	24 (3.3)	28 (3.9)	290 (5.9)	201 (4.1)
Dermatitis and eczema	119 (3.1)	65 (1.7)	5 (3.0)	4 (2.4)	2 (1.6)	5 (4.2)	8 (1.1)	8 (1.1)	134 (2.7)	82 (1.7)
Eczema*	50 (1.3)	25 (0.6)	3 (1.8)	2 (1.2)	1 (0.8)	1 (0.8)	2 (0.3)	3 (0.4)	56 (1.1)	31 (0.6)
Dermatitis allergic*	36 (0.9)	23 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	36 (0.7)	27 (0.6)
Dermatitis*	21 (0.5)	14 (0.4)	1 (0.6)	1 (0.6)	1 (0.8)	2 (1.7)	4 (0.5)	1 (0.1)	27 (0.5)	18 (0.4)
Dermatitis contact*	8 (0.2)	3 (0.1)	1 (0.6)	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.3)	1 (0.1)	11 (0.2)	6 (0.1)
Dermatitis atopic*	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)
Rashes, eruptions and exanthems NEC	103 (2.7)	77 (2.0)	14 (8.5)	6 (3.6)	10 (7.8)	7 (5.8)	16 (2.2)	17 (2.3)	143 (2.9)	107 (2.2)
Rash**	93 (2.4)	72 (1.9)	14 (8.5)	5 (3.0)	10 (7.8)	6 (5.0)	16 (2.2)	17 (2.3)	133 (2.7)	100 (2.0)
Rash generalised**	7 (0.2)	3 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.1)	4 (0.1)
Rash macular**	3 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	1 (0.0)
Rash maculo-papular**	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Rash vesicular**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Other HLTs	12 (0.3)	8 (0.2)	0 (0.0)	1 (0.6)	1 (0.8)	0 (0.0)	0 (0.0)	3 (0.4)	13 (0.3)	12 (0.2)
Angiodema and urticaria	27 (0.7)	28 (0.7)	2 (1.2)	4 (2.4)	2 (1.6)	0 (0.0)	3 (0.4)	3 (0.4)	34 (0.7)	35 (0.7)
Total PTs	261 (6.7)	178 (4.6)	21 (12.8)	15 (9.1)	15 (11.6)	12 (13.3)	27 (3.7)	31 (4.3)	324 (6.6)	236 (4.8)

* in set P; ** not in set P; D = Denosumab, P = Placebo

For the HALT studies, there were no significant differences found when treatment arms were compared under various MedDRA levels. This was true when the studies were either analyzed individually or pooled together.

Additional exploratory MedDRA levels analysis was done by pooling all four pivotal studies (PMO and HALT). The results were similar to what was found in the PMO studies. That is, significant differences between treatment arms were found for all the MedDRA levels in column two of Table 3 when considering set P PTs and in column two of Table 4 when considering set S PTs. Because no significant differences between treatment arms were found in the HALT studies, the PMO studies were the main driver of these results.

In Table 5, the number of events under the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs generally have higher crude incidences in the denosumab arm over placebo (2.7% vs 1.7% and 2.9% vs 2.2%, respectively) when events from set S were pooled together using all four pivotal studies. For the Epidermal and dermal conditions HLGT, the crude incidence of events in denosumab over placebo was 5.9% vs 4.1%. Because the Angioedema and urticaria HLGT was balanced between arms, the large difference between arms in the Epidermal and dermal conditions HLGT was the main factor for the large differences between treatment arms when considering the Skin SOC level (6.6% vs 4.8%, for denosumab vs placebo, respectively).

In PMO study 20030216, there were 4 each of Dermatitis atopic and Toxic skin eruption events found under the denosumab arm but none in the placebo. None of these events were found in all other pivotal studies. One case of Toxic skin eruption was reported to be serious in Section 4.1.3. Furthermore, there were 9 vs 2 Bronchospasm events, in denosumab vs placebo, respectively. Of the denosumab cases, 7 were from study 20030216 and 1 each from studies 20040135 and 20040138. The two placebo cases were from study 20030216. The

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Bronchospasm events were mostly mild and the rest were moderate. None of them were reported as serious.

All PTs in the entire adverse event database under the following primary SOCs were also reviewed: (1) Skin and subcutaneous tissue disorders (2) Immune system disorders (3) General disorders and administration site conditions. There were no significant findings found in these primary SOCs.

4.1.2 Frequency of Events, SMQs and Baseline and Demographic Characteristics

The frequencies of the hypersensitivity events within treatment periods are given in Table 6. Table 6 shows that most of the events occurred only once and only a few occurred more than once. Furthermore, the denosumab arm has many more events than placebo (195 vs 138) for study 20030216 only but not for the other pivotal studies.

Table 6: Frequencies of Adverse Events Per Subject.

	Set P						Set S							
	Denosumab			Placebo			Denosumab				Placebo			
Study	1	2	3	1	2	3	1	2	3	4	1	2	3	4
PMO	195	12	2	142	6	2	285	35	2	1	221	18	2	0
20030216	183	11	1	130	6	2	266	31	2	0	207	16	2	0
20040132	12	1	1	12	0	0	19	4	0	1	14	2	0	0
HALT	23	0	0	21	2	0	45	2	0	0	38	6	0	0
20040135	7	0	0	5	2	0	16	0	1	0	10	3	0	0
20040138	16	0	0	16	0	0	29	2	0	0	28	3	0	0

Table 7 summarizes the set P events according to SMQs. None of the event counts were large enough to show significant differences between treatment arms. Toxic skin reaction

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occurred only in the denosumab arm and not in placebo as seen earlier, and constitutes an adverse skin reaction. One case was considered serious in the following section.

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Table 7: Summary of SMQ Events (Set P)

	PMO				HALT				TOTAL	
	20030216		20040132		20040135		20040138			
SMQ and PT	D	P	D	P	D	P	D	P	D	P
Safety Population	3886 (%)	3876 (%)	164 (%)	165 (%)	129 (%)	120 (%)	731 (%)	725 (%)	4910 (%)	4886 (%)
Angioedema	38 (1.0)	41 (1.1)	6 (3.7)	6 (3.6)	2 (1.6)	1 (0.8)	4 (0.5)	6 (0.8)	50 (1.0)	52 (1.1)
Allergic oedema	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)
Angioedema	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)
Conjunctival oedema	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)
Corneal oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Eye oedema	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Eye swelling	1 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	2 (1.1)	2 (0.0)	3 (0.1)
Eyelid oedema	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Face oedema	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Gingival swelling	0 (0.0)	3 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Laryngeal oedema	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)
Lip swelling	0 (0.0)	1 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	2 (0.0)
Pharyngeal oedema	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Swelling face	2 (0.1)	2 (0.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	3 (0.1)
Swollen tongue	1 (0.0)	1 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)
Tongue oedema	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Urticaria	27 (0.7)	26 (0.7)	2 (1.2)	4 (2.4)	1 (0.8)	0 (0.0)	3 (0.4)	3 (0.4)	33 (0.7)	33 (0.7)
Anaphylactic shock	5 (0.1)	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	5 (0.1)	5 (0.1)
Anaphylactic shock	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Circulatory collapse	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.0)	1 (0.0)
Shock	4 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	2 (0.0)
Severe cutaneous adverse reaction	6 (0.2)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	6 (0.1)	4 (0.1)
Erythema multiforme	2 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)
Exfoliative rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Skin necrosis	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.0)
Toxic skin reaction	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)
Total PTs	49 (1.3)	47 (1.2)	6 (3.7)	6 (3.6)	2 (1.6)	1 (0.8)	5 (0.7)	8 (1.1)	61 (1.2)	61 (1.2)

D = Denosumab, P = Placebo

The baseline and demographic characteristics of subjects who have events from set P are shown in Table 8. For study 20030216, there were many more events from set P in the denosumab arm than placebo as seen earlier (195 vs 138; see also Sex category) even though the arms were balanced in terms of the number of subjects in the safety population (3886 vs 3876). The subcategories where there were many more events from set P in the denosumab arm than in the placebo were the following:

- 70-74 age group: 76 denosumab vs 49 placebo (safety population: 1634 denosumab vs 1628 placebo)
- White or Caucasian race: 181 denosumab vs 129 placebo (safety population: 3594 denosumab vs 3600 placebo)
- Geographical region: 66 denosumab vs 38 placebo (safety population: 1337 denosumab vs 1317 placebo) for Eastern Europe and 38 denosumab vs 20 placebo (safety population: 467 denosumab vs 460 placebo) for Latin America

For study 20040132, the following subcategories were slightly imbalanced in terms of the number of events in set P:

- 50-54 age group: 7 denosumab vs 1 placebo (safety population: 1634 denosumab vs 1628 placebo)
- Menopause ($\leq$ 5 years): 10 denosumab vs 3 placebo (safety population: 77 denosumab vs 80 placebo)
- Menopause ($>$ 5 years): 4 denosumab vs 9 placebo (safety population: 87 denosumab vs 85 placebo)

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Table 8: Baseline and Demographic Characteristics of Subjects With Set P Events

	PMO				HALT			
	20030216		20040132		20040135		20040138	
	D	P	D	P	D	P	D	P
Safety Population	3886	3876	164	165	129	120	731	725
Age (years)								
< 50	-	-	1	0	1	0	0	0
$50 - 54$	-	-	7	1	1	3	0	0
$55 - 59$	-	-	3	6	4	1	0	0
$60 - 64$	12	7	1	2	1	1	0	1
$65 - 69$	46	37	2	2	0	2	0	1
$70 - 74$	76	49	0	1	0	0	9	6
$75 - 79$	53	38	0	0	0	0	5	4
$80 \leq$	8	7	0	0	0	0	2	4
Sex								
Male	-	-	-	-	-	-	16	16
Female	195	138	14	12	7	7	-	-
Race								
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Asian	1	0	1	2	0	0	0	0
Black or African American	1	0	0	0	0	1	1	1
Hispanic or Latino	11	7	0	0	0	0	2	2
Japanese	1	1	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	1	0	0
White or Caucasian	181	129	13	10	6	5	13	13
Other	0	1	0	0	1	0	0	0
Geographical Region								
Eastern Europe	66	38			0	0	0	0
Europe					0	0	3	1
Latin America	38	20			0	0	0	0
North America	15	9	14	12	7	7	13	15
Western Europe	76	71			0	0	0	0
Menopause								
≤ 5 years	-	-	10	3	-	-	-	-
> 5 years	-	-	4	9	-	-	-	-
AIT								
≤ 6 months	-	-	-	-	1	3	-	-
> 6 months	-	-	-	-	6	4	-	-
ADT (months)								
≤ 6 (age < 70 years)	-	-	-	-	-	-	0	0
≤ 6 (age ≥ 70 years)	-	-	-	-	-	-	1	5
> 6 (age < 70 years)	-	-	-	-	-	-	0	2
> 6 (age ≥ 70 years)	-	-	-	-	-	-	15	9

D = Denosumab; P = Placebo; AIT = aromatase inhibitor therapy;
ADT = androgen deprivation therapy

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There were no remarkable differences in the categories or subcategories between treatment arms in studies 20040135 and 20040138.

4.1.3 Severity, Toxicity Grade and Seriousness

Severity data was available only for the PMO studies. Adverse events for the HALT studies were assessed by toxicity grade using the National Cancer Institute (NCI) grading scale.

This review analyzed severity at two levels: (1) all hypersensitivities irrespective of event and (2) hypersensitivity based on a given event. For (1), the most severe hypersensitivity event was chosen for each subject. The order from most to least severe is death, life threatening, severe, moderate and mild. For (2), the most severe of a given hypersensitivity event was chosen. For example, a subject may have two types of hypersensitivity events: eczema and rash. For this patient, the most severe eczema and rash episodes were chosen.

Table 9: Severity Irrespective of Hypersensitivity Event, Level (1).

	Set P						Set S					
	20030216		20040132		Total		20030216		20040132		Total	
Severity	D	P	D	P	D	P	D	P	D	P	D	P
Mild	106	87	6	5	112	92	174	150	14	6	188	156
Moderate	78	45	7	5	85	50	112	67	9	7	121	74
Severe	9	6	1	2	10	8	11	8	1	3	12	11
Life Threatening	1	0	0	0	1	0	1	0	0	0	1	0
Fatal	1	0	0	0	1	0	1	0	0	0	1	0
Total	195	138	14	12	209	150	299	225	102	108	323	241

D = Denosumab, P = Placebo

Table 9 shows the number of hypersensitivities irrespective of type [level (1)] classified by severity. There was one life threatening and one fatal case from study 20030216. The life threatening case was Shock (reported term: Circulatory failure; subject id: (b) (6)

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This event occurred about 17-18 months after the first dose was given, lead to patient hospitalization but not withdrawal from the study. The fatal case was also Shock (reported term: Mixed shock; subject id: (b) (6)

Table 10: Severity for Epidermal and dermal conditions HLGT [Set S, PMO, Level (2)].

	Mild		Moderate		Severe		Total	
HLT and PT	D	P	D	P	D	P	D	P
Dermatitis and eczema HLT	67 (54.0)	49 (71.0)	54 (43.5)	20 (29.0)	3(2.4)	0 (0.0)	124	69
Eczema*	26 (49.1)	21 (77.8)	25 (47.2)	6 (22.2)	2 (3.8)	0 (0.0)	53	27
Dermatitis allergic*	18 (50.0)	14 (58.3)	18 (50.0)	10 (41.7)	0 (0.0)	0 (0.0)	36	24
Dermatitis*	15 (68.2)	11 (73.3)	7 (31.8)	4 (26.7)	0 (0.0)	0 (0.0)	22	15
Dermatitis contact*	6 (66.7)	3 (100.0)	2 (22.2)	0 (0.0)	1 (21.1)	0 (0.0)	9	3
Dermatitis atopic*	2 (50.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	4	0
Rashes, eruptions and exanthems NEC HLT	77 (65.8)	55 (66.3)	39 (33.3)	25 (30.1)	1 (0.9)	3 (3.6)	117	83
Rash**	72 (67.3)	51 (66.2)	34 (31.8)	24 (31.2)	1 (0.9)	2 (2.6)	107	77
Rash generalised**	3 (42.9)	3 (0.8)	4 (57.1)	1 (0.2)	0 (0.0)	0 (0.0)	7	4
Rash macular**	2 (66.7)	1 (100.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	3	1
Rash maculo-papular**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0	1
Other HLTs	8 (66.7)	7 (77.8)	3 (0.3)	2 (22.2)	1 (8.0)	0 (0.0)	12	9
Total	152 (60.1)	111 (68.9)	96 (37.9)	47 (29.2)	5 (2.0)	3 (0.0)	253	161

* in set P; ** not in set P; D = Denosumab, P = Placebo

Table 10 gives the summary for Epidermal and dermal conditions HLGT broken down into counts at lower MedDRA levels when considering severity in hypersensitivity of a given event [level (2)]. For Eczema, there is a large difference in number (25 vs 6) between the denosumab and placebo arms at moderate severity. There were also 2 severe cases in the denosumab arm versus 0 from placebo. The two severe cases were from subjects (b) (6) (reported term: Worsening eczema on both hands) and (b) (6) [reported term: Eczema (Keratosis on the whole body - especially heels)]. Subject (b) (6) completed the study whereas (b) (6) discontinued treatment and withdrew from the study.

Toxicity grades were reported from 1-5 with 1 having the lowest toxicity grade and 5 the highest. For the HALT studies, there were no significant differences between arms across

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Table 11: Serious Hypersensitivity Events (set S)

	PMO				HALT					
	20030216		20040132		20040135		20040138		TOTAL	
SOC and PT	D	P	D	P	D	P	D	P	D	P
Immune system disorders	1	1	0	0	0	0	1	0	2	1
Anaphylactic shock*	0	1	0	0	0	0	0	0	0	1
Drug hypersensitivity*	1	0	0	0	0	0	1	0	2	0
Respiratory, thoracic and mediastinal disorders	1	3	0	0	0	0	0	0	1	3
Bronchospasm**	1	0	0	0	0	0	0	0	1	0
Laryngeal oedema*	0	2	0	0	0	0	0	0	0	2
Pharyngeal oedema*	0	1	0	0	0	0	0	0	0	1
Skin and subcutaneous tissue disorders	3	4	0	0	0	0	0	1	3	5
Angioedema*	0	1	0	0	0	0	0	0	0	1
Dermatitis*	1	0	0	0	0	0	0	0	1	0
Dermatitis allergic*	1	0	0	0	0	0	0	0	1	0
Rash maculo-papular**	0	1	0	0	0	0	0	0	0	1
Skin necrosis*	0	0	0	0	0	0	0	1	0	1
Toxic skin eruption**	1	0	0	0	0	0	0	0	1	0
Urticaria**	0	2	0	0	0	0	0	0	0	2
Vascular disorders	2	0	0	0	0	0	3	0	5	0
Circulatory collapse*	0	0	0	0	0	0	3	0	3	0
Shock*	2	0	0	0	0	0	0	0	2	0
Total	6	7	0	0	0	0	4	1	10	9

* in set P; ** not in set P; D = Denosumab, P = Placebo

toxicity grades. There were also no reported toxicity grades higher than 3.

Table 11 summarizes the events that were classified as serious. The crude incidences were very low and do not appear to be imbalanced between treatment arms. One case each of Drug hypersensitivity in the denosumab arm was reported in 20030216 and 20040138. One of the four cases of Toxic skin reaction in the denosumab arm seen in the previous section is reported here as serious. Two cases of Shock in the denosumab arm, reported as life threatening and fatal in previous sections, is reported here as serious. Three cases of Circulatory collapse in the denosumab arm were reported as serious in 20040138 but occurred only on the same subject (subject id: (b) (6)). This subject was hospitalized but did not

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withdraw from the study.

4.1.4 Eczema and Rash

Onset Time of Eczema and Rash

In this section, the analysis for onset time was limited to study 20030216 because the other pivotal studies only had a few of the events in each arm and had different lengths of completion. All start dates of adverse events were imputed by the sponsor to the first day of the month for events with missing days.

Figure 1 shows the onset time or time to the first occurrence (in months) of Eczema for study 20030216. For denosumab (50 subjects), there were two epochs that had high incidence: within a month of the first dose administration and immediately before the third dose administration or 8-12 months. The other cases were more or less uniformly spread throughout the entire study. The mean onset time was 15.40 months, standard deviation (SD) 10.48 months, median 12.16 months, range 33.84 months, minimum (min) 0.36 months and maximum (max) 34.20 months. For placebo (25 subjects), there were no marked spikes in incidence but there were three notable clusters at 2-12 months, 18-28 months and 29-36 months. More than half of all occurrences were towards the end of the study. The mean onset time was 21.05 months, SD 11.81 months, median 24.34 months, range 33.54 months, min 2.33 months, max 35.88 months.

Figure 2 shows the onset time (in months) of Rash in study 20030216. For denosumab (93 subjects), there was higher incidence within the first two months than placebo (72 subjects) but thereafter, incidence in both arms were very similar. The mean onset time under the denosumab arm was 11.33 months, SD 10.61 months, median 8.31 months, range 35.29 months, min of 0.00 months and max of 35.29 months. The mean onset time under placebo

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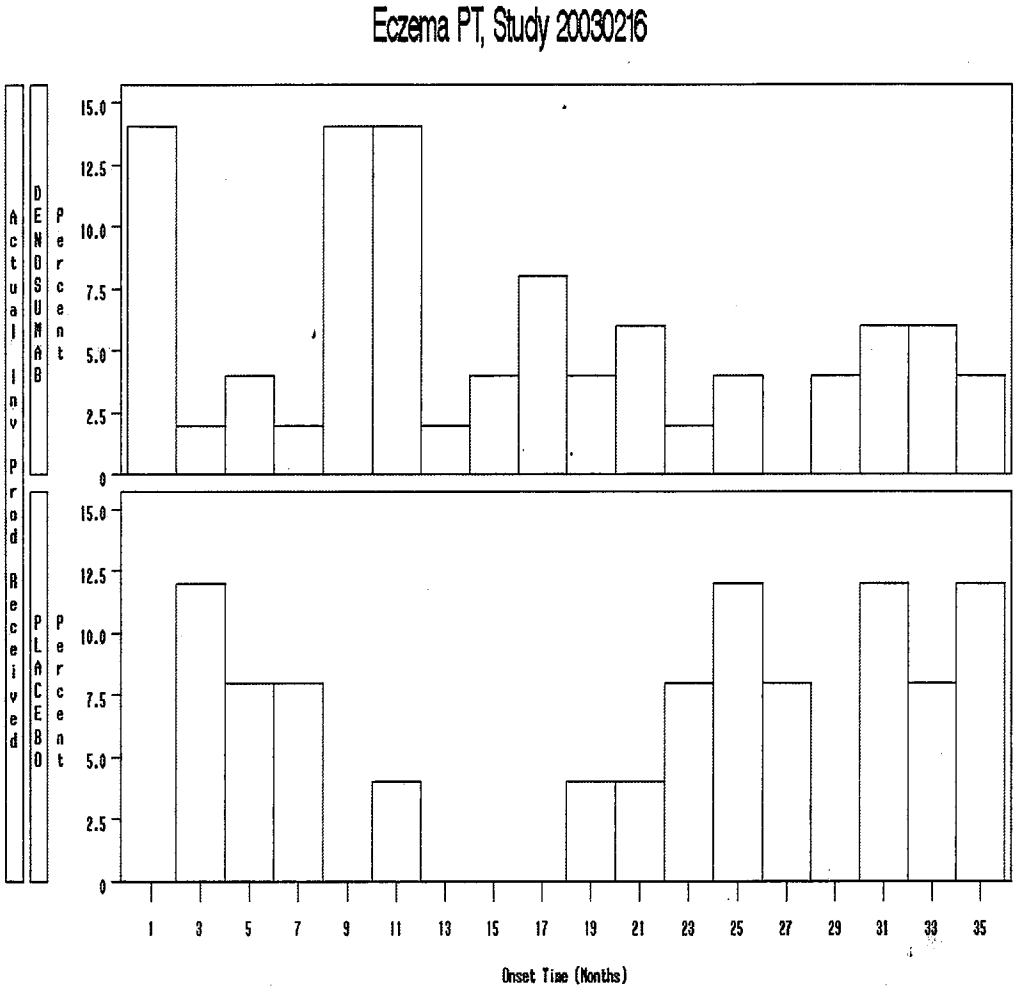

Figure 1: Onset Time of Eczema (Study 20030216)

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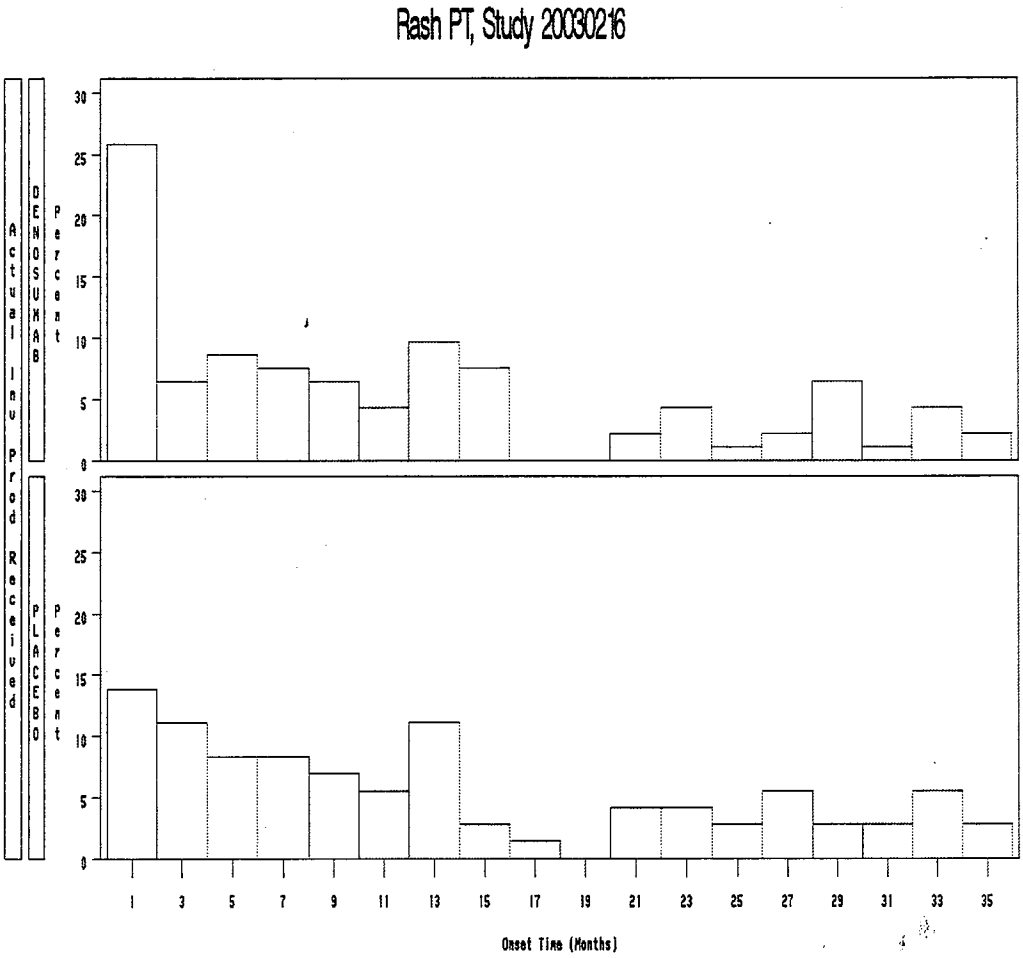

Figure 2: Onset Time of Rash (Study 20030216)

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was 13.14 months, SD 10.95 months, median 10.89 months, range 35.81 months, min 0.00 months and max 35.81 months.

Duration of Eczema

Table 12: Duration Statistics (in Months) for Eczema (Study 20030216).

Eczema PT Status	Treatment Arm	n (%)	Mean	SE	Min	Median	Max	Range
Not continuing	Denosumab	29 (56.9)	4.06	5.41	0.20	2.35	26.17	25.97
	Placebo	15 (60.0)	4.74	5.65	0.26	2.04	22.26	22.00
Continuing	Denosumab	22 (43.1)	15.76	10.43	1.44	14.22	33.69	32.24
	Placebo	10 (40.0)	5.95	4.76	0.03	5.48	12.21	12.18
Combined	Denosumab	51 (100.0)	8.88	9.71	0.20	3.91	33.69	33.49
	Placebo	25 (100.0)	5.16	5.30	0.03	3.78	22.26	22.23

n = number of cases; SE = standard error; Min = minimum; Max = maximum

Some end dates for Eczema had the day of the month missing and no imputation was done by the sponsor. In order to compute duration, this review imputed these end dates to the first day of the month. Furthermore, the Eczema events were reviewed and the end dates were chosen, when necessary, to yield realistic durations. For example, cases that were recorded multiple times for one subject, with the same start date, but were different only in the location of the subject's body where the Eczema occurred was considered as one Eczema case only. For a complete description of how the end dates were chosen, see Appendix C.

Table 13: Characteristics of Subjects With Eczema (Study 20030216).

	Denosumab		Placebo	
Event	Yes	No	Yes	No
Medication Taken	36 (71%)	15 (29%)	17 (68%)	8 (32%)
Discontinuation of Treatment	2 (4%)	49 (96%)	1 (4%)	24 (96%)
Withdrawal from Study	1 (2%)	50 (98%)	1 (4%)	24 (96%)
Study Completer	48 (94%)	3 (6%)	24 (96%)	1 (4%)

Table 12 shows the summary statistics for the duration of Eczema. Both treatment arms

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have approximately the same rate of continuing and not continuing cases (40% and 60%, respectively). For cases that were not continuing, denosumab had a slightly lower average time to resolution than placebo, although the median and maximum cases were slightly higher. The durations for continuing cases were taken to be the reference end dates minus the adverse event start dates. In this case, the mean, standard error and median for denosumab were significantly higher than placebo. When both continuing and not continuing cases were combined, the mean and standard error for denosumab were still higher than placebo and the median was only slightly higher. As observed previously, most of the cases for denosumab occurred early on compared to placebo which had many cases late in the study. It appears that most continuing cases for denosumab had earlier onset times than placebo. Because of continuing cases, a comparative assessment of duration between treatment arms is not feasible.

Table 13 gives a summary of the characteristics of Eczema cases. Approximately 70% of subjects in both treatment arms have taken medication for Eczema. Only at most two subjects discontinued treatment but only one subject withdrew from the study in each arm. No subjects had their dose altered nor were there any hospitalized. None of the cases were reported as serious.

Medical History of Subjects with Eczema

There were 9 subjects in the denosumab arm and 1 in the placebo who had histories of Eczema and also had Eczema during the study. Of the 9 denosumab subjects, 3 where classified as mild, 5 moderate and 1 severe. The placebo case was mild. All cases were reportedly continuing except for 2 in the denosumab arm. When all these cases were excluded in the MedDRA levels analysis, the results were still significant within the 0.05 level.

Other Reported Skin Adverse Events of Subjects With Eczema and Rash

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All subjects with Eczema and Rash were reviewed for other adverse events reported in the Skin SOC. The results for study 20030216 are summarized in Tables 23 and 24 in Appendix D. In Table 23, the first row shows that there was one subject in the denosumab arm that had Eczema. This subject was previously reported to have Dermatitis contact and then Dermatitis prior to Eczema and later was reported to have Skin Lesion. In Table 23, at least 80% of all subjects with Eczema in both arms reported Eczema as the first adverse event in the Skin SOC. A few cases may have possibly been reported as early stages of Eczema, e.g Rash or Dry skin, before actually developing into Eczema or these cases may have been concomitant Skin SOC PTs to Eczema.

In Table 24, around 90% of all cases in both arms reported Rash as the first adverse event in the Skin SOC. Only 3 and 1 cases in the denosumab and placebo arms, respectively, reported Eczema cases later.

4.2 Other Phase 2 and 3 PMO Studies

This section summarizes adverse events crude incidence rates obtained from other phase 2 and phase 3 PMO studies. Some details about the specific studies are given in Tables 14 and 15.

Each study has a treatment arm with a dose of 60 mg of the investigational product and administered subcutaneously every 6 months (Table 15). This is the dose that was used in the pivotal studies and is the dose for which the sponsor is seeking approval. Age should not be a major issue in pooling studies (Table 14) because only study 20050141 had 11 subjects over 80 years. Except for subjects each 85, 88 and 91 years old, the rest of the subjects were at most 83 years old.

The major issues for pooling the studies are (1) the population for study 20050172 are

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Table 14: Summary of Other Phase 2 and 3 Studies

Study	Phase	Population	Denosumab Doses	Study Duration
20010223	2	PMO women with low BMD; $\leq$ 80 yr	6, 14, 30 mg SC every 3 months and 14, 60, 100, 210 mg SC every 6 months; other	24 months; months 24-48
20050172	2	Japanese PMO women with low BMD; $\leq$ 80 yr	14, 60, 100 mg SC every 6 months	12 months
20050179	2	PMO women with low BMD; 50-70 yr; stratify by $\leq$ 60 yr or $>$ 60 yr	60 mg SC every 6 months	12 months
20050141	3	PMO women with low BMD	60 mg SC every 6 months	12 months
20050234	3	PMO women with low BMD; prior AL therapy: 6-12, 12-24 or $>$ 24 months	60 mg SC every 6 months	12 months

BMD = bone mineral density; AL = alendronate; SC = subcutaneous

Table 15: Safety Population Sizes of Other Phase 2 and 3 Studies

	Phase 2			Phase 3		
Arm	20010223	20050172	20050179	20050141	20050234	Total
Alendronate 70 MG QW	46	0	82	586	249	963
Denosumab 60 MG Q6M	47	54	83	593	253	1030
Placebo	46	55	82	0	0	183
Denosumab 210 MG Q6M	46	0	0	0	0	46
Denosumab 100 MG Q6M	41	50	0	0	0	91
Denosumab 30 MG Q3M	40	0	0	0	0	40
Denosumab 14 MG Q6M	53	53	0	0	0	106
Denosumab 14 MG Q3M	44	0	0	0	0	44
Denosumab 6 MG Q3M	43	0	0	0	0	43
Total	406	212	247	1179	502	2546

MG = milligrams; QW = weekly; Q6M = every 6 months; Q3M = every 3 months

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Japanese women whereas all the other studies are mainly Caucasian (2) study 20010223 has 48 months duration whereas all the other studies have 12 months (3) the population for study 20050234 have a history of alendronate (a bisphosphonate) use whereas all the other studies do not. This may be an issue because alendronate could have hypersensitivity effects that may confound denosumab. Item (2) can be resolved by considering only the adverse events within 12 months from the start of the study. Therefore, crude incidence rates are shown separately for studies 20010223, 20050141 and 20050179 combined, 20050234 (have history of alendronate use) and 20050172 (Japanese women). The crude incidences of set S events are presented in Table 16.

It should be noted that the crude incidences in Table 16 are only for a 12 month duration and that the PMO pivotal studies are 24 (20040132) and 36 (20030216) months duration. Furthermore, the placebo is a pooling from studies 20010223, 20050172, and 20050179. Care should be taken in interpreting this column because 20050172 has a different population (Japanese women) as 20010223 and 20050179 (mostly Caucasian). This pooling nonetheless can give a sense of how the incidences compare with the other treatment arms. The Skin SOC in Table 16 reports very similar events as those in Table 5 for the PMO pivotal studies. Perhaps due to trial differences (e.g. sample sizes), the events in these two tables do not match exactly.

Table 17 summarizes the events by SOCs for studies 20010223 and 20050172 separately under different dose arms and treatment frequencies and the placebo. It is difficult to discern any definitive trends because of the low counts of events. However, in study 20010223, Rash occurred in all denosumab arms and none in the placebo. For the 6 month frequency, the largest count was 5 in the highest dose (210 mg) versus only 2 in all other doses. The counts in the 3 and 6 month frequencies were both nondecreasing by increasing dose.

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Table 16: Hypersensitivity Events in Other Phase 2 and 3 Studies (Set S)

	Denosumab			
SOC and PT	20010223, 20050141 and 20050179	20050234	20050172	Placebo***
Safety Population	723 (%)	253 (%)	54 (%)	183 (%)
Blood and lymphatic system disorders				
Eosinophilia**	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Eye disorders				
Eye oedema*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Eyelid oedema*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Corneal oedema*	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Immune system disorders				
Hypersensitivity*	4 (0.6)	1 (0.4)	0 (0.0)	1 (0.5)
Drug hypersensitivity*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders				
Rash**	19 (2.6)	2 (0.8)	0 (0.0)	2 (1.1)
Eczema*	1 (0.1)	1 (0.4)	4 (7.4)	5 (2.7)
Dermatitis contact*	3 (0.4)	1 (0.4)	0 (0.0)	2 (1.1)
Dermatitis*	3 (0.4)	1 (0.4)	0 (0.0)	1 (0.5)
Urticaria**	3 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)
Dermatitis allergic*	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)
Dermatitis atopic*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Exfoliative rash*	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Rash erythematous**	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Rash generalised**	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)
Skin exfoliation**	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders				
Peripheral circulatory failure**	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

* in set P; ** not in set P; *** from 20010223, 20050172 and 20050179

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Table 17: Hypersensitivity Events in Study 20010223/20050172 By Dose (Set S)

	Denosumab Doses							
	3 Months (Q3M)			6 Months (Q6M)				
SOC and PT	6	14	30	14	60	100	210	Placebo
Sample size	43	44	40	53/53	47/54	41/50	46	46/55
Eye disorders								
Corneal oedema*	0	0	1	0/0	0/0	0/0	0	0/0
Eyelid oedema*	0	0	0	0/0	0/0	0/1	0	0/0
Eye swelling*	0	0	0	0/1	0/0	0/0	0	1/1
Gastro-intestinal disorders								
Gingival swelling*	0	0	0	0/0	0/0	0/1	0	0/0
General disorders and administration site conditions								
Face oedema*	0	0	0	0/0	0/0	0/1	0	0/0
Immune system disorders								
Drug hypersensitivity*	0	0	0	0/0	0/0	1/1	0	0/0
Hypersensitivity*	2	0	0	0/0	3/0	0/1	0	1/0
Skin and subcutaneous tissue disorders								
Dermatitis*	0	0	1	0/0	0/0	0/1	0/0	0/1
Dermatitis allergic*	0	0	0	0/0	0/0	1/0	0	0/0
Dermatitis contact*	2	1	2	1/1	0/0	3/1	0/0	0/1
Eczema*	0	0	0	1/6	0/4	1/6	0	0/5
Rash**	1	1	3	2/0	2/0	2/0	5/0	0/1
Rash erythematous**	1	0	0	0/0	0/0	0/0	0/0	0/0
Rash generalised**	0	0	0	0/0	0/0	2/0	1/0	1/0
Skin exfoliation**	0	0	0	0/0	1/0	0/0	1/0	0/0
Urticaria**	0	0	2	2/0	0/0	0/0	0/0	0/0
Vascular disorders								
Peripheral Circulatory Failure**	0	0	0	0/0	0/1	0/0	0/0	0/0

* in set P; ** not in set P

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4.3 Additional MedDRA Levels Analyses

4.3.1 Pooled PMO Studies

In this section, the denosumab (60 mg dose every 6 months subcutaneously) and placebo arms in the pivotal (20030216 and 20040132) and other phase 2 and 3 (20010223, 20050172, 20050179, 20050141 and 20050234) PMO studies were all pooled together ignoring (1) the duration of each study (2) race (mostly Caucasian in all studies except 20050172 who were all Japanese) and (3) no history of alendronate use in all studies except 20050234. Moreover, all the studies were placebo-controlled except for 20050141 and 20050234 which were both active-controlled. The resulting total population sizes were 5080 in the denosumab versus 4224 in the placebo arm. The results are shown in Tables 18 and 19.

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Table 18: MedDRA Level Analysis (Set P, Denosumab vs Placebo, Pooled PMO)

MedDRA Level	Name	No. of PTs		Pearson's Chi-square p-value	Fisher's Exact p-value	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
		Denosumab	Placebo					
PT	Eczema	59	32	0.049	0.056	1.539 (0.983,2.452)	1.533 (0.999,2.353)	0.004 (0.000,0.008)
HLT	Dermatitis and eczema	142	78	0.003	0.003	1.528 (1.147,2.047)	1.513 (1.151,1.989)	0.009 (0.003,0.016)
HLGT	Epidermal and dermal conditions	151	83	0.002	0.002	1.528 (1.157,2.028)	1.512 (1.160,1.970)	0.010 (0.004,0.016)
SOC	Skin and subcutaneous tissue disorders	183	116	0.020	0.021	1.323 (1.039,1.691)	1.311 (1.043,1.649)	0.009 (0.001,0.016)

Table 18 gives similar results as those for the pivotal PMO studies (Table 3) except that Eczema is no longer conclusively significant at 0.05 when comparing treatment arms at the PT level because the p-values and risk assessments are not in agreement. The results in Table 19 are also similar to those for the pivotal PMO studies (Table 4) except that Eczema is not conclusively significant and Rash is insignificant at 0.05 when comparing treatment arms at the PT level.

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Table 19: MedDRA Level Analysis (Set S, Denosumab vs Placebo, Pooled PMO)

MedDRA Level	Name	No. of PTs		Pearson's Chi-square p-value	Fisher's Exact p-value	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
		Denosumab	Placebo					
PT	Eczema	59	32	0.049	0.056	1.539 (0.983,2.452)	1.533 (0.999,2.353)	0.004 (0.000,0.008)
	Rash	128	79	0.034	0.040	1.356 (1.013,1.824)	1.347 (1.021,1.778)	0.006 (0.001,0.012)
HLT	Dermatitis and eczema	142	78	< 0.003	< 0.003	1.528 (1.147,2.047)	1.513 (1.151,1.989)	0.007 (0.003,0.016)
	Rashes, eruptions and exanthems NEC	139	86	0.029	0.030	1.353 (1.023,1.797)	1.343 (1.030,1.752)	0.007 (0.001,0.013)
HLGT	Epidermal and dermal conditions	296	173	< 0.001	< 0.001	1.447 (1.189,1.764)	1.421 (1.183,1.706)	0.017 (0.008,0.026)
SOC	Skin and subcutaneous tissue disorders	328	206	0.001	0.001	1.345 (1.120,1.617)	1.322 (1.116,1.567)	0.016 (0.006,0.025)

4.3.2 Denosumab Versus Active-Control

The hypersensitivity adverse events in the denosumab arm were also compared to those in the active-control arm (alendronate) for studies 20050141 and 20050234 (see Tables 14 and 15). There were no significant differences between treatment arms when analysis was done at various MedDRA levels. Table 20 shows the counts and crude incidence rates of the Skin SOC. The MedDRA level groups listed are the same as in Table 5. In general, denosumab has about the same incidence rate for Skin SOC events than alendronate when considering either both studies or each study separately.

Table 20: Skin and subcutaneous tissue disorders SOC (Set S, Active-control)

	20050141		20050234		Total	
HLGT, HLT, and PT	Denosumab	Alendronate	Denosumab	Alendronate	Denosumab	Alendronate
Safety Population	593 (%)	586 (%)	253 (%)	249 (%)	846 (%)	835 (%)
Epidermal and dermal conditions	19 (3.2)	14 (2.4)	7 (2.8)	7 (2.8)	26 (3.1)	21 (2.5)
Dermatitis and eczema	6 (1.0)	2 (0.3)	4 (1.6)	2 (0.8)	10 (1.2)	4 (0.5)
Dermatitis*	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)	2 (0.2)	2 (0.2)
Dermatitis allergic*	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)
Dermatitis atopic*	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Dermatitis contact*	3 (0.5)	0 (0.0)	1 (0.4)	0 (0.0)	4 (0.5)	0 (0.0)
Eczema*	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)	2 (0.2)	2 (0.2)
Rashes, eruptions and exanthems NEC	11 (1.9)	10 (1.7)	3 (1.2)	3 (1.2)	14 (1.7)	13 (1.6)
Rash**	11 (1.9)	8 (1.4)	2 (0.8)	3 (1.2)	13 (1.5)	11 (1.3)
Rash generalised**	0 (0.0)	2 (0.3)	1 (0.4)	0 (0.0)	1 (0.1)	2 (0.2)
Other HLTs	2 (0.3)	2 (0.3)	0 (0.0)	2 (0.8)	2 (0.2)	4 (0.5)
Angiodema and urticaria	3 (0.5)	4 (0.7)	0 (0.0)	1 (0.4)	3 (0.4)	5 (0.6)
Total PTs	22 (3.7)	18 (3.1)	7 (2.8)	8 (3.2)	29 (3.4)	26 (3.1)

* in set P; ** not in set P

4.4 Follow-up and Extension Phases of Pivotal Studies

Study 20030216 has a follow-up open-label and single-arm extension study, 20060289. All subjects enrolled in Study 20060289, regardless of treatment arm in Study 20030216, re-

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ceived denosumab 60 mg subcutaneously every six months for two years. Studies 20040132, 20040135 and 20040138 each has a 24-month safety follow-up period where no investigational product was administered. The follow-up and extension phase studies were still ongoing at the time this report was written.

5 Immunogenicity

As a biologic product, denosumab has the potential of inducing countering antibodies or cell-based immune responses. Specific adverse events that may indicate an immunogenicity include reactions due to systemic infusion, local injection site and hypersensitivity. The sponsor conducted two types of tests: the presence or formation of (1) binding antibodies and (2) neutralizing antibodies. Two was only conducted when patients tested positive or found to be reactive for (1) at the same time point. Tests (1) and (2) used electrochemiluminescent (ECL) bridging immunoassay and cell-based chemiluminescent mRNA expression assay, respectively. The data for antibody testing was in a domain called AB (in Standard Data Tabulation Model or SDTM format) and AAB (ADaM format). Neither datasets contained antibody titers/concentration levels or measurements and only positive or negative test results for antibody formations.

A summary of the results for positive binding antibodies testing is given in Table 21. In study 20030216, the largest study, only 25 of 3886 or about 0.6% of all subjects developed binding antibodies. The largest incidence in any of the studies was about 1.6% (study 20040135). Table 22 shows the subject visits when the positive test results where collected for study 20030216. This table shows that there were $7+5+3+2+0+2 = 19$ subjects that tested positive for only one binding antibody test and most of them were on the first and

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Table 21: Positive Binding Antibody Test Results.

Study	Size	Pre-existing	Developing	Frequency 1	2	3
20030216	3886	5	25	19	5	1
20010223	314	0	2	2	0	0
20040132	164	0	2	2	0	0
20040135	129	0	2	2	0	0
20040138	731	0	1	1	0	0
20050233*	200	0	1	1	0	0

* ongoing at the time of BLA submission

sixth months. There were 5 subjects that tested positive in two occasions during the study and most of the positive tests were on the sixth and twelfth months. Only one subject tested positive thrice (on months 1, 6 and 12). No pre-existing nor developing antibodies were found in any of the subjects in studies 20040245, 20050141, 20050172, 20050179, 20050234 and 20050237. Furthermore, there were no positive test results for neutralizing antibodies in any of the studies.

Table 22: Positive Binding Antibody Tests Per Visit (Study 20030216).

No. of positive tests	Analysis Visit Month 1	6	12	18	24	30
1	7	5	3	2	0	2
2	1	0	1	0	0	0
2	0	1	0	1	0	0
2	0	1	1	0	0	0
2	0	1	1	0	0	0
2	0	1	1	0	0	0
3	1	1	1	0	0	0
Total	9	10	8	3	0	2

The presence or formation of binding antibodies may result in adverse events or hypersensitivity reactions. Thus, the adverse event profiles of subjects who were positive for binding

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antibodies were reviewed. The results are summarized in Table 25 of Appendix E for study 20030216. Table 25 categorizes the adverse events according to severity and occurrence since the last antibody testing that was positive. There were 5 severe adverse cases reported, two of which were from the same subject: Subject IDs (b) (6) (Urinary incontinence), (b) (6) (Arthralgia and Osteoarthritis), (b) (6) (Gastric perforation) and (b) (6) (Ligament rupture). The Osteoarthritis and Gastric perforation cases were considered serious and lead to hospitalization. None of the 5 cases were considered life-threatening, nor were there discontinuation or alteration of treatment and withdrawal. However, only subjects (b) (6) and (b) (6) completed the study. Most of the other cases were either mild or moderate in severity and there were more adverse events after 6 months of positive tests than within 6 months. Finally, of all adverse events reported in subjects with positive binding antibody tests, only Eczema PTs was a potential hypersensitivity case.

6 Summary and Conclusions

This safety review considered primary (P) and secondary (S) sets of preferred terms for hypersensitivity analysis. The events in set P were considered, reviewed and analyzed by the sponsor except for a few that were added by the statistical safety reviewer. Based on the analysis of the pooled pivotal PMO studies, the Skin SOC was found to be significantly different between treatment arms with p-value of ≤ 0.001 when considering either set P or S. The denosumab arm had higher relative risk [1.515 with 95% CI (1.190, 1.928) for set P and 1.455 with 95% CI (1.218,1.738) for set S] and risk difference [0.0135 with 95% CI (0.006, 0.021) for set P and 0.022 with 95% CI (0.011,0.032) for set S] when compared to placebo. When considering set S, the crude incidence rate of events in study 20030216 (the

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largest of the 4 pivotal studies) was 6.7% (261/3886) for denosumab and 4.6% (178/3876) for placebo. Significant differences were also found in the following MedDRA levels within the Skin SOC: Epidermal and dermal conditions HLGT, Dermatitis and eczema HLT, Rashes, eruptions and exanthems NEC HLT, Eczema PT and Rash PT. The Epidermal and dermal conditions HLGT, Dermatitis and eczema HLT, and Eczema PT were significant whether set P or S was considered whereas the Rashes, eruptions and exanthems NEC HLT and Rash PT were significant only when set S was considered. Most results were mainly driven by study 20030216 but for the Rash, significance was only found in study 20030132. No significant results were found for the HALT studies.

For set P events, the three SMQs searched, baseline and demographic characteristics, and events considered serious were largely balanced between treatment arms for the four pivotal studies. Severity and toxicity grade were assessed at the level of a specific event and across events and differences between arms were found for Eczema. Mild cases were about the same in both arms but moderate to severe cases were significantly higher in denosumab (27) than placebo (6). The onset time patterns were very different in both arms. Most denosumab cases happened early on whereas those in placebo happened late in the study. As many subjects in both arms were continuing cases, it was difficult to assess duration. However, almost all subjects with Eczema in either arm completed the study and did not discontinue treatment. For Rash, the onset time was higher in the beginning for denosumab but was similar to placebo thereafter.

Two cases of Shock (an Anaphylactic Reaction SMQ) was reported as life-threatening and fatal in study 20030216. There were 3 cases of Circulatory collapse in study 20040138 that were reported as serious but occurred only on the same subject. The subject was hospitalized but did not withdraw from the study. There were 9 vs 2, mostly mild, Bronchospasm in

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the denosumab and placebo arms, respectively across all four pivotal studies. Other less common events that were noted as occurring only in the denosumab arm and not in the placebo were 4 cases each of Dermatitis atopic and Toxic skin eruption. One case of Toxic skin eruption was considered serious.

The review of secondary studies did not suggest different events nor crude incidence rates when compared to the pivotal studies. Furthermore, no dose-varying adverse events were observed. In the analysis of denosumab versus the active-control alendronate, there were no significant differences found between treatment arms.

For immunogenicity, the sponsor conducted two antibody tests. The first was a test for binding antibodies and the second test was a follow-up on the first one to confirm if the binding antibodies were neutralizing or not. Based on the data submitted by the sponsor, 6 of 12 studies with antibody tests had positive results: 20030216 (25/3886 or 0.6%), 20010223 (2/314 or 0.6%), 20040132 (2/164 or 1.2%), 20040135 (2/129 or 1.6%), 20040138 (1/731 or 0.1%) and 20050233 (1/200 or 0.5%). In 20030216, 19 subjects tested positive once only, 5 were positive twice and 1 was positive thrice. There was no correlation observed between subjects with positive binding antibody tests and their adverse event profiles. None of the subjects that were positive for binding antibodies were positive for neutralizing antibodies.

In conclusion, denosumab does not appear to be immunogenic but there are some hypersensitivity concerns when it comes to particular types or groups of Skin SOC events. Specific cases that were found to be significant were Eczema and Rash. For Eczema, the main difference between treatment arms were those classified as moderate and severe. The Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs, which contained the Eczema and Rash events, respectively, were also of concern because of higher incidences of other PTs in denosumab compared to placebo. Although most of the subjects with Eczema and Rash

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completed the study, it is recommended that the labeling of denosumab should indicate the potential occurrence of these events while on treatment. Additionally, it is recommended that the label includes the potential occurrence of other PTs within the Dermatitis and eczema and Rashes, eruptions and exanthems NEC HLTs. Furthermore, it is recommended that safety monitoring in postmarketing should record and evaluate the occurrences of all these events.

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7 APPENDICES

A. Standardised MedDRA Queries (SMQ) Searched for Set P

ANGIOEDEMA SMQ:

Allergic oedema	Angioedema	Circumoral oedema
Conjunctival oedema	Corneal oedema	Epiglottic oedema
Eye oedema	Eye swelling	Eyelid oedema
Face oedema	Gingival oedema	Gingival swelling
Gleich's syndrome	Hereditary angioedema	Idiopathic urticaria
Laryngeal oedema	Laryngotracheal oedema	Lip oedema
Lip swelling	Oculorespiratory syndrome	Oedema mouth
Oropharyngeal swelling	Palatal oedema	Periorbital oedema
Pharyngeal oedema	Scleral oedema	Small bowel angioedema
Swelling face	Swollen tongue	Tongue oedema
Tracheal oedema	Urticaria	Urticaria cholinergic
Urticaria chronic	Urticaria papular	

ANAPHYLACTIC REACTION SMQ:

Anaphylactic reaction	Anaphylactic shock	Anaphylactoid reaction
Anaphylactoid shock	Circulatory collapse	First use syndrome
Shock	Type I hypersensitivity	

SEVERE CUTANEOUS ADVERSE REACTION SMQ:

Acute generalised exanthematous pustulosis	Cutaneous vasculitis	Dermatitis bullous
	Dermatitis exfoliative generalised	Epidermal necrosis
Dermatitis exfoliative	Exfoliative rash	Skin necrosis
Erythema multiforme	Toxic epidermal necrolysis	Toxic skin eruption
Stevens-Johnson syndrome		

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B. Additional Potential Hypersensitivity Preferred Terms Searched For Set S

Anaphylaxis treatment	Bronchospasm	Circulatory collapse
Drug eruption	Eosinophilia	Erythema multiforme
Exfoliative rash	Peripheral circulatory failure	Rash
Rash erythematous	Rash generalised	Rash macular
Rash maculo-papular	Rash morbilliform	Rash vesicular
Skin exfoliation	Toxic skin eruption	Urticaria

C. Computation of Duration for Eczema Preferred Terms (Study 20030216)

- Subjects 20030216 (b) (6), 20030216 (b) (6), 20030216 (b) (6) had the same start dates for the same PT but were coded multiple times for different location of occurrence on the body. The multiple records were counted as one PT.
- Subject 20030216 (b) (6) was coded with one eczema case (aeterm: "worsening eczema on both hands") with a start date of (b) (6) and an end date of (b) (6). However, another eczema case (aeterm: "eczema both hands") was reported as having started on (b) (6) and reported as continuing (aecont='Y'). Another eczema case (aeterm: "eczema in the face") was reported with start date of (b) (6) with an end date of (b) (6). For this subject, all three cases were considered as one eczema case with start date of (b) (6) and reported as continuing.
- Subject 20030216- (b) (6) had two coded eczema events that were both continuing. For

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this subject, only one case was included in the analysis using the earliest start date of [redacted].

- Subject 20030216-[redacted] had eczema (aeterm: "eczema both palms") with start date of [redacted] and end date of [redacted]. Three other cases (aeterms: "eczema left palm", "eczema on sole right foot", and "eczema right palm") were reported with the same start date of [redacted] and reported as continuing. For this subject, one case of eczema was reported with start date of [redacted] and continuing.

- For subject 20030216[redacted], eczema (aeterm: worsening eczema) was reported to have started on [redacted] and ended on [redacted]. However, another eczema case with the same aeterm was reported to have started on [redacted] and continuing. For this subject, only one case of eczema was included in the analysis with start of [redacted] and continuing.

- Usubjid 20030216[redacted] had two reported cases of eczema (aeterm: "eczema" for both) with start dates of [redacted] and [redacted]. Both were treated as separate cases in the analysis. 20030216-[redacted] had two continuing cases. Only one case was considered using the earliest start date. 20030216[redacted] had two continuing cases with same start date and only one was considered in analysis.

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D. Other Reported Skin Adverse Events of Subjects With Eczema and Rash (Study 20030216)

Table 23: Other Reported Skin Primary SOC Adverse Events of Subjects With Eczema (Study 20030216)

Adverse events	No. of Subjects	
	Denosumab	Placebo
Dermatitis contact, Dermatitis, Eczema, Skin lesion	1	0
Skin inflammation, Pruritus, Eczema, Rash	1	0
Eczema, Hyperkeratosis, Lichen planus, Pruritus	1	0
Rash, Eczema, Pruritus	1	1
Urticaria, Eczema, Dermatitis allergic	0	1
Eczema, Dermal cyst	1	0
Eczema, Dry skin	1	0
Eczema, Pruritus	0	1
Eczema, Skin nodule	0	1
Eczema, Toxic skin eruption	1	0
Eczema, Urticaria	1	1
Alopecia areata, Eczema	1	0
Dry skin, Eczema	1	0
Pain of skin, Eczema	1	0
Pruritus, Eczema	2	1
Rash, Eczema	1	0
Skin ulcer, Eczema	1	0
Urticaria, Eczema	1	0
Eczema	34	19
Total	50	25

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Table 24: Other Reported Skin Primary SOC Adverse Events of Subjects With Rash (Study 20030216)

Adverse events	No. of Subjects	
	Denosumab	Placebo
Rash, Onychoclasis, Psoriasis, Nail disorder, Nail dystrophy	1	0
Onychoclasis, Dry skin, Hyperhidrosis, Rash	0	1
Skin inflammation, Pruritus, Eczema, Rash	1	0
Rash, Blister, Pruritus	1	0
Rash, Eczema, Pruritus	1	1
Rash, Ingrowing nail, Alopecia	1	0
Rash macular, Rash, Rash pruritic	1	0
Dermatitis allergic, Rash, Pruritus	1	0
Dermatitis contact, Seborrhoeic Dermatitis	1	0
Dry skin, Rash, Rash pruritic	1	0
Skin discolouration, Rash, Skin lesion	1	0
Rash, Actinic keratosis	1	0
Rash, Alopecia	1	0
Rash, Dermal cyst	1	0
Rash, Dermatitis	1	0
Rash, Dermatitis allergic	0	2
Rash, Dermatitis contact	1	0
Rash, Dry skin	1	1
Rash, Eczema	1	0
Rash, Granuloma annulare	1	0
Rash, Pain of skin	1	0
Rash, Parapsoriasis	0	1
Rash, Pruritus	0	1
Rash, Purpura	0	1
Rash, Rash generalised	2	0
Rash, Rash macular	1	0
Rash, Rash pruritic	2	0
Rash, Rosacea	0	1
Rash, Skin nodule	0	1
Rash, Skin ulcer	1	1
Rash, Urticaria	2	1
Dermatitis, Rash	0	1
Dermatitis allergic, Rash	0	2
Dry skin, Rash	1	0
Erythema, Rash	1	0
Prurigo, Rash	1	0
Pruritus, Rash	2	1
Purpura, Rash	0	1
Swelling face, Rash	0	1
Rash	61	54
Total	93	72

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E. Adverse Events For Subjects Who Were Positive For Binding Antibodies (Study 20030216)

	0-6 Months*			> 6 Months*		
System Organ Class	Mild	Moderate	Severe	Mild	Moderate	Severe
Musculoskeletal and connective tissue disorders	4	5	0	4	8	2
Back pain	2	3	0	2	2	0
Arthralgia	0	0	0	2	2	1
Osteoarthritis	0	0	0	0	1	1
Pain in extremity	0	1	0	0	1	0
Intervertebral disc space narrowing	1	0	0	0	0	0
Muscle rigidity	0	0	0	0	1	0
Spinal osteoarthritis	1	0	0	0	0	0
Joint swelling	0	0	0	0	1	0
Musculoskeletal pain	0	1	0	0	0	0
Infections and infestations	5	5	0	4	4	0
Nasopharyngitis	3	0	0	2	1	0
Influenza	0	1	0	0	1	0
Viral infection	0	0	0	2	0	0
Gastroenteritis	1	0	0	0	0	0
Furuncle	1	0	0	0	0	0
Gingival infection	0	0	0	0	1	0
Lower respiratory tract infection	0	1	0	0	0	0
Tooth abscess	0	0	0	0	1	0
Herpes ophthalmic	0	1	0	0	0	0
Upper respiratory tract infection	0	1	0	0	0	0
Urinary tract infection	0	1	0	0	0	0
Gastrointestinal disorders	0	2	0	1	3	1
Abdominal pain upper	0	1	0	1	0	0
Constipation	0	0	0	0	2	0
Diarrhoea	0	1	0	0	0	0

Continued on next page

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Table 25 – continued from previous page

	0-6 Months*			> 6 Months*		
System Organ Class	Mild	Moderate	Severe	Mild	Moderate	Severe
Gastric perforation	0	0	0	0	0	1
Gastroduodenal ulcer	0	0	0	0	1	0
Injury, poisoning and procedural complications	2	3	1	0	1	0
Procedural pain	0	0	0	0	1	0
Limb injury	0	1	0	0	0	0
Contusion	1	0	0	0	0	0
Fall	0	1	0	0	0	0
Foot fracture	0	1	0	0	0	0
Ligament rupture	0	0	1	0	0	0
Rib fracture	1	0	0	0	0	0
Nervous system disorders	0	1	0	1	4	0
Headache	0	0	0	1	1	0
Dizziness	0	1	0	0	0	0
Hyperreflexia	0	0	0	0	1	0
Paraesthesia	0	0	0	0	1	0
Sciatica	0	0	0	0	1	0
Metabolism and nutrition disorders	2	0	0	2	0	0
Hypercholesterolaemia	1	0	0	1	0	0
Hyperlipidaemia	0	0	0	1	0	0
Type 2 diabetes mellitus	1	0	0	0	0	0
Psychiatric disorders	1	0	0	2	1	0
Anxiety	1	0	0	1	0	0
Depression	0	0	0	0	1	0
Insomnia	0	0	0	1	0	0
Skin and subcutaneous tissue disorders	2	1	0	0	0	0
Alopecia	1	0	0	0	0	0
Onychoclasis	1	0	0	0	0	0
Eczema	0	1	0	0	0	0
Reproductive system and breast disorders	0	0	0	3	0	0

Continued on next page

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Table 25 – continued from previous page

	0-6 Months*			> 6 Months*		
System Organ Class	Mild	Moderate	Severe	Mild	Moderate	Severe
Breast mass	0	0	0	1	0	0
Genital haemorrhage	0	0	0	1	0	0
Vaginal haemorrhage	0	0	0	1	0	0
General disorders and administration site conditions	0	0	0	1	2	0
Gait disturbance	0	0	0	0	1	0
Oedema peripheral	0	0	0	1	0	0
Non-cardiac chest pain	0	0	0	0	1	0
Renal and urinary disorders	0	1	0	0	0	1
Urinary incontinence	0	0	0	0	0	1
Dysuria	0	1	0	0	0	0
Eye disorders	0	0	0	2	0	0
Lacrimation increased	0	0	0	1	0	0
Cataract	0	0	0	1	0	0
Vascular disorders	1	0	0	0	0	0
Haematoma	1	0	0	0	0	0
Ear and labyrinth disorders	1	0	0	1	0	0
Tinnitus	0	0	0	1	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1	0
Bronchitis chronic	0	0	0	0	1	0
Total	18	18	1	21	24	4

* since last positive binding antibody test

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8 References

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SIGNATURES/DISTRIBUTION LIST

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John Stephen Yap, PhD

Mathematical Statistician, Division of Biometrics VII

Secondary Statistical Reviewers

July 28, 2009

Paul Schuette, PhD

Mathematical Statistician, Division of Biometrics VII

7/28/09

C. George Rochester, PhD, RAC

Acting Director, Division of Biometrics VII

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HFD-Number/Office of Biostatistics Director: Robert O'Neill, PhD

Yap

Reference ID: 3168397

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA /

NDA Number: 125320 Applicant: Amgen Stamp Date: 12/19/09

Drug Name: Prolia (Denosumab) NDA/BLA Type: Standard

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.				
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.				
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.				
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.				

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

Reference ID: 3168397

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Paul R. Schuette — January 29, 2009
Reviewing Statistician — Date

[signature] — 1/29/09
Supervisor/Team Leader — Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

Reference ID: 3168397

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

MICROBIOLOGY/VIROLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: September 9, 2009
To: Administrative Files, STN 125320, STN 125331, STN 125332, STN 125333
From: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT 9/14/09
Subject: Team Leader Microbiology Product Quality review memo and assessment of Manufacturing Establishments
Applicant: Amgen, Inc.
US License: 1080
Facilities: Drug Substance:

1. Amgen Inc. (ACO) LakeCentre Facility, Boulder, CO 80301 (FEI = 3003072024
2. Boehringer Ingelheim Pharma GmbH & Co. Kg Biberach an der Riss, Germany (FEI=3002806518)

Drug Product:

1. Amgen Manufacturing, Limited (AML), Juncos, Puerto Rico 00777 (FEI=1000110364)

Product: Prolia™ (Denosumab, AMD 162)
Dosage: Single-use, sterile preservative-free solution for subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial.
Indication: Treatment for prevention of osteoporosis in postmenopausal women (STN 125320)
Prevention of osteoporosis in postmenopausal women (STN 125331)
Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer (STN 125332) or prostate cancer (STN125333)
PDUFA date: 19 October 2009

RECOMMENDATION FOR BLA APPROVABILITY:

CMC Microbiology Product Quality Assessment:

BLA 125320, as amended, is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. Data and information supporting the recommendation for approval are presented in the review memos of Kalavati Suvarna, Ph.D., Ph.D., CDER/OC/DMPQ/BMT for the drug substance and Donald Obenhuber, Ph.D., CDER/OC/DMPQ/ NGDM for the drug product part of the application.

Establishment Assessment:

The manufacturing and testing facilities listed in the BLA have an acceptable compliance status.

1. Pre-approval inspections of the following drug substance manufacturing and testing sites were conducted by a team of investigators from OBP/DMA and OC/BMT during the review of this BLA:
    a. Amgen Colorado LakeCentre facility, Boulder Colorado, FEI 3003072024
    b. Boehringer ingelheim GmbH & Co, Biberach an der Riss, Germany, FEI= 3002806518

    Both sites were found to be acceptable from a compliance perspective.

2. The drug product is manufactured at Amgen Manufacturing Limited (AML), Juncos, Puerto Rico (FEI=1000110364). This site was inspected by the district on January 8-12, 2007 and currently has an acceptable compliance status. A surveillance inspection of the AML site was conducted during the review of this BLA and is currently on-going.

Review Summary

Drug substance:

The drug substance is a fully human IgG2 monoclonal antibody that is expressed in Chinese Hamster Ovary (CHO) cells during cell culture at the (b) (4) bioreactor scale at the Amgen LakeCentre (ACO) manufacturing facility in Colorado, Boulder, and at the (b) (4) (b) (4) bioreactor scale at Boerhinger Ingelheim Pharma in Biberach, Germany. Adequate in-process microbial controls, including endotoxin, are in place at various steps of the manufacturing process. In addition, in-process holds for intermediates and buffers, cleaning, sanitization and storage of purification (b) (4) are validated and microbial methods are qualified.

During the review cycle, the sponsor provided a calculation of the endotoxin limit based on worst-case minimal patient weight of 50 kg and the maximum single human dose for denosumab to determine the safety margin for the proposed endotoxin specification. The endotoxin drug substance specification is (b) (4) is well below the threshold of human pyrogenic response. The endotoxin results for batches manufactured at ACO site (b) (4) varied from that manufactured at BI Pharma (b) (4) due to the differences in testing methods (LAL turbidimetric at ACO versus chromogenic kinetic LAL method at BI Pharma). Both methods comply with USP <85> and Ph.Eur .2.6.14 compendial methods. The results from the two sites were within the acceptance criteria and well below the threshold of human pyrogenic response.

All drug substance review issues were resolved in the course of the review and six amendments were submitted to the BLA.

A pre-license inspection of the ACO establishment was conducted on June 8-12, 2009 by BMT and OPB reviewers (Kalavati Suvarna, Ph.D., Maan Abduldayem, and Sarah Kennett, Ph.D.) and by district inspectors (Nancy Schmidt and Kimberly Hoefen). The

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inspection was classified as NAI and was acceptable from a compliance perspective. The BI Pharma facility was inspected by a BMT and OBP reviewers (Kalavati Suvarna, Ph.D., Chana Fuchs, Ph.D. and Sarah Kennett, Ph.D.) on May 11-19, 2009. The firm was cited with a one item 483 observation because (b) (4) . In response to the 483 observation, the firm indicated that (b) (4) (b) (4) The response was also reviewed by the International Compliance Team in OC/DMPQ and was deemed acceptable.

Drug product:

The drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial presentation with a 1.0 mL deliverable volume. No issues that would prevent BLA recommendation for approval were identified by the primary microbiology reviewer. The drug product vials and pre-filled syringes are manufactured in AML (FEI=1000110364). This facility was inspected January 8-12, 2007 and classified VAI and currently has an acceptable compliance status. A surveillance inspection in progress during the review of this application revealed several complaints of broken syringes for other products of Amgen especially using auto injection device. This does not affect the recommendation for approval of this BLA since this application is for the vial and PFS final dosage form presentations.

Conclusion

I. The BLA, as amended, is recommended for approval from a microbial control, sterility assurance and product quality microbiology perspective.

II. Information and data in this submission not related to microbial control, sterility assurance and product quality microbiology should be evaluated by OBP reviewers.

III. All establishments involved in the manufacture and testing of the drug substance and drug product have an acceptable compliance status.

Cc: WO51: Obenhuber
WO 51:Suvarna
WO51: Hughes
WO22: Peacock
WO:22 Pierce

WO51: eCTD Files (STN 125320, STN 125331, STN 125332, STN 125333)

Archived File: S:\archive\BLA\125320\125320.TL.rev.mem.BLA.9-8 -2009.doc
Archived File: S:\archive\BLA\125331\125331.TL.rev.mem.BLA.9-8 -2009.doc
Archived File: S:\archive\BLA\125332\125332.TL.rev.mem.BLA.9-8 -2009.doc
Archived File: S:\archive\BLA\125333\125333.TL.rev.mem.BLA.9-8 -2009.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA:	125320, 125331, 125332, and 125333
Type/Category:	New molecular entity, First in class
Brand Name:	Prolia™
Generic Name:	Denosumab
Proposed Indication:	Treatment (BLA 125320) and prevention (BLA 125331) of osteoporosis; Treatment and prevention of bone loss in patients undergoing hormone ablation therapy (HALT) for breast (BLA 125332) or prostate (BLA 125333) cancer
Dosage Form:	Injection
Route of Administration:	Subcutaneous
Dosing Regimen and Strength:	60 mg/ml every 6 months
Sponsor:	Amgen Inc.
OCP Division:	Division of Clinical Pharmacology 3 (DCP3); Division of Clinical Pharmacology 5 (DCP5)
OND Division:	Division of Reproductive and Urologic Products (DRUP); Division of Biologics and Oncology Products (DBOP)
Submission Date:	December 19, 2008 (original)
Primary Reviewers:	Chongwoo Yu, Ph.D.; Sarah Schrieber, Ph.D.
Secondary Reviewers:	Jang-Ik Lee, Pharm.D., Ph.D.; Hong Zhao, Ph.D.
Pharmacometrics Primary Reviewer:	Ping Ji, Ph.D.
Pharmacometrics Secondary Reviewer:	Pravin Jadhav, Ph.D.

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1 EXECUTIVE SUMMARY

Denosumab is a fully human IgG2 monoclonal antibody that inhibits receptor activator of nuclear factor kappa B (RANK) ligand, proposed for the treatment (BLA 125320) and prevention (BLA 125331) of osteoporosis in postmenopausal women (PMO) and for the treatment and prevention of bone loss in patients undergoing hormone ablation therapy (HALT) for breast (BLA 125332) or prostate (BLA 125333) cancer. Denosumab is considered to be a new molecular entity (NME) and the first monoclonal antibody proposed for the indications above (i.e., first in class). The proposed proprietary name for denosumab, Prolia™ was found to be acceptable to the Division of Medication Error Prevention and Analysis (DMEPA) and the Sponsor was notified via a letter on May 20, 2009.

This application includes 30 clinical studies including 13 Clinical Pharmacology and Biopharmaceutics studies conducted in healthy volunteers and patients performed from June 2001 to September 2008. Among the 13 Clinical Pharmacology and Biopharmaceutics studies subject to review, there were 4 pharmacokinetics (PK) and tolerability studies conducted in healthy volunteers, 2 PK and tolerability studies conducted in cancer patients, 2 dose-ranging studies conducted in PMO patients, 1 intrinsic factor PK study conducted in patients with renal impairment, and 1 extrinsic factor PK study conducted in patients with prior exposure to bisphosphonates.

The Division of Reproductive and Urologic Products (DRUP) has conducted review for the PMO related indications (BLAs 125320 and 125331) while the Division of Biologics and Oncology Products (DBOP) has conducted review for the cancer related indications (BLAs 125332 and 125333).

A required office-level Clinical Pharmacology briefing was held on Tuesday, August 11, 2009 with approximately 40 attendees. An Advisory Committee (AC) meeting was held on Thursday, August 13, 2009 to discuss about this product.

1.1 RECOMMENDATIONS

The Division of Clinical Pharmacology 3 (DCP-3) has reviewed BLA 125320 and 125331 and the Division of Clinical Pharmacology 5 (DCP-5) has reviewed BLA 125332 and 125333. The overall Clinical Pharmacology and Biopharmaceutics data submitted to support the approval of BLAs 125320, 125332, and 125333 are acceptable provided that a satisfactory agreement is reached regarding the labeling language.

With regards to BLA 125331(prevention of PMO), while the general pharmacokinetics of denosumab should be unchanged in this indication, (b) (4)

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(b) (4)

1.2 PHASE IV COMMITMENTS

The Clinical Pharmacology Review Team recommends the following post marketing commitments (PMC):

Anti-cytokine antibodies such as tocilizumab, an anti-IL-6 monoclonal antibody, showed the alteration of CYP substrate drug exposure by affecting the effect of cytokine on drug metabolism. Thus, denosumab may affect the exposure to CYP substrate drugs by altering the concentration of RANKL, a cytokine that affects B- and T-cell differentiation, and dendritic cell maturation.

Therefore, the Clinical Pharmacology Review Team recommends the sponsor conduct an in vitro study to assess whether RANKL modulate expression of major CYP enzymes (e.g., CYP 3A4, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 2D6). If, upon review, there is no significant modulation of any of the major CYP enzyme(s) observed, further exploration would not be necessary. If the results of the in vitro study are positive, a drug interaction study or studies will be needed to further characterize the effect of denosumab on the metabolism of CYP probe drugs in PMO patients.

As an alternative to the in vitro study and the subsequent drug interaction study above, the sponsor may conduct a drug interaction study to determine the potential of denosumab to alter CYP substrate metabolism in PMO patients (e.g., using a cocktail of the major CYP probe drugs).

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Pharmacokinetics

It should be noted that early clinical studies (Studies 20010124, 20030180, 20030148, 20030164, 20010123, and parts of 20010223) were conducted using denosumab drug substance manufactured using an initial version of the commercial process, designated CP1 at Amgen Thousand Oaks (ATO) (see more information under *Comparability* section below).

In an open-label, randomized, single-dose, parallel-group study (Study 20050146) in healthy men and women volunteers (n=73) having a mean age of 33.6 years (range 18 to 64 years), the mean maximum serum denosumab concentrations (C_{max}) of 6.75 µg/ml (standard deviation [SD]: 1.89 µg/ml) was reached in the median time of 10 days (range: 3 to 21 days) following a 60 mg SC dose after at least 12 hrs of fasting prior to

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denosumab administration. After C_{max}, serum denosumab concentrations decline over a period of 4 to 5 months with a mean half-life of 25.4 days (SD: 8.5 days; n=46; Study 20010223). No accumulation in serum denosumab concentrations was observed with repeated doses of 60 mg once every 6 month (Q6M), and denosumab PK did not appear to change with time (up to 4 years exposure). Denosumab PK was not affected by the formation of binding antibodies to denosumab and was similar in men and women.

The serum concentration time profiles of denosumab were best characterized as a two-compartment model with first-order absorption and a parallel linear and non-linear elimination. Approximately dose-proportional increases in exposure (based on $AUC_{0\text{-}tau}$) were observed for doses ≥ 60 mg (i.e., in the range of fixed doses of 60 to 210 mg in Study 20010223 in the PMO population). Across the range of doses tested, denosumab plasma concentrations declined at a faster rate when serum denosumab concentration dropped below approximately 1 µg/ml. The mechanism behind this change in elimination rate is likely related to denosumab binding to RANKL (i.e target-mediated disposition) . This non-linear elimination mechanism predominates at low serum denosumab concentrations (i.e., < 1 µg/ml in this case) and becomes saturated as serum denosumab concentration increases.

Because denosumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms (e.g., by cytochrome P450 [CYP] enzymes), hepatic impairment and drug interaction studies (e.g., with CYP inhibitors or inducers) were not considered appropriate by the Sponsor and have therefore not been conducted. However, considering that the effect of denosumab, an anti-cytokine antibody, on CYP activities is unknown, a post-marketing commitment (PMC) recommendation is being made to the Sponsor to address denosumab's effect on CYP activities and drug interaction potential.

A study including transition from a bisphosphonate to denosumab was conducted (Study 20050241) and showed that the PK of denosumab was not altered in subjects who transitioned from bisphosphonates to denosumab.

A renal impairment study (Study 20040245) was conducted and included 55 patients with normal, mild, moderate, severe, and end-stage renal disease, defined by creatinine clearance (CrCL). Overlap was observed in denosumab exposure across renal impairment cohorts, and no notable relationship was apparent between denosumab PK and renal impairment. No dose adjustment is necessary in patients with renal impairment.

Pharmacodynamics

Denosumab administration resulted in significant inhibition of bone resorption, as assessed by reductions in serum levels of Type 1 C-telopeptide (CTX1). In clinical studies, treatment with 60 mg of denosumab resulted in rapid reduction in the bone resorption marker serum CTX1 (sCTX1) within 6 hours of SC administration by approximately 70% (Studies 20030216 and 20040132), with reductions of approximately 85% occurring by 3 days (Study 20010223). sCTX1 reductions in bone turnover appeared to be maintained throughout the dosing interval (6 months). At the end of the

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dosing cycle, some attenuation of bone resorption inhibition was observed, indicating that reduction of bone turnover associated with denosumab administration is reversible when serum concentrations of denosumab diminish. Bone mineral density (BMD) continuously increased during treatment. The effects of denosumab on BMD were rapid, with significant increases in lumbar spine BMD and hip BMD observed as early as 1 month following initiation of treatment, and sustained, with greater increases compared with placebo observed at each time point through the end of treatment (up to 3 years, depending on the study) in these subject populations.

No relationship between denosumab exposure and changes in serum calcium following denosumab administration was observed.

Exposure-Response Relationship
In Study 20010223, the percent change from baseline in sCTX1 and lumbar spine BMD following 2 consecutive doses of various denosumab concentrations given every 3 or 6 months to postmenopausal women with low BMD was assessed. Denosumab treatment was associated with an increase in BMD of the lumber spine. The gain in lumbar spine BMD of all active treatment groups was significantly greater compared to placebo. The gain in lumbar spine BMD following 60 mg Q6M dosing is comparable to that observed following 100 and 210 mg Q6M dosing and greater than that observed following 14 mg Q6M dosing. However, all dose groups achieved similar increases in BMD after 48 months. There was no dose-response relationship for safety established.

Intrinsic Factors
Based on the pharmacometrics review (attached), age and gender were not significant covariates in the population PK analysis. In the population PK analysis both race (as Black and Hispanic) and solid tumor were identified as covariates for clearance. The PK of denosumab did not appear to be affected by these covariates as shown in the simulation results.

The appropriateness of fixed dosing regimen of 60 mg Q6M was evaluated through the effect of body weight on new vertebral fractures and BMD levels. Although body weight was identified as a covariate for clearance, body weight did not appear to affect the incidence of new vertebral fracture over the 36 months period and change in the BMD levels. While denosumab PK parameters are dependent on body weight, these differences in exposure did not affect the response to denosumab. Therefore, the proposed dosing regimen was found to be appropriate for all patients recommended for use.

Comparability
The Biopharmaceutics program demonstrated the comparability between denosumab drug substance and drug product produced for the pivotal Phase 3 clinical trials and those intended for commercial use.

Drug substance: During the development of denosumab, there were process changes of manufacturing the drug substance. Denosumab drug substance used in the nonclinical and early clinical studies (Studies 20010124, 20030180, 20030148, 20030164, 20010123,

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and parts of 20010223) was manufactured using an initial version of the commercial process, designated CP1 at Amgen Thousand Oaks (ATO). Denosumab drug substance manufactured at ATO using an optimized process with increased product yields and improved process robustness, designated as CP2 has been used in all of the later clinical trials. Although the Sponsor has assessed the comparability of denosumab produced using the CP1 and CP2 processes in a nonclinical study with cynomolgus monkeys, the PK comparability of denosumab produced using CP1 and CP2 processes in human is unknown. It should be noted that the Sponsor is proposing to use PK data obtained from studies conducted using CP2 process drug substance for labeling purpose.

Manufacturing site change and product preparation: The drug substance used in the pivotal Phase 3 trials was manufactured at ATO while the to-be-marketed drug substance was manufactured at Amgen Colorado (ACO) and Boehringer-Ingelheim Pharma (BIP). The Sponsor is proposing to have both a vial and a prefilled syringe (PFS) product preparation. PK and PD comparability assessments were conducted by the Sponsor to establish comparability across the different manufacturing sites as well and the different product preparations. Assessments of PK and PD comparability were based on the rate (maximum observed serum denosumab concentration [C_{max}]) and extent (area under the serum denosumab concentration-time curve from time zero to 16 weeks [$AUC_{0\text{-}16\ weeks}$]) of denosumab exposure and were supported by PD parameters (e.g., area under the effect curve from time zero to 16 weeks [$AUEC_{0\text{-}16\ weeks}$] for reductions in sCTX1). In addition, the safety profiles including immunogenicity were also compared and appeared to be consistent between the drug substances from the three different manufacturing sites. In the Clinical Pharmacology studies performed in healthy volunteers (Studies 20050227, 20060286, and 20050146), the PK and PD comparability of denosumab drug substances manufactured at 3 manufacturing sites (ATO, ACO, and BIP) and using 2 drug product preparations (PFS and vial) was established.

Immunogenicity

Immunogenicity testing (using a validated electrochemiluminexcent bridging immunoassay) has been performed in all denosumab clinical studies. The immunogenicity potential with denosumab is low. Less than 1% (43 out of 8113) of patients treated with denosumab tested positive for binding antibodies. No patients tested positive for neutralizing antibodies. No evidence of altered PK, PD, safety profile, or clinical response has been observed in patients who tested positive for binding antibodies.

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1.4 SIGNATURES

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Date: 08/21/2009

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QUESTION BASED REVIEW

2.1 General Attributes

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?

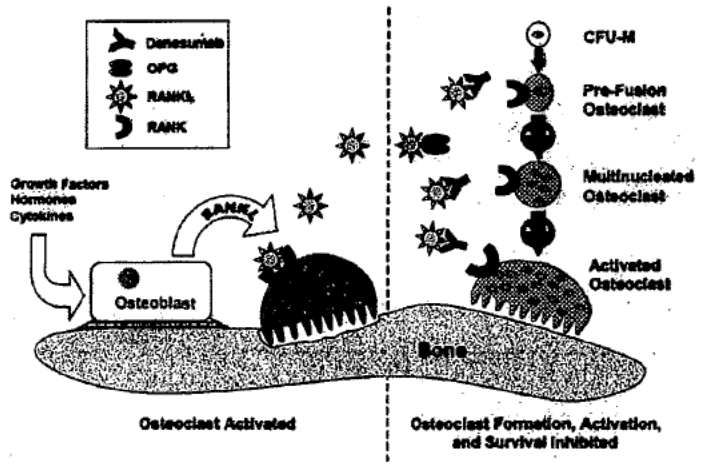
Denosumab (molecular weight: 147 kDa) is a fully human IgG2 κ-type monoclonal antibody to receptor activator of nuclear factor-kB (RANK) ligand (RANKL; a member of the tumor necrosis factor [TNF] family of proteins) that binds with high affinity and specificity to RANKL (K_d 3 x 10^{-12} M). Denosumab binds only to RANKL and does not bind to other members of the TNF family of proteins, including TNFα, TNFβ, TNF-related apoptosis-inducing ligand, or CD40 ligand (Elliott *et al*, 2006).

Denosumab drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in either a 60 mg/ml prefilled syringe (PFS) or 60 mg/ml vial presentation with a 1.0 ml deliverable volume to support dosing of 60 mg every 6 months (Q6M).

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Denosumab is a fully human IgG2 monoclonal antibody binding to RANKL. This binding prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts (Figure 1), the result of which is a reduction in the number and function of osteoclasts and, consequently, a decrease in bone resorption and an increase in cortical and trabecular bone mass, volume, and strength (Kostenuik, 2005). As a result of its mechanism of action, denosumab is being investigated as a therapy for postmenopausal osteoporosis (PMO) and bone loss associated with hormone ablation therapy (HALT).

Figure 1: Mechanisms of Action for Denosumab, Osteoprotegerin, and RANKL



CFU-M - colony-forming unit-macrophage; OPG = Osteoprotegerin; RANK = receptor activator of nuclear factor-κB; RANKL = RANK ligand

Adapted from Boyle et al, 2003

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2.1.3 What are the proposed dosage and route of administration?

The Sponsor's proposed dose of denosumab is 60 mg subcutaneously once every six monthly (Q6M). The proposed dosing regimen of denosumab was evaluated up to a length of 4 years and was generally well tolerated.

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?

The Clinical Pharmacology program was designed to: characterize the initial safety, tolerability, PK, PD, and exposure-response properties of denosumab in healthy volunteers (men [≥ 50 yrs old] and postmenopausal women [≥ 40 yrs old]) and in patients with BMD or osteoporosis or bone loss associated with hormone ablation therapy (HALT); guide the selection of the dose regimens for Phase 2 and 3 studies; evaluate the effect of covariates (gender, body weight, body mass index (BMI), race, and age) on the PK and PD of denosumab; explore possible relationships between the presence of denosumab binding antibodies and denosumab PK and PD properties; and explore the relationship between serum concentrations of denosumab and calcium. Furthermore, the Clinical Pharmacology program was designed to assess the impact of renal impairment on the PK, PD, and safety profiles of denosumab, and to explore the effect of transitioning from a bisphosphonate on the, PK, PD, and safety profiles of denosumab.

The Biopharmaceutics program demonstrated the PK and PD comparability between denosumab drug substance and drug product produced for the pivotal Phase 3 clinical trials and those intended for commercial use.

The Clinical Pharmacology and Biopharmaceutics studies are outlined in Section 5.1 of the Appendix.

The PMO clinical development program is supported by 2 pivotal Phase 3 studies (Studies 20030216 and 20040132). Study 20030216 was a 3-year randomized, double-blind, placebo-controlled study in postmenopausal women with osteoporosis to determine whether denosumab treatment can reduce the incidence of new vertebral (primary endpoint), and nonvertebral and hip fractures (secondary endpoints) as compared with control. Denosumab decreased the incidence of new vertebral fractures (primary endpoint) by approximately two thirds, from 7.2% in the placebo group to 2.2% (risk ratio: 0.32; $p < 0.0001$).

Study 20040132 is a randomized, double-blind, placebo-controlled study in postmenopausal women with low bone mass to determine whether denosumab treatment can prevent lumbar spine bone loss. Denosumab statistically significantly increased BMD (based on dual energy x-ray absorptiometry [DXA]) at the lumbar spine, total hip, femoral neck, trochanter, distal 1/3 radius, and total body at month 24 ($p < 0.0001$ after

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multiplicity adjustment) for both early and late postmenopausal women and for both strata combined.

To support the approval in breast cancer, the Sponsor conducted two Phase 1 studies, one Phase 2 study, and one Phase 3 study. Patients in the Phase 1 studies and Phase 2 study were assigned to receive various doses (0.1-3 mg/kg and 30-180 mg, respectively) of denosumab administered at various intervals (single, or every 4 or 12 weeks). The dose and dosing regimen for the Phase 3 study was based on data obtained from a dose ranging Phase 2 study in post-menopausal women. The Phase 1 and Phase 2 breast cancer studies provided supportive data for the 60 mg dose used in the Phase 3 study. In the Phase 3 study, 252 patients were randomly assigned to receive placebo or denosumab 60 mg subcutaneously every 6 months for 18 months (i.e., 4 total doses). Results indicate that treatment with denosumab statistically significantly increased BMD, as assessed by DXA, at the lumbar spine, total hip, and femoral neck at Months 6 and 12 ($p < 0.0001$), as compared to placebo.

To support the approval in prostate cancer, the Sponsor conducted one Phase 3 study. In the Phase 3 study, 1,468 patients were randomly assigned to receive placebo or denosumab 60 mg subcutaneously every 6 months for 30 months (i.e. 6 total doses). Results indicate that treatment with denosumab statistically significantly increased BMD, as assessed by DXA, at the lumbar spine, total hip, and femoral neck at Month 24 and Month 36 (adjusted $p < 0.0001$), as compared to placebo.

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?

Clinical Endpoints

Postmenopausal Osteoporosis

Bone fracture is considered to be the primary clinical endpoint for 'treatment' of osteoporosis. BMD will be considered as the primary clinical endpoint for the 'prevention' indication only if the Sponsor already has an approval for the indication of 'treatment' of osteoporosis. Per *Guidelines for Preclinical and Clinical Evaluation of Agents used in the Prevention or Treatment of Postmenopausal Osteoporosis* (Division of Metabolic and Endocrine Drug Products, April, 1994), if an agent has already been approved to treat osteoporosis, increased BMD may be an appropriate efficacy endpoint for prevention since fracture protection has already been shown in the treatment approval.

Because PMO is characterized by increases in fracture risk and reductions in BMD, the efficacy endpoints in the denosumab clinical studies included vertebral fractures, nonvertebral fractures, hip fractures, and BMD at several anatomical sites (lumbar spine, total hip, femoral neck, trochanter, 1/3 distal radius, and total body) (Table 1). In order to further characterize the mechanism of action of denosumab, serum biochemical markers of bone turnover were also evaluated as endpoints.

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Table 1: Efficacy Endpoints in the Pivotal and Supportive Phase 3 Studies in Postmenopausal Women with Low Bone Mass or Osteoporosis

	Pivotal Phase 3 Efficacy Studies		Supportive Efficacy Studies			Other Studies
Endpoint	Study 20030216	Study 20040132	Study 20050141 (phase 3)	Study 20050234 (phase 3)	Study 20050179 (phase 2)	Study 20050233 (phase 3)[a]
Incidence of new vertebral fractures	Primary	Tertiary	--	--	--	--
Time to first non-vertebral fracture	Secondary	--	--	--	--	--
Time to first hip fracture	Secondary	--	--	--	--	--
Percent change from baseline in lumbar spine BMD	Tertiary	Primary	Secondary	Secondary	--	Secondary
Percent change from baseline in total hip BMD	Tertiary	Secondary	Primary	Primary	Secondary	Secondary
Percent change from baseline in femoral neck, trochanter, 1/3 distal radius, and total body BMD	Tertiary	Secondary	--	--	Secondary	--
Percent change from baseline in femoral neck, trochanter, and 1/3 distal radius	--	--	Secondary	Tertiary	--	Secondary
Percent change from baseline in trabecular, cortical, and total volumetric BMD of the distal radius	Tertiary	Secondary	--	--	Secondary	--
Percent change from baseline in cortical thickness at the distal radius by XtremeCT	--	--	--	--	Primary	--
Percent change from baseline in bone markers (serum CTX1, P1NP, BSAP and TRAP 5b)	Tertiary	Tertiary	Tertiary (CTX1 and P1NP only)	Secondary (serum CTX1 only)	Secondary (CTX1, P1NP, TRAP 5b only)	Secondary (CTX1 and BSAP only)

[a] The primary objective was to evaluate the long-term safety of denosumab administration in postmenopausal women with low BMD who completed the parent Study 20010223.

Breast and Prostate Cancer

The endpoints for both of the pivotal Phase 3, multicenter, randomized, double-blinded, placebo-controlled studies were percentage change from baseline in lumbar spine BMD.

Bone Turnover Markers

sCTX1 is a product of the proteolytic process of bone resorption brought about by osteoclasts and is a recognized biochemical marker for bone resorption. Changes in sCTX1 concentrations have been shown to correlate with changes in BMD in elderly, osteopenic and osteoporotic, postmenopausal women treated with alendronate (Greenspan *et al*, 2000). The Sponsor believes that rapid and sustained effect of denosumab on bone turnover markers has been demonstrated and therefore, is proposing to include a summary of the effects of denosumab on bone turnover markers, notably sCTX1, in the PD section of the label.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. A validated, conventional sandwich enzyme-linked immunosorbent assay (ELISA) was used to quantify serum denosumab concentrations (see Section 2.6 for detail information).

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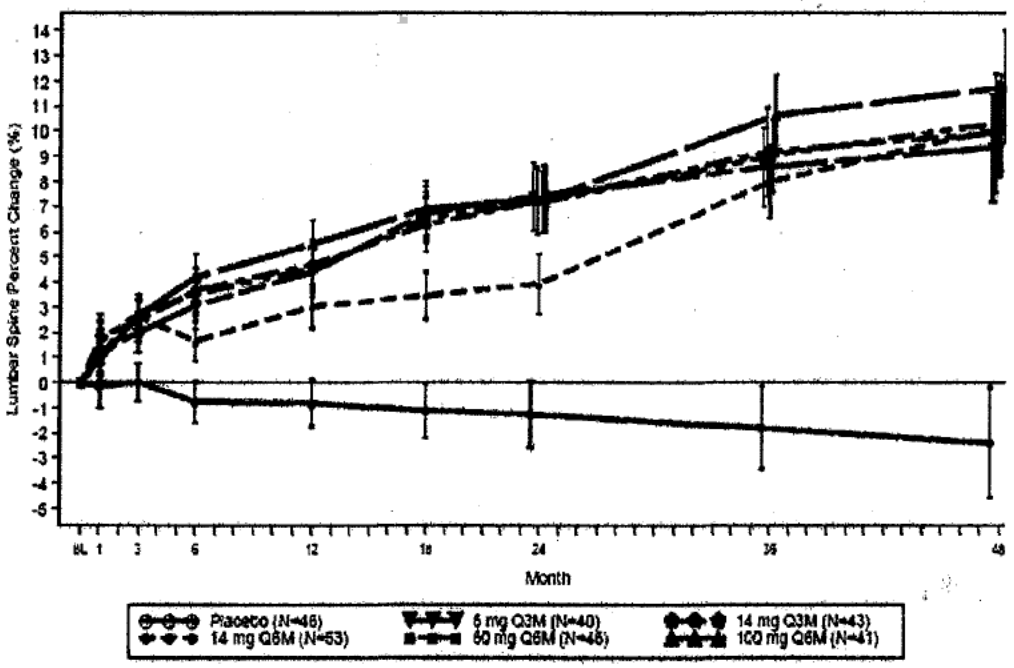
2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

In Study 20010223, the percent change from baseline in sCTX1 and lumbar spine BMD following 2 consecutive doses of various denosumab concentrations given every 3 or 6 months to postmenopausal women with low BMD was assessed. Denosumab treatment was associated with increase in BMD of the lumber spine and the effect was significant compared to placebo. The gain in lumbar spine BMD following 60 mg Q6M dosing is comparable to that observed following 100 and 210 mg Q6M dosing and greater than that observed following 14 mg Q6M dosing (Figure 2). This result indicates that longer durations of maximal reductions in bone resorption for doses ≥ 60 mg does not result in greater gains in BMD. There was no dose-response relationship for efficacy established.

Figure 2: Least Squares Mean (+ 95% Confidence Interval [CI]) Percent Change from Baseline in Lumbar Spine BMD for Subjects in the Continuous Treatment Cohorts (Study 20010223, 48-month Analysis)



Population includes all subjects who had at least one baseline and at least one postbaseline measurement.
Note: Least squares means and its 95% confidence intervals are from a linear model with percent change from baseline value as the dependent variable and treatment, geographic location and baseline value as independent variables.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The overall incidence of adverse events, serious adverse events, and adverse events leading to treatment withdrawal were generally similar between denosumab and placebo groups. No relationship between denosumab exposure and changes in serum calcium following denosumab administration was observed. Refer to Section 1.1.3 of Dr. Ping

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Ji's pharmacometrics review attached separately. There was no dose-response relationship for safety established.

2.2.4.3 Does this drug prolong the QT or QTc interval?

According to Dr. Vaishali Popat's (clinical primary reviewer) clinical review, denosumab is not anticipated to have a direct effect on ion channels. Therefore, a thorough QT study was not required.

In preclinical studies, no effect of denosumab on QTc interval was observed. The clinical development program included an intensive assessment of the effects of denosumab on electrocardiograms, with particular emphasis on the QTc interval. There were no significant differences in the changes from baseline in QTcF across the denosumab and placebo treatment groups, however, several outliers with QTcF value > 500 ms and QTcF change from baseline > 60 ms were noted more frequently in the denosumab group. A QT consult was requested from QT-IRT team to evaluate effect of denosumab on QT interval. The QT-IRT Team's opinion is that the sponsor's ECG evaluations appear adequate and there are no large effects on the QT interval due to denosumab. Outliers (patients with absolute post-dose QTcF over 500 ms or over 60 ms change from baseline) have been noted in several studies although underlying ECG abnormalities were noted in several of the studies except Study 20050172 and Study 20040114. It is important to note that subjects were not excluded because of baseline QTc prolongation. There was no imbalance in the reports of sudden death between the denosumab and comparator groups.

In addition, no relationship was observed between change from baseline in QTc and change from baseline in serum calcium concentration. There is no discernible relationship between denosumab exposure and changes in serum calcium. There was no relationship between denosumab serum concentration and change in QTcF. For Details, please refer to Dr. Suchitra Balakrishnan's QT-IRT consult review.

2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Figure 3 illustrates the mean serum denosumab concentrations and percent change from baseline in sCTX1 and lumbar spine BMD following 2 consecutive doses of 60-mg denosumab Q6M to postmenopausal women with low BMD in Study 20010223. Eligible subjects in this study were postmenopausal women with low BMD ($-4.0 \leq$ T-score ≤ -1.8 for the lumbar spine or $-3.5 \leq$ T-score ≤ -1.8 for the total hip or femoral neck) who were ≤ 80 years of age at the time of randomization, not receiving medication that affected bone metabolism, and free from any underlying condition that might have resulted in abnormal bone metabolism. C_{max} for denosumab is typically attained at 1 month post-dose, which coincides with a rapid, extensive, and sustained reduction in the bone resorption marker, sCTX1. Following C_{max}, serum denosumab concentrations decrease with a mean half-life of approximately 30 days. During the last 2 months (on average) of the Q6M dose interval, serum denosumab concentrations decrease to a level at which

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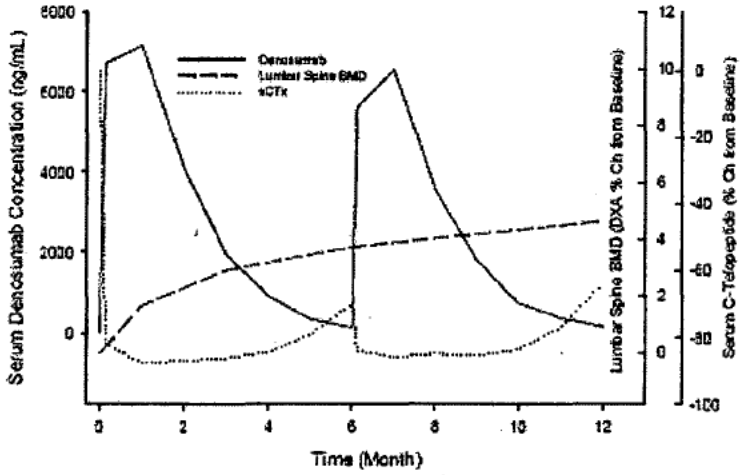
binding to RANKL is no longer saturated. This level corresponds to more rapid elimination of denosumab and a lessening in denosumab's effect on sCTX1 levels, although significant suppression remains (≥ approximately 55%). This partial attenuation in denosumab's effect on sCTX1 does not impact denosumab's effect on lumbar spine BMD

Figure 3: Mean Serum Denosumab Concentration and Mean Percent Change From Baseline for Serum CTX1 and Lumbar Spine BMD Following Two 60-mg Q6M Doses of Denosumab to Postmenopausal Women with Low BMD (Study 20010223)



As mentioned in Section 2.2.4.1, the 60 mg Q6M dose was selected by the sponsor because no additional efficacy was observed at higher doses. The Sponsor's PK based argument on the appropriateness of fixed dose (60 mg 6QM) was evaluated through the effect of body weight on new vertebral fractures and BMD levels and was found to be appropriate for all patients recommended for use in treatment of PMO (see Dr. Ping Ji's pharmacometrics review attached separately)

Reviewer's Comment to the Sponsor:

The proposed dosing regimen of 60 mg Q6M was based on a Phase 2 dose ranging study, Study 20010223. Eligible subjects in this study were postmenopausal women with low BMD (-4.0 ≤ T-score ≤ -1.8 for the lumbar spine or -3.5 ≤ T-score ≤ -1.8 for the total hip or femoral neck) who were ≤ 80 years of age at the time of randomization, not receiving medication that affected bone metabolism, and free from any underlying condition that might have resulted in abnormal bone metabolism. The proposed dosing regimen of 60 mg Q6M was found to be acceptable for the indication of treatment of PMO. (b) (4)

(b) (4)

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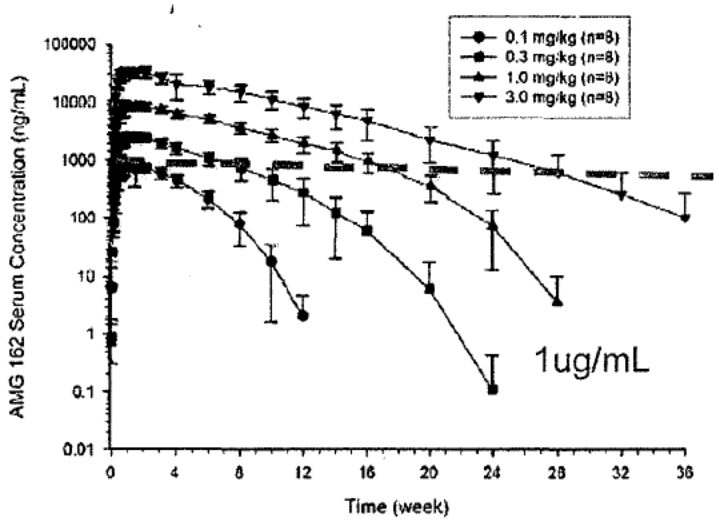
2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose (SD) and multiple dose (MD) PK parameters?

PK of Healthy Volunteers and PMO Patients

As shown in Figure 4 below, mean concentration-time profiles of the 1.0 and 3.0 mg/kg dose cohorts declined in parallel over a long duration (up to 20 weeks post-dose where the denosumab serum concentrations were > 1 μg/ml), which represented a large proportion of the total exposure ($AUC_{0\text{-}16\ weeks}$) to denosumab, due to the higher serum denosumab concentration maintained. Approximately dose-proportional increases in exposure (based on $AUC_{0\text{-}tau}$) were observed for doses ≥ 60 mg (in the range of fixed doses of 60 to 210 mg in Study 20010223 in the PMO population).

Figure 4: Mean (± SD) Serum Concentrations of Denosumab After Single-dose SC Administration to Healthy Men 50 Years and Older (Study 20030148)



The serum concentration time profiles of denosumab were best characterized as a two-compartment model with first-order absorption and a parallel linear and non-linear elimination. Denosumab was eliminated with a faster rate when serum denosumab concentration dropped below approximately 1 μg/ml. As shown in Figure 4, this phenomenon becomes apparent earlier in the lower dose groups (i.e., 0.1 and 0.3 mg/kg) compared to the higher dose groups (i.e., 1.0 and 3.0 mg/kg). The mechanism behind this change in elimination rate is likely related to denosumab binding to RANKL (i.e target-mediated disposition) . This mechanism predominates at low serum denosumab concentrations (i.e., < 1 μg/ml in this case) and becomes saturated as serum denosumab concentration increases.

Target-mediated disposition refers to a phenomenon wherein a significant proportion of a drug (relative to dose) is bound with high affinity to a pharmacological target, such as this interaction is reflected in the PK properties of the drug. Although a few small molecular weigh compounds have been identified to exhibit target-mediated disposition, the incidence of target-mediated disposition is likely to increase particularly among

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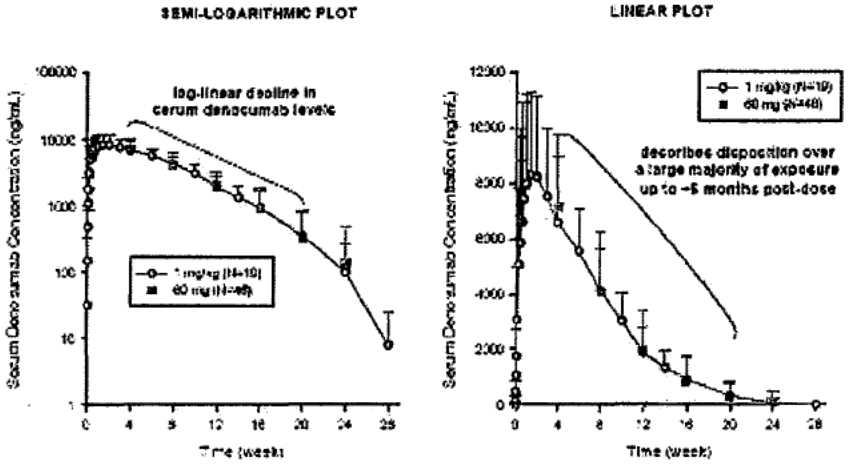
biologic drug products. Similar target-mediated drug disposition has been reported for several monoclonal antibodies (Hayashi *et al*, 2006; Ng *et al*, 2006; Ng *et al*, 2005).

Figure 5 shows the PK profile of the proposed 60 mg fixed dose and also compares it to the 1.0 mg/kg weight based dose showing comparable PK profiles.

Figure 5: Mean Serum Denosumab Concentration-Time Profiles following SC Administration of 60 mg or 1 mg/kg to Postmenopausal Women (From Studies 20010124, 20010223, 20030164, and 20030180)



In an open-label, randomized, single-dose, parallel-group study (Study 20050146) in healthy men and women volunteers (n=73) having a mean age of 33.6 years (range 18 to 64 years), the mean maximum serum denosumab concentrations (C_{max}) of 6.75 µg/ml (standard deviation [SD]: 1.89 µg/ml) was reached in the median time of 10 days (range: 3 to 21 days) following a 60 mg SC dose after at least 12 hrs of fasting prior to denosumab administration. After C_{max}, serum denosumab concentrations declined over a period of 4 to 5 months with a mean half-life of 25.4 days (SD: 8.5 days; n=46; Study 20010223). Mean (Standard Deviation) denosumab PK Parameters are summarized in Table 2.

It should be noted that the Phase 1 healthy volunteer PK studies (Studies 20010124, 20010223, 20030164, and 20030180) were conducted using denosumab drug substance manufactured using an initial version of the commercial process, designated CP1 at ATO while denosumab drug substance manufactured using an optimized process with increased product yields and improved process robustness, designated as CP2, has been used in all of the later clinical trials.

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Table 2: Mean (Standard Deviation) Denosumab PK Parameters

Study Number	Denosumab treatment cohort	AUC (µg·day/ml)	C_{max} [a] (ng/ml)	T_{max} [b] (day)	$t_{½,\beta}$ (day)	CL/F [c] (ml/day/kg)
Healthy Volunteer PK and Tolerability Studies						
20010124	SD SC (n=3-7)	$AUC_{0-\infty}$				(ml/hr/kg)
	0.01 mg/kg	0.77 (0.27)	49.9 (16.0)	7 (3, 7)	N/A	0.62 (0.17)
	0.03 mg/kg	3.77 (2.04)	157 (67.3)	7 (5, 14)	23.3 (2.44)	0.52 (0.40)
	0.1 mg/kg	20.4 (4.08)	721 (103)	7 (3, 14)	19.5 (3.15)	0.21 (0.04)
	0.3 mgkg	115 (42.1)	2230 (873)	14 (7, 56)	33.2 (9.5)	0.13 (0.06)
	1.0 mg/kg	538 (224)	8990 (3340)	18 (7, 42)	30.2 (7.04)	0.09 (0.04)
	3.0 mg/kg	2070 (483)	36200 (7280)	10 (5, 42)	29.5 (5.46)	0.06 (0.01)
	MD SC (n=5-6)					
	0.1 mg/kg (1st dose)	23.3 (9.04)	730 (243)	11 (7, 21)	5.3 (0.60)	0.24 (0.13)
	0.1 mg/kg (last dose)	22.2 (6.75)	724 (231)	14 (3, 28)	9.2 (2.0)	0.24 (0.13)
	SD IV (n=6)					
	0.01 mg/kg	2.16 (0.83)	506 (153)	0 (0, 0.2)	N/A	0.22 (0.06)
	0.03 mg/kg	6.00 (0.73)	1040 (36.5)	0 (0, 0.2)	8.3 (1.16)	0.19 (0.02)
	0.1 mg/kg	33.7 (5.71)	3830 (779)	0 (0, 0.0)	12.7 (3.30)	0.13 (0.02)
	0.3 mg/kg	180 (48.3)	10600 (1730)	0.0 (0, 0.0)	24.4 (5.83)	0.08 (0.02)
	1.0 mg/kg	688 (195)	35200 (10400)	0.0 (0, 0.0)	35.1 (4.96)	0.06 (0.02)
	3.0 mg/kg	2760 (738)	110000 (26600)	0.0 (0, 0.2)	37.3 (6.96)	0.05 (0.02)
20030148	SD SC (n=8)	AUC_{0-t}				
	0.1 mg/kg	24.9 (6.5)	0.85 (0.23)	7 (3, 14)	-	4.24 (1.05)
	0.3 mg/kg	105 (22)	2.60 (0.40)	10 (7, 14)	-	2.96 (0.60)
	1.0 mg/kg	479 (74)	8.85 (1.91)	7 (5, 14)	-	2.14 (0.40)
	3.0 mg/kg	1990 (540)	34.9 (6.6)	10 (4, 14)	-	1.60 (0.40)
20030164	SD SC (n=6)	AUC_{0-t}				
	0.03 mg/kg	2.06 (0.53)	99.6 (25.8)	7 (7, 10)	-	15.3 (4.2)
	0.1 mg/kg	15.2 (6.7)	492 (166)	12 (7, 21)	-	8.31 (4.97)
	0.3 mg/kg	84.3 (20.1)	1910 (658)	14 (7, 21)	-	3.72 (0.89)
	1.0 mg/kg	481 (131)	8690 (2170)	14 (10, 21)	-	2.20 (0.56)
	3.0 mg/kg	1790 (650)	27400 (7880)	14 (14, 42)	-	1.85 (0.58)
20030180	SD SC (n=6-8)	AUC_{0-t}				
	0.03 mg/kg	3.63 (2.59)	201 (129)	7 (3, 10)	-	13.2 (9.13)
	0.1 mg/kg	14.8 (6.0)	563 (149)	9 (7, 14)	-	7.84 (3.34)
	0.3 mg/kg	78.3 (44.6)	2050 (876)	10 (7, 14)	-	5.52 (3.69)
	1.0 mg/kg	476 (201)	9530 (4270)	7 (2, 14)	-	2.64 (1.68)
	3.0 mg/kg	1660 (227)	30800 (8510)	7 (1, 10)	-	1.84 (0.27)
Patients PK and Initial Tolerability Studies						
20010123	BC SD SC (n=3-7)	AUC_{0-t} (µg·hr/ml)				
	0.1 mg/kg	234 (101)	448 (282)	14 (3, 21)	N/E	-
	0.3 mg/kg	1400 (754)	1430 (758)	14 (7, 28)	20.7 (4.5)	-
	1.0 mg/kg	5870 (2940)	4850 (2550)	14 (7, 28)	29.7 (6.7)	-
	3.0 mg/kg	27200 (10500)	19800 (6520)	21 (14, 28)	46.3 (16.7)	-
	MM SD SC (n=3-9)	AUC_{0-t} (µg·hr/ml)				
	0.1 mg/kg	502 (270)	625 (314)	7 (7, 14)	N/E	-
	0.3 mg/kg	2460 (787)	2420 (572)	7 (7, 14)	19.5 (3.1)	-
	1.0 mg/kg	11300 (5430)	8260 (3590)	21 (7,28)	38.6 (13.9)	-

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	3.0 mg/kg	20800 (9780)	20000 (6420)	14 (3, 21)	33.3 (21.7)	-
20040176	SD SC (n=5-6)	AUC_{0-t}				
	60 mg	351 (144)	7730 (3130)	8 (7, 28)	24.7 (2.44)	-
	180 mg	1320 (640)	31100 (14900)	10 (4, 28)	29.1 (7.15)	-
	MD SC (n=6)					
	180 mg (dose 1)	545 (123)	24100 (5130)	18 (7, 28)	N/A	-
	180 mg (dose 2)	1210 (240)	48000 (9340)	14 (7, 21)	N/A	-
Intrinsic Factor PK Study						
20040245	SD SC 60 mg	$AUC_{0-16\ weeks}$				-
	Normal (n=9-11)	217 (76)	5160 (1770)	10 (3, 14)	-	-
	Mild (n=11-13)	266 (143)	6200 (2880)	10 (2, 28)	-	-
	Moderate (n=13)	322 (154)	7040 (3060)	10 (3, 28)	-	-
	Severe (n=9)	295 (120)	6020 (2320)	10 (7, 14)	-	-
	ESRD (n=8)	208 (107)	5370 (2590)	10 (5, 21)	-	-
Extrinsic Factor PK Studies						
20050241	SD SC	AUC_{0-t}				
	15 mg (n=3)	41.5 (27.6)	1100 (610)	21 (14, 21)	-	-
	60 mg (n=10-12)	332 (176)	7570 (4410)	13 (3, 28)	34.1 (6.7)	-
PK and PD Comparability Studies						
20050227	SD SC	$AUC_{0-16\ weeks}$				
	1 mg/kg ACO (n=58)	432 (150)	9420 (3090)	7.0 (2.0, 21)	-	-
	1 mg/kg ATO (n=59)	440 (110)	9070 (2310)	7.0 (2.0, 21)	-	-
20060286	SD SC	$AUC_{0-16\ weeks}$				
	60 mg ATO (n=58)	258 (81)	5330 (1530)	10 (3.0, 21)	-	-
	60 mg BIP (n=58)	259 (91)	5430 (1820)	7 (3.0, 28)	-	-
20050146	SD SC	$AUC_{0-16\ weeks}$				
	60 mg PFS (n=74)	331 (111)	7110 (2040)	10 (3.0, 21)	-	-
	60 mg GS (n=73)	316 (101)	6750 (1890)	10 (3.0, 21)	-	-
Dose-ranging Study						
20010223	MD SC	AUC_{0-tau}				
	14 mg dose 1 (n=53)	64.4 (39.0)	0 (0)	4 (2.0, 35)	N/A	-
	14 mg dose 2 (n=49)	59.8 (36.5)	0 (0)	21 (2.0, 37)	N/A	-
	60 mg dose 1 (n=46)	503 (239)	7930 (2950)	26 (2.9, 32)	25.4 (8.48)	-
	60 mg dose 2 (n=44)	448 (239)	6940 (3180)	29 (1.9, 42)	27.1 (8.99)	-
	100 mg dose 1 (n=40)	937 (341)	288 (397)	28 (2.9, 38)	30.1 (10.3)	-
	100 mg dose 2 (n=36)	863 (319)	262 (358)	22 (2.0, 37)	28.7 (7.39)	-
	210 mg dose 1 (n=46)	2230 (865)	1390 (1430)	26 (2.9, 35)	32.6 (8.84)	-
	210 mg dose 2 (n=42)	2140 (988)	1470 (1470)	27 (2.9, 39)	33.7 (11.9)	-

SD= Single Dose; MD= Multiple Dose; ESRD= End-state renal disease; IV= Intravenous; SC= Subcutaneous; N/A: Not Applicable; N/E: Not Accurately Estimable; AUC_{0-tau}: Area under the serum denosumab concentration-time curve over the dosing interval

[a] C_0 (initial concentration) for IV doses

[b] median (range)

[c] clearances for intravenous doses

It should be noted that the Sponsor is proposing to use PK data from Studies 20040245, 20050241, 20050146, 20060286, and 20010223 for labeling purposes and these studies were conducted with drug substance manufactured with the CP2 process. While the Sponsor's proposal of using PK data generated with the CP2 process is appropriate, it

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should be noted that PK parameters on the label should be from the most reliable single study rather than combining PK parameters from multiple studies.

PK of Cancer Patients

Phase 1 – Breast cancer: The Sponsor conducted a single dose study in breast cancer and multiple myeloma patients and a single and multiple dose study in Japanese breast cancer patients. The single dose study utilized weight-based dosing (0.1, 0.3, 1, and 3 mg/kg) while the other study used fixed doses of 60 and 180 mg; multiple dosing was only conducted at the 180 mg dose level. Additionally, this was the only multiple dosing Phase 1 study in the oncology setting. The sampling times are summarized below:

In the single dose study, samples were obtained at:

- pre-dose and post-dose at 1, 2, 4, 8, and 24h, Days 3, 4, 8, 15, 22, 29, 43, 57, 71, and 85.

In the single dose part of the single and multiple dose study, blood samples for were obtained at:

- pre-dose, and post-dose at 6h; Days 2, 3, 8, 15, 22, 29, 57, and 85.

In the 180 mg multiple dosing arm, samples were obtained at:

- pre-dose, and Days 8, 15, 22, 29, 57, 64, 71, 78, 85, 113, and 141.

Following a single dose, denosumab demonstrated nonlinear PK and a dose-dependent increase in half-life (Table 3, Figure 6). After SC administration, denosumab demonstrated rapid and prolonged absorption, with serum levels that were detectable as early as 1 hour post-dose and mean maximum serum concentrations of 448 ng/ml (0.1-mg/kg cohort) to 3,100 ng/ml (180 mg cohort) occurring 8 to 21 days post-dose. Mean half-lives increased with increased dose (0.1-3 mg/kg) from 20.7 to 46.3 days. Following multiple dosing, an approximate 2.2-fold accumulation was observed by the third dose relative to the first dose (Table 4).

Table 3: Mean (SD) Single Dose Denosumab Pharmacokinetic Parameters in Breast Cancer.

Study #	Dose	Cmax (ng/ml)	Cmax / D (ng/ml / mg/kg)	Tmax* (day)	AUC0-t (µg•h/ml)	t1/2, β (day)
20010123	0.1 mg/kg, N=7	448 (282)	4480 (2820)	14 (3 – 21)	234 (101)	NA
	0.3 mg/kg, N=7	1430 (758)	4770 (2530)	14 (7 – 28)	1400 (754)	20.7 (4.5)
	1.0 mg/kg, N=7	4850 (2550)	4850 (2550)	14 (7 – 28)	5870 (2970)	29.7 (6.7)
	3.0 mg/kg, N=3	19800 (6520)	6610 (2170)	21 (14 – 28)	27200 (10500)	46.3 (16.7)
20040176	60 mg, N=6	7730 (3130)	-	8.0 (7 – 28)	8424 (3456)	24.7 (2.44)
	180 mg, N=6	31100 (14900)	-	10 (4 –28)	31680 (15360)	29.1 (7.15)

*Data presented as: median (range)

NA= Not applicable

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Figure 6: Mean (±SD) Denosumab Concentrations Time Profiles in Breast Cancer Patients. Panel A. Study # 20010123: Single Dose. Panel B. Study # 20040176: Single and Multiple Dose.

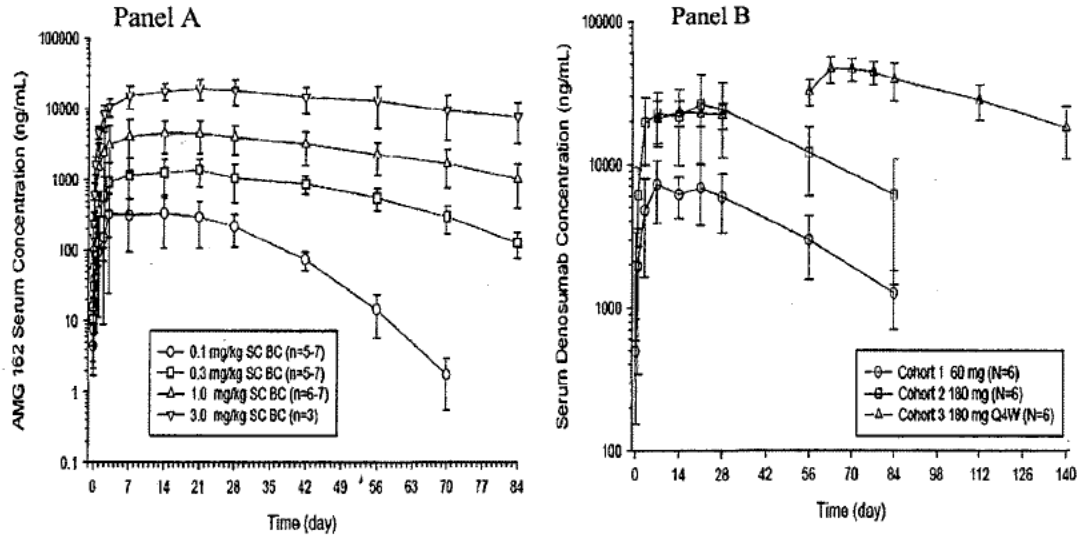

Table 4: Study # 20040176: Mean (SD) Denosumab Pharmacokinetic Parameters Following Multiple Dose Administration of 180 mg Denosumab Every 4 Weeks.

Dose (mg)	Dose	Cmax (ng/ml)	Tmax* (day)	AUC0-28 (µg•h/ml)	AR
180 Q4W, N=6	1st	24100 (5130)	18 (7.0 – 28)	13080 (2952)	2.2 (0.18)
	3rd	48000 (9340)	14 (7.0 – 21)	29040 (5760)	

*Data presented as: median (range)
AR = Accumulation ratio, calculated as AUC0-28 (dose 3) / AUC0-28 (dose 1)

Phase 3 - Cancer (breast or prostate): In the two Phase 3 clinical studies in bone loss associated with hormone-ablative therapy, breast cancer: Study 20040135 and prostate cancer: Study 20040138, approximately 100 and 700 patients, respectively, had denosumab concentrations determined at each sampling time point; the Sponsor's results are listed in Table 5. Denosumab 60 mg was administered as a SC injection every 6 months.

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Table 5: Serum Denosumab Concentrations (ng/ml) After SC Administration of 60 mg Denosumab Every 6 Months in Women with Breast Cancer (up to 24 months) and Men with Prostate Cancer (up to 36 months).

Summary Statistics	Month							
	1		3		6		12	
	Breast	Prostate	Breast	Prostate	Breast	Prostate	Breast	Prostate
N	117	701	112	695	112	673	101	648
Mean (SD)	5890 (2500)	4280 (1930)	1730 (1200)	942 (737)	63 (183)	40 (286)	50 (97)	26 (113)
Median	5560	4040	1520	798	1.1	BLQ	BQL	BLQ
Range	1430 - 12200	BLQ - 13800	79.2 - 6920	BLQ- 5000	BLQ - 1480	BLQ - 4340	BLQ - 486	BLQ - 2250
BLQ = Below the lower limit of quantification (LLOQ = 0.8 ng/ml)								

Table 5 cont.

Summary Statistics	Month							
	15		18		24		30	36
	Breast	Prostate	Breast	Prostate	Breast	Prostate	Prostate	Prostate
N	100	624	100	608	95	539	485	462
Mean (SD)	1430 (886)	1060 (832)	116 (413)	35 (104)	76 (196)	40 (174)	43 (130)	47 (142)
Median	1290	895	1.29	BLQ	1.5	BLQ	BLQ	BLQ
Range	40.2 - 5490	BLQ - 6680	BLQ - 3270	BLQ - 932	BLQ - 1510	BLQ - 2960	BLQ - 1310	BLQ - 1830
BLQ = Below the lower limit of quantification (LLOQ = 0.8 ng/ml)								

Within each study, mean and median concentrations at Months 3 and 15 (approximately 3 months post-dose) were similar; indicating that PK did not change with time and that there was no accumulation with repeated dosing (Table 5). When comparing across the 2 studies, the mean concentrations appear to be greater in women with breast cancer compared to men with prostate cancer at months 1, 3, 6, 12, 15, 18, and 24. However, upon population PK analysis, the respective patient populations did not affect denosumab PK, as summarized by Clearance (L/h). Refer to Dr. Ping Ji's Pharmacometrics Review attached separately.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Denosumab PK was similar between healthy volunteers, postmenopausal women with low BMD or osteoporosis, or patients with breast or prostate cancer receiving HALT. No metabolism studies were conducted. Refer to Section 1.1.3 of Dr. Ping Ji's pharmacometrics review attached separately.

2.2.5.3 What are the characteristics of drug absorption?

Following a 60 mg SC dose, bioavailability was 61% based on the population PK analysis. Maximum mean serum denosumab concentrations (C_{max}) of 6.75 µg/ml (SD 1.89 µg/ml) occurred in a median time of 10 days (range 3 to 21 days).

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2.2.5.4 What are the characteristics of drug distribution?

Plasma protein binding has not been conducted. Based on non-compartmental analysis (1 mg/ml IV), the mean (SD) V_{ss} is 54.1 (5.67) ml/kg. Based on population PK analysis (2-compartment model), the volume of the central compartment and the volume of the peripheral compartment is 2,460 ml and 1,300 ml, respectively.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Denosumab is a monoclonal antibody product and no mass balance study was conducted.

2.2.5.6 What are the characteristics of drug metabolism?

Denosumab is a monoclonal antibody product and is not expected to be eliminated via hepatic metabolic mechanisms (e.g., CYP enzymes). Thus, no metabolism studies were conducted.

2.2.5.7 What are the characteristics of drug excretion?

Denosumab is a monoclonal antibody product and is not expected to be excreted via the kidney and/or bile as an intact form. Thus, no excretion studies were conducted.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

The early Phase 1 studies of denosumab conducted in healthy postmenopausal women and healthy men ≥ 50 years of age using CP1 as drug substance (Studies 20010124, 20030148, 20030164, and 20030180) explored a wide range of weight-based SC doses (0.01 to 3.0 mg/kg) with intensive PK sampling.

Denosumab displayed approximately dose-proportional increases in exposure (based on $AUC_{0\text{-}tau}$) in the dose range of 1.0 mg/kg to 3.0 mg/kg.

As noted previously, denosumab was eliminated with a faster rate when serum denosumab concentration drops below approximately 1 μg/ml. The mechanism behind this change in elimination rate is likely related to denosumab binding to RANKL (i.e target-mediated disposition) . This mechanism predominates at low serum denosumab concentrations (i.e., < 1 μg/ml in this case) and becomes saturated as serum denosumab concentration increases. As shown in Figure 4, this phenomenon becomes more apparent in the lower dose groups (i.e., 0.1 and 0.3 mg/kg) compared to the higher dose groups (i.e., 1.0 and 3.0 mg/kg). Consistent with this observation, mean apparent clearance (CL/F) was approximately 8-fold higher at a dose of 0.03 mg/kg (i.e., faster rate of elimination as the plasma levels are below saturation) compared to a higher dose of 3.0 mg/kg (where levels are above the saturation point for the majority of the dosing interval). In addition, mean CL/F values were similar (< 35% difference), in the dose range of 1.0

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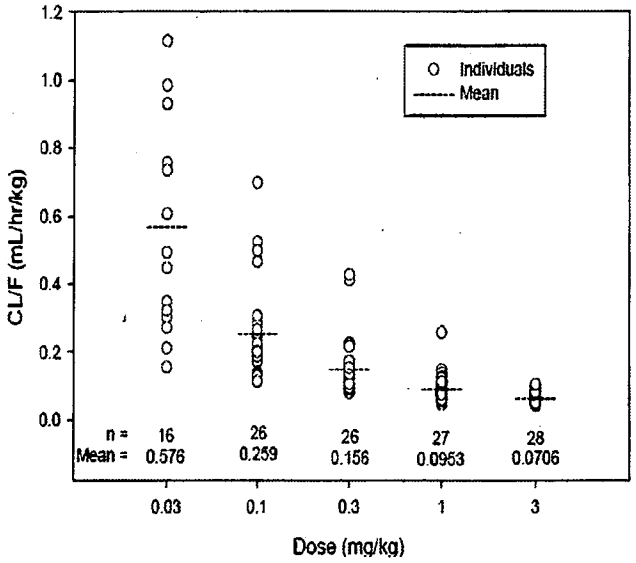
and 3.0 mg/kg (Figure 7), again the lack of difference between the doses being related to the amount of time plasma concentrations are above 1ug/mL.

Figure 7: Apparent Clearance (CL/F) vs. Dose for Weight-Based SC Doses of Denosumab in Healthy Postmenopausal Women and Healthy Men ≥ 50 Years (Studies 20010124, 20030148, 20030164, and 20030180)



Dose linearity was also assessed in Study 20010223 where denosumab was given 6 to 30 mg every 3 months and 14 to 210 mg every 6 months. Mean $AUC_{0\text{-}tau}$ values increased in an approximately dose-proportionately manner between the 60 and 210 mg every 6 months doses. Additionally, exposure based on mean C_{max} values increased approximately dose-proportionately across both the every 3 months and every 6 months dose ranges.

Table 6: Mean (SD) Denosumab PK Parameters
Following Administration of 6, 14, or 30 mg Denosumab Every 3 Months

Dose (mg)	Dose number	T_{max}[a] (day)	C_{max} (ng/mL)	$AUC_{0\text{-}tau}$ (day•µg/mL)	C_{min} (ng/mL)	AR
6	1	3.0 (2.9 – 32)	554 (244)	17.4 (8.54)	2.25 (9.80)	1.23
	3	3.9 (1.9 - 35)	638 (276)	20.6 (11.4)	2.36 (5.23)	
14	1	4.0 (2.8 - 39)	1450 (621)	60.3 (25.5)	58.2 (87.2)	1.27
	3	27 (2.0 - 93)	1550 (693)	68.3 (34.5)	97.2 (144)	
30	1	5.0 (2.9 - 34)	3540 (1590)	170 (87.5)	446 (360)	1.04
	3	4.0 (1.9 - 37)	3760 (1830)	193 (108)	799 (720)	

[a] Median (range)
T_{max} = time of maximum observed serum denosumab concentration (C_{max})
$AUC_{0\text{-}tau}$ = area under the serum denosumab concentration-time curve over the dosing interval
C_{min} = trough serum denosumab concentration
AR = accumulation ratio

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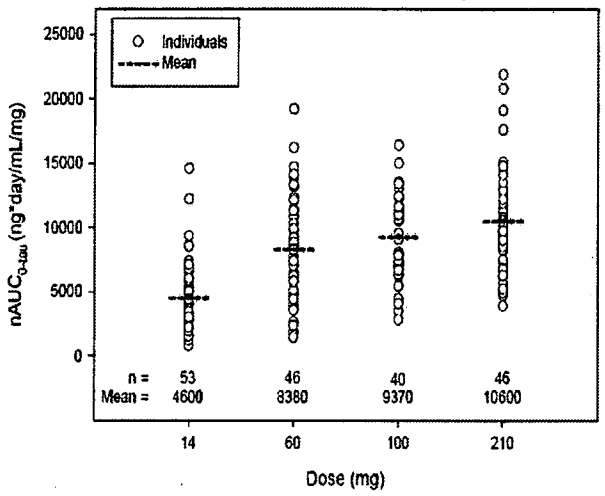
Table 7: Mean (SD) Denosumab PK Parameters Following Administration of 14, 60, 100, and 210 mg Denosumab Every 6 Months

Dose (mg)	Dose number	T_{max}[a] (day)	C_{max} (ng/mL)	$AUC_{0\text{-}tau}$ (day•µg/mL)	$t_{1/2}$ (day)	C_{min} (ng/mL)	AR
14	1	4.0 (2.0 – 35)	1490 (681)	64.4 (39.0)	NA	0 (0)	1.74
	2	21 (2.0 - 37)	1390 (672)	59.8 (36.5)	NA	0 (0)	
60	1	26 (2.9 - 32)	7930 (2950)	503 (239)	25.4 (8.47)	137 (334)	0.910
	2	29 (1.9 - 42)	6940 (3180)	448 (239)	27.1 (8.99)	132 (334)	
100	1	28 (2.9 - 38)	14200 (5300)	937 (341)	30.1 (10.3)	288 (397)	1.02
	2	22 (2.0 - 37)	13200 (4550)	863 (319)	28.7 (7.39)	262 (358)	
210	1	26 (2.9 - 35)	32300 (11900)	2230 (865)	32.6 (8.84)	1390 (1430)	1.02
	2	27 (2.9 - 39)	30000 (12700)	2140 (988)	33.7 (11.9)	1470 (1470)	

[a] Median (range)
T_{max} = time of maximum observed serum denosumab concentration (C_{max})
$AUC_{0\text{-}tau}$ = area under the serum denosumab concentration-time curve over the dosing interval
$t_{1/2}$ = half-life describing a large majority of exposure
C_{min} = trough serum denosumab concentration
AR = accumulation ratio

Consistent with weight-based dosing, mean dose-normalized $AUC_{0\text{-}tau}$ values increased approximately 2-fold for fixed doses of 14 to 60 mg Q6M (equivalent to approximately 0.3 to 1.0 mg/kg), but were *similar* (< 27% different) for fixed doses of 60 to 210 mg Q6M, with notable overlap observed in individual values (Study 20010223, Figure 8).

Figure 8: Mean and Individual Dose-normalized AUC0-tau (nAUC0-tau) Values Following SC Administration of 14 to 210 mg Denosumab to Postmenopausal Women with Low BMD (Study 20010223, Q6M First Dose)



$nAUC_{0\text{-}tau}$ = dose-normalized area under the serum concentration curve during the dosing interval

Mean dose-normalized C_{max} (nC_{max}) values did not vary markedly (> 50%) across the entire 14 to 210 mg dose range, with differences of < 17% observed for doses ≥ 60 mg (Figure 9). Thus, denosumab exposure, based on both C_{max} and AUC, increases approximately dose-proportionally for a fixed dose range between 60 and 210 mg.

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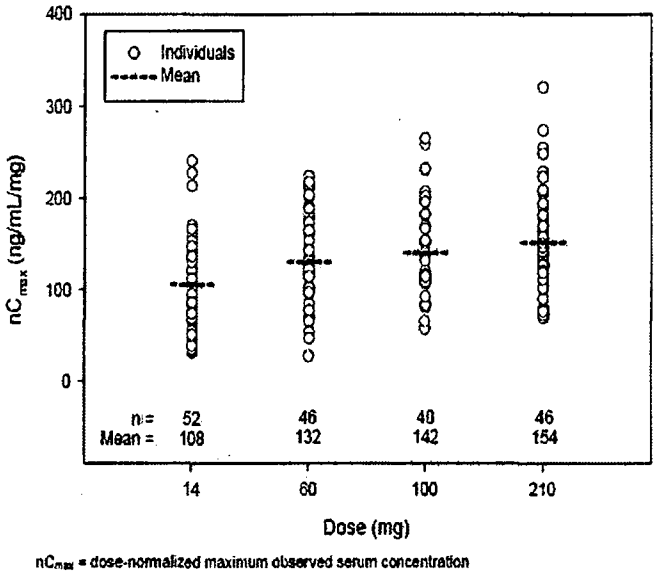
Figure 9: Mean and Individual Dose-normalized Cmax (nCmax) Values Following SC Administration of 14 to 210 mg Denosumab to Postmenopausal Women with Low BMD (Study 20010223, Q6M First Dose)



nC_{max} = dose-normalized maximum observed serum concentration

2.2.5.9 How do the PK parameters change with time following chronic dosing?

No accumulation in serum denosumab concentrations was observed with repeated doses of 60 mg once every 6 month (Q6M), nor would it be expected to with an observed plasma half-life of ~ 1 month. Denosumab PK did not appear to change following up to 4 years exposure.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The serum concentration time profiles of denosumab were best characterized as a two-compartment model with first-order absorption and a parallel linear and non-linear elimination. The following parameters were allometrically scaled on the basis of body weight: linear clearance (CL), central volume of distribution (V_c), inter-compartmental clearance (Q), and peripheral volume of distribution (V_p), absorption rate constant (k_a), Michaelis-Menten rate constant (K_m) and maximal velocity (V_{max}). In addition, disease type as solid tumor and subject type as Black and Hispanic were also identified as categorical covariates of CL. After adjusting these covariates, the inter-subject variability (%CV) of CL, V_{max}, V_c, and k_a was 40, 51, 50, and 43, respectively. The residual variability (%CV) of the PK model was 26 and 81 for high concentration and low concentration, respectively.

2.2.6 What are the PD characteristics of denosumab?

In clinical studies, treatment with 60 mg of denosumab resulted in rapid reduction in the bone resorption marker, sCTX1 within 6 hours of SC administration by approximately 70% (Studies 20030216 [Figure 10] and 20040132), with reductions of approximately

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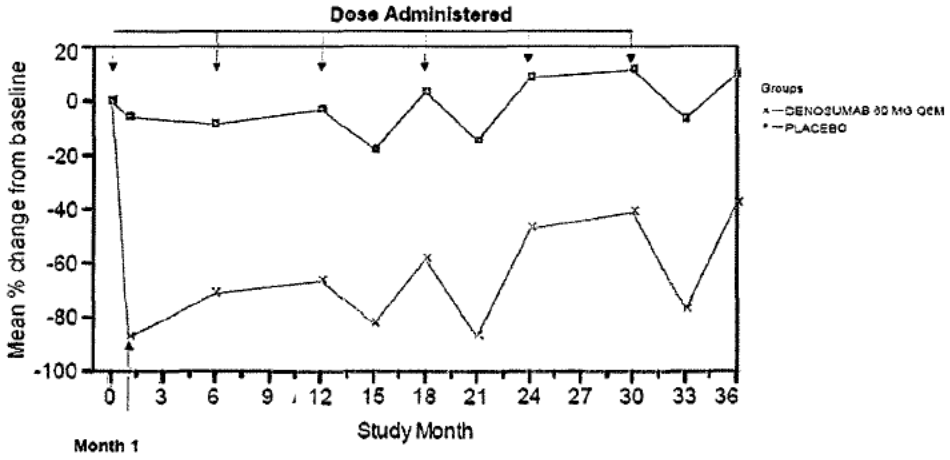
85% occurring by 3 days (Study 20010223). Peaks in sCTX1 levels were each time before the dose was due and valleys were at 3 months after the dose.

Figure 10: sCTX1 levels by visit in Study 20030216



sCTX1 reductions were maintained over the 6-month dosing interval (Figure 11). At the end of each dosing interval, sCTX1 reductions were partially attenuated from maximal reduction of ≥ 87% to ≥ 45% (range 45% to 80%), reflecting the reversibility of the effects of denosumab on bone remodeling once serum levels diminish (Studies 20040135, 20040138, 20040132, and 20030216; Table 8). These effects were sustained with continued treatment. Consistent with the physiological coupling of bone formation and resorption in skeletal remodeling, subsequent reductions in bone formation markers were observed beginning 1 month after the first dose of denosumab.

Figure 11: Mean Serum Denosumab Concentration and Mean Percent Change From Baseline for Serum CTX1 and Lumbar Spine BMD Following Two 60-mg Q6M Doses of Denosumab to Postmenopausal Women with Low BMD (Study 20010223)

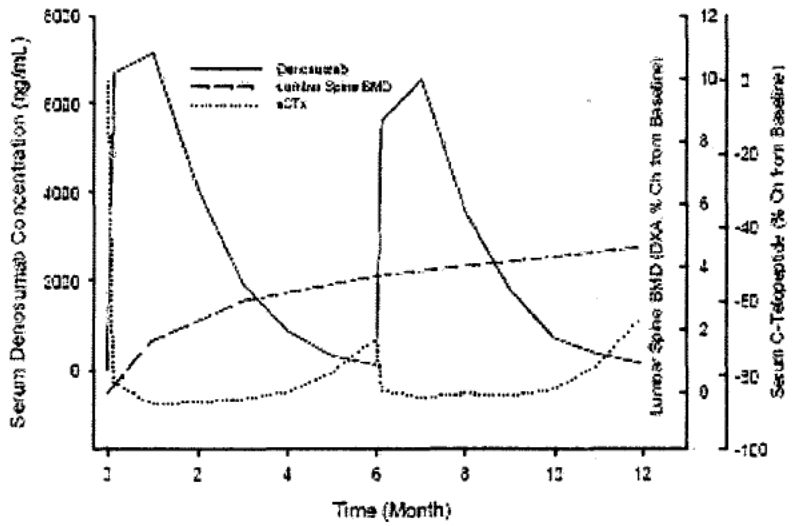


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Table 8: Summary Statistics for Percent Reduction in sCTX1 at 1 Month after SC Administration of 60 mg Denosumab

	Healthy Adults	Postmenopausal women			Subjects with cancer and bone loss associated with HALT	
		With low BMD		With osteoporosis	Breast	Prostate
Study No.	20050146	20040132	20050233[a]	20030216	20040135	20040138[b]
N	140	160	22	93	109	671
Mean	82	87	90	87	88	87
SD	11	8	6	8	8	13

BMD = bone mineral density, HALT = hormone ablation therapy

[a] Change from Study 20010223 baseline in subjects who were switched from placebo in Study 20010223 to 60 mg Q6M denosumab in Study 20050233;this study included women with low BMD and osteoporosis.

[b] Excluding subject with outlier sCTX1 value (Subject 138134013 with 1060% change from baseline).

Bone turnover markers generally reached pretreatment levels within 9 months after the last 60 mg SC dose (Studies 20040132 and 20010223). Upon reinitiation, the degree of inhibition of sCTX1 by denosumab was similar to that observed in patients initiating denosumab treatment.

In pivotal Studies 20040135 and 20040138 for cancer indications, baseline sCTX1 were similar between treatment groups. Median percentage changes from baseline in concentrations of sCTX1 at the time points assessed were greatest in the denosumab group at Month 1. Treatment with denosumab resulted in sustained decreases in concentrations of sCTX1 relative to placebo at each post-baseline assessment ($p<0.0001$ at all time points).

In a clinical study (Study 20050241) of postmenopausal women with low bone mass (n=20) who were previously treated with alendronate with a median duration of 3 years, those transitioning to receive alendronate experienced additional reduction in sCTX1, compared with women who remained on alendronate. Fourteen days after dosing, the mean percent change from baseline in sCTX1 concentration was approximately -60% and -73% for subjects in the 15 mg and 60 mg denosumab groups, respectively. These changes were generally maintained from study Day 14 through study Day 84. The mean percent change from baseline for sCTX1 for subjects who continued on alendronate treatment ranged from approximately -40% to +20%, with no change, on average at study Day 107. Please refer to Section 2.4.2 for further discussion.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Gender

Mean serum denosumab concentration-time profiles for healthy men ≥ 50 years in Study 20030148 (Figure 12) were also similar to those observed for postmenopausal women administered the same doses in Study 20010124 (Figure 13).

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Figure 12: Mean (± SD) Serum Concentrations of Denosumab After Single-dose SC Administration to Healthy Men 50 Years and Older (Study 20030148)

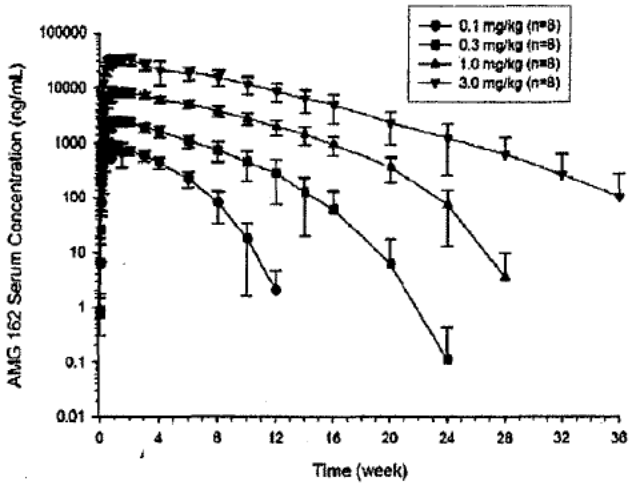
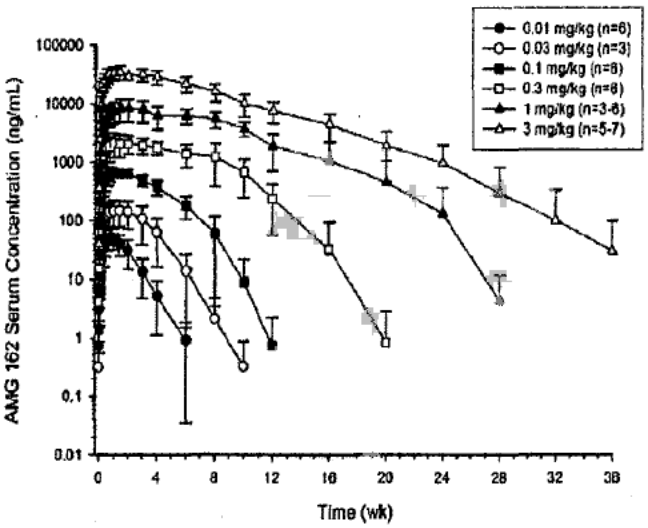


Figure 13: Mean (± SD) Serum Concentration-time Profiles of Denosumab in Healthy Postmenopausal Women (Study 20010124, SC Single-dose Cohorts)



Body Weight

Although body weight was identified as a covariate for clearance, body weight did not appear to affect the incidence of new vertebral fracture and change in the BMD levels (Figures 14 and 15).

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Figure 14: The Incidence of Any New Vertical Fracture versus Body Weight (From Study 20030216)

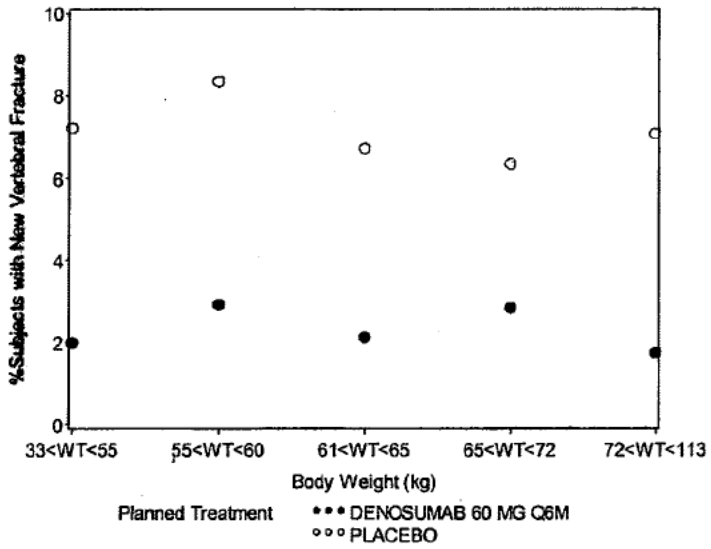
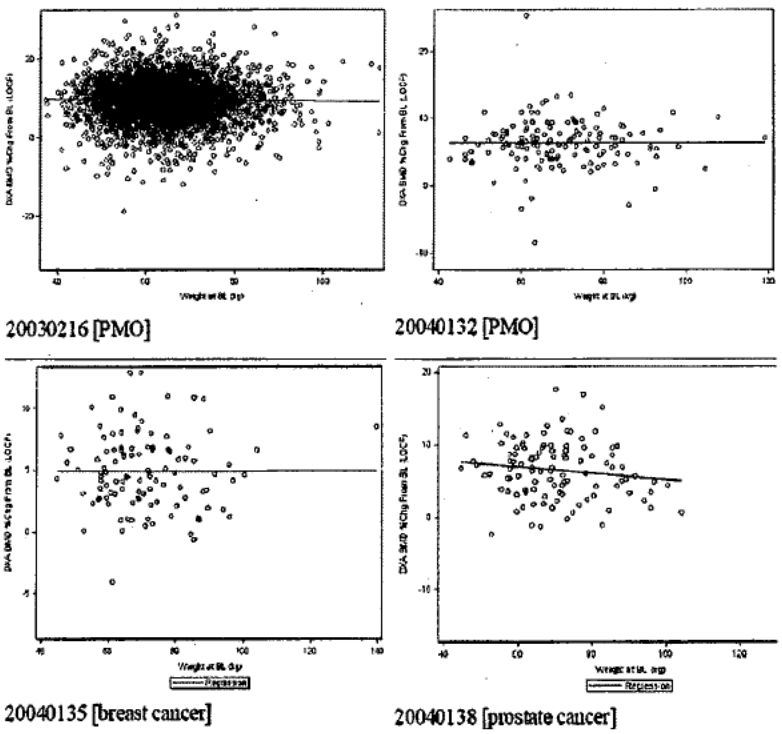


Figure 15: Scattered Plots of Lumber Spine Bone Mass Density versus Body Weight (From Studies 20030216, 20040132, 20040135, and 20040138)



Denosumab PK parameters are dependent on body weight. However, differences in exposure do not affect response to denosumab. Figure 5 in Section 2.2.5.1 further illustrates that exposures following a weight based dose of 1 mg/kg and a fixed dose of 60 mg to postmenopausal women are comparable. Therefore, fixed dose of 60 mg

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appears to be appropriate for all patients recommended for use. Please refer to Sections 1.1.1 and 1.1.2 of Dr. Ping Ji's pharmacometrics review attached separately.

Other Intrinsic Factors

Based on the pharmacometrics review attached separately, Sponsor's population PK analysis is generally adequate and the population PK analysis showed that denosumab's bioavailability is 61%. Age and gender are not significant covariates in the population PK analysis. Subject type as solid tumor and race (as black and Hispanic) were identified as covariates for clearance in the population PK model (Amgen Pharmacometric report 100957) and the significant covariates identified by the sponsor were reproduced (see Section 3 of Dr. Ping Ji's pharmacometrics review attached separately). The PK of denosumab did not appear to be affected by race and solid tumor as shown in the simulation results.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

A pediatric indication is not being sought at this time, and a pediatric waiver has been requested.

2.3.2.2 Renal impairment

Study 20040245 investigating the effect of renal impairment on the PK of denosumab was completed in male and female patients with varying degrees of renal impairment and a normal renal function control group. During screening, subjects were assigned to a renal function group based on creatinine clearance (CrCL) as calculated by the Cockcroft-Gault equation. All subjects were administered a single SC dose of 60 mg denosumab. The renal function groups are defined in Table 9.

Table 9: Definition of Renal Impairment Cohorts.

Group	Creatinine Clearance (CrCL), ml/min
Normal	CrCL > 80
Mild chronic kidney disease (CKD	CrCL 50 - 80
Moderate CKD	CrCL 30 - 49
Severe CKD	CrCL < 30
End-stage renal disease (ESRD)	hemodialysis

Blood samples for analysis of denosumab were collected up to 113 days after dosing. Specifically, PK samples were collected at pre-dose, and post-dose Days 2, 3, 6, 8, 11, 15, 22, 29, 43, 57, 85, and 113. A total of 55 subjects were enrolled in this study. The

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patient demographics between cohorts were comparable and a summary of the demographics can be found in the individual study report.

Overlap was observed in denosumab maximum concentrations and exposures across renal function groups, and no clear trend was apparent between denosumab PK and renal function group (Figure 16). Mean C_{max} and $AUC_{0\text{-}16\ weeks}$ values differed by 4% to 48% when each renal impairment group was compared with the normal renal function group (Table 10). Linear regression analyses did not demonstrate a significant relationship between baseline CrCL and any of the denosumab PK parameters (Table 13). Based on these data, the conclusion can be made that the PK profile of denosumab was not significantly affected by varying degrees of renal impairment.

Figure 16: C_{max} (Panel A) and $AUC_{0\text{-}16\ weeks}$ (Panel B) vs. Renal Function Group After SC Administration of 60 mg Denosumab.

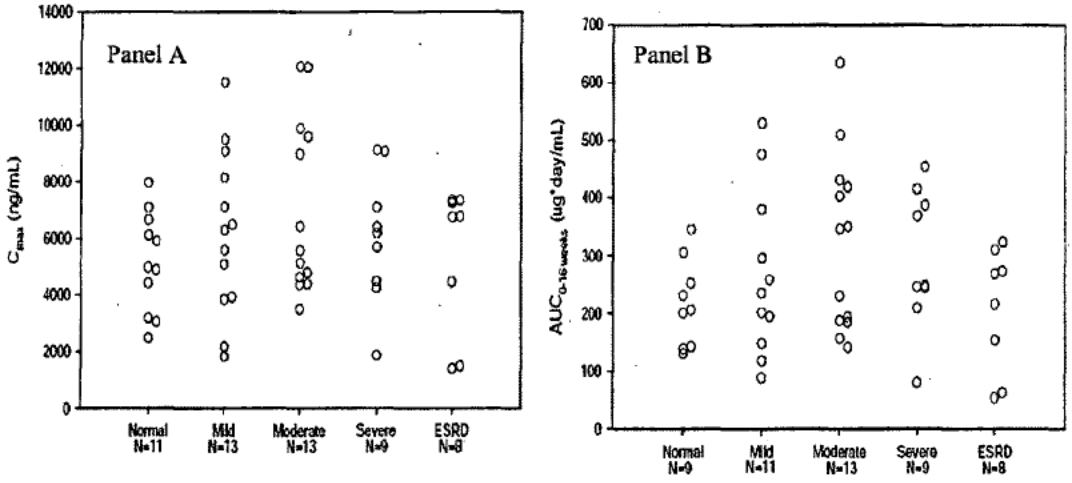

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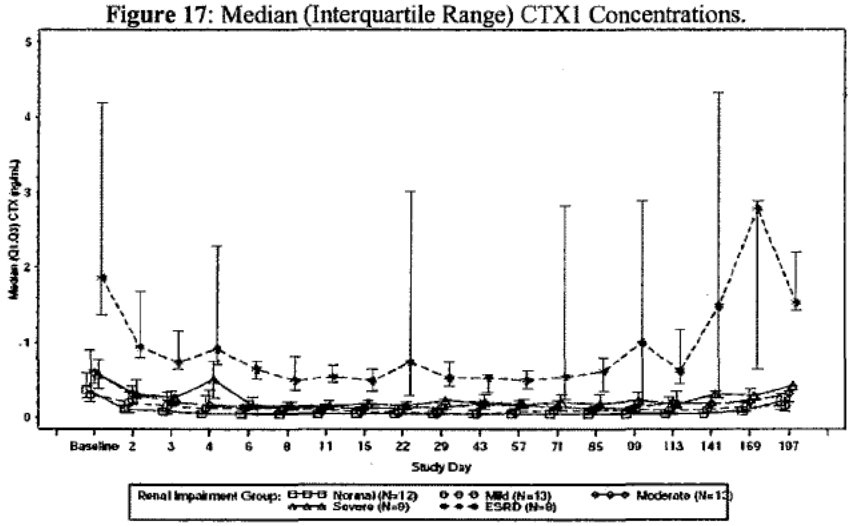
Table 10: Mean (SD) [%CV] Serum Denosumab Pharmacokinetic Parameter Estimates After SC Administration of 60 mg Denosumab.

PK Parameter	Renal Impairment Group					p-Value	
	Normal (n=11)	Mild (n=13)	Moderate (n=13)	Severe (n=9)	ESRD (n=8)	Jonckheere -Terpstra [d]	Linear Regression [e]
AUC0-16weeks [a] (µg*d/ml)	217 (76) [35]	266 (143) [54]	322 (154) [48]	295 (120) [41]	208 (107) [51]	0.595	0.173 (estimate= -0.0028
% Change vs. Normal [b]	-	23%	48%	36%	-4%		
Cmax (µg/ml)	5160 (1770) [34]	6200 (2880) [46]	7040 (3060) [43]	6020 (2320) [39]	5370 (2590) [48]	0.511	0.334 (estimate= -0.0018)
% Change vs. Normal*	-	20%	36%	17%	4%		
Tmax [c] (day)	10 (3 – 14)	10 (2 -28)	10 (3-28)	10 (7 -14)	10 (5-21)	-	-

[a] N for AUC0-16weeks: 9, 11, 13, 9, 8 for Normal, Mild, Moderate, Severe, end ESRD, respectively
[b] % Change vs Normal was calculated as the mean % difference in AUC and Cmax for each renal group compared to the normal group.
[c] Tmax is presented as median (range).
[d] p-value was obtained by sponsor from nonparametric Jonckheere-Terpstra trend test.
[e] Regression analysis of the relationship between CrCL and PK Parameters

Denosumab treatment resulted in decreases from baseline in sCTX1 concentration in all of the renal function groups, which were sustained from the first observation at Day 2 through the end of study (Figure 17). Median percent decreases from baseline in sCTX1 concentrations during the study (65% to 85% once maximal reductions were achieved) were generally similar across the renal function groups (see the individual study review for complete data).

Figure 17: Median (Interquartile Range) CTX1 Concentrations.



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In conclusion, renal impairment does not appear to alter denosumab PK. Denosumab treatment resulted in decreases from baseline in sCTX1 concentration in all of the renal function groups, which were sustained from the first observation at Day 2 through the end of study.

2.3.2.3 Hepatic impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK of denosumab.

2.3.2.4 What pregnancy and lactation use information is there in the application?

No data regarding the excretion of denosumab in the milk of humans or animals was provided.

2.3.3 Immunogenicity (NOT applicable to small molecule drugs)

2.3.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Overall, the incidence rate of developing binding antibodies was 0.5% (43 of 8,113) in denosumab-treated subjects and 0.3% (16 of 5,320) placebo-treated subjects in the studies included in this BLA. The rate of positive pre-existing binding antibodies was 0.2% in placebo patients and 0.1% in denosumab patients. In most of these subjects, the antibodies were transiently detected. Samples for immunogenicity were collected at adequate time points to assess for anti-product antibody formation at early onset, during study, and during study follow-up. Table 11 summarizes the sample collection times in the pivotal trials. For information on immunogenicity sampling in other clinical trials conducted, see the individual study reviews. In summary, the denosumab immunogenicity incidence is low and not associated with any clinical consequence.

Table 11: Immunogenicity Sample Collection Times in the Pivotal Trials.

Pivotal Study #	Patient Population	Immunogenicity Sample Collection Times
20030216	PMO	• Day 1 (baseline) • Months 1, 6, 12, 18, 24, 30, and 36/early termination
20040138	Prostate Cancer	
20040132	PMO	• Day 1 (baseline) • Months 1, 6, 12, 18, and 24/early termination
20040135	Breast Cancer	

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2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

No evidence of altered PK or PD has been observed in subjects who tested positive for binding antibodies. Examples of patients with positive samples for immunogenicity in the 4 pivotal trials are presented in Tables 12 and 13.

Denosumab concentrations were determined in all patients at 1 month post-dose. Patients with positive samples for immunogenicity during the study each had denosumab concentrations at 1 month within the range at that time point observed for all patients in the denosumab treatment arm.

Table 12: Serum Denosumab Concentrations at Month 1 Post-dose for Antibody-positive Patients.

Study #	Subject #	Time of Positive Ab Results (month)	Denosumab Conc at 1 Month post-dose (ng/ml)	Range of Denosumab Conc at 1 Month post-dose (ng/ml)*
20040132	132105014	1	4710	1620†, 11800
	132103012	24	5140	
20030216	6633313	12	4900	842, 17100
20040135	135185004	1, 12	3020	4130, 12200
	135434001	18	8070	
20040138	138646019	1	13800	<0.8, 13200

* Range of denosumab concentrations observed at 1 Month post-dose for antibody negative-subjects.
† Excludes 2 subjects as described in Section 10 of the 24-month study report.

Percent change from baseline in lumbar spine and total hip BMD at Month 12 (or 24) were determined in all patients. Patients with positive samples for immunogenicity during the study each had percent change BMD values within the range at that time point observed for all denosumab-treated patients in the study.

Table 13: Percent Change from Baseline in Lumbar Spine and Total Hip BMD at Month 12 (or 24) for Antibody-positive Patients.

Study #	Subject #	Time of Positive Ab Results (month)	Lumbar Spine BMD (%)	Lumbar Spine BMD Range (%)	Total Hip BMD (%)	Total Hip BMD Range (%)
20040132	132105014	1	4.59	-4.2, 21.2	0.75	-2, 6.5
	132103012*	24	12.65	-8.4, 25.4	7.89	-3.1, 7.9
20030216	6633313	12	NR	N/A	5.77	-12.5, 15.1
20040135	135185004	1, 12	3.46	-4.1, 12.9	4.21	-12.5, 13.3
	135434001*	18	9.19	-2.4, 17.7	6.51	-12.5, 13.3
20040138	138646019	1	4.36	-6.8, 18.2	5.74	-6.8, 11

NR, not reported; N/A, not applicable
*Patient BMD and study range values reported at Month 24 due to timing of positive antibody result.

No evidence of altered PK or PD has been observed in subjects who tested positive for binding antibodies.

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2.3.3.3 Do the anti-product antibodies have neutralizing activity?

Neutralizing antibodies have not been detected in any subject who tested positive for binding antibodies.

2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?

The denosumab immunogenicity incidence was low and was not associated with any clinical consequences.

2.3.3.5 What is the impact of anti-product antibodies on clinical safety? (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?

No evidence of altered safety profiles has been observed in subjects who tested positive for binding antibodies.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The extrinsic factor influence on dose-exposure and/or –response was not explored.

2.4.2 Drug-drug interactions

None of the general drug-drug interaction questions in the QBR is applicable to this biologics product, denosumab. Because denosumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms (e.g., by CYP enzymes), hepatic impairment and drug interaction studies (e.g., with CYP inhibitors or inducers) were not considered appropriate by the Sponsor and have therefore not been conducted.

However, considering that the effect of denosumab, an anti-cytokine antibody, on CYP activities is unknown, a PMC recommendation is being made to the Sponsor to address denosumab's effect on CYP activities and drug interaction potential (see Section 1.2 for details).

In a clinical study (Study 20050241) of postmenopausal women with low bone mass (n=20) who were previously treated with alendronate with a median duration of 3 years, those transitioning to receive alendronate experienced additional reduction in sCTX1, compared with women who remained on alendronate. As shown in Table 12, the PK of denosumab was not altered in subjects who transitioned from bisphosphonates to denosumab.

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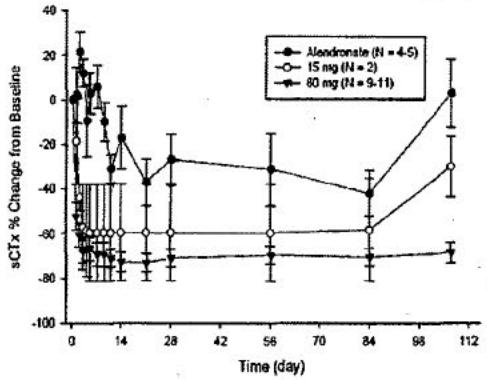
Table 12: Mean (SD) Denosumab Serum PK Parameters following 60 mg SC Dose (Study 20050234)

Treatment Groups	T_{max} [a] (day)	C_{max} (ng/ml)	AUC_{0-t} (µg·day/ml)
Alendronate pre-exposed postmenopausal women (n=12)	13 (3, 28)	7570 (4410)	332 (176)
Postmenopausal women (n=73)[b]	10 (3, 21)	6750 (1890)	316 (101)

[a] Median (range)
[b] Study 20050146 (vial)

Mean percent change from baseline for sCTX1 versus time profiles are presented in Figure 18. Fourteen days after dosing, the mean percent change from baseline in sCTX1 concentration was approximately -60% and -73% for subjects in the 15 mg and 60 mg denosumab groups, respectively. These changes were generally maintained from study Day 14 through study Day 84. The mean percent change from baseline for sCTX1 for subjects who continued on alendronate treatment ranged from approximately -40% to +20%, with no change, on average at study Day 107. In this study, change in serum calcium was similar between the two groups.

Figure 18: Mean (± SE) Serum C-Telopeptide Percent Change From Baseline Profiles for Postmenopausal Women With Low Bone Mass Density Following a Single Subcutaneous Administration of Denosumab 15 mg or 60 mg Dose, or Continuation on Alendronate Therapy (Study 20050241)



2.5 General Biopharmaceutics

Sections 2.5.1 through 2.5.9 are not applicable to therapeutic proteins.

2.5.10 What is the PK and PD comparability of the proposed to-be-marketed formulation to pivotal clinical trial?

The biopharmaceutics program demonstrated the PK and PD comparability between denosumab drug substance and drug product produced for the pivotal Phase 3 clinical trials and those intended for commercial use.

(b) (4)

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3 REFERENCES

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4 LABELING

The following are Clinical Pharmcology revelant parts of the Sponsor's proposed labeling with preliminary labeling recommendations from the Clinical Pharmacology review team. Labeling review will be completed later at the time of label negotiation with the Sponsor.

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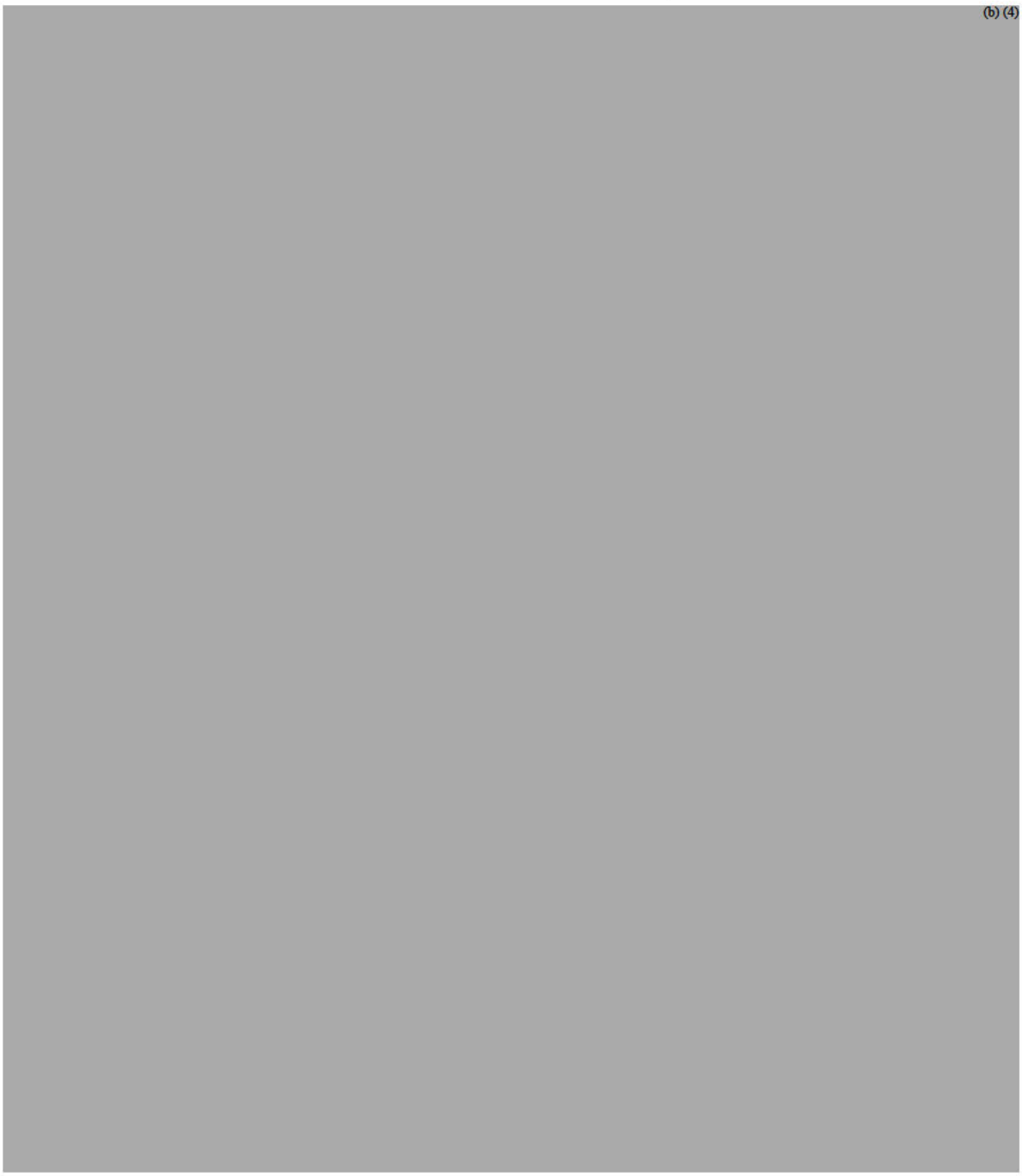

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5 APPENDIX

5.1 Summary of Clinical Pharmacology and Biopharmaceutics Studies

Table 5.1-1. Clinical Pharmacology and Biopharmaceutics Study Designs and Key Results

Study Number	Study Design & Objectives	Study Population	Key Results
Healthy volunteer PK and initial tolerability studies			
20010124	Phase 1, randomized, double-blind, placebo-controlled, single- and multiple-dose study to assess safety, tolerability, PK, PD, and antibody response	Healthy, postmenopausal women; Age: 40 to 70 yr	Denosumab was generally well tolerated and demonstrated dose-dependent, nonlinear PK. Denosumab doses ≥ 1.0 mg/kg maintained decreases in bone turnover markers for ≥ 6 months post-dose.
20030148	Phase 1, randomized, blinded, , placebo-controlled, single-dose study to assess PK, PD, safety, and tolerability	Healthy men; Age: ≥ 50 yr	Denosumab was well tolerated and demonstrated dose-dependent, nonlinear PK. All doses resulted in a rapid suppression of bone turnover markers relative to placebo; suppression was more sustained at higher doses. No differences in PK were apparent between men 50 to 64 years and ≥ 65 years of age.
20030164	Phase 1, randomized, double-blind, placebo-controlled, single-dose study to assess safety, tolerability, PK, and PD	Postmenopausal Japanese women; Age: 40 to 64 yr	Denosumab was well tolerated; demonstrated dose-dependent, nonlinear PK; and rapidly suppressed bone turnover markers relative to placebo. The duration of suppression increased with dose.
20030180	Phase 1, randomized, blinded, placebo-controlled, single-dose study to assess PK, PD, safety, and tolerability	Healthy postmenopausal women; Age: 40 to 64 yr	Denosumab was well tolerated; demonstrated dose-dependent, nonlinear PK; and rapidly suppressed bone turnover markers relative to placebo. The duration of suppression increased with dose.
Patient PK and initial tolerability studies			
20010123	Phase 1, randomized, double-blind, active-controlled, double-dummy, single-dose study to assess the safety, tolerability, PD compared with pamidronate, PK, and antibody response for Denosumab	Men or women with either multiple myeloma or breast cancer, with documented bone lesions/metastases, and estimated survival ≥ 6 months	All doses of denosumab were well tolerated and resulted in rapid suppression of uNTX/Cr. The extent of suppression was dose-dependent for denosumab doses ≤ 1.0 mg/kg. Levels were notably suppressed through 12-weeks postdose for all doses, except 0.1 mg/kg in subjects with BC. Denosumab demonstrated dose-dependent, nonlinear PK.
20040176	Phase 1, open-label, dose-ascending, single- and multiple-dose study	Japanese women with confirmed breast cancer,	Denosumab was well tolerated when administered SC as a single dose of 60 or 180 mg and as

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	to assess safety, PK, antibody response, and PD	radiological evidence of ≥ 1 bone metastasis, and ECOG score ≤ 2	multiple doses of 180 mg. Denosumab demonstrated approximately dose-linear PK. As expected, an approximate 2.2-fold accumulation was observed by the third dose relative to the first dose for the 180-mg Q4W cohort. All doses resulted in a rapid and sustained suppression of bone turnover markers.
Intrinsic factor PK study			
20040245	Phase 1, open-label, single-dose study to assess PK, safety, and tolerability	Men and women with normal renal function (healthy subjects) and varying degrees of renal impairment	Renal impairment does not impact the PK of denosumab and, therefore, no dose adjustments are required when denosumab is administered to patients with impaired renal function. Denosumab treatment resulted in rapid and sustained suppression in serum CTX1 concentration in all of the renal function groups. In addition, the incidence and ypes of adverse events reported in this study were generally similar to those reported in other studies with denosumab. As expected with an antiresorptive therapeutic and consistent with other studies, transient decreases in median serum calcium concentration were observed following administration of denosumab. The potential for hypocalcemia in subjects with severe kidney disease and ESRD, however, appeared greater compared with subjects with mild or moderate kidney disease and subjects with normal renal function. This observation is likely due to the fact that subjects with severe kidney disease or ESRD rely more heavily on the bone to provide a source of calcium, due to their impaired ability to reabsorb calcium from the urine and to absorb calcium in the gastrointestinal tract. Therefore, with antiresorptive therapy, these subjects may be more susceptible to reductions in serum calcium. In this study, supplementation with calcium and vitamin D was effective in mitigating the risk of clinically significant hypocalcemia
Extrinsic factor PK study			

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20050241	Phase 1, randomized, open-label, single-dose study to assess safety (changes in serum calcium for subjects switched from alendronate to denosumab)	Postmenopausal women who have received alendronate (70 mg QW or equivalent) for ≥ 1 year with low BMD (-4 ≤ T-score ≤ -1 for spine or total hip); Age: ≤ 80 yr	Transitioning from alendronate to denosumab was generally well tolerated. No clinically significant differences between serum calcium profiles were observed after subjects transitioned from alendronate to denosumab. Denosumab demonstrated dose-dependent, nonlinear PK. All doses tested resulted in a rapid suppression of serum CTX1 relative to alendronate, with a greater extent and duration of suppression observed for the 60-mg dose than the 15-mg dose.
Dose-ranging studies			
20010223	Phase 2, randomized, double-blind, placebo and active-controlled, dose-finding study to assess efficacy (BMD), selection of denosumab dose regimen for future studies, safety, and tolerability	Postmenopausal women with low BMD (-4.0 ≤ T-score ≤ -1.8 for lumbar spine or -3.5 ≤ T-score ≤ -1.8 for total hip or femoral neck); Age: ≤ 80 yr	Denosumab was well tolerated and effectively increased trabecular and cortical BMD and decreased bone turnover markers in postmenopausal women with low BMD. The effects of denosumab are reversible, since BMD returned to baseline levels upon discontinuation of treatment. The dose selected for future clinical trials in the bone loss setting was 60 mg Q6M because no additional efficacy for BMD and bone turnover markers was observed at higher doses. Denosumab displayed dose-dependent, nonlinear PK, which did not change with time or upon multiple Q3M or Q6M dosing.
20050172	Phase 2, randomized, double-blind, placebo controlled, dose-response study to assess efficacy (BMD), safety, tolerability, selection of denosumab dose for future studies, PK, and PD	Japanese women with PMO (-4.0 ≤ T-score ≤ -2.5 for lumbar spine or -3.5 ≤ T-score ≤ -2.5 for total hip or femoral neck); Age: ≤ 80 yr	Denosumab was well tolerated and effectively increased trabecular and cortical BMD and decreased bone turnover markers in Japanese postmenopausal women with osteoporosis. Denosumab displayed dose-dependent, nonlinear PK, which did not change with time or upon multiple Q6M dosing.
Biopharmaceutics studies			
20050146	Phase 1, randomized, open label, single-dose study to compare PK of denosumab after administration with a PFS vs. a GS (drawn from a vial)	Healthy volunteers; Age: 18 to 65 yr	Denosumab PFS is bioequivalent to denosumab GS. Denosumab administered from a PFS and in a GS was considered well tolerated in this study.
20050227	Phase 1, randomized, openlabel, single-dose	Healthy volunteers;	Denosumab ACO is bioequivalent to denosumab ATO. Denosumab

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	study to compare PK of denosumab drug substance produced at ACO vs. ATO	Age: 18 to 65 yr	ACO and ATO were considered well tolerated in this study.
20060286	Phase 1, randomized, open label, single-dose study to compare PK of denosumab drug substance produced at ATO vs. BIP	Healthy volunteers; Age: 18 to 65 yr	Denosumab BIP is bioequivalent to denosumab ATO. Denosumab BIP and ATO were considered well tolerated in this study.

Please refer to the individual study reviews for details of the Clinical Phamracology and Biopharmaceutics studies.

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5.2 Summary of denosumab and sCTX1 bioanalytical assay performances

Table 5.2-1: Denosumab Clinical Studies included in the Summary of Clinical Pharmacology, Summary Statistics for Standard and QC Inter-Assay Performance for Serum Denosumab and CTX1 Concentrations

Study #	Sample Type	Analyte			
		Denosumab		CTX1	
		Accuracy (%Diff)	Precision (%CV)	Accuracy (%Diff)	Precision (%CV)
Healthy Volunteer Pharmacokinetics and Initial Tolerability Studies					
20010124	Standards	-2 to 3	6 to 10	NA	NA
	Quality Controls	-4 to 3	8 to 17	NA	NA
20030148	Standards	-6 to 7	2 to 4	-6 to 7	2 to 8
	Quality Controls	-3 to 7	5 to 7	-8 to 1	4 to 8
20030164	Standards	-8 to 6	2 to 4	-8 to 8	2 to 4
	Quality Controls	-5 to 6	8 to 10	-5 to 4	3 to 8
20030180	Standards	-9 to 7	2 to 3	-5 to 7	2 to 5
	Quality Controls	-1 to 11	5 to 8	-3 to 3	3 to 8
Patient Pharmacokinetics and Initial Tolerability (Advanced Cancer) Studies					
20010123	Standards	-4 to 3	5 to 9	NA	NA
	Quality Controls	-7 to 2	8 to 14	NA	NA
20040176	Standards	-11 to 10	2 to 6	-4 to 4	2 to 7
	Quality Controls	-6 to 7	5 to 8	-2 to 5	3 to 7
Intrinsic Factor Pharmacokinetics Study					
20040245	Standards	-11 to 8	2 to 3	-3 to 6	2 to 7
	Quality Controls	-7 to 4	6 to 9	1 to 7	4 to 7
Extrinsic Factor Pharmacokinetics Study					
20050241	Standards	-9 to 10	2 to 4	-4 to 2	3 to 9
	Quality Controls	6	5 to 8	4 to 15	8 to 12
Other Studies Contributing Pharmacokinetic and Pharmacodynamic Data					
Biopharmaceutics Studies					
20050146	Standards	0 to 2	2 to 4	-5 to 6	2 to 8
	Quality Controls	-4 to -2	4 to 8	1 to 8	4 to 7
20050227	Standards	-1 to 2	1 to 5	-4 to 5	2 to 6
	Quality Controls	-1 to 1	4 to 6	-1 to 4	3 to 9
20060286	Standards	-2 to 3	2 to 4	-4 to 5	2 to 8
	Quality Controls	0 to 2	4 to 7	1 to 9	4 to 8
20060446	Standards	-2 to 2	2 to 4	-6 to 7	2 to 7
	Quality Controls	-4 to -1	4 to 5	2 to 7	4 to 7
Dose-ranging Studies in Postmenopausal Women					
20010223	Standards	-9 to 7	3	-7 to 7	2 to 5
	Quality Controls	-3 to 5	7 to 9	-6 to 3	4 to 6
20050172	Standards	-7 to 8	2 to 4	-4 to 3	4 to 10
	Quality Controls	2 to 6	5 to 9	7 to 25	4 to 10
Safety and Efficacy Studies in the Prevention and Treatment of PMO					
20030216	Standards	-6 to 8	3 to 4	-4 to 3	2 to 12
	Quality Controls	1 to 4	7 to 12	0 to 3	4 to 16
20040132	Standards	-10 to 8	3	-3 to 3	2 to 8
	Quality Controls	-6 to 4	7 to 12	1 to 3	4 to 8
20050233	Standards	-7 to 7	3 to 4	-5 to 2	3 to 9
	Quality Controls	3 to 4	6 to 10	-8 to 20	4 to 13
Safety and Efficacy Studies in the Treatment of Bone Loss Associated with HALT					
20040135	Standards	-11 to 8	2 to 3	-3 to 2	2 to 7
	Quality Controls	-6 to 6	7 to 11	0 to 4	3 to 8
20040138	Standards	-11 to 8	3	-4 to 3	2 to 9
	Quality Controls	-7 to 4	7 to 11	0 to 4	4 to 12
Safety and Efficacy Studies in Other Indications					
20040144	Standards	-11 to 8	3	-4 to 3	2 to 9
	Quality Controls	-7 to 3	8 to 10	-1 to 3	4 to 8
20040113	Standards	-11 to 8	3	-3 to 4	3 to 8
	Quality Controls	-6 to 4	7 to 10	-2 to 5	4 to 16
20040114	Standards	-10 to 7	3	-3 to 3	2 to 8
	Quality Controls	-8 to 5	6 to 13	-1 to 3	4 to 10
20050134	Standards	-9 to 9	3 to 4	-4 to 3	4 to 10
	Quality Controls	4 to 6	6 to 11	-16 to 16	4 to 17

Reference ID: 3168397

5.2 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology Biologics License Application Filing and Review Form			
General Information About the Submission			
	Information		Information
BLA Number	125-320, 125-331	Brand Name	Prolia
OCP Division	DCP3	Generic Name	Denosumab
Medical Division	DRUP	Drug Class	Monoclonal antibody
OCP Reviewer	Chongwoo Yu, Ph.D	Indication(s)	Treatment (BLA 125-320) and prevention (BLA 125-331) of osteoporosis in postmenopausal women
OCP Team Leader	Myong Jin Kim, Pharm. D.	Dosage Form	Injection
Secondary Reviewer	Bo Lee, Ph.D.	Dosing Regimen	60 mg/ml every 6 months
Date of Submission	December 19, 2008	Route of Administration	subcutaneous
Estimated Due Date of OCP Review	August 19, 2009	Sponsor	Amgen
PDUFA Due Date	October 19, 2009	Priority Classification	Standard
Division Due Date	September 28, 2009		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		20030148, 20030184, 20030180
multiple dose:	x	1		20040124
Patients-				
single dose:	x	1		20040123
multiple dose:	x	1		20040179
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
in-vivo effects on primary drug:				
in-vitro effects of primary drug:				
in-vitro:				
Subpopulation studies -				
ethnicity:				Pop-PK
gender:				Pop-PK
pediatrics:	NA			Pediatric waiver request
geriatrics:				Pop-PK
renal impairment:		1		20040245
hepatic impairment:	NA			

Reference ID: 3168397

PD:				
Phase 1:		1		20050241
Phase 2:		5		20050172, 20040144, 20040153, 20040114, 20050124
Phase 3:		11		20050218, 20040132, 20050145, 20050179, 20050234, 20050233, 20050232, 20050289, 20040135, 20040138, 20050209
PK/PD:				
Phase 1 and/or 2, proof of concept:		1		20010223
Phase 3 clinical trial:				
Population Analyses -				
PK:	x	1		109657
PD:	X	1		110184
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		4		20050148, 20050227, 20050286, 20050448
replicate design; single / multi dose:				
Food-drug interaction studies:	NA			
Dissolution:				
(MIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile		1		20050237
Literature References				
Total Number of Studies		32		

Other comments	
	Comments
OBR questions (key issues to be considered)	1. Acceptability of comparability studies. 2. Sufficient drug interaction information? 3. Population PK analyses. 4. Acceptability of immunogenicity. 5. Sufficient bioanalytical assay validation information?
Other comments or information not included above	1. Need to request a consult to the OCP Pharmacometrics (PM) group. 2. Need to request a consult to the Office of Biotechnology Products (OBP) for review of antibody assays 3. Need to request a consult to OSI for inspection of sites where the comparability studies were conducted.

Reference ID: 3168397

5.3 Pharmacometric Review

Attached Separately

Reference ID: 3168397

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	BLA125320 BLA125331 BLA125332 BLA125333
Submission Number (Date)	Dec 19, 2008
Clinical Division	Division of Reproductive and Urology Products (DRUP) Division of Biologics and Oncology Products (DBOP)
Primary PM Reviewer	Ping Ji, Ph.D.
Secondary PM Reviewer	Pravin Jadhav, Ph.D.

1 Summary of Findings 2

1.1 Key Review Questions 2

1.1.1 Is there evidence to support fixed dosing regimen (60 mg Q6M) for all patients? 2

1.1.2 Are the proposed labeling claims based on PopPK analysis appropriate? . 4

1.1.3 Does exposure-response analysis provide evidence of effectiveness and are there any exposure related safety events? 4

1.1.4 Does immunogenicity affect the PK and effectiveness? 6

1.2 Recommendations 7

1.3 Labeling Statements 9

2 Pertinent regulatory background 9

3 Results of Sponsor's Analysis 10

4 Appendix A: Reviewer's results for the Population PHarmacokinetic Analysis 13

5 Appendix A: Reviewer's results for the Population pharmacodynamic Analysis.... 14

Reference ID: 3168397

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

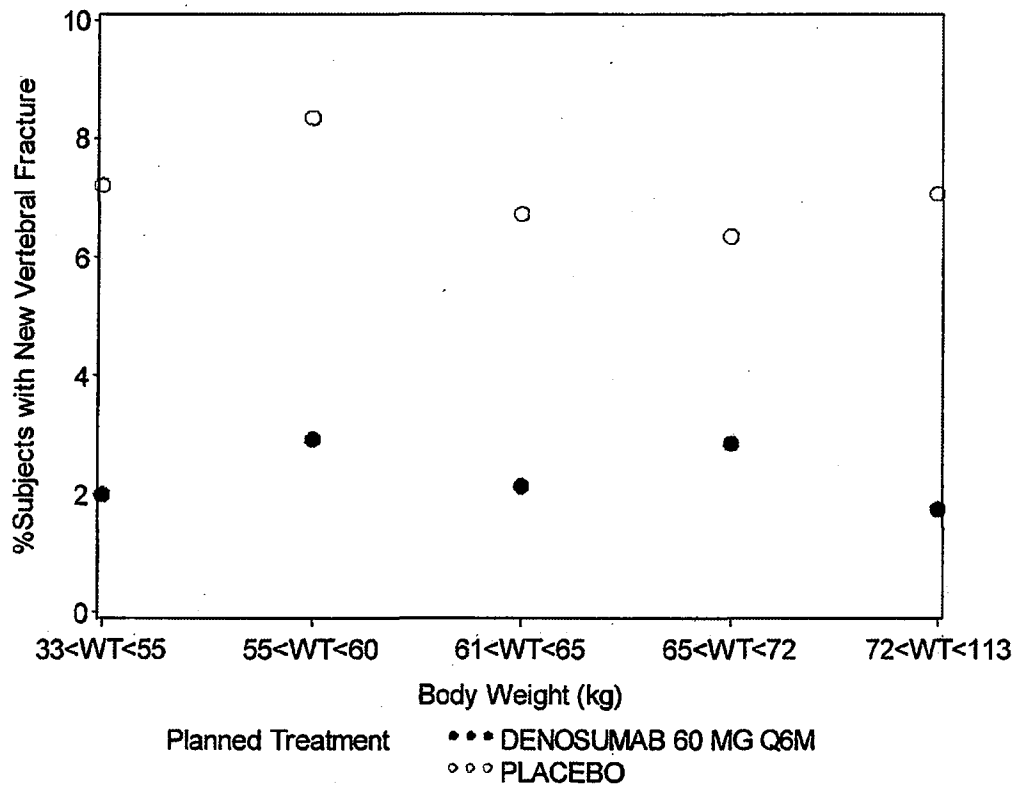
The purpose of this review is to address the following key questions.

1.1.1 Is there evidence to support fixed dosing regimen (60 mg Q6M) for all patients?

Yes, fixed dosing regimen (60 mg Q6M) is appropriate for all the patients.

The effect of body weight on the incidence of new vertebral fracture over the 36 months period, the primary efficacy point, was investigated in study 200302016. Body weight did not appear to affect the incidence of new vertebral fracture over the 36 months period.

Figure 1. The incidence of any new vertebral fracture versus body weight in study 200302016.

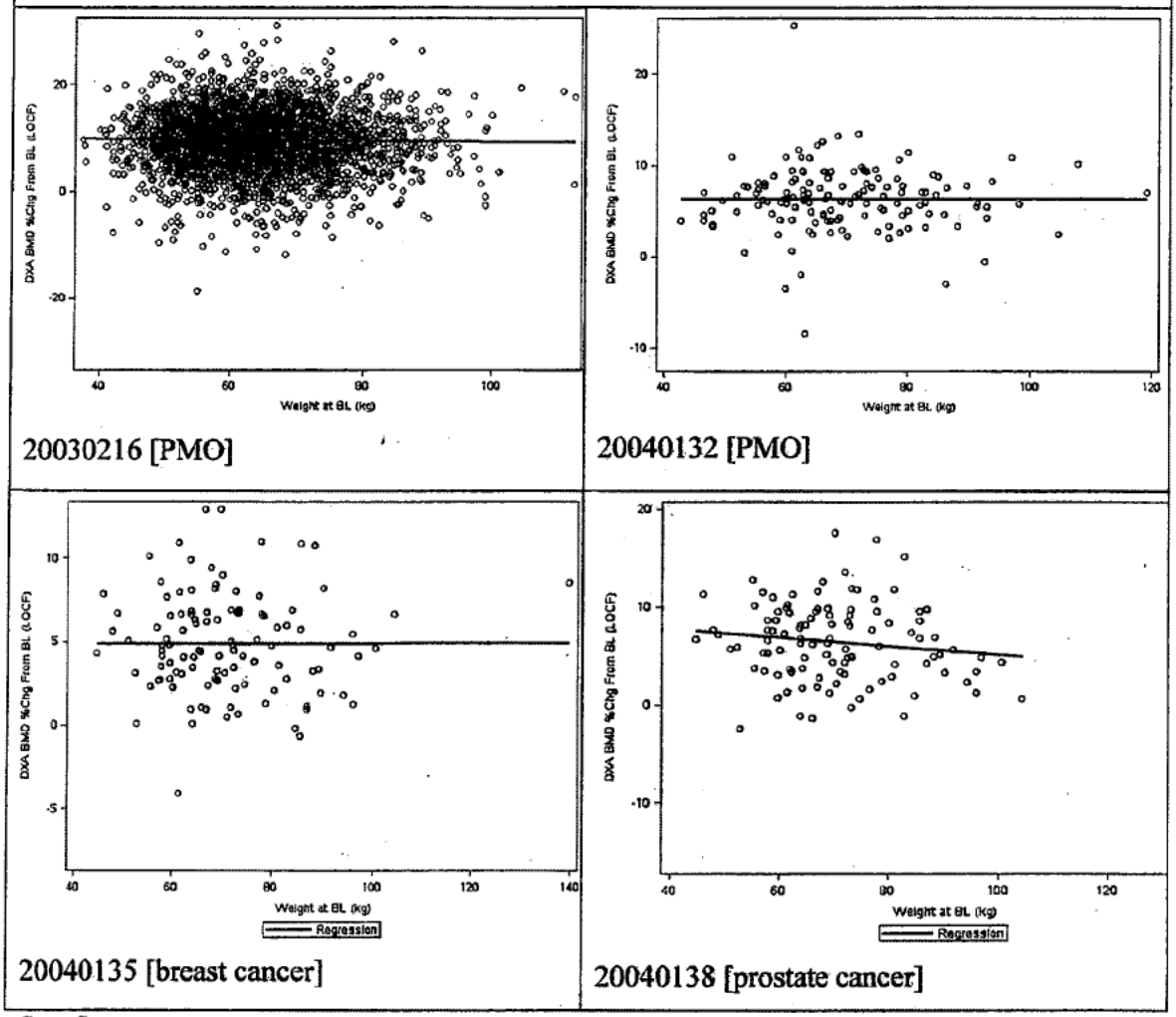


Data used in creating this plot are summarized in Appendix 1

The effect of body weight on the bone mineral density (BMD) in lumber spine was also explored in the phase III pivotal efficacy studies (200302016 [PMO], 20040132 [PMO 24 month data], 20040135 [breast cancer patients], and 20040138 [prostate cancer patients]). The increase of body weight was not associated with any change in the BMD level.

Reference ID: 3168397

Figure 2. Scatter plots of lumber spine bone mineral density versus body weight in studies 200302016, 20040132, 20040135, and 20040138.



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\\Cbsap58\m\eCTD_Submissions\STN125320\0000\m5\datasets\20040132-36-Month\analysis\aslbase.xpt abmdxa.xpt

\\Cbsap58\m\eCTD_Submissions\STN125320\0000\m5\datasets\200401356\analysis\aslbase.xpt abmdxa.xpt

\\Cbsap58\m\eCTD_Submissions\STN125320\0000\m5\datasets\20040138\analysis\aslbase.xpt abmdxa.xpt

Denosumab pharmacokinetic parameters are dependent on body weight. However, differences in exposure do not affect response to denosumab, therefore, fixed dose for all patients can be supported.

Reference ID: 3168397

1.1.2 Are the proposed labeling claims based on PopPK analysis appropriate?

Yes, the proposed labeling appeared to be appropriate.

Age and gender are not significant covariates in the population PK analysis (See Appendix 4 for distribution of subject demographics). Subject type as solid tumor and race as black and Hispanic were identified as covariates for clearance in the population PK model (*Amgen Pharmacometric report 100957*). However, the pharmacokinetics of denosumab did not appear to be affected by race and solid tumor as shown in the simulation results.

Table 1. Mean and SD of the AUC, Cmax, and the duration the serum concentration above 200 ng/mL after 60 mg single dose for black, Hispanic and solid tumor subjects with respect to the Caucasian postmenopausal women (reference).

Parameter	Reference		Black		Ratio	
	Mean	SD	Mean	SD	Mean	Quartiles
AUC (mg·h/L)	10200	4820	9300	4470	0.908	0.928, 0.884
C_{Max} (ng/mL)	11300	4630	10300	4120	0.915	0.938, 0.912
T > 200 ng/mL (days)	130	28.7	127	29.1	0.979	0.952, 1.00
	Reference		Hispanic		Ratio	
	Mean	SD	Mean	SD	Mean	Quartiles
AUC (mg·h/L)	10200	4820	9770	4630	0.954	0.948, 0.942
C_{Max} (ng/mL)	11300	4630	10700	4300	0.951	0.966, 0.952
T > 200 ng/mL (days)	130	28.7	129	29.4	0.990	0.952, 1.00
	Reference		Solid Tumor		Ratio	
	Mean	SD	Mean	SD	Mean	Quartiles
AUC (mg·h/L)	10200	4820	9920	4580	0.969	0.980, 0.959
C_{Max} (ng/mL)	11300	4630	11100	4530	0.979	0.974, 0.998
T > 200 ng/mL (days)	130	28.7	129	28.6	0.995	0.952, 1.00

Mean (SD) bodyweight in kg for each population: Reference 66.0 (10.2); Black 72.2 (13.9); Hispanic 68.5 (12.4); Solid Tumor 69.6 (15.7)

Source: page 63 of Amgen pharmacometrics report: 109957.

1.1.3 Does exposure-response analysis provide evidence of effectiveness and are there any exposure related safety events?

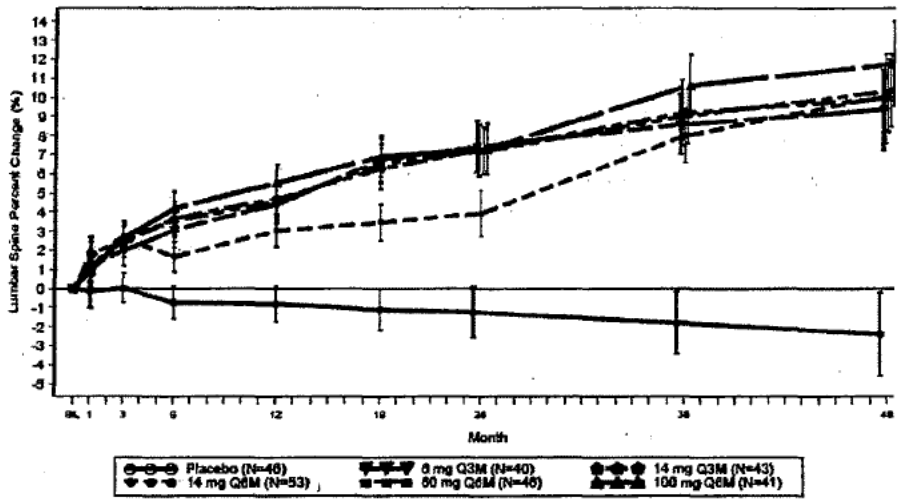
Effectiveness

Denosumab treatment was associated with increase in BMD of the lumber spine in dose dependent manner. The effect was significant compared to placebo. Denosumab treatment was associated with significant decrease in the bone-turnover-marker (BALP, CTX, or NTX_UCR) of the lumber spine than placebo treatment.

The effect of denosumab dose on BMD of the lumber spine in postmenopausal women with low BMD was investigated in study 20010223. All drug treated cohorts had significantly greater increase in BMD of the lumber spine than placebo cohort. Across denosumab dose cohorts, the magnitude of the increase in BMD was similar with the exception of the 14-mg-Q6M dose cohort.

Reference ID: 3168397

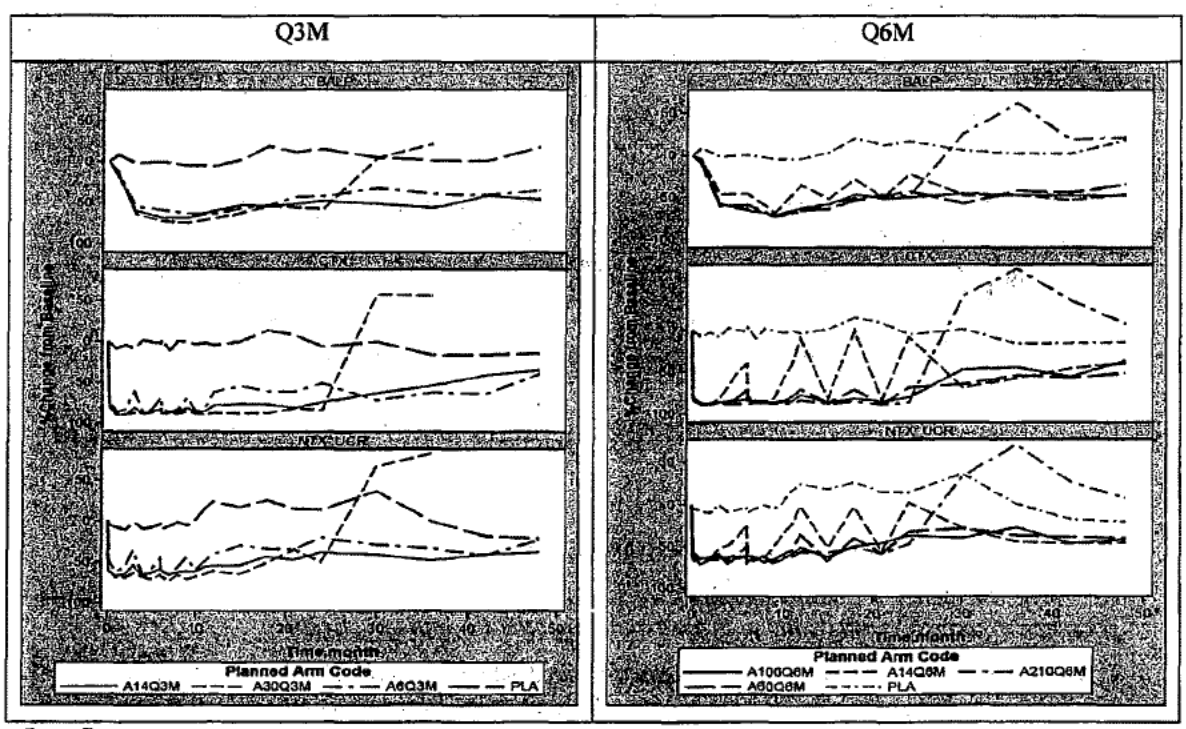
Figure 3. %Change (95% CI) from baseline in lumber spine BMD for subjects in the continuous treatment cohorts (*Study 20010223*)



Source: Page 66 in Module 2.72. Summary of Clinical Pharmacology Studies

Further, Denosumab treatment resulted in a rapid and sustained decrease in median serum C-TX of type I collagen (CTX), bone-specific alkaline phosphatase (BALP), and N-telopeptide (NTX) concentrations (Figure 4). Across the denosumab dose cohorts, the maximal suppression of serum turnover markers was similar.

Figure 4. Median percent change from baseline in the bone-turnover-marker (CTX, BALP, and NTX_UCR) versus time (*study 20010223*).



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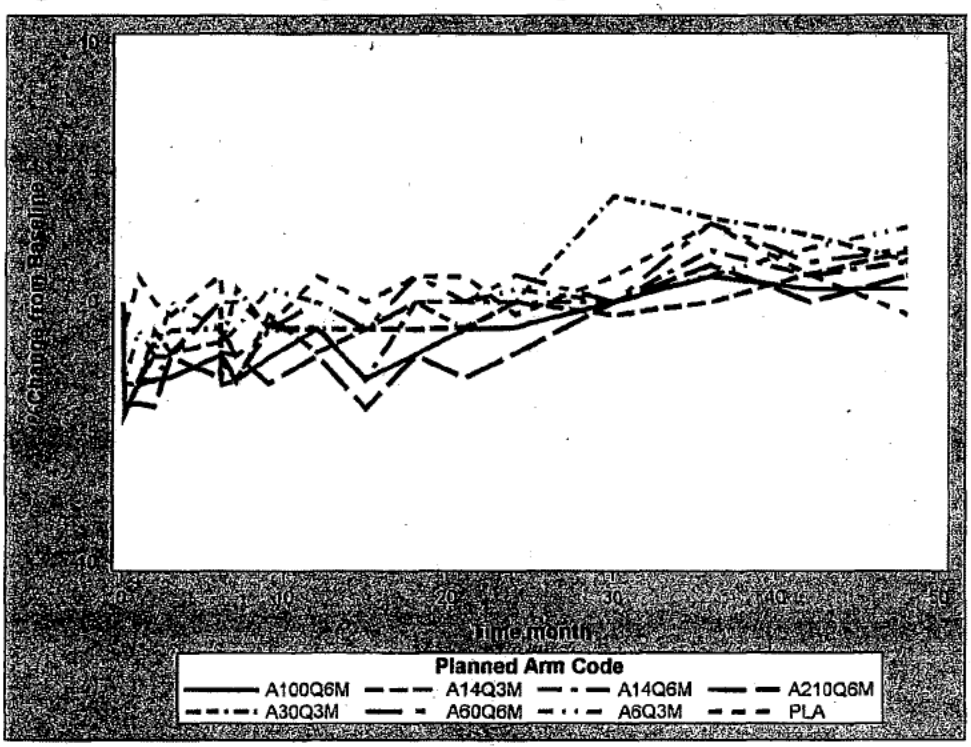
Reference ID: 3168397

Safety

The overall safety profile was comparable between denosumab group and placebo group. Denosumab administration was associated with mild transient decreases in the concentration of serum calcium, an event of interest.

The overall incidence of adverse events, serious adverse events, and adverse events leading to treatment withdrawal were generally similar between denosumab and placebo groups. In this application, hypocalcemia was considered an event of interest due to the potential for denosumab to lower serum calcium levels. The effects of denosumab dose on the percent change of calcium levels were investigated in study 20010223 as shown in Figure 5. Denosumab administration was associated with mild transient decrease in serum calcium level. However, no subjects had albumin-adjusted serum calcium below the normal range at the scheduled visits. For details, please refer to the medical review.

Figure 5. Median % change from baseline in plasma calcium.



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1.1.4 Does immunogenicity affect the PK and effectiveness?

No. The incidence of immunogenicity of denosumab in humans appears to be low and the presence of immunogenicity did not appear to affect the PK and effectiveness.

Overall, 43 out of 8113 (0.5%) denosumab-treated subjects were positive for development of binding antibodies. In most of these subjects, the antibodies were transiently detected. In addition, neutralizing antibodies were not been detected in any subject. Table 2 summarizes the serum denosumab concentrations at 1 month postdose and the changes in lumbar spine and total hip

Reference ID: 3168397

BMD at month 12 or 24 for subjects who developed transient binding antibodies to denosumab during the phase 3 studies in subjects with low BMD (*Study 20040132*) or PMO (*Study 20030216*) or bone loss due to HALT (Studies 20040135 and 20040138). The serum denosumab concentrations and changes in BMD for these subjects were all within the ranges observed for the other subjects in the studies, except for the month-1 serum denosumab concentration for subject 138646019 in Study 20040138. This subject had the highest serum concentration at that time point; however, this value was < 5% greater than that of the next highest value in an antibody-negative subject. Thus, there is no evidence that the transient occurrence of binding antibodies to denosumab alters its pharmacokinetic or pharmacodynamic profiles.

Table 2. Serum denosumab concentrations at Month 1 and percent change from baseline in lumber spine and total hip BMD at Month 12 or 24 for antibody-positive subjects.

(Studies 20040132, 20040135, 20040138, and 20030216)

Study	Subject	Time of Positive Ab Result (month)	C1month (ng/mL)	Range C1month[a] (ng/mL)	Lumbar Spine BMD (%)	Range: Lumbar Spine BMD (%)	Total Hip BMD (%)	Range: Total Hip BMD (%)
20040132	132103012[b]	24	5140	1620[c], 11800	12.65	-8.4, 25.4	7.89	-3.1, 7.9
20040132	132105014	1	4710	1620[c], 11800	4.59	-4.2, 21.2	0.75	-2.0, 8.5
20040135	135185004	1, 12	3020	1430, 12200	3.46	-4.1, 12.9	4.21	-12.5, 13.3
20040135	135434001[b]	18	8070	1430, 12200	9.19	-2.4, 17.7	8.51	-12.5, 13.3
20040138	138646019	1	13800	<0.8, 13200	4.36	-8.8, 18.2	5.74	-6.8, 11.0
20030216	6833313	12	4900	842,17100	NR	-5.1, 15.9	5.77	-12.5, 15.1

Ab = antibody; BMD = bone mineral density (percent change from baseline at month 12); C1month = serum denosumab concentration at 1 month postdose; NR = not reported

[a] For antibody-negative subjects

[b] Lumbar spine and total hip BMD individual values and ranges at month 24 (due to timing of positive antibody result).

[c] Excludes 2 subjects as described in Section 10 of the Study 20040132 24-month clinical study report

Source: Page 131 in Module 2.7.2 Summary of clinical pharmacology studies

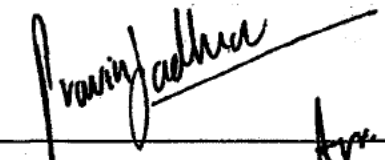
1.2 Recommendations

None.

Reference ID: 3168397

Signature Page

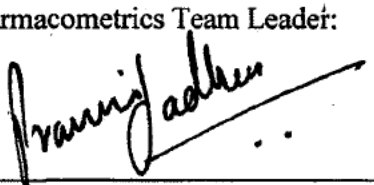
Pharmacometrics Reviewer:



for Dr. Ping Ji

Ping Ji, Ph.D., 8/21/09

Pharmacometrics Team Leader:



Pravin Jadhav, Ph.D., 8/21/09

Reference ID: 3168397

1.3 Labeling Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

7 Drug Interactions:

[redacted]

12.3 Pharmacokinetics:

[redacted]

[redacted] (b) (4) **populations**

[redacted]

Race: The pharmacokinetics of denosumab were not affected by race.

Renal Impairment: In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab; thus, dose adjustment for renal impairment is not necessary.

6.2 Immunogenity:

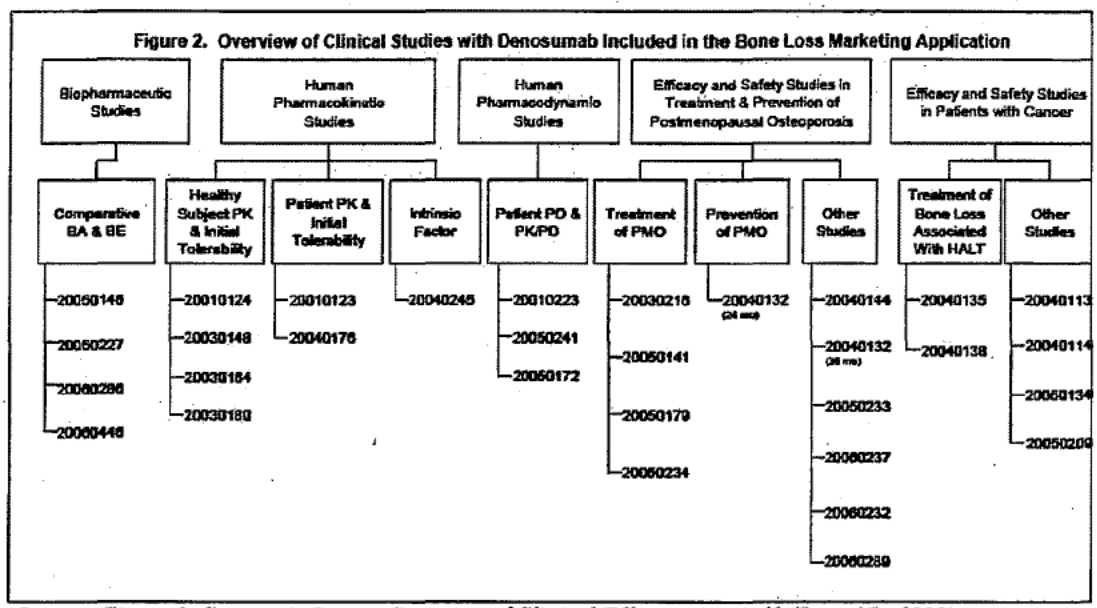
[redacted]

2 PERTINENT REGULATORY BACKGROUND

The sponsor, Amgen Inc., submitted an original BLA on Dec 19, 2008 for denosumab, a receptor activator of nuclear factor kappa B (RANK) ligand inhibitor indicated for the treatment and prevention of postmenopausal osteoporosis and of bone loss in patients undergoing hormone ablation for prostate or breast cancer. Denosumab is developed for subcutaneous administration 60 mg once every six month. A total of 30 clinical studies are included in this submission (Figure 6). Among which, twenty-three clinical studies contributed data on the safety, tolerability, and pharmacokinetic profiles for denosumab.

Reference ID: 3168397

Figure 6. Overview of clinical studies with denosumab included in the bone loss.



Source: Figure 2- Sponsor's Report Summary of Clinical Efficacy-pmo.pdf (Page 17 of 220)

3 RESULTS OF SPONSOR'S ANALYSIS

The key findings from sponsor's population PK analysis (*study report: 109957*) in healthy subjects, cancer patients, and postmenopausal women are summarized below:

Reference ID: 3168397

1. A two-compartment pharmacokinetic model with linear distribution to the peripheral compartment, parallel linear and non-linear elimination, and first-order absorption after subcutaneous administration is suitable to describe the pharmacokinetics of denosumab after intravenous and subcutaneous administrations of different dosing schedules to healthy subjects, osteopenic and osteoporotic postmenopausal women and subjects with cancer.

2. After subcutaneous administration, denosumab absolute bioavailability was 61% and the mean absorption time was estimated to be 7 days. The rate and the extent of absorption were similar across the range of doses evaluated.

3. Denosumab is eliminated through a non-specific (linear) elimination through the rethiculoendothelial system and a receptor-mediated (nonlinear) clearance, which results in a concentration dependent clearance that increases from 3.0 mL/hr for high concentrations to 18 mL/hr for low concentrations, achieving half of that change at concentrations of 216 ng/mL. With the 60 mg (or 1 mg/kg), the receptor mediated pathway was saturated at least 40% during approximately 6 months period, and the RANKL production over 6 month period was estimated to be lower 925 nmol. Taken together, these values support the selection of a 60 mg (417 nmol) dose every 6 months for clinical use.

4. Denosumab exhibited time-independent kinetics and its systemic exposure is consistent following repeat subcutaneous administration of 60 mg every 6 months, which evidenced minimal accumulation.

5. Body weight was associated with denosumab pharmacokinetic parameters; however, given the between-subject variability in pharmacokinetics parameters, a fixed dose of 60-mg denosumab administered to postmenopausal women with osteoporosis provides similar pharmacokinetic profiles compared with a 1-mg/kg denosumab dose. Thus, dose adjustments on the basis of body weight are not warranted

6. Age, race (Caucasian, Hispanic, black, Japanese/Asian, others), disease status (namely healthy subjects, osteopenic or osteoporotic postmenopausal women, subjects with solid tumors, subjects with multiple myeloma), and treatment with aromatase inhibitors had no considerable effect on the denosumab pharmacokinetic parameters. Consequently, dose adjustments on the basis of these covariates are not warranted.

7. The variability in the pharmacokinetics parameters of denosumab appeared to be moderate to high.

Reference ID: 3168397

Reviewer's comments:
Sponsor's population PK analysis is generally adequate and the significant covariates identified by the sponsor were reproduced (see Appendix 2).
The sponsor's pharmacokinetic based argument on the appropriateness of fixed dose (60mg 6QM) was evaluated through the effect of body weight on new vertebral fractures and BMD levels (Key question 1.1.1).

The key findings from sponsor's population PD analysis (*study report: 110184*) in healthy subjects, cancer patients, and postmenopausal women with osteopenia or osteoporosis are summarized below:

- A complex pharmacodynamic model was developed that describes the time course of serum CTX and BMD changes for denosumab dose-response and, in particular, for 60 mg Q6M dosing. The model describes the rapid, dose-dependent, and reversible effects of denosumab on serum CTX. A maximum reduction in serum CTX of 91% was estimated, and reductions (>55%) were sustained throughout the dosing interval. The model also described the association between these reductions in serum CTX and the continuous increases in lumbar spine BMD.

- Based on the covariate analysis, body weight, age, race, disease status (healthy subjects, postmenopausal women with osteopenia or osteoporosis, or subjects with cancer), or treatment with aromatase inhibitors do not impact the pharmacodynamic effects of denosumab. Thus, dose adjustments are not warranted based on these covariates.

- The variability in the pharmacodynamic parameters of denosumab appeared to be moderate to high.

- The means and distributions for changes in sCTX and BMD profiles following SC administration of 1 mg/kg versus 60 mg every 6 months for 4 years are highly comparable as demonstrated through simulation analysis.

Reviewer's comments:
Sponsor's population PD analysis is generally adequate and the results were reproduced by the reviewer (see Appendix 3).

Reference ID: 3168397

APPENDIX 1: SUMMARY OF SUBJECTS WITH NEW VERBRAL FRACTURE IN STUDY 200302016.

TRTP	WT Range	New Fracture Count	Number of Subjects	Min	Max	Median	Percent
60 MG Q6M	33kg<WT<55kg	15	752	37	55	52	2.0
	55kg<WT<60kg	21	717	55	60	58	2.93
	61kg<WT<65kg	16	748	61	65	63	2.14
	65kg<WT<72kg	22	770	65	72	69	2.86
	72kg<WT<113kg	13	744	72	113	77	1.75
PLACEBO	33kg<WT<55kg	57	790	33	55	51	7.22
	55kg<WT<60kg	59	706	55	60	58	8.36
	61kg<WT<65kg	51	758	61	65	63	6.73
	65kg<WT<72kg	48	756	65	72	69	6.35
	72kg<WT<113kg	50	707	72	112	78	7.07

APPENDIX 2: REVIEWER'S RESULTS FOR THE POPULATION PHARMACOKINETIC ANALYSIS

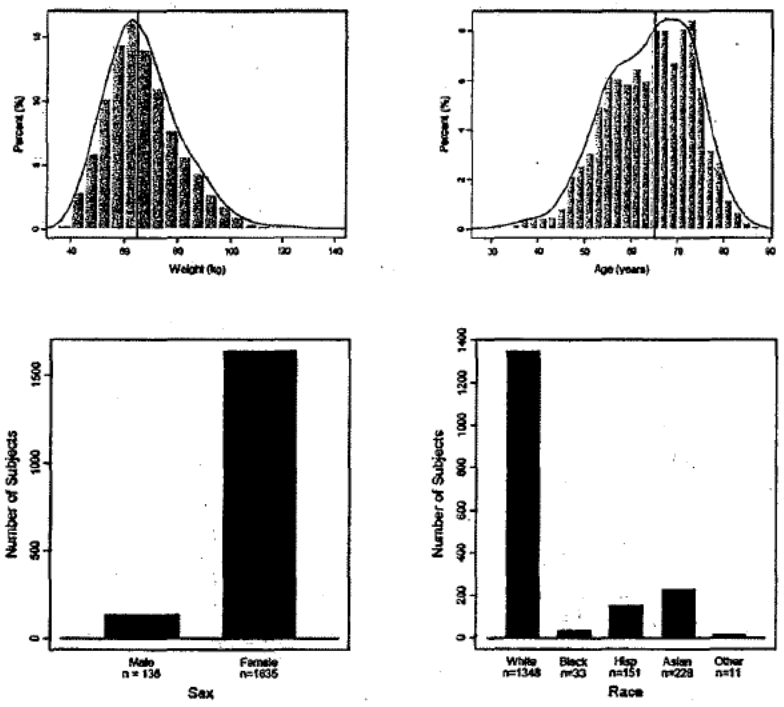
Parameters	Units	Typical Value (RSE%)	Between Subject Variability (RSE)%
Linear Clearance (CL) - Solid Tumor factor - Black factor - Hispanic factor	mL/h	3.01 (2.08) 2.1 (1.66) 1.49 (1.74) 1.54 (0.81)	40.1 (34.7)
Central Volume (Vc)	mL	2520 (2.86)	50.5 (5.45)
Intercompartmental Clearance (Q)	mL/h	12.5 (5.32)	—
Peripheral Volume (V2)	mL	1260 (3.43)	—
Maximal Velocity (Vmax)	µg/h	3.29 (2.41)	50.5 (6.63)
Michaelis-Menten Rate Constant (Km)	ng/mL	239 (2.75)	—
- Exponent Body Weight Scaling	—	-0.771 (6.03)	—
Absorption Rate (Ka)	/h	0.00623 (1.77)	42.7 (6.10)
- Exponent Body Weight Scaling	—	0.242 (16.5)	—
Bioavailability (F)	%	59.2 (1.91)	—
Residual Variability:			
- Cut-off High vs Low Cp	ng/mL	341 (1.53)	—
- High Cp	%	26.3 (0.710)	
- Low Cp	%	80.7 (1.16)	

Reference ID: 3168397

APPENDIX 3: REVIEWER'S RESULTS FOR THE POPULATION PHARMACODYNAMIC ANALYSIS

Parameter (unit)	Typical Value (RSE)	Between Subject Variability, % (RSE)
k_{DE} (1/month)	0.364 (2.99)	14.2 (14.3)
IR_{50} (mg/yr)	1.33 (11.8)	61.1 (11.5)
I_{Max}	0.917 (0.149)	72.5 (3.60)
λ	1.68 (3.53)	NA
γ	0.0573 (1.34)	29.4 (12.2)
τ	3.95 (9.72)	238 (18.1)
k_{out}(sCTX) (1/day)	0.341 (0.63)	20.3 (23.2)
k_{out}(BMD) (1/year)	0.307 (1.57)	41.0 (20.5)
sCTX at baseline* (ng/mL)	0.419 (3.99)	68.7 (25.6)
Residual variability (%):		
sCTX	33.0 (1.11)	
BMD	2.26 (2.07)	

APPENDIX 4: DISTRIBUTION OF SUBJECT DEMOGRAPHICS



Reference ID: 3168397

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	BLA 125332, 125333	Brand Name	Prolia
OCP Division (I, II, III, IV, V)	V	Generic Name	Denosumab
Medical Division	DBOP	Drug Class	Monoclonal antibody
OCP Reviewer	Sarah J. Schrieber	Indication(s)	Bone loss prevention
OCP Team Leader	Hong Zhao	Dosage Form	60mg/ml solution
Pharmacometrics Reviewer	n/a	Dosing Regimen	60 mg q 6 months
Date of Submission	12/19/08	Route of Administration	SC
Estimated Due Date of OCP Review	8/30/09	Sponsor	Amgen
Medical Division Due Date	8/30/09	Priority Classification	Standard
PDUFA Due Date	10/19/09		

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:	n/a			
Isozyme characterization:	n/a			
Blood/plasma ratio:	n/a			
Plasma protein binding:	n/a			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	n/a			
multiple dose:	n/a			
Patients-				
single dose:	x	1	1	Study # 20010123
multiple dose:	x	5	5	Study # 20040176, 20040135, 20040138, 2004113, 2004114
Dose proportionality -				
fasting / non-fasting single dose:	n/a			
fasting / non-fasting multiple dose:	n/a			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	n/a			
In-vivo effects of primary drug:	n/a			
In-vitro:	n/a			
Subpopulation studies -				
ethnicity:	n/a			
gender:	n/a			
pediatrics:	n/a			Requested waiver

Reference ID: 3168397

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

geriatrics:	n/a			
renal impairment:	n/a			
hepatic impairment:	n/a			
PD -				
Phase 2:	n/a			
Phase 3:	n/a			
PK/PD -				
Phase 1 and/or 2, proof of concept:	n/a			
Phase 3 clinical trial:	n/a			
Population Analyses -				
Data rich:	n/a			
Data sparse:	n/a			
II. Biopharmaceutics				
Absolute bioavailability	n/a			
Relative bioavailability -				
solution as reference:	n/a			
alternate formulation as reference:	n/a			
Bioequivalence studies -				
traditional design; single / multi dose:	n/a			
replicate design; single / multi dose:	n/a			
Food-drug interaction studies	n/a			
Bio-waiver request based on BCS	n/a			
BCS class	n/a			
Dissolution study to evaluate alcohol induced dose-dumping	n/a			
III. Other CPB Studies				
Genotype/phenotype studies	n/a			
Chronopharmacokinetics	n/a			
Pediatric development plan	n/a			Requested waiver
Literature References	x			
Total Number of Studies		6	6	

Other Comments	
	Comments
QBR (key issues to be considered)	What are the PK parameter values in the proposed indicated population? What is the immunogenicity rate and does it impact the PK? Is there an exposure-response relationship? Do intrinsic or extrinsic factors impact the PK in the patient population?
Other comments or information not included above	n/a

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 BLA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the	x			

Reference ID: 3168397

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	BLA legible so that a substantive review can begin?				
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an BLA (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			popPK study under BLA 125320, 125331
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Waiver submitted
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Waiver submitted
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.

- n/a

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

- None have been identified at this time.
- See DRUP BLA 125320, 125331 OCP filing form for additional information.

Frank Schmidt — 1/29/09

Reviewing Clinical Pharmacologist — Date

Hong Zhao — 1/29/09

Team Leader/Supervisor — Date

Reference ID: 3168397

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology
Biologics License Application Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	125-320, 125-331	Brand Name	Prolia
OCP Division	DCP3	Generic Name	Denosumab
Medical Division	DRUP	Drug Class	Monoclonal antibody
OCP Reviewer	Chongwoo Yu, Ph.D	Indication(s)	Treatment (BLA 125-320) and prevention (BLA 125-331) of osteoporosis in postmenopausal women
OCP Team Leader	Myong Jin Kim, Pharm. D.	Dosage Form	Injection
Secondary Reviewer	Ike Lee, Ph.D.	Dosing Regimen	60 mg/ml every 6 months
Date of Submission	December 19, 2009	Route of Administration	subcutaneous
Estimated Due Date of OCP Review	August 19, 2009	Sponsor	Amgen
PDUFA Due Date	October 19, 2009	Priority Classification	Standard
Division Due Date	September 26, 2009		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		20030148, 20030164, 20030180
multiple dose:	x	1		20010124
Patients-				
single dose:	x	1		20010123
multiple dose:	x	1		20040176
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:				Pop-PK
gender:				Pop-PK
pediatrics:	NA			Pediatric waiver request
geriatrics:				Pop-PK
renal impairment:		1		20040245
hepatic impairment:	NA			

Reference ID: 3168397

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

PD:				
Phase 1:		1		20050241
Phase 2:		5		20050172, 20040144, 20040113, 20040114, 20050134
Phase 3:		11		20030216, 20040132, 20050141, 20050179, 20050234, 20050233, 20060232, 20060289, 20040135, 20040138, 20050209
PK/PD:				
Phase 1 and/or 2, proof of concept:		1		20010223
Phase 3 clinical trial:				
Population Analyses -				
PK:	x	1		109957
PD:	X	1		110184
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		4		20050146, 20050227, 20060286, 20060446
replicate design; single / multi dose:				
Food-drug interaction studies:	NA			
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile		1		20060237
Literature References				
Total Number of Studies		32		

Other comments

	Comments
QBR questions (key issues to be considered)	1. Acceptability of comparability studies. 2. Sufficient drug interaction information? 3. Population PK analyses. 4. Acceptability of Immunogenicity. 5. Sufficient bioanalytical assay validation information?
Other comments or information not included above	1. Need to request a consult to the OCP Phamacometrics (PM) group. 2. Need to request a consult to the Office of Biotechnology Products (OBP) for review of antibody assays 3. Need to request a consult to DSI for inspection of sites where the comparability studies were conducted.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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		See filing memo below
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		x		See filing memo below
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate 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	Pediatric waiver submitted
6	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Pediatric waiver submitted
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				

Reference ID: 3168397

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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.

- *N/A*

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

- *We acknowledge the submission of the comparability studies in your submission. We notice the following and these will be review issues:*
  - *There is no direct bridging between the ATO vial and the ACO PFS formulation.*
  - *Pharmacodynamics comparability in target population needs to be assessed.*
- *We remind you that bioanalytical method validation reports for all analytes (i.e., biomarkers) assessed to support this application need to be submitted.*
- *We recommend that you assess denosumab's effect on CYP activities in vitro.*

Chongwoo Yu — 1/28/2009

Reviewing Clinical Pharmacologist — Date

Hae Young Ahn — 1/28/2009

Team Leader/Supervisor — Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo

Clinical Pharmacology Review

BLA: 125-320 and 125-331
Compound: Prolia (60 mg/ml Denosumab)
Sponsor: Amgen

Date: 1/26/2009
Reviewer: Chongwoo Yu, Ph.D.

Introduction:
Denosumab is a fully human IgG2 monoclonal antibody that inhibits receptor activator of nuclear factor kappa B (RANK) ligand, for the treatment (BLA 125-320) and prevention (BLA 125-331) of osteoporosis in postmenopausal women (PMO) and for the treatment and prevention of bone loss in patients undergoing hormone ablation therapy (HALT) for breast (BLA 125-332) or prostate (BLA 125-333) cancer. The Division of Reproductive and Urologic Products (DRUP) will be responsible for reviewing BLAs 125-320 and 125-331. Denosumab is considered to be a new molecular entity (NME). The proposed proprietary name for denosumab in these indications is Prolia™.

Denosumab drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in either a 60 mg/ml prefilled syringe (PFS) or 60 mg/ml vial presentation with a 1.0 ml deliverable volume to support dosing of 60 mg every 6 months (Q6M).

This marketing application includes 30 clinical studies in normal volunteers and patients with osteoporosis (approximately 10,500 subjects), bone loss associated with hormone ablation therapy (approximately 1700 subjects), rheumatoid arthritis, and advanced cancer performed from June 2001 to September 2008. Twenty-three of the 30 clinical studies supporting this marketing application contributed data on the safety, tolerability, and pharmacokinetic (PK) profiles for denosumab. Eight of these 23 studies were primarily designed as clinical pharmacology studies to assess healthy volunteer pharmacokinetics and initial tolerability (Studies 20010124, 20030148, 20030164, and 20030180), patient PK and initial tolerability (Studies 20010123 and 20040176), intrinsic factor PK (Study 20040245), or extrinsic factor PK (Study 20050241). The other 15 studies were primarily designed to address other objectives (i.e., "Biopharmaceutic" and "Efficacy and Safety" studies), but provide supportive PK and pharmacodynamic (PD) data. Of these 15 studies, (b) (4) The PMO clinical development program is supported by 2 pivotal phase 3 studies (Studies 20030216 and 20040132). Study 20030216 was a 3-year randomized, double-blind, placebo controlled study in postmenopausal women with osteoporosis to determine whether denosumab treatment can reduce the incidence of new vertebral (primary endpoint), and nonvertebral and hip fractures (secondary endpoints) as compared with control. Study 20040132 is a randomized, double-blind, placebo-controlled study in postmenopausal women with low bone mass to determine whether denosumab treatment can prevent lumbar spine bone loss.

The Sponsor believes that the criteria for priority review are met for denosumab for the indications listed above and justifications were submitted in this marketing application.

Bioavailability and ADME (Absorption, Distribution, Metabolism, and Excretion):
Safety, tolerability, PK, PD, and exposure-response properties of denosumab were characterized in healthy volunteers and in patients with low BMD or osteoporosis or bone loss associated with HALT. The dose-exposure-response relationship for denosumab has also been studied. Data obtained in these characterizations were instrumental in the selection of the dose regimens for phase 2 and 3 studies, the evaluation of the effect of covariates (sex, body weight/body mass index (BMI), race, and age) on the PK and PD of denosumab, and exploring the relationship between serum concentrations of denosumab and calcium. Oral absorption studies have not been conducted because denosumab is administered subcutaneously. Bioavailability, plasma protein binding, and other human biomaterials studies were not considered appropriate by the Sponsor and have therefore not been conducted.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Drug-drug interactions:

Because denosumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms (e.g., by cytochrome P450 (CYP) enzymes), drug-drug interaction studies (e.g., with CYP inhibitors) were not considered appropriate by the Sponsor and have therefore not been conducted. However, studies including transition from a bisphosphonate to denosumab or studies including concomitant hormone ablation therapies allowed an indirect evaluation of drug interactions when compared to results from other studies.

Special population:

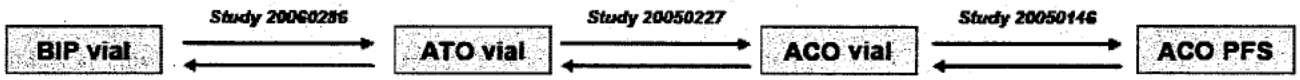
A study evaluating the effect of renal impairment on the PK of denosumab have been conducted and data is available for review. Because denosumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms (e.g., by CYP enzymes), hepatic impairment were not considered appropriate by the Sponsor and have therefore not been conducted.

Population PK/PD Analyses:

Population PK and PD analyses in healthy subjects, postmenopausal women with low BMD or osteoporosis, and subjects with cancer were performed using NONMEM. Population PK and PD reports are submitted for review.

Comparability studies for drug substance and drug product presentation

Data from biopharmaceutics studies that were conducted to demonstrate clinical comparability between denosumab drug substance produced for the pivotal phase 3 studies and that intended for commercial use and clinical comparability between the drug product presentations proposed for commercial use are submitted in this marketing application. Drug substance for the pivotal phase 3 studies was manufactured at Amgen Thousand Oaks (denosumab ATO). In preparation for commercialization of denosumab, manufacturing process was subsequently scaled-up and transferred from ATO to both Amgen Colorado (ACO) and Boehringer Ingelheim Pharma GmbH & Co Kg (BI Pharma), with minor changes to improve process robustness and ensure facility fit. Drug product preparations proposed for commercial use in this marketing application are the 60 mg/ml vial and 60 mg/ml PFS. It is noted that PK and PD profiles were only assessed in healthy volunteers.



Bioanalytical Method validation:

Serum denosumab and serum type 1 C-telopeptide (CTX1) concentrations in study samples were determined with an enzyme-linked immunosorbent assay (ELISA) following validated analytical procedures. For immunogenicity testing, sensitive and specific assays were developed and validated for detecting antibodies in nonclinical and clinical studies. Samples were screened for binding antibodies using an electrochemiluminescent (ECL) bridging immunoassay. If confirmed positive or reactive samples were then characterized for neutralizing antibodies using a cell-based chemiluminescent mRNA expression assay. Bioanalytical method validation reports are submitted for review.

Food Effect:

The effect of food on denosumab PK has not been studied.

Genomics Information:

This submission contains limited genomics information. The potency of denosumab's drug substance has been assessed using 3 different assays: homogenous time resolved fluorescence (HTRF), Reporter Gene, and tartrate-resistant acid phosphatase (TRAP) assays

Immunogenicity:

Immunogenicity testing (using validated assays) has been performed in all denosumab clinical studies. More than 13,000 subjects have been tested for antidenosumab antibodies in studies described in this marketing application, including > 8000 subjects who have received at least 1 dose of denosumab.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for BLAs 125-320 AND 125-331 is fileable with potential review issues.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: **August 24, 2011**

To: Melanie Pierce, Senior Regulatory Health Project Manager
Division of Biologic Oncology Products (DBOP)
Office of Oncology Drug Products
Center for Drug Evaluation and Research

From: Karen Munoz, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Shefali Doshi, DTC Group Leader, DDMAC
Kathleen Klemm, Regulatory Review Officer, DDMAC
Carole Broadnax, Regulatory Review Officer, DDMAC
Andrew Haffer, Professional Group Leader, DDMAC
Olga Salis, Regulatory Health Project Manager, DDMAC
Michael Wade, Regulatory Health Project Manager, DDMAC
Becki Vogt, Regulatory Health Project Manager, DDMAC

Subject: **Prolia (denosumab) Injection, for subcutaneous use**
BLA 125320/5 and 6
DDMAC Comments on draft product labeling - Medication Guide

In response to DBOP's Request for Consultation dated April 28, 2011, DDMAC has reviewed the proposed Medication Guide for Prolia. Please note that our comments are based on the substantially complete version of the proposed Medication Guide, titled, "sp draft-med-guide-text (2).doc" sent via email to DDMAC by Melanie Pierce on August 17, 2011.

Supplement 5 provides for a new indication – treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer. Supplement 6 provides for a new indication – treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer.

The comments on the attachment that follows are only on the Medication Guide (Patient Labeling) for Prolia. Professional review comments on the PI were sent previously under separate cover on August 18, 2011 from Carole C. Broadnax, R.Ph., Pharm.D., Regulatory Review Officer.

Thank you for the opportunity to comment on these proposed materials.
If you have any questions, please contact LCDR Karen Munoz at (301) 796-3274 or karen.munoz@fda.hhs.gov.

4 Page(s) have been Withheld in Full as Draft Labeling immediately following this page

Reference ID: 3168397

Division of Drug Marketing, Advertising, and Communications

Internal Consult

****Pre-decisional Agency Information****

To: Melanie Pierce, Regulatory Project Manager
Division of Biologic Oncology Products (DBOP)
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications (DDMAC)

C Broadnax 8/18/11

Date: August 18, 2011

Re: **Prolia (denosumab) Injection, for subcutaneous use**
BLA 125320/5 and 6
Comments on draft product labeling

In response to DBOP's Request for Consultation dated April 28, 2011, DDMAC has reviewed the proposed professional package insert (PI) for Prolia. Please note that our comments are based on the substantially complete version of the proposed PI sent via email to DDMAC from DBOP on August 10, 2011.

Supplement 5 provides for a new indication – treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer

Supplement 6 provides for a new indication – treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer

DDMAC offers the following comments in the attached proposed PI document. Please note that in the attached document we hid DBOP's and Amgen's comments, deletions, and formatting changes so that DDMAC's comments are easier to read.

DDMAC appreciates the opportunity to provide comments on this material. If you have any questions, please contact:

- Carole Broadnax (Professional directed materials), 301-796-0575, or carole.broadnax@fda.hhs.gov

15 Page(s) have been Withheld in Full as Draft Labeling immediately following this page

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

PATIENT LABELING REVIEW

Date:	August 16, 2011
To:	Patricia Keegan, MD, Director **Division of Biologic Oncology Products (DBOP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN 8/16/11 Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management (DRISK)**
	Barbara Fuller, RN, MSN, CWOCN 8/16/2011 Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management (DRISK)**
From:	Steve L. Morin, RN, BSN, OCN 8/16/11 Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name (established name):	Prolia (denosumab) Injection
Application Type/Number:	BLA 125320/5 and BLA 125320/6
Applicant:	Amgen
OSE RCM #:	2011-1386

1 INTRODUCTION

Prolia (denosumab) REMS consisting of a Medication Guide, Communication Plan, and Timetable for Submission of Assessments was initially approved June 1, 2010 by the Division of Reproductive and Urologic Products (DRUP). November 18, 2010 denosumab was approved by the Division of Biologic Oncology Products (DBOP) without a REMS. There is a Prior Approval Supplement (PAS) open in DRUP that provides for the addition of information advising patients of the availability of denosumab under two distinct proprietary names, "Xgeva" and "Prolia".

This review is written in response to a request by the Division of Biologic Oncology Products (DBOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for (denosumab) Injection.

On March 18, 2011 Amgen submitted a Complete Response to address deficiencies listed in the FDA Complete Response (CR) action letter dated October 19, 2009 for Biologic License Application (BLA), 125320/5 and 125360/6. Efficacy supplement BLA 125320/5 proposes the new indication for the treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer to the Prescribing Informaton. Efficacy supplement BLA 125320/6 proposes to add the new indication for the treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer to the Prescribing Information.

DRISK's review of the proposed denosumab REMS was sent to DBOP under separate cover August 1, 2011.

2 MATERIAL REVIEWED

- Draft Prolia (denosumab) Injection Medication Guide (MG) received on March 18, 2011 and revised by the review division throughout the review cycle and sent to DRISK on August 3, 2011.
- Draft Prolia (denosumab) Injection prescribing information (PI) received March 18, 2011 revised by the Review Division throughout the current review cycle and received by DRISK on July 29, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss.* The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

12 Page(s) have been Withheld in Full as Draft Labeling immediately following this page

CC List

DBOP
Patricia Keegan
Jeff Summers
Melanie Pierce

DRUP
Theresa Kehoe

OSE
Claudia Karwoski
Mary Dempsey
LaShawn Griffiths
Barbra Fuller
Amarilys Vega
Cynthis LaCivita,
Sue Kang

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
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Maternal Health Team Memorandum

Date: October 9, 2009 **Date Consulted:** September 23, 2009

From: Jeanine Best, MSN, RN, PNP J. Howard for Jeanine Best 10/14/09
Clinical Analyst, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff KBFeibus 10/14/09

Lisa Mathis, MD LLM 10/14/09
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Reproductive and Urologic Products (DRUP)

Drug: Denosumab for Subcutaneous Injection, BLA 125320

Subject: Pregnancy Registry Protocol, dated September 8, 2009

Consult Request
The Division of Reproductive and Urologic Products (DRUP) consulted the Maternal Health Team to review the draft denosumab pregnancy registry protocol submitted to BLA 125320 on September 8, 2009.

Background
AMGEN submitted an original BLA (125320) on December 19, 2008, for Denosumab for Subcutaneous Injection, for the treatment and prevention of osteoporosis in postmenopausal women and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. The application was administratively split for review purposes into BLA 125320 for the treatment and prevention of osteoporosis in postmenopausal women (Division of Reproductive and Urologic Products – DRUP) and BLA 125333 for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer (Division of Biologic Oncology Products). Amgen submitted a draft pregnancy registry protocol for denosumab on September 8, 2009. DRUP consulted the MHT to review the

draft pregnancy registry protocol. A Complete Response will be issued for densosumab this review cycle, and indications for approval and labeling are not complete at this time.

Additional Background

Denosumab is a human monoclonal antibody (IgG2) that inhibits receptor activator of nuclear factor kappa B (RANK) ligand (a TNF-family molecule). RANK ligand (RANKL), also known as osteoprotegerin ligand, is a key regulator (with its receptor RANK) of bone remodeling and essential for the development and activation of osteoclasts. RANKL also regulates T cell/dendritic cell survival and lymph node organogenesis and is involved with the formation of lactating mammary glands in pregnancy.[1] Published reports[2,3] of reproductive and developmental toxicity studies in pregnant and neonatal mice lacking the RANKL signaling pathway resulted in fetal lymph node agenesis (prenatal exposure) and impaired dentition and bone growth (neonatal exposure). Pregnant mice showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum. Reproductive and developmental toxicity studies were performed in cynomolgus monkeys; however, maternal dosing was only done during the period of organogenesis, so the effects of denosumab on later fetal development were not assessed. In addition, lymph nodes were not examined in the fetal monkeys, even though previous mouse studies demonstrated that signaling via RANKL was necessary for lymph node development. Neither perinatal nor postnatal studies were performed in cynomolgus monkeys.

Discussion

MHT is not able to complete a review of the draft denosumab pregnancy registry protocol until indications to be approved are known and labeling is near complete; however, we are able to provide preliminary comments and recommendations. A complete review of the pregnancy registry protocol with additional comments and recommendations will be done when a Complete Response is submitted for denosumab.

(b) (4)

(b) (4). Ordinarily, MHT would not have requested pregnancy registry at this time for denosumab because the current proposed denosumab indications do not include females of childbearing potential and complete preclinical embryo-fetal toxicity studies have not been done to support use in females of childbearing potential. MHT acknowledges AMGEN's intent to capture potential pregnancy exposures that may result from off-label use in the clinical setting.

---

[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

(b) (4)

Recommendations

Please convey the following denosumab pregnancy registry protocol deficiencies to the Sponsor:

1. (b) (4)
2. (b) (4)
3. Resubmit your revised draft denosumab pregnancy registry protocol at the time of your denosumab Complete Response submission.

Please re-consult the revised draft denosumab pregnancy registry protocol to the MHT when it is resubmitted with the Complete Response submission.

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: September 17, 2011

Applicant Name: Amgen, Incorporated
U.S. License #: 1080
STN(s):125320/6
Product(s) Prolia (denosumab)
Short summary of application: Class II Resubmission; Efficacy Supplement

125320/5: treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer.

FACILITY INFORMATION

Manufacturing Location:
Firm Name: Amgen Inc. (ACO)
Address: 5550 Airport Boulevard
Boulder, CO 80301
(LakeCentre facility)

FEI: 1724812

Short summary of manufacturing activities performed:
Working cell bank storage

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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: 3168397

Raw material storage, testing and release
Drug substance manufacture
Drug substance in-process and release testing
Drug substance stability testing
Drug substance storage

Inspected by DEN-DO from 8/23/10-9/3/10 and classified VAI. This was a GMP inspection that found the CBI profile updated and 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 from 8/23/10-9/3/10 and classified VAI. This was a GMP inspection that found the CBI profile updated and 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 4/1/2008 and revealed that the firm has no planned commercial production. The firm continues GMP activities such as: warehousing and distribution of all Amgen products, complaint intake and resolution for all Amgen products, stability testing for various drug substances and drug products, cell bank storage, sterility testing on commercial products, annual product review evaluation, and final release of products manufactured under contract. This site is acceptable for the purposes of this suppelement

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 from 4/18/11-4/29/11 and classified VAI. This GMP inspection found the BTP and TRP profiles acceptable.

Manufacturing Location:
Firm Name: Boehringer Ingelheim Pharma
GmbH & Co. Kg
Address: Birkendorfer Strasse 65
88397 Biberach an der Riss
Germany

FEI: 3002806518

Short summary of manufacturing activities performed:
Working cell bank storage
Raw material storage, testing and release
Drug substance manufacture
Drug substance in-process and release testing
Drug substance storage

Inspected by IOG from 5/15/10-5/26/10 and classified VAI. This GMP inspection found the TRP profile updated and acceptable.

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: October 19, 2009

Applicant Name: Amgen, Incorporated
U.S. License #: 1080
STN(s): 125320/0, 125331/0, 125332/0, 125333/0
Product(s): Prolia (denosumab)
Short summary of application: New BLA

FACILITY INFORMATION

Manufacturing Location: Newbury Park, CA
Firm Name: Amgen, Inc.
Address: One Amgen Center Drive
FEI: 2026154/055513
Short summary of manufacturing activities performed: Master cell bank and working cell bank storage; working cell bank production; raw materials testing, storage, and release Drug substance storage

Inspected by LOS-DO, April 7-11, 2008 and classified NAI. The inspection covered the manufacturing and control laboratory processes and focused on the Quality and Laboratory Systems. The CBI and CTL profiles were covered and are considered acceptable.

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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."

Manufacturing Location: Germany
Firm Name: Boehringer Ingleheim Pharma
Address: Birkendorfer Strasse 65
88397 Biberach an der Riss, Germany
FEI: 3002806518
Short summary of manufacturing activities performed: Working cell bank storage Raw material storage, testing and release Drug substance manufacture Drug substance in-process and release testing Drug substance storage

Inspected by CDER DMPQ, May 11-19, 2009 and initially classified VAI. The inspection was comprehensive, systems-based, and performed as a pre-approval inspection for denosumab. Although a final classification for this site has not been made, we consider this site acceptable for the purposes of these applications.

Manufacturing Location: Boulder, CO
Firm Name: Amgen Inc.
Address: 5550 Airport Boulevard, Boulder, CO
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 and release testing Drug substance stability testing Drug substance storage

Inspected by CDER-DMPQ, June 8-12, 2009 as a comprehensive, systems-based pre-approval inspection for denosumab and classified NAI. The CBI profile was updated and is considered acceptable.

Manufacturing Location: Longmont, CO
Firm Name: Amgen Inc.
Address: 400 Nelson Road, Longmont, CO
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 CDER-DMPQ, January 31, 2009 as a control testing laboratory and classified NAI. Raw material, drug substance, and drug product testing were covered and are considered acceptable.

Manufacturing Location: Juncos, Puerto Rico
Firm Name: Amgen Manufacturing, Limited
Address: State Road 31, Kilometer 24.6
Juncos, Puerto Rico
FEI: 1000110364
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 release testing Drug product stability testing Packaging/Labeling Drug product storage

Inspected by SJN-DO, July 27-September 11, 2009 and initially classified OAI due to GMP deficiencies related to Quality Systems failure. Although the compliance status of this site is OAI, this site is considered to be acceptable for the purposes of these applications based on the most recent information provided by the district office.

[redacted]

Manufacturing Location: Amgen Fremont
Firm Name: Amgen (AFR)
Address: 6701 Kaiser Drive
Fremont, CA
FEI: 3005925062
Short summary of manufacturing activities performed: Container closure testing for vials for stability

Inspected by SAN-DO, September 3-10, 2008 and classified NAI. This was a comprehensive, biennial cGMP inspection covering all six systems. The TRP profile was updated and is considered acceptable.

[redacted] (b) (4)



Manufacturing Location: Newbury Park, CA
Firm Name: Amgen Inc
Address: 1840 De Haviland Drive
Newbury Park, CA
FEI: 2026154
Short summary of manufacturing activities performed: Drug product storage and distribution

Inspected by LOS-DO, April 7-11, 2008 and classified NAI. The inspection covered the manufacturing and control laboratory processes and focused on the Quality and Laboratory Systems. The CBI and CTL profiles were covered and are considered acceptable.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 6, 2009

TO: Melanie Pierce, Regulatory Project Manager
Suzanne Demko, Senior Clinical Analyst
Division of Biologic Oncology Products

FROM: John Lee, MD, Medical Officer
Division of Scientific Investigations

THROUGH: Jean M. Mulinde, MD
Acting Team Leader, Good Clinical Practice Branch II
Division of Scientific Investigations

10/7/09

SUBJECT: Evaluation of Clinical Inspections

SUBMISSION: BLA 125332

APPLICANT: Amgen, Inc.

DRUG: Prolia (denosumab)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer

CONSULTATION REQUEST DATE: January 23, 2009

DIVISION ACTION GOAL DATE: October 19, 2009

PDUFA DATE: October 19, 2009

I. BACKGROUND

The so-called RANKL (receptor activator of nuclear factor-k-beta ligand), a member of the tumor necrosis factor family of proteins, is important in formation and activation of osteoclasts. Increased RANKL production in decreased estrogen states (menopause, hormonal ablation) has been known to be associated with increased bone resorption.

Denosumab is a human monoclonal IgG2 anti-RANKL which inhibits osteoclast formation and activation to decrease bone resorption and increase bone mass. Amgen, Inc. has developed denosumab as a therapeutic agent to treat bone loss associated with hormone ablation therapy in patients with breast or prostate cancer. Two international, multicenter, randomized, double-blind, placebo-controlled studies were conducted as pivotal studies to support these treatment indications.

Study 20040135 (pivotal study for BLA 125333) was conducted in women with non-metastatic breast cancer and low bone mass on aromatase inhibitor therapy (AIT). The primary objective was to compare denosumab with placebo in preserving lumbar spine bone mineral density after 12 months of AIT. Subjects were randomized in equal ratio to receive either placebo or denosumab (60 mg by subcutaneous injection every 6 months) for 24 months (total 4 doses) followed by a 24-month safety follow-up period. All subjects were instructed to take daily supplemental calcium and vitamin D.

Under BLA 125332, the sponsor seeks the following clinical indication for Prolia (denosumab): treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer.

II. CLINICAL INSPECTIONS

Two clinical sites were selected for inspection based on high numbers of responders and/or protocol violations relative to other clinical sites in the study. Safety results (numbers of deaths and serious adverse events), similar for both study arms, did not play a role in site selection.

The efficacy data could not be audited at clinical sites. Dual X-ray absorptiometry (DXA) scans obtained at clinical sites were sent to (b) (4) a contract research organization (CRO), where efficacy data were generated electronically from the scans received from the clinical sites. The electronic efficacy data were then uploaded to a central shared server, which Amgen accessed to compile the final efficacy dataset. In addition to the clinical sites, the sponsor (Amgen) and the CRO (b) (4) sites were also inspected to evaluate the database management systems and associated procedures used to generate the efficacy data.

Inspection Results

No serious deficiencies were identified at the 4 inspections. The overall inspectional outcome is shown in **Table 1**, followed by a discussion of each inspection.

Table 1: Inspectional Outcome

	Clinical Investigator and Site	Site No. Subjects	Inspection Dates	Classification	
				Field	CDER
1	Nicholas Iannotti, MD Hem/Onc Associates of the Treasure Coast 1871 SE Tiffany Avenue, Suite 100 Port St. Lucie, FL 34952	Site 159 19 subjects	April 15-21 2009	NAI	NAI
2	Shaker Dakhil, MD Cancer Center of Kansas 818 North Emporia St, Suite 403 Wichita, KS 67214	Site 183 32 subjects	Jul 20-22 2009	VAI	VAI
3	Amgen, Inc. One Amgen Center Drive Thousand Oaks, CA 91320	Sponsor	Apr 20-May 1 2009	NAI	NAI
4	(b) (4)	Contract Research Organization	(b) (4)	Pending Preliminary classification of VAI	Pending Preliminary classification of VAI

NAI: No action indicated (no deviations from regulations)
VAI: Voluntary action indicated (no significant deviations from regulations)
OAI: Official action indicated (significant deviations from regulations)

Pending: EIR has not been received from the field and post-inspectional correspondence has not been issued.

1. **Nicholas Iannotti, MD (Site 159)**

   Hem/Onc Associates of the Treasure Coast
   1871 SE Tiffany Avenue, Suite 100
   Port St. Lucie, FL 34952

   a. What was inspected:

   - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, and adherence to protocol and applicable regulations
   - Data verification: adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation

- Subjects: 39 subjects were screened, 19 enrolled, and 11 completed the study. Subject records were reviewed for all enrolled subjects, including complete review for the 11 subjects completing the study.

b. General observations and commentary:

All audited study data were verified to be accurate. No unreported adverse events were noted. Study monitoring oversight appeared to be adequate. No significant deficiencies were observed and a Form FDA 483 was not issued.

c. Assessment of data integrity:

The data from this study site appear to be reliable.

2. **Shaker Dakhil, MD (Site 183)**

Cancer Center of Kansas
818 North Emporia St, Suite 403
Wichita, KS 67214

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, and adherence to protocol and applicable regulations
- Data verification: adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
- Subjects: 42 subjects were screened to enroll 32 subjects into the study. Fourteen subjects completed the study. Subject case records were reviewed for all enrolled subjects, including complete records review for 4 subjects.

b. General observations and commentary:

All audited study data were verified to be accurate. No unreported adverse events were noted. IRB oversight and study monitoring appeared to be adequate. A Form FDA 483 was issued for the following GCP deficiencies:

- The study drug was stored at temperatures ranging from -1° C to 10° C, in deviation of the study protocol which specified a storage temperature range of 2° C to 8° C. Within a period of about 20 months (between January 28, 2005 and October 9, 2006), the study drug was exposed to temperatures outside the protocol-specified range on 19 days, which included 6 days in March 2006 (up to 10° C) and 4 days in July 2006 (up to 9° C).
- Subject (b) (6) was enrolled in another clinical study about Exemestane, an approved drug in the United States and being investigated for a new clinical indication. Despite being enrolled in another clinical study, the subject was enrolled into this study, in deviation of the study protocol which specified enrollment in another clinical study as a subject exclusion criterion.
- In Subject (b) (6), a subject with a history of hyperthyroidism, a thyroid stimulating hormone (TSH) level was not determined at study enrollment, in deviation of the study protocol which specified the determination of the TSH level (between Day -28 and Day 1) in subjects with a history of hyperthyroidism to confirm adequate treatment and euthyroid state.
- Study records did not include documentation of adequate staff training towards assuring study conduct according to the investigational plan.

c. Assessment of data integrity:

The product efficacy and safety implications of small excursions in the storage temperature below or above the protocol-specified range was discussed with the review division previously in the context of the inspectional findings at Site 129 (Feldman, Study 20040138, BLA 125333). Small temperature excursions were not considered to importantly affect product stability, efficacy, or safety, provided that the product is not exposed to repeated freezing and thawing. As a protein solution, the product was not likely to freeze at the low temperatures observed at this inspection. Further, freezing is expected to be associated with decreased efficacy, in which case the sponsor's efficacy claims in the BLA remain valid, and/or increased adverse events (decreased safety), a possible study outcome specifically investigated and not observed at this inspection. Other GCP deficiencies noted at FDA inspection are also not expected to importantly affect overall primary efficacy and safety outcomes of the study. In general, the data from this study site appear reliable.

3. **Amgen, Inc. (Sponsor)**

Kevin Sharer
Chief Executive Officer, Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320

a. What was inspected:

- Scope of inspection: an assessment of the sponsor's responsibilities as transferred to multiple contract research organizations (CROs), and an evaluation of the CROs' performance in adhering to the contractual agreements and established standard operating procedures (SOPs) for the transferred study functions, including efficacy data management by (b) (4) and clinical site monitoring by other CROs.
- Data verification: data obtained from the clinical sites linked with the sponsor inspection (Studies 20040135 and 20040138)

b. General observations and commentary:

No major deficiencies were observed and a Form FDA 483 was not issued. The sponsor's study records revealed no significant deficiencies and indicated adequate monitoring (by CROs) of study conduct at clinical sites. The performance of the CROs appeared to be adequate, including database management by (b) (4) A limited audit of the study data from the four clinical sites linked with the sponsor inspection revealed no inconsistencies among source documents, case report forms, and data listings submitted under the BLA. The regulatory files for the linked clinical sites were consistent with the inspectional findings at those clinical sites.

c. Assessment of data integrity:

The data reported under the BLA appear reliable.

4. (b) (4)

a. What was inspected:

(b) (4)

b. General observations and commentary:

(b) (4)

c. Assessment of data integrity:

Specific evidence of unreliable data system or procedures was not observed. (b) (4) adequately

addressed the citations on the Form FDA 483 (post-inspectional correspondence to FDA, [(b)(4)] and a review of [(b)(4)] inspectional history revealed no significant deficiencies at recent inspections. The efficacy data appear reliable, as managed by [(b)(4)] and reported by the sponsor under BLA 125332.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

A total of 4 inspections were performed to support review of BLA 125332: two clinical sites, the sponsor site, and a CRO site [(b)(4)] The sponsor and CRO inspections were important to evaluating the reliability of the efficacy data.

No significant deficiencies were identified at the 4 inspections. At the two clinical sites, all audited study data were verified to be accurate and no unreported adverse events were noted. The sponsor's oversight of the study appeared to be adequate. At [(b)(4)], documentation to support the validation and/or the robustness of all aspects of efficacy data management was not consistently available. However, specific evidence of unreliable data systems or procedures was not observed, [(b)(4)]c readily and adequately addressed the observed deficiencies, and a review of [(b)(4)] inspectional history revealed no significant deficiencies at recent inspections. The study data, including efficacy data as managed by [(b)(4)] appear reliable in support of the proposed indication under BLA 125332.

Note: The final inspection report for the inspection of [(b)(4)] is pending; upon receipt and review of the final inspection reports, an addendum to this clinical inspection summary will be provided if additional observations of clinical or regulatory significance are discovered.

10/7/09

John Lee, MD
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

Jean M Mulinde MD 10/7/09

Jean M. Mulinde, MD
Acting Team Leader, Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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

Date:	September 24, 2009
To:	Scott Monroe, MD Director, Division of Reproductive and Urologic Products Patricia Keegan, MD Director, Division of Biologic Oncology Products
Through:	Carlos Mena-Grillasca, RPh, Team Leader C Mena 9/24/09 Denise Toyer, PharmD, Deputy Director D.P. Toyer 9/24/09 Carol Holquist, RPh, Director D.P. Toyer for 9/24/09 Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Labeling Review
Drug Name(s):	Prolia (Denosumab) Injection 60 mg/mL
Application Type/Number:	BLA 125320 BLA 125331 BLA 125332 BLA 125333
Applicant:	Amgen
OSE RCM #:	2009-162

Reference ID: 3168397

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APPENDICES 5

Reference ID: 3168397

1 INTRODUCTION

This review is in response to a January 14, 2009 request from the Division of Reproductive and Urologic Products and the Division of Biologic Oncology Products for an evaluation of the container labels, carton and insert labeling of Prolia to identify areas that could lead to medication errors.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis,[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels and carton labeling submitted on December 19, 2008 and June 12, 2009, and insert labeling submitted on May 4, 2009 to identify vulnerabilities that could lead to medication errors.

3 RECOMMENDATION

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling Section 3.1, *Comments to the Division*. Section 3.2 *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Sandra Griffith, OSE Project Manager for DBOP at 301-796-2445 or Maria Waslik, OSE Project Manager for DRUP at 301-796-2084.

3.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. Revise the presentation of the drug name, dosage form and route of administration as the following on the first page:

   Prolia (denosumab)
   Injection
   For Subcutaneous Use

2. Delete trailing zeros (e.g. 1.0 mL under *Description* section) and abbreviations (e.g. SC) throughout the labeling. FDA launched a national campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. The abbreviation "SC" and trailing zeros are specifically listed in the ISMP's List of Error-Prone Abbreviations, Symbols and Dose Designation. As part of this campaign, FDA agreed not to approve such abbreviations in the approved labeling.

3. Under *Dosage and Administration, Preparation and Administration* section, clarify if the product must reach room temperature before administration or it can be administered straight out of refrigeration.

4. Under *How Supplied* section, revise the presentation of strength (i.e. 60 mg) as "60 mg/mL."

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.2 COMMENTS TO THE APPLICANT

A. General Comment for All Labels and Labeling

1. Present the established name so that the active ingredient is in parenthesis and the finished dosage form (e.g. injection) immediately follows the active ingredient as this is the customary presentation of established names.
2. Add the statement "Discard unused portion" immediately following the statement "Single use vial" or "Single use prefilled syringe".

B. Container Label - Syringe

1. If space permits, include the route of administration (i.e. For subcutaneous use) per 21 CFR 200.100(b)(3) to avoid wrong route of administration errors.
2. Relocate the strength so that it immediately follows the established name and dosage form.

C. Carton Labeling – Syringe

1. Remove the line between the drug name and strength so that it does not interfere with the presentation of the drug name, dosage form and strength.
2. Relocate the strength so that it immediately follows the established name and dosage form.
3. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."
4. Per 21 CFR 208.24(d), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient).

C. Syringe Topweb Labeling

1. Relocate the strength so that it immediately follows the established name and dosage form.
2. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."

D. Container Label – Vial

1. If space permits, include the route of administration (i.e. For subcutaneous use) per 21 CFR 200.100(b)(3) to avoid of wrong route of administration errors.
2. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."

E. Carton Labeling – Vial

1. Remove the line between the drug name and strength so that it does not interfere with the presentation of the drug name, dosage form and strength.
2. Revise the strength unit in the green circle (i.e. 60 mg) as "60 mg/mL."
3. Increase the prominence of the route of administration (i.e. For subcutaneous use only) to avoid wrong route of administration errors.
4. Per 21 CFR 208.24(d), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient).

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Maternal Health Team Review

Date: September, 11, 2009 **Date Consulted:** January 22, 2009

From: Jeanine Best, MSN, RN, PNP
Clinical Analyst, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Biological Oncology Products (DBOP)
Division Reproductive and Urologic Products (DRUP)

Drug: Prolia™ (denosumab) for Subcutaneous Injection

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Prolia™ (denosumab) for Subcutaneous Injection labeling, BLAs 125320 and 125333, dated December 19, 2008, and revised by Sponsor September 4, 2009

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of Denosumab labeling.

Reference ID: 3168397

INTRODUCTION

AMGEN submitted an original BLA (125320) on December 19, 2008, for Prolia™ (denosumab) for Subcutaneous Injection, for the treatment and prevention of osteoporosis in postmenopausal women and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer. The application was administratively split for review purposes into BLA 125320 for the treatment and prevention of osteoporosis in postmenopausal women (Division of Reproductive and Urologic Products – DRUP) and BLA 125333 for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer (Division of Biologic Oncology Products).

Densosumab was discussed at an August 13, 2009, Advisory Committee Meeting. Identified safety concerns from clinical trials include serious infections, development of new malignancies, tumor progression with existing malignancies, suppression of bone remodeling, and dermatologic adverse events.[1] Based on these safety concerns the Advisory Committee members recommended approval of densoumab with a Risk Evaluation and Mitigation Strategy (REMS), to ensure the drug benefits outweigh its risks, for treatment of osteoporosis in postmenopausal women and the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate cancer. The Advisory Committee did not recommend approval of denosumab for the prevention of osteoporosis in postmenopausal women or for the treatment and prevention of bone loss in patients undergoing hormone ablation for breast cancer due to the above mentioned safety concerns.

Division of Drug Biologic Products and the Division of Reproductive and Urologic Products consulted MHT to review the pregnancy and Nursing Mothers section of Prolia™ labeling.

BACKGROUND

Denosumab

Denosumab is a human monoclonal antibody (IgG2) that inhibits receptor activator of nuclear factor kappa B (RANK) ligand (a TNF-family molecule). RANK ligand (RANKL), also known as osteoprotegerin ligand, is a key regulator (with its receptor RANK) of bone remodeling and essential for the development and activation of osteoclasts. RANKL also regulates T cell/dendritic cell survival and lymph node organogenesis and is involved with the formation of lactating mammary glands in pregnancy.[2] Published reports[3,4] of reproductive and developmental toxicity studies in pregnant and neonatal mice lacking the RANKL signaling pathway resulted in fetal lymph node agenesis (prenatal exposure), and impaired dentition and bone growth (neonatal exposure). Pregnant mice showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum. Reproductive and developmental toxicity studies were performed in cynomolgus monkeys; however, maternal dosing was only done during the period of organogenesis, so the effects of denosumab on later fetal development were not assessed. In addition, lymph nodes were not examined in the fetal monkeys, even though previous mouse studies demonstrated that signaling via RANKL was necessary for lymph node development. Neither perinatal nor postnatal studies were performed in cynomolgus monkeys. The Pharmacology/Toxicology reviewers from both DRUP and

[1] See FDA Background Document for Meeting of Advisory Committee for Reproductive Health Drugs, July 21, 2009, amended August 3, 2009

[2] Nakashima T, Wada T, Penninger J. RANKL and RANM as novel therapeutic targets for arthritis. Curr Opin in Rheumat, 2003, 15:280-7

[3] 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

[4] Hororweg K, Cupedo T. Development of human lymph nodes and peyer's patches. Sem in Immune, 2008, 20:166-70

Reference ID: 3168397

DBOP determined that the partial reproductive and developmental preclinical studies performed were acceptable for the proposed indicated populations. Complete reproductive and developmental toxicity studies will be required if the denosumab population is expanded to include women of childbearing potential.

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides MHT's suggested revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Prolia™ (denosumab) for Sucuntaeous Injection labeling.

SUMBMITTED LABELING

Sponsors Proposed Pregnancy and Nursing Mothers Labeling (September 4, 2009 version)

(b) (4)



8.3 Nursing Mothers

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

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for denosumab is provided on pages 4-5 of this review. Appendix A of this review also provides a track changes version of labeling

MATERNAL HEALTH TEAM LABELING RECOMMENDATIONS
HIGHLIGHTS OF PRESCRIBING INFORMATION



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REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Biologic Oncology Products

Application Numbers:
STN: BL 125320/0
STN: BL 125331/0
STN: BL 125332/0
STN: BL 125333/0

Name of Drug: Denosumab

Applicant: Amgen, Incorporated

Material Reviewed:

Submission Date(s): December 19, 2008

Receipt Date(s): December 19, 2008

Submission Date of Structure Product Labeling (SPL): December 19, 2008

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

General Comments:

1. Include a Boxed Warnings section in the Highlights, Full Prescribing Information (FPI): Contents, and FPI sections of the label to include warnings regarding osteonecrosis, infection and hypocalcemia adverse reactions. Please reference the following: *Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed*

Warning Section of Labeling for Human Prescription Drug and Biological Products-Content and Format found at http://www.fda.gov/CBER/gdlns/boxwarlb.htm.

2. Use "active voice" throughout the label.

Highlights:

3. Delete the white space between the major headings and the text underneath.

4. Do not use "TM" after the drug names in Highlights or Table of Contents. Use "TM" only once in the content of labeling (FPI).

5. For biologic products, the dosage form and route of administration are not part of the product name. Relocate the dosage form and route of administration to the next line below.

6. Please revise the DOSAGE AND ADMINISTRATION section, to say "Administer 60 mg every 6 months as a subcutaneous (SC) injection."

7. Reword sentence in the DOSAGE FORMS AND STRENGTHS section to read "Single use prefilled syringe containing 60 mg in a 1 mL solution," and "Single use vial containing 60 mg in a 1 mL solution."

8. Include "Skin Infections," and "Hypocalcemia," in the WARNINGS AND PRECAUTIONS section

9. In the USE IN SPECIFIC POPULATION, add the headers "Pregnancy," and "Pediatric Use," and "Renal Impairment" and one of the following statements, as appropriate: "Based on animal data, may cause fetal harm," or "No human or animal data. Use only if clearly needed." [redacted] (b) (4)

10. Add "Revised [Month/Year]" as the last item in Highlights. [Note: For this new BLA, the revision date will be the month /year that the application is approved].

Full Prescribing Information (FPI):

11. Revise the ADVERSE REACTIONS; Section 6.2 Immunogenicity, to include the following standard verbatim statement.

[redacted] (b) (4)

(b) (4)

12. USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: the labeling must include the appropriate required regulatory statement for Pregnancy Category C. Refer to 21 CFR 201.57(c)(9)(i)(A)(3).

13. USE IN SPECIFIC POPULATIONS: 8.3 Nursing Mothers: If a drug is absorbed systemically and is known to be excreted in human milk or excretion in human milk is unknown, this subsection must describe if the drug is associated with serious adverse reactions or has known tumorigenic potential and include required statements, as appropriate. Reference [21 CFR 201.57(C)(9)(iii)].

Please address the identified deficiencies/issues and re-submit labeling by (April 3, 2009). This updated version of labeling will be used for further labeling discussions.

Melanie Pierce
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Karen D. Jones
Chief, Project Management Staff

Drafted: Melanie Pierce/2.23.09
Revised/Initialed: 3.02.09 and 3.03.09
Finalized:3.03.09
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

FINAL REMS MODIFICATION REVIEW

Date:	September 14, 2011
To:	Patricia Keegan, M.D., Director Division of Biologic Oncology Products
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK) Claudia B Karwoski 9/14/11
From:	Amarilys Vega, M.D., M.P.H. Risk Management Analyst, DRISK Kate Heinrich Oswell, MA Health Communications Analysts, DRISK Cynthia LaCivita, Pharm.D. Cynthia LaCivita 9/14/11 Risk Management Analyst Team Leader, DRISK
Subject:	Denosumab (Prolia) Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification Review.
Drug Name	
(Established Name):	Denosumab (Prolia)
Therapeutic Class:	Osteoclast inhibitor (RANKL inhibitor)
Dosage and Route:	60 mg every 6 months as a subcutaneous injection
Application Type/Number:	BLA 125320/5/6
Applicant:	Amgen Inc.
OSE RCM #:	2011-1386
TSI #:	000991, 000992, 000998

1 INTRODUCTION

This review provides recommendations by the Division of Risk Management (DRISK) regarding Amgen's amendments of the approved Prolia® Risk Evaluation and Mitigation Strategy (REMS).

The proposed REMS modification was included with an efficacy supplement for the proposed indication for treatment and prevention of bone loss associated with hormone ablation therapy (HALT) in patients with breast or prostate cancer submitted to the FDA on March 18, 2011. Three previous reviews on this REMS modification were completed by DRISK on July 29, 2011; August 25, 2011; and September 2, 2011.

The purpose of this review is to determine if this amendment is acceptable and includes all the necessary changes that were conveyed to the sponsor.

The Medication Guide is reviewed under a separate cover, dated August 16, 2011.

2 MATERIALS REVIEWED

DRISK reviewed the following documents:

- Amgen, Denosumab REMS-related documents submitted by email September 8, 2011 and September 14, 2011: REMS Document, Dear Healthcare Provider Letter, Medication Guide, REMS Website Screenshots, and REMS Supporting Document.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

The DRISK Review Team finds the proposed REMS modifications provided via e-mail on September 14, 2011 to be acceptable. The REMS is appended.

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

Reference ID: 3168397

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Biologic Oncology Products

DBOP REVIEW

RISK EVALUATION AND MITIGATION STRATEGY MODIFICATION REVIEW

BLA/Serial Number:	125320/5 and 125320/6
Drug Name:	Prolia (Denosumab)
Purpose:	REMS Modification associated with efficacy supplement for expanded indication to hormone ablation therapy cancer patient population
Applicant:	Amgen
Date(s):	Received 3/18/11: Amendment 64 to both Supplements 125320/5 and 125320/6 representing a Complete Response submission to the FDA CR Letter of 10/19/09
Medical Division:	Division of Biological Oncology Products
Reviewer:	Jeff Summers, M.D. Review Date September 6, 2011
Through:	Patricia Keegan M.D., Director Division of Biologic Oncology Products
Review Team:	Pat Keegan, M.D.; Claudia Karwoski, Pharm.D.; Amarilys Vega, M.D., MPH; Cynthia LaCivita, Pharm.D.; Grace Carmouze, Kate Heinrich, Shan Pradhan, M.D.; Steven Lemery, M.D.
Project Manager:	Melanie Pierce
TSIs Referenced	000991, 000992, 000998

sponsor submitted an efficacy supplement for the proposed indication for the treatment and prevention of bone loss associated with HALT in patients with breast or prostate cancer.

Listed below is a chronological summary of the regulatory history for this Prolia supplement.

- December 19, 2008: Amgen submitted an application requesting Prolia approval for 2 indications:
  - treatment and prevention of osteoporosis in postmenopausal women and
  - treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer.
- October 19, 2009: Complete Response Letter for the HALT cancer indications issued.
- June 1, 2010: Approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture with a REMS. It was approved with a REMS that included a Medication Guide (MG) and Communication Plan (CP).
- November 18, 2010: Denosumab was approved under the proprietary name Xgeva (BL 125320/7) for the prevention of skeletal related events in patients with bone metastases from solid tumors. Xgeva was approved without a REMS for that indication.
- March 18, 2011: Amgen submitted a Complete Response (CR) addressing the Agency's October 19, 2009 action letter comments on the HALT indication.
- June 8, 2011: The FDA sent the sponsor a REMS Information Request indicating that a CP was required for Prolia's HALT indication.
- July 1, 2011: Amgen submitted a revised REMS document including a CP for the HALT indication.
- August 5, 2011: FDA sent comments to Amgen regarding necessary changes to the REMS document and REMS materials.
- August 12, 2011: Amgen submitted a revised REMS and REMS materials in response to the FDA e-mail comments of August 5, 2011.
- August 26, 2011: FDA sent additional comments regarding necessary changes to the REMS document and REMS materials.
- August 30, 2011: Amgen responded by e-mail to the changes requested on August 26.
- September 1, 2011: A final set of comments were set to Amgen

Amgen's March 18, 2011 submission included changes to reflect the HALT indications in the Medication Guide, REMS document, and REMS supporting document. Amgen's proposed modifications to the REMS (b) (4) FDA sent Amgen a REMS Information Request on June 8, 2011 indicating that the CP should also apply to the oncology healthcare providers. Amgen resubmitted REMS materials on July 1, 2011 to address this request. An internal Safety Issues Team meeting to include DRISK, DRUP, and DBOP was held on August 5, 2011 to discuss the DRISK proposed changes to the REMS and REMS materials. Comments were sent to Amgen on August 5, 2011 (see Appendix 1) and a formal submission in response was received on August 12, 2011. Additional comments were sent to Amgen on August 26, 2011 (see Appendix 11) and an e-mail response was received on August 30th. A final set of comments were sent to the Amgen on September 2, 2011.

3 REVIEW

The current REMS, approved June 1, 2010 includes a Medication Guide and a CP. The goals of the approved REMS are to:

- inform healthcare providers (HCP) about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover associated with Prolia (denosumab)
- inform patients about the serious risks associated with the use of Prolia.

The initial REMS Communication plan consisted of a Dear Health Care Provider Letter that was targeted to physicians who were likely to treat osteoporosis patients or who had prescribed an osteoporosis medication in the 12 months preceding the approval of Prolia. A number of professional societies also received the DHCPL with the request that their members be provided the letter. Any newly identified prescribers of Prolia that had not previously been sent the DHCPL would be sent a DHCPL for up to two years after approval of the Prolia REMS. REMS assessments are currently scheduled at 18 months, 3 years and 7 years from the date of the approval of the REMS.

Review of Materials Approved

The following is an overview of the changes agreed to for each REMS document provided. It does not identify every change but highlights the major changes. The DRISK reviews that delineates the changes can be found in Appendix 2 and Appendix 13.

Concise REMS document

- The original June 1, 2010 approved Prolia REMS can be found in Appendix 3. The initial proposed REMS modifications for this efficacy supplement can be found in Appendix 9. The Sponsor proposed (b) (4) as shown below in track changes.

(b) (4)

DRISK recommended that we revert to the original REMS language as approved in 2010 and that the risk of osteonecrosis of the jaw also be included (see Appendix 4).

- Amgen did not propose a communication plan for the new physicians (oncologists and urologists) that would prescribe Prolia for the expanded indication. In addition, Amgen proposed altering the communication plan such that (b) (4) not previously sent the Dear Health Care Provider Letter (DHCPL) would be sent the DHCPL as shown below in track changes.

(b) (4)

DBOP requested on June 8, 2011 that Amgen include a communication plan that also targeted oncologists and urologists. Amgen's response to this request on July 1, 2011 consisted of a REMS document with (b) (4) DRISK proposed a consolidated communication plan that removed the (b) (4) language (see Appendix 4). The changes proposed by DRISK to Amgen's proposed communication plan appear reasonable. These were discussed and agreed to at a SIT meeting between DBOP, DRUP, and DRISK on August 5, 2011. Amgen agreed to all the FDA proposed concise REMS document revisions in their response of August 12, 2011 and proposed one additional change to the REMS document in the communication plan section as follows:

(b) (4)

The Amgen proposed revision was discussed with the DBOP clinical review team and determined to be acceptable. However, a request was made to Amgen on August 26th to explain in the REMS supporting document the methods that would be used to identify these physicians and a request made to modify the language in the concise REMS document to the following:

> *"The CP consists of a Dear Health Healthcare Provider Letter (DHCPL), which will be sent within 60 days of the most recent REMS approval to oncologists and urologists who are likely to prescribe or have prescribed hormone ablation as a method of treatment for patients with prostate or breast cancer by mass mailing or electronic mailing."*

Amgen provided the requested information for the REMS supporting document and accepted the changes described above for the concise REMS in their e-mail response of August 30, 2011. Additional editorial changes were proposed by Amgen to the REMS supporting document and found to be acceptable.

Dear Health Care Provider Letter

The originally approved June 1, 2010 Dear Health Care Provider Letter can be found in Appendix 5. Amgen's proposed new DHCPL for Oncologists and Urologists can be found in Appendix 6. The following statement has been deleted from the introductory paragraph:

> "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. (b) (4)"

In addition, the section on the Prolia Post-marketing Active Safety Surveillance Program (b) (4) (b) (4) The inclusion of patients with cancer in the voluntary adverse events of special interest registry could provide useful information, however, this "experience" data would likely be more confounded then that obtained from the postmenopausal patient population. The registry would need to capture data from the two different patient populations separately.

Amgen, in their July 1, 2011 submission, intended on [redacted]. DRISK is of the opinion that a single letter and website should be used for the REMS [redacted] program. Amgen accepted all of the changes proposed by FDA to the DHCPL with the exception of the indication statements that were modified as follows:

The Amgen proposed revision of the indication statements in the DHCPL accurately reflect the label indications and are therefore acceptable. The August 26th FDA comments sent after the DDMAC review was complete requested that additional safety information from the label be included in the DHCPL as follows:

In their August 30th e-mail Amgen stated that although this information and language is in the Prescribing Information, that it was included in the label originally in regards to a theoretical risk with no data to support the statement. They also argued that the statement is not relevant to the HALT indications [redacted]. FDA responded on September 2, 2011 that this information is included in the label and provides important guidance to prescribers. Additionally, this letter will be resent to professional societies and

Important Information about the Risks of Prolia

The REMS associated with Prolia is intended to ensure the benefits of the drug outweigh the risks of:

- **serious infections,**
- **dermatologic adverse events, and**
- **suppression of bone turnover, including osteonecrosis of the jaw.**

Serious infections

[redacted] In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were

included in the initial communication plan to any new prescriber for all the indications. FDA requested that the following sentence now be added to the end of the "Serious Infections" section to be more consistent with the PI:

[redacted]

Please see Appendix 14 for the 02-SEP-11 comments to Amgen regarding editorial changes to the REMS and REMS supporting documents and the changes necessary to the DHCPL.

The REMS Supporting document

Amgen proposed changes in the REMS supporting document to reflect their proposed changes in the REMS document. These changes included [redacted]

(b) (4) (b) (4) with the additional inclusion of osteonecrosis of the jaw and that the communication plan should consist of a single plan and letter. Amgen was instructed to revise the REMS supporting document to reflect the FDA requested changes regarding the REMS document, communication plan, and REMS website. In addition, the REMS supporting document should be updated to include the current assessment plan and methods. The Amgen submission of August 12 updated the REMS supporting document to accurately describe activities that had already occurred in the past and to reflect the new information and changes in the REMS program agreed to under this REMS modification submission. Amgen's response of August 30th also incorporated the changes requested regarding identification of prescribers who had prescribed hormone ablation therapy. The additional proposed changes by Amgen that were mostly editorial or for clarification purposes were also acceptable.

Website Revisions

Amgen proposed modifications to the website that were consistent with their proposed changes to the goals in the REMS document. They proposed (b) (4) The Sponsor's proposed web site changes as well as DRISK's were reviewed. DRISK proposed a single web site and single DHCPL for the two indications. DRISK identified a link that goes to (b) (4) that needs to be removed from the top of the web page (see the DRISK review of the ms-word-version of the Website in Appendix 7). DRISK proposed the revisions below in track-changes. The language (b) (4) (b) (4) could be made more direct and state instead (b) (4) (b) (4) " This recommendation was discussed with DRISK and they proposed the following revision that is more consistent with language used in other REMS: *"To learn about the serious risks of Prolia.."*

Amgen accepted the FDA proposed Website revisions of August 5th with the following proposed alternative language which is acceptable.

(b) (4)

Medication Guide

Amgen's changes to the Medication Guide reflected information relevant to the new HALT indications to include the following:

What is Prolia?

(b) (4)



The DBOP clinical review team proposed the following revisions to the Medication Guide:



The sections of the Medication Guide *"What is osteoporosis?" and "What can I do to treat osteoporosis"* were previously removed from the Medication Guide on July 22, 2011 (see Appendix 8). Based on this, the following DBOP proposed revision to "(b) (4) will also be deleted.

(b) (4)

A labeling meeting was held on September 1, 2011 to address DDMAC comments and some minor additional changes were made to clarify the indicated patient populations to be those where the cancer has not spread to other parts of the body. See Appendix 12 for the final Medication Guide comments sent to Amgen on September 2, 2011.

4 CONCLUSION

This review documents the modifications to the Prolia REMS that occurred under supplements 125320/5 and 125320/6 (REMS Modification submitted with the Complete Response for the HALT efficacy supplements). The recommendations provided by DRISK were discussed at a SIT meeting on August 5, 2011, and sent to the Sponsor on August 5, 2011. Amgen agreed to all of the FDA requested changes with some minor modifications that were determined to be acceptable as described in this review. Subsequently, additional comments were sent to Amgen on various components of the REMS materials based on DDMAC recommendations on August 26th. Amgen accepted these changes except for language in the DHCPL. DBOP and DRISK did not accept Amgen's argument that this omission of safety information from the DHCPL was valid and informed them on September 2nd that these changes were required. Once Amgen agrees to the changes requested on September 2nd they should be requested to resubmit all the final REMS materials to include the concise REMS document, DHCPL, REMS supporting document, Website screen shots, and Medication guide so that a single submission can be referenced for the approved REMS and REMS materials. The REMS modification should be approved at that time.

5 APPENDICES

Appendix 1 05-AUG-11 Comments to Amgen
Appendix 2 DRISK REMS Mod Review 29-JUL-11
Appendix 3 Original approved Prolia REMS
Appendix 4 DRISK Concise REMS proposed language
Appendix 5 Originally approved 01-JUN-10 DHCPL
Appendix 6 Amgen's proposed 07-JUL-11 DHCPL
Appendix 7 DRISK review ms word version website
Appendix 8 Medication Guide Approval 22-JUL-11
Appendix 9 Amgen's initial 18-MAR-11 Proposed REMS modifications
Appendix 10 Amgen's 01-JUL-11 Proposed REMS in response to FDA June 8 request
Appendix 11 26-AUG-11 Comments to Amgen
Appendix 12 02-SEP-11 Labeling meeting DDMAC Revisions Medication Guide
Appendix 13 DRISK REMS Mod Review 02-SEP-11
Appendix 14 02-SEP-11 Comments to Amgen

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Appendix 13

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS MODIFICATION REVIEW

Date:	September 02, 2011
To:	Patricia Keegan, M.D., Director Division of Biologic Oncology Products
Through:	Cynthia LaCivita, Pharm.D. Cynthia LaCivita 9/2/2011 Risk Management Analyst Team Leader, DRISK
From:	Amarilys Vega, M.D., M.P.H. Amarilys Vega 9/2/2011 Risk Management Analyst, DRISK Kate Heinrich Oswell, MA Health Communications Analysts, DRISK
Subject:	Denosumab (Prolia) Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification Review: DRISK comments on Amgen's 8-31-2011 submission.
Drug Name	
(Established Name):	Denosumab (Prolia)
Therapeutic Class:	Osteoclast inhibitor (RANKL inhibitor)
Dosage and Route:	60 mg every 6 months as a subcutaneous injection
Application Type/Number:	BLA 125320/5/6
Applicant:	Amgen Inc.
OSE RCM #:	2011-1386
TSI #:	000991, 000992, 000998

Reference ID: 3168397

1 INTRODUCTION

This review provides recommendations by the Division of Risk Management (DRISK) regarding Amgen's proposed modification of the approved Prolia® Risk Evaluation and Mitigation Strategy (REMS) submitted to the FDA on August 31, 2011.

On August 26, 2011, FDA sent Amgen a memorandum providing comments on their REMS modification submission received by the FDA on August 12, 2011. Amgen responded to FDA's comments on August 31, 2011.

2 MATERIALS REVIEWED

DRISK reviewed the following documents:

- Amgen, Denosumab REMS-related documents submitted August 31, 2011; REMS Document, REMS materials, REMS Supporting Document, and Amgen's justification for not including the additional sentence proposed by FDA in the Serious Infections section of the Dear Healthcare Provider Letter.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

DRISK concurred with most of the modifications proposed by Amgen and requests that the recommendations on the Prolia REMS included in section 4 below be sent to the applicant as soon as possible, including the following appended materials with our track changes:

- Attachment A: REMS Document
- Attachment B: Dear Healthcare Provider Letter (DHCP Letter)
- Attachment C: REMS Supporting Document

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

Please request that the applicant respond to these comments as soon as possible to facilitate further review in order to meet the action date for this BLA.

4 RECOMMENDATIONS FOR THE APPLICANT

1. REMS Document

a. Change acronym for "Dear Healthcare Provider Letter" from DHCPL to DHCP Letter in the REMS document and REMS Supporting document.

Rationale: We recommend this modification to maintain internal consistency in all REMS materials.

b. Attach to the REMS document the following materials: Medication Guide, DHCP Letter, and Prolia REMS website screenshot.

Rationale: These materials are part of the REMS and must be appended.

Reference ID: 3168397

c. Additional minor edits in track changes.

See track changes in attachement A.

2. Dear Healthcare Provider Letter

a. Add the following sentence as the end of the "Serious Infections" section.

(b) (4)

[redacted]

Rationale: This information is included in the label and provides important guidance to prescribers. Additionally, please note that this letter will be resent to the professional societies included in the initial communication plan and to any new prescribers.

See track changes in attachement B.

3. REMS Supporting Document

a. Change acronym for "Dear Healthcare Provider Letter" from DHCPL to DHCP Letter in the REMS document and REMS Supporting document.

Rationale: We recommend this modification to maintain internal consistency in all REMS materials.

b. Additional minor edits in track changes.

See track changes in attachement C.

4. Submission Instructions

a. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document.

b. Format Request:

i. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it m akes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

ii. Submit the REMS and the REMS Suppor ting Document as two separate WORD documents. It is p referable that the entire REM S document and attached materials be in a single WORD document.

5. Attachments

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

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS MODIFICATION REVIEW

Date:	September 02, 2011
To:	Patricia Keegan, M.D., Director Division of Biologic Oncology Products
Through:	Cynthia LaCivita, Pharm.D. Cynthia LaCivita 9/2/2011 Risk Management Analyst Team Leader, DRISK
From:	Amarilys Vega, M.D., M.P.H. Amarilys Vega 9/2/2011 Risk Management Analyst, DRISK Kate Heinrich Oswell, MA Health Communications Analysts, DRISK
Subject:	Denosumab (Prolia) Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification Review: DRISK comments on Amgen's 8-31-2011 submission.
Drug Name	
(Established Name):	Denosumab (Prolia)
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Application Type/Number:	BLA 125320/5/6
Applicant:	Amgen Inc.
OSE RCM #:	2011-1386
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1 INTRODUCTION

This review provides recommendations by the Division of Risk Management (DRISK) regarding Amgen's proposed modification of the approved Prolia® Risk Evaluation and Mitigation Strategy (REMS) submitted to the FDA on August 31, 2011.

On August 26, 2011, FDA sent Amgen a memorandum providing comments on their REMS modification submission received by the FDA on August 12, 2011. Amgen responded to FDA's comments on August 31, 2011.

2 MATERIALS REVIEWED

DRISK reviewed the following documents:

- Amgen, Denosumab REMS-related documents submitted August 31, 2011; REMS Document, REMS materials, REMS Supporting Document, and Amgen's justification for not including the additional sentence proposed by FDA in the Serious Infections section of the Dear Healthcare Provider Letter.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

DRISK concurred with most of the modifications proposed by Amgen and requests that the recommendations on the Prolia REMS included in section 4 below be sent to the applicant as soon as possible, including the following appended materials with our track changes:

- Attachment A: REMS Document
- Attachment B: Dear Healthcare Provider Letter (DHCP Letter)
- Attachment C: REMS Supporting Document

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

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4 RECOMMENDATIONS FOR THE APPLICANT

1. REMS Document

a. Change acronym for "Dear Healthcare Provider Letter" from DHCPL to DHCP Letter in the REMS document and REMS Supporting document.

Rationale: We recommend this modification to maintain internal consistency in all REMS materials.

b. Attach to the REMS document the following materials: Medication Guide, DHCP Letter, and Prolia REMS website screenshot.

Rationale: These materials are part of the REMS and must be appended.

Reference ID: 3168397

c. Additional minor edits in track changes.

See track changes in attachement A.

2. Dear Healthcare Provider Letter

a. Add the following sentence as the end of the "Serious Infections" section.

(b) (4)

Rationale: This information is included in the label and provides important guidance to prescribers. Additionally, please note that this letter will be resent to the professional societies included in the initial communication plan and to any new prescribers.

See track changes in attachement B.

3. REMS Supporting Document

a. Change acronym for "Dear Healthcare Provider Letter" from DHCPL to DHCP Letter in the REMS document and REMS Supporting document.

Rationale: We recommend this modification to maintain internal consistency in all REMS materials.

b. Additional minor edits in track changes.

See track changes in attachement C.

4. Submission Instructions

a. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document.

b. Format Request:

i. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

ii. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.

5. Attachments

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS MODIFICATION REVIEW

Date:	August 25, 2011
To:	Patricia Keegan, M.D., Director Division of Biologic Oncology Products
Through:	Cynthia LaCivita, Pharm.D. C LaCivita 8/25/2011 Risk Management Analyst Team Leader, DRISK
From:	Amarilys Vega, M.D., M.P.H. Amarilys Vega 8/25/2011 Risk Management Analyst, DRISK Kate Heinrich Oswell, MA Health Communications Analysts, DRISK
Subject:	Denosumab (Prolia) Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification Review-DRISK comments on Amgen's 8-12-2011 submission.
Drug Name	
(Established Name):	Denosumab (Prolia)
Therapeutic Class:	Osteoclast inhibitor (RANKL inhibitor)
Dosage and Route:	60 mg every 6 months as a subcutaneous injection
Application Type/Number:	BLA 125320/5/6
Applicant:	Amgen Inc.
OSE RCM #:	2011-1386
TSI #:	000991, 000992, 000998

Reference ID: 3168397

1 INTRODUCTION

This review provides recommendations by the Division of Risk Management (DRISK) regarding Amgen's proposed modification of the approved Prolia® Risk Evaluation and Mitigation Strategy (REMS) submitted to the FDA on August 12, 2011.

On August 5, 2011, FDA sent Amgen a memorandum providing comments on their REMS modification submission received by the FDA on July 1, 2011. Amgen responded to FDA's comments on August 12, 2011.

2 MATERIALS REVIEWED

The following documents were reviewed by DRISK:

- Amgen, Denosumab, REMS Document, REMS materials, and REMS Supporting Document submitted August 12, 2011.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

DRISK concurred with most of the modifications proposed by Amgen and requests that the recommendations on the Prolia REMS included in section 4 below be sent to the applicant as soon as possible, including the following appended materials with our track changes:

- Attachment A: REMS Document
- Attachment B: Dear Healthcare Provider Letter (DHCPL)
- Attachment C: REMS Supporting Document

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

Please request that the applicant respond to these comments as soon as possible to facilitate further review in order to meet the action date for this BLA.

4 RECOMMENDATIONS FOR THE APPLICANT

1. REMS Document

a. Deletion of the (b) (4) from the REMS document.

Rationale: A statement indicating that the Medication Guide (MG), Dear Healthcare Provider Letter (DHCPL), and REMS web page screenshots are appended is sufficient. However, you may include (b) (4) in the REMS Supporting document.

b. Please, describe in the REMS Supporting document the methods for (b) (4) (b) (4) (b) (4). In addition, edit the statement to include providers who are likely to prescribe Prolia for the HALT indications in the future. We suggest the following language:

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*"The CP consists of a Dear Health Healthcare Provider Letter (DHCPL), which will be sent within 60 days of the most recent REMS approval to oncologists and urologists who **are likely to prescribe or have prescribed** hormone ablation as a method of treatment for patients with prostate or breast cancer by mass mailing or electronic mailing."*

Rationale: The REMS Supporting document does not describe how will prescribers, who have utilized hormone ablation as a method of treatment for patients with prostate or breast cancer, be uniquely identified. In addition, it is important to include potential prescribers of Prolia for these indications.

c. Append the MG, DHCPL, and web page screenshot to the REMS document.

Rationale: All REMS documents must be appended.

See track changes in attachement A.

2. Dear Healthcare Provider Letter

a. Add the following sentence as the first sentence of the paragraph under the subheading "Serious Infections": (b) (4)

Rationale: This statement is an important component of the risk message communicated in this REMS.

See track changes in attachement B.

3. REMS Supporting Document

a. Add the following text to the end of section 4.1.1: (b) (4) (b) (4)

Rationale: The REMS Supporting document (b) (4) containing the MG.

b. Please, describe in the REMS Supporting document the methods for (b) (4) (b) (4) .. (b) (4) (b) (4) In addition, edit the statement to include providers who are likely to prescribe Prolia for the HALT indications in the future. We suggest the following language:

*"The CP consists of a Dear Health Healthcare Provider Letter (DHCPL), which will be sent within 60 days of the most recent REMS approval to oncologists and urologists who **are likely to prescribe or have prescribed** hormone ablation as a method of treatment for patients with prostate or breast cancer by mass mailing or electronic mailing."*

Rationale: The REMS Supporting document does not describe how will prescribers, who have utilized hormone ablation as a method of treatment for patients with

prostate or breast cancer, be uniquely identified. In addition, it is important to include potential prescribers of Prolia for these indications.

c. Add the following text to the end of section 4.1.2:

"The DHCP Letter was revised to include new indications for Prolia and will replace the initial letter in subsequent mailings to professional societies and newly identified prescribers. [redacted (b) (4)]*".*

Prolia REMS Website: [redacted (b) (4)] *will describe the risks associated with the use of Prolia and instruct Healthcare Providers on how to obtain additional safety information."*

Rationale: Provide additional clarification points to the CP.

See track changes in attachement C.

4. Submission Instructions

a. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document.

b. Format Request:

i. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

ii. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.

5. Attachments

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Appendix 2

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS MODIFICATION REVIEW

Date:	July 29, 2011
To:	Patricia Keegan, M.D., Director Division of Biologic Oncology Products
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK) Claudia B Karwoski 8/1/11
From:	Amarilys Vega, M.D., M.P.H. Amarilys Vega 8/1/2011 Risk Management Analyst, DRISK Kate Heinrich Oswell, MA Health Communications Analysts, DRISK Cynthia LaCivita, Pharm.D. Risk Management Analyst Team Leader, DRISK
Subject:	Denosumab (Prolia) Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification Review
Drug Name	
(Established Name):	Denosumab (Prolia)
Therapeutic Class:	Osteoclast inhibitor (RANKL inhibitor)
Dosage and Route:	60 mg every 6 months as a subcutaneous injection
Application Type/Number:	BLA 125320/5/6
Applicant:	Amgen Inc.
OSE RCM #:	2011-1386
TSI #:	000991, 000992, 000998, 001075

Reference ID: 3168397

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6 RECOMMENDATIONS FOR THE APPLICANT 8

Reference ID: 3168397

1 INTRODUCTION

This review provides DRISK's recommendations on Amgen's proposed Risk Evaluation and Mitigation Strategy (REMS) modification of the approved Prolia® REMS.

The proposed REMS modification was included with an efficacy supplement for the proposed indication for treatment and prevention of bone loss associated with hormone ablation therapy (HALT) in patients with breast or prostate cancer submitted to the FDA on March 18, 2011.

2 MATERIALS REVIEWED

The following documents were reviewed by DRISK:

- Amgen, Denosumab, REMS Document, REMS materials, and REMS Supporting Document submitted March 18, 2011 and July 1, 2011 Amgen, Denosumab, Clinical overview, submitted December 19, 2008
- Amgen, Denosumab, Prior Approval Supplement, November 18, 2010

3 BACKGROUND

Prolia is a RANK ligand (RANKL) inhibitor indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture (original approval date June 1, 2010).[1] The sponsor submitted an efficacy supplement for the proposed indication for the treatment and prevention of bone loss associated with HALT in patients with breast or prostate cancer.

Listed below is an abbreviated chronological summary of the regulatory history for denosumab.

- **December 19, 2008:** Amgen submitted an application requesting Prolia approval for 2 indications: (1) treatment and prevention of osteoporosis in postmenopausal women and (2) treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer.
- **October 2, 2009:** FDA, Division of Reproductive and Urologic Products, sent the sponsor a REMS Notification Letter for Prolia's osteoporosis indication.
- **October 16, 2009:** The FDA issues a Complete Response Action Letter for Prolia's osteoporosis indication.
- **October 19, 2009:** The FDA issues a Complete Response Action Letter for Prolia's HALT indication.
- **January 25, 2010:** Amgen submitted a Complete Response (CR) addressing the Agency's October 16, 2009 action letter regarding Prolia's osteoporosis indication.

[1] RANK ligand (RANKL) is an essential mediator of osteoclast formation, function, and survival.

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- **June 1, 2010:** Denosumab was approved under the proprietary nam e Prolia (BL 125320) for the treatm ent of postmenopaus al women with osteoporosis at high risk for fracture. It was approved with a REMS that included a Medication Guide (MG) and Communication Plan (CP).
- **November 18, 2010:** Denosumab was approved under the proprietary nam e Xgeva (BL 125320/7) for the the prevention of skeletal related events in patients with bone metastases from solid tumors. Xgeva was approved without a REMS for that indication.
- **December 23, 2010:** A labeling revision supplem ent for Prolia was received by the FDA. This Prior Approval Supplem ent proposed revisions to Prolia's Prescribing Information and MG with the objective of ensuring that patients are aware denosumab is available under two di stinct proprietary na mes (i.e., Prolia and Xgeva) and to instruct th em to inform the Healthcare Provider if they are taking Xgeva before they receive Prolia.
- **March 18, 2011:** Amgen submitted a Com plete Response (CR) add ressing the Agency's October 19, 2009 action letter regarding Prolia's HALT indication. The proposed REMS modification (b) (4)
- **June 8, 2011:** The FDA sent the sponsor a REMS Inform ation Request indicating that a CP was required for Prolia's HALT indication.
- **July 1, 2011:** Amgen submitted a revised REMS document including a CP for the HALT indication.

Clinical Development Program

Denosumab's clinical develop m ent program consisted of 30 clinical studies in norm al volunteers and patients with osteoporosis (approximately 10,500 subjects), bone loss associated with HALT (approxim ately 1,700 subjects), rheumatoid arthritis, and advanced cancer performed from June 2001 to September 2008.[2] This program included:

- 12 studies – conducted in subjects w ith postmenopausal osteoporosis or low bone mass
- 2 studies – conducted in subjects w ith breast cancer or prostate cancer who had bone loss associated with HALT (arom atase inhibitor and androgen deprivation therapy, respectively)
  - Study 20040138 - a random ized, double-blind, placebo-controlled study in subjects undergoing androgen deprivation therapy for nonm etastatic prostate cancer to determine the treatment effect of denosum ab on lumbar spine BMD compared with control
  - Study 20040135 - a random ized, double-blind, placebo-controlled study in subjects undergoing arom atase inhibitor therapy for nonmetastatic breast cancer to determine the treatment effect of denosum ab on lumbar spine BMD compared with control

[2] Denosumab, Clinical Overview, submitted December 19, 2008.

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- 1 study – conducted in subjects with breast cancer receiving aromatase inhibitor therapy (ongoing and remains blinded to treatment assignment)
- 9 studies – provide bio pharmaceutic and clinical pharmacology information as well as information on initial efficacy and tolerability of denosumab.
- 6 studies – conducted in patient populations outside of the bone loss indications (i.e., inhibition of structural damage in subjects with rheumatoid arthritis, prevention of skeletal-related events in subjects with advanced cancer and bone metastases, and treatment of multiple myeloma).

Denosumab administration was generally well tolerated across the 30 studies. The safety profile of denosumab was comparable with that of placebo. Data from approximately 9,800 evaluable subjects in these studies showed the following important adverse drug reactions: hypocalcemia, eczema, skin infections leading to hospitalization, and cataracts in men with prostate cancer receiving androgen deprivation therapy. Other potential risks that will continue to be evaluated because they occur infrequently, include hypersensitivity, fracture healing complications, and osteonecrosis of the jaw.

A REMS, including a MG and a CP, was required for Prolia's osteoporosis indication to address the risk of serious infections, dermatologic adverse reactions, and suppression of bone turnover.

4 REMS SUMMARY

4.1 Approved REMS for Prolia

The current REMS, approved on June 1, 2010, include a MG and a CP. The goals of the approved REMS are to: (1) inform healthcare providers (HCP) about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover associated with Prolia (denosumab) and (2) inform patients about the serious risks associated with the use of Prolia.

The current CP consists of a Dear Healthcare Provider Letter (DHCPL), which was distributed via mass mailing or electronic mailing, targeting endocrinologists, rheumatologists, gynecologists, and primary care physicians who had written at least one prescription for an osteoporosis medication in the 12 months prior to Prolia's launch. In addition, Amgen distributed the DHCPL to the following professional societies: National Osteoporosis Foundation, American Society of Bone Mineral Research, American College of Rheumatology, American Association of Clinical Endocrinologists, the American College of Physicians, the American Academy of Family Physicians, and the Endocrine Society. Amgen requested that these societies provide the letter to their members. Following the initial distribution, Amgen will resend the DHCPL to these professional societies annually for up to 3 years after approval, again with a request that they provide the letter to their members. Any known new prescribers of Prolia, who were not previously sent the DHCPL, would be sent a DHCPL for up to 2 years after approval of the REMS or Prolia launch. REMS assessments are scheduled at 18 months, 3 years, and 7 years from the date of the approval of the REMS.

Reference ID: 3168397

4.2 Applicant's Proposed REMS Modifications

4.2.1 Consolidated REMS document

4.2.1.1 REMS Goals: The sponsor proposed changing the current REMS goals to the following, (b) (4) (b) (4) (b) (4)

DRISK Comments: DRISK does not agree with the changes proposed by the sponsor because these (b) (4). *Please note that osteonecrosis of the jaw is listed as a separate entity in the Warnings and Precautions section of the label.*

DRISK recommends keeping the current REMS goals with the addition of osteonecrosis of the jaw to the list of risks mentioned.

See Attachment A, REMS Document, for DRISK recommendations in track changes.

4.2.1.2 Communication Plan: In the March 18, 2011 submission for the HALT indication, the sponsor proposed (b) (4).

DRISK comments: The need to communicate information regarding the risks associated with Prolia is the same for both indications, thus, a CP will be necessary for the new indication.

We recommend (b) (4) *a single CP that will cover both indications.*

We recommend removing the initial CP from the REMS document and adding to the CP section of the Supporting Document a description of what occurred with regard to the initial communication plan (include who was targeted (i.e., endocrinologists, rheumatologists) and why and when the CP activities occurred).

We agree with targeting the CP to urologists and oncologists, as proposed by the sponsor in the July 1, 2011 submission. The DHCPL should be sent to the American Society of Clinical Oncology (ASCO) for distribution among its members.

The revised CP should describe the process for sending the DHCPL to newly identified prescribers annually for up to 2 years after product approval and for resending the DHCPL annually, up to 3 years after Prolia approval, to the selected professional societies.

See Attachment A, REMS Document, for DRISK recommendations in track changes.

- **DCHPL** – Amgen did not suggest any changes to the DHCPL in the March 18, 2011 submission, but proposed some changes to the initial DHCPL in the July 1, 2011 submission.

  DRISK comments: See Attachment B, DHCPL, for DRISK recommendations in track changes.

4.2.1.3 Elements to Assure Safe Use: The REMS for Prolia does not include Elements to Assure Safe Use.

4.2.1.4 Implementation System: The REMS for Prolia does not include Elements to Assure Safe Use. Therefore, an Implementation System is not required.

4.2.2 REMS Supporting Document

- Amgen proposed changing the current REMS goals to those proposed in the consolidated REMS document.

  DRISK comments: See DRISK comments and recommendations in section 4.2.1.1 above regarding modification of the REMS goals.

- Amgen proposed the addition of section 2.2.1 and 2.2.2 – Amgen proposed adding these sections to address the differences in the communication strategies for the osteoporosis and the HALT indications.

  DRISK comments: DRISK does not agree. See section 4.2.1.2 above.

4.2.3 REMS webpage

- Amgen proposed changing the current REMS goals to those described in the REMS document.

  DRISK comments: DRISK does not agree. See section 4.2.1.1 above.

- Amgen proposed changing the name of the DHCPL link from "Dear Health Care Professional Letter" to (b) (4) or (b) (4)

  DRISK comments: DRISK does not agree and recommends keeping the original text. See attached MS Word version of the website with track changes.

- Additional comments by DRISK

  DRISK comments: The hyperlink at the top of the webpage, (b) (4) *This hyperlink should be removed as we believe that REMS websites should not* (b) (4)

See Attachment C (MS Word version of the website) with DRISK recommendations in track changes.

5 RECOMMENDATIONS FOR THE REVIEW DIVISION

DRISK requests that the recommendations on the Prolia REMS included in section 6 below be sent to the applicant as soon as possible, including the following appended materials with our track changes:

- Attachment A: REMS Document
- Attachment B: Dear Healthcare Provider Letter (DHCPL)
- Attachment C: MS Word version of the Prolia REMS website

Please copy DRISK on the comm unication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

Please request that the applicant respond to these comments as soon as possible to facilitate further review in order to meet the action date for this BLA.

6 RECOMMENDATIONS FOR THE APPLICANT

1. REMS Document

a. Goals

i. FDA does not agree with the propo sed revisions to the go als because these [redacted] (b) (4). Please note that osteonecrosis of the jaw is listed as a separate entity in the Warnings and Precautions section of the label.

ii. Revise the goal to include the addition of osteonecrosis of the jaw to the list of risks mentioned.

See Attachment A, REMS Document, for the necessary changes.

b. Communication Plan

i. Communication Plan and DHCPL – F DA does not agree with having a [redacted] (b) (4).

Make the following necessary changes:

→ remove the initial CP from the REMS document,

→ add to the Supporting Docum ent CP section a description of what occurred with regard to the initia l communication plan (include who was targeted (i.e., endocrinologists, rheu matologists) and why and when the CP activities occurred),

→ [redacted] (b) (4) a single CP that will address both indications,

→ send the DHCPL to the Am erican Society of Clinical Oncology (ASCO) for distribution among its members,

→ resend the DHCPL to newly iden tified prescribers for up to 2 years afte r Prolia approval, and

→ resend the DHCPL yearly to all th e selected professional societies mentioned in the initial CP for up to 3 years after Prolia approval.

See Attachment A (REMS docum ent) and Attachm ent B (DHCPL) with FDA recommendations in track changes.

2. REMS Supporting Document

a. Update the REMS Supporting Document to reflect the modifications to the REMS Document and currently implemented REMS assessment methods.

3. REMS webpage

a. [redacted] (b) (4).

b. Change the current REMS goals to be consistent with the REMS document, as described above.

c. Keep the original text for the DHCPL link.

d. Remove the hyperlink at the top of the page, [redacted] (b) (4)

[redacted] (b) (4)

See Attachment C, MS W ord version of th e website, with FDA recomm endations in track changes.

4. Submission Instructions

a. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document.

b. Format Request:

i. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it m akes review of th ese materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

ii. Submit the REMS and the REMS Suppor ting Document as two separate WORD documents. It is p referable that the entire REM S document and attached materials be in a single WORD document.

5. Attachments

a. Attachment A: REMS Document

b. Attachment B: Dear Healthcare Provider Letter (DHCPL)

c. Attachment C: MS Word version of the Prolia REMS website

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

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

Date:	July 29, 2011
To:	Patricia Keegan, M.D., Director Division of Biologic Oncology Products
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	Amarilys Vega, M.D., M.P.H. Risk Management Analyst, DRISK
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Subject:	Denosumab (Prolia) Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification Review
Drug Name	
(Established Name):	Denosumab (Prolia)
Therapeutic Class:	Osteoclast inhibitor (RANKL inhibitor)
Dosage and Route:	60 mg every 6 months as a subcutaneous injection
Application Type/Number:	BLA 125320/5/6
Applicant:	Amgen Inc.
OSE RCM #:	2011-1386
TSI #:	000991, 000992, 000998, 001075

Reference ID: 3168397

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1 INTRODUCTION

This review provides DRISK's recommendations on Amgen's proposed Risk Evaluation and Mitigation Strategy (REMS) modification of the approved Prolia® REMS.

The proposed REMS modification was included with an efficacy supplement for the proposed indication for treatment and prevention of bone loss associated with hormone ablation therapy (HALT) in patients with breast or prostate cancer submitted to the FDA on March 18, 2011.

2 MATERIALS REVIEWED

The following documents were reviewed by DRISK:

- Amgen, Denosumab, REMS Document, REMS materials, and REMS Supporting Document submitted March 18, 2011 and July 1, 2011 Amgen, Denosumab, Clinical overview, submitted December 19, 2008
- Amgen, Denosumab, Prior Approval Supplement, November 18, 2010

3 BACKGROUND

Prolia is a RANK ligand (RANKL) inhibitor indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture (original approval date June 1, 2010).[1] The sponsor submitted an efficacy supplement for the proposed indication for the treatment and prevention of bone loss associated with HALT in patients with breast or prostate cancer.

Listed below is an abbreviated chronological summary of the regulatory history for denosumab.

- **December 19, 2008:** Amgen submitted an application requesting Prolia approval for 2 indications: (1) treatment and prevention of osteoporosis in postmenopausal women and (2) treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer.
- **October 2, 2009:** FDA, Division of Reproductive and Urologic Products, sent the sponsor a REMS Notification Letter for Prolia's osteoporosis indication.
- **October 16, 2009:** The FDA issues a Complete Response Action Letter for Prolia's osteoporosis indication.
- **October 19, 2009:** The FDA issues a Complete Response Action Letter for Prolia's HALT indication.
- **January 25, 2010:** Amgen submitted a Complete Response (CR) addressing the Agency's October 16, 2009 action letter regarding Prolia's osteoporosis indication.

[1] RANK ligand (RANKL) is an essential mediator of osteoclast formation, function, and survival.

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- **June 1, 2010:** Denosumab was approved under the proprietary name Prolia (BL 125320) for the treatment of postmenopausal women with osteoporosis at high risk for fracture. It was approved with a REMS that included a Medication Guide (MG) and Communication Plan (CP).
- **November 18, 2010:** Denosumab was approved under the proprietary name Xgeva (BL 125320/7) for the the prevention of skeletal related events in patients with bone metastases from solid tumors. Xgeva was approved without a REMS for that indication.
- **December 23, 2010:** A labeling revision supplement for Prolia was received by the FDA. This Prior Approval Supplement proposed revisions to Prolia's Prescribing Information and MG with the objective of ensuring that patients are aware denosumab is available under two distinct proprietary names (i.e., Prolia and Xgeva) and to instruct them to inform the Healthcare Provider if they are taking Xgeva before they receive Prolia.
- **March 18, 2011:** Amgen submitted a Complete Response (CR) addressing the Agency's October 19, 2009 action letter regarding Prolia's HALT indication. The proposed REMS modification (b) (4).
- **June 8, 2011:** The FDA sent the sponsor a REMS Information Request indicating that a CP was required for Prolia's HALT indication.
- **July 1, 2011:** Amgen submitted a revised REMS document including a CP for the HALT indication.

Clinical Development Program

Denosumab's clinical development program consisted of 30 clinical studies in normal volunteers and patients with osteoporosis (approximately 10,500 subjects), bone loss associated with HALT (approximately 1,700 subjects), rheumatoid arthritis, and advanced cancer performed from June 2001 to September 2008.[2] This program included:

- 12 studies – conducted in subjects with postmenopausal osteoporosis or low bone mass
- 2 studies – conducted in subjects with breast cancer or prostate cancer who had bone loss associated with HALT (aromatase inhibitor and androgen deprivation therapy, respectively)
  - Study 20040138 - a randomized, double-blind, placebo-controlled study in subjects undergoing androgen deprivation therapy for nonmetastatic prostate cancer to determine the treatment effect of denosumab on lumbar spine BMD compared with control
  - Study 20040135 - a randomized, double-blind, placebo-controlled study in subjects undergoing aromatase inhibitor therapy for nonmetastatic breast cancer to determine the treatment effect of denosumab on lumbar spine BMD compared with control

[2] Denosumab, Clinical Overview, submitted December 19, 2008.

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- 1 study – conducted in subjects with breast cancer receiving aromatase inhibitor therapy (ongoing and remains blinded to treatment assignment)
- 9 studies – provide biopharmaceutic and clinical pharmacology information as well as information on initial efficacy and tolerability of denosumab.
- 6 studies – conducted in patient populations outside of the bone loss indications (i.e., inhibition of structural damage in subjects with rheumatoid arthritis, prevention of skeletal-related events in subjects with advanced cancer and bone metastases, and treatment of multiple myeloma).

Denosumab administration was generally well tolerated across the 30 studies. The safety profile of denosumab was comparable with that of placebo. Data from approximately 9,800 evaluable subjects in these studies showed the following important adverse drug reactions: hypocalcemia, eczema, skin infections leading to hospitalization, and cataracts in men with prostate cancer receiving androgen deprivation therapy. Other potential risks that will continue to be evaluated because they occur infrequently, include hypersensitivity, fracture healing complications, and osteonecrosis of the jaw.

A REMS, including a MG and a CP, was required for Prolia's osteoporosis indication to address the risk of serious infections, dermatologic adverse reactions, and suppression of bone turnover.

4 REMS SUMMARY

4.1 Approved REMS for Prolia

The current REMS, approved on June 1, 2010, include a MG and a CP. The goals of the approved REMS are to: (1) inform healthcare providers (HCP) about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover associated with Prolia (denosumab) and (2) inform patients about the serious risks associated with the use of Prolia.

The current CP consists of a Dear Healthcare Provider Letter (DHCPL), which was distributed via mass mailing or electronic mailing, targeting endocrinologists, rheumatologists, gynecologists, and primary care physicians who had written at least one prescription for an osteoporosis medication in the 12 months prior to Prolia's launch. In addition, Amgen distributed the DHCPL to the following professional societies: National Osteoporosis Foundation, American Society of Bone Mineral Research, American College of Rheumatology, American Association of Clinical Endocrinologists, the American College of Physicians, the American Academy of Family Physicians, and the Endocrine Society. Amgen requested that these societies provide the letter to their members. Following the initial distribution, Amgen will resend the DHCPL to these professional societies annually for up to 3 years after approval, again with a request that they provide the letter to their members. Any known new prescribers of Prolia, who were not previously sent the DHCPL, would be sent a DHCPL for up to 2 years after approval of the REMS or Prolia launch. REMS assessments are scheduled at 18 months, 3 years, and 7 years from the date of the approval of the REMS.

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4.2 Applicant's Proposed REMS Modifications

4.2.1 Consolidated REMS document

4.2.1.1 REMS Goals: The sponsor proposed changing the current REMS goals to the following, (b) (4)

(b) (4)

(b) (4)

DRISK Comments: DRISK does not agree with the changes proposed by the sponsor because these (b) (4)
Please note that osteonecrosis of the jaw is listed as a separate entity in the Warnings and Precautions section of the label.

DRISK recommends keeping the current REMS goals with the addition of osteonecrosis of the jaw to the list of risks mentioned.

See Attachment A, REMS Document, for DRISK recommendations in track changes.

4.2.1.2 Communication Plan: In the March 18, 2011 submission for the HALT indication, the sponsor proposed (b) (4)

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DRISK comments: The need to communicate information regarding the risks associated with Prolia is the same for both indications, thus, a CP will be necessary for the new indication.

We recommend (b) (4)
a single CP that will cover both indications.

We recommend removing the initial CP from the REMS document and adding to the CP section of the Supporting Document a description of what occurred with regard to the initial communication plan (include who was targeted (i.e., endocrinologists, rheumatologists) and why and when the CP activities occurred).

We agree with targeting the CP to urologists and oncologists, as proposed by the sponsor in the July 1, 2011 submission. The DHCPL should be sent to the American Society of Clinical Oncology (ASCO) for distribution among its members.

The revised CP should describe the process for sending the DHCPL to newly identified prescribers annually for up to 2 years after product approval and for resending the DHCPL annually, up to 3 years after Prolia approval, to the selected professional societies.

See Attachment A, REMS Document, for DRISK recommendations in track changes.

- **DCHPL** – Amgen did not suggest any changes to the DHCPL in the March 18, 2011 submission, but proposed some changes to the initial DHCPL in the July 1, 2011 submission.

  DRISK comments: See Attachment B, DHCPL, for DRISK recommendations in track changes.

4.2.1.3 Elements to Assure Safe Use: The REMS for Prolia does not include Elements to Assure Safe Use.

4.2.1.4 Implementation System: The REMS for Prolia does not include Elements to Assure Safe Use. Therefore, an Implementation System is not required.

4.2.2 REMS Supporting Document

- Amgen proposed changing the current REMS goals to those proposed in the consolidated REMS document.

  DRISK comments: See DRISK comments and recommendations in section 4.2.1.1 above regarding modification of the REMS goals.

- Amgen proposed the addition of [redacted] (b) (4) – Amgen proposed adding [redacted] (b) (4).

  DRISK comments: DRISK does not agree. See section 4.2.1.2 above.

4.2.3 REMS webpage

- Amgen proposed changing the name of the DHCPL link from "Dear Health Care Professional Letter" to [redacted] (b) (4) or [redacted] (b) (4).

  DRISK comments: DRISK does not agree and recommends keeping the original text. See attached MS Word version of the website with track changes.

- Additional comments by DRISK

  DRISK comments: The hyperlink at the top of the webpage, [redacted] (b) (4) *This hyperlink should be removed as we believe that REMS websites should not* [redacted] (b) (4).

See Attachment C (MS Word version of the website) with DRISK recommendations in track changes.

5 RECOMMENDATIONS FOR THE REVIEW DIVISION

DRISK requests that the recommendations on the Prolia REMS included in section 6 below be sent to the applicant as soon as possible, including the following appended materials with our track changes:

- Attachment A: REMS Document
- Attachment B: Dear Healthcare Provider Letter (DHCPL)
- Attachment C: MS Word version of the Prolia REMS website

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

Please request that the applicant respond to these comments as soon as possible to facilitate further review in order to meet the action date for this BLA.

6 RECOMMENDATIONS FOR THE APPLICANT

1. REMS Document

a. Goals

i. FDA does not agree with the proposed revisions to the goals because these [redacted] (b) (4) Please note that osteonecrosis of the jaw is listed as a separate entity in the Warnings and Precautions section of the label.

ii. Revise the goal to include the addition of osteonecrosis of the jaw to the list of risks mentioned.

See Attachment A, REMS Document, for the necessary changes.

b. Communication Plan

i. Communication Plan and DHCPL – FDA does not agree with having a [redacted] (b) (4)

Make the following necessary changes:

- remove the initial CP from the REMS document,
- add to the Supporting Document CP section a description of what occurred with regard to the initial communication plan (include who was targeted (i.e., endocrinologists, rheumatologists) and why and when the CP activities occurred),
- [redacted] (b) (4) single CP that will address both indications,
- send the DHCPL to the American Society of Clinical Oncology (ASCO) for distribution among its members,
- resend the DHCPL to newly identified prescribers for up to 2 years after Prolia approval, and
- resend the DHCPL yearly to all the selected professional societies mentioned in the initial CP for up to 3 years after Prolia approval.

See Attachment A (REMS document) and Attachment B (DHCPL) with FDA recommendations in track changes.

2. REMS Supporting Document

a. Update the REMS Supporting Document to reflect the modifications to the REMS Document and currently implemented REMS assessment methods.

3. REMS webpage

a. [redacted] (b) (4)

b. Change the current REMS goals to be consistent with the REMS document, as described above.

c. Keep the original text for the DHCPL link.

d. Remove the hyperlink at the top of the page. [redacted] (b) (4)

See Attachment C, MS Word version of the website, with FDA recommendations in track changes.

4. Submission Instructions

a. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document.

b. Format Request:

i. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

ii. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.

5. Attachments

a. Attachment A: REMS Document

b. Attachment B: Dear Healthcare Provider Letter (DHCPL)

c. Attachment C: MS Word version of the Prolia REMS website

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

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

Date:	04 September 2009
To:	Scott Monroe, M.D., Director Division of Reproductive and Urologic Products
	Patricia Keegan, M.D., Director Division of Biologic Oncology Products
Thru:	Claudia Karwoski, Pharm. D., Director Division of Risk Management (DRISK), OSE
From:	Elizabeth Donohoe, M.D., Medical Officer, DRISK
	Kathryn O'Connell, M.D., PhD, Medical Officer, DRISK
Subject:	Review of proposed Risk Management Plan
Drug Name(s):	Denosumab [Prolia]
Application Type/Number:	BLA 125320, BLA 125331
Applicant/sponsor:	Amgen
OSE RCM #:	2009-133

Mary Willy, PhD
for Claudia Karwoski

INTRODUCTION

This review responds to the request by the Division of Reproductive and Urologic Products (DRUP) for the Office of Surveillance and Epidemiology's (OSE) Division of Risk Management (DRISK) to review and comment on the sponsor's proposed Risk Management Plan (RMP) for denosumab (Prolia). The sponsor submitted a Risk Management Plan (RMP) for BLA 125320, BLA 125331 on December 19, 2008. Additional information related to risk management activities was submitted by the sponsor for the Advisory Committee meeting held August 13, 2009.

BACKGROUND

Denosumab, trade name Prolia, has proposed indications for treatment and prevention of post-menopausal osteoporosis and treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast or prostate cancer. Denosumab is a human monoclonal antibody targeting RANK ligand, an important factor in regulation of bone loss. This product is a subcutaneous injection given every six months. This review does not specifically address the indications related to bone loss in cancer patients as a DRISK consult was only requested from DRUP. The sponsor submitted an RMP with its NDA application which provides the basis for this review.

Post-menopausal osteoporosis is a disease associated with significant morbidity with estimates of over 8 million persons afflicted in the United States. There are a number of treatment options with varied dosing regimens currently on the market for post-menopausal osteoporosis including five bisphosphonates, an estrogen agonist/antagonist, a Parathyroid Hormone analog and three calcitonin products. Denosumab is a New Molecular Entity (NME) and the first biologic developed for treatment of osteoporosis. There are other monoclonal antibodies on the market with serious risks, such as infections, which have warranted issuance of Medication Guides. Denosumab shares some risks with the bisphosphonates: hypocalcemia and osteonecrosis of the jaw (ONJ); these risks are currently addressed through product labeling for bisphosphonates.

The Food and Drug Administration Amendments Act (FDAAA) of 2007 gives the FDA the authority to require the submission of a REMS from a sponsor for a given product if the FDA determines a REMS is warranted. A sponsor may submit a "risk management" plan, but it is not considered a "REMS" unless the FDA determines that a REMS is warranted. Given the early stage of this products application process, the FDA has not yet determined if a REMS is warranted. The review below addresses the format of the submitted information in general but does not imply that the FDA has agreed that this product requires submission of a REMS from the sponsor.

MATERIAL REVIEWED

- Risk Management Plan (RMP) submitted by the sponsor December 19, 2008.
- Background Information for the August 13, 2009 Advisory Committee meeting
    - submitted by sponsor; and
    - submitted by DRUP
- Advisory Committee findings, August 13, 2009

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RESULTS OF REVIEW

Sponsor's RMP Submitted December 2008
The sponsor's RMP submitted in December 2008 largely utilizes routine risk minimization activities through product labeling and routine pharmacovigilance (PV). No "REMS" elements are mentioned in the sponsor's RMP.

The sponsor categorizes associated risks as follows [all requiring routine risk minimization in the RMP]:

Identified Risk: hypocalcemia
Potential Risks: infections, hypersensitivity, cataracts in men with prostate cancer
Important Missing (or Limited) Information: pregnant and lactating women, children and potential off-label use.

With the exception of "potential off-label use", all risks would be addressed through language in Prescribing Information [PI]. The sponsor does not plan any "Additional Risk Minimization Activities" for any of the identified risks. The sponsor's RMP focuses on "product information, labeling, health care professional and patient education where appropriate" yet these efforts are not further defined. There are also additional safety concerns identified by the review division which the sponsor does not specifically include in its RMP; these will be addressed in the discussion below.

In addition to routine PV of the aforementioned risks, the sponsor proposes proactive surveillance [explained below] related to fracture healing complications, ONJ, infections, cataracts and use in children.

Sponsor's Background Materials for the AC Meeting
There is minimal variation between the RMP submitted in December 2008 and the RMP the sponsor included in the background materials for the AC. In the slide set for the AC meeting, the sponsor identifies the following:

Risk Minimization [included in "Warnings and Precautions" Highlights in the PI]:
- Hypocalcemia
- Skin infections
- ONJ

Additional Risk Communication: Labeling
- Eczema
- Cataracts [males with prostrate cancer]

It is not clear if "labeling" in this category refers just to the PI or to a possible Patient Package Insert or Medication Guide but, as "additional risk minimization activities" are not identified by the sponsor, it is likely the sponsor planned to limit this information to the PI.

The sponsor's Background Materials includes all risk management activities under "Pharmacovigilance Program" as described below:

Pharmacovigilance:
- Routine: utilizing AE reporting, periodic safety reports [PSRs] and periodic safety update reports [PSURs].

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- Proactive:
    - Targeted surveillance and focused questionnaires for specific adverse events of interest [hypocalcemia, skin infections leading to hospitalization, infections, fracture healing complications, ONJ, hypersensitivity, immunogenicity, cataracts, cardiovascular, malignancy, potential off-label use for other indications] that are reported in clinical trials and from the postmarketing experience.
    - Use of health care databases to further elucidate the risk and incidence of adverse events of interest which will detect rare events occurring with a frequency as low as 2.5/100,000.
    - Continued monitoring and adjudication of ONJ.
    - A prospective study related to cataracts.
    - A prospective observational pregnancy exposure registry

Ongoing Risk Assessment

- A comprehensive postmarketing pharmacovigilance program including evaluation of ongoing long-term safety studies in post-menopausal osteoporosis [PMO] and hormone ablation therapy [HALT] trials and from the advanced cancer program. Over 8000 patients are currently enrolled with denosumab exposure planned for up to 10 years.

The sponsor states: "The risks associated with denosumab use and the relevant risk minimization and management of events will be discussed under the appropriate sections of the proposed prescribing information". These "Risk Minimization Activities" include, by risk:

Hypocalcemia: contraindicated for persons with hypocalcemia; monitor patients predisposed to hypocalcemia; recommend calcium and Vitamin D supplementation
Skin Infections Leading to Hospitalization: advise patients to seek prompt medical attention if they develop signs or symptoms of cellulitis
ONJ: advise patients that good oral hygiene should be practiced during treatment
Potential Off-Label Use for Other Indications: recommended use only in approved indications

DISCUSSION

The safety profile of denosumab carries a number of identified risks (described above). In its RMP, the sponsor has proposed addressing these risks largely through "routine risk minimization activities" in the form of the product label [Prescribing Information]. Additional efforts are warranted to communicate these serious risks to patients and prescribers. The sponsor further proposes monitoring a number of these risks through its planned PV activities, which appear adequate. However, not all safety concerns are specifically included in the sponsor's proposed RMP.

The review division raised specific safety concerns at the AC, including: occurrence of serious infections, development of new malignancies, dermatologic adverse events and possible oversuppression of bone remodeling. It seems that the risks of infection [including skin, ear, urinary tract, endocarditis, infective arthritis and endocarditis] and dermatologic events remain as significant safety concerns. The sponsor's RMP includes "infections" but focuses on "skin infections (predominantly cellulitis)" as the related adverse reaction. Additional infections, as noted above and identified by the review division, are not further defined.

If the review division decides to approve this drug, these risks should be communicated to patients and prescribers. It appears that these risks may not be well characterized and additional

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data needs should be considered through post-marketing requirements [PMR] overseen by the review division. It is DRISK's understanding that a number of PMRs are being considered, including a post-approval surveillance study, which may address these safety concerns.

The risk of development of new malignancies is difficult to characterize since carcinogenicity studies were not done [no animal studies were done as denosumab is not active in rodent] and the question of oversuppression of bone remodeling requires long-term follow-up for better understanding. Additionally, tumor metastases is a concern for the indications related to bone loss and HALT. These risks could also be addressed through PMRs.

The sponsor's RMP appears to limit its communication efforts to Prescribing Information. Under FDAAA, enacted in 2007, the FDA has authority to require a Risk Evaluation and Mitigation Strategies (REMS) program if it is determined that it is necessary for the benefits of the drug to outweigh the risks. Under FDAAA, a Medication Guide may be required if FDA determines that: patient labeling could help prevent serious adverse events; the product has serious risks that could affect the patient's decision to use or continue to use the drug; or patient adherence to directions is crucial to product effectiveness. A Communication Plan may also be warranted to support risk mitigation and may include a letter to healthcare providers.

Given that other monoclonal antibodies have similar serious risk of infection and require MGs, it is reasonable to require a MG informing patients about the risks of denosumab [infections, skin infections, hypocalcemia, and other risks as identified by the review division]. These risks would also be delineated in the labeling. The support of the Advisory Committee for a Communication Plan is also an important factor. Since denosumab is a new Molecular Entity, targeted education to providers through a health care provider letter informing providers of associated risks could be seriously considered.

The Advisory Committee also recommended that the REMS for denosumab include a patient registry. It is not clear what the intent of that "registry" would be, based on discussion at the AC meeting. It appears that the AC recommended collection of patient safety data for use in long-term adverse event monitoring and analyses.

It is DRISK's opinion that use of a patient "registry" as part of a REMS is important when the point of prescribing or dispensing the drug requires specific patient data. It does not appear that either of these two criteria applies to denosumab. Collection of long-term safety information through a post-marketing requirement [PMR] for such a study, however, may be an option the review division may consider.

RECOMMENDATIONS

DRISK recommends that a REMS including a Medication Guide [MG] and Communication Plan [CP] be considered if the review division decides to approve denosumab. The MG and CP, informing patients and prescribers of the serious risks of denosumab, would necessitate a REMS. Further characterization of known risks and additional risks, including occurrence of new malignancies and suppression of bone remodeling, may be addressed in PMR efforts specified by the review division.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

PROPRIETARY NAME REVIEW(S)

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

Date:	April 7, 2009
To:	Scott Monroe, MD Director, Division of Reproductive and Urologic Products Patricia Keegan, MD Director, Division of Biologic Oncology Products
Through:	Carlos Mena-Grillasca,, RPh, Acting Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Errors and Technical Support
Subject:	Proprietary Name Review
Drug Name(s):	Prolia (Denosumab) for Solution for Subcutaneous Injection 60 mg/mL
Application Type/Number:	BLA 125320 BLA 125331 BLA 125332 BLA 125333
Applicant:	Amgen
OSE RCM #:	2008-1362

****Note: This review contains proprietary and confidential information that should not be released to the public.****

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EXECUTIVE SUMMARY

DMEPA identified 29 names as having potential orthographic and/or phonetic similarity to Prolia. Additionally, the Applicant submitted an external risk assessment of the proprietary name, which identified an additional two names. Thus, DMEPA analyzed 31 names for their potential to cause confusion with Prolia. Our Failure Mode Effects Analysis determined that the name similarity between Prolia and the 31 names was unlikely to result in medication errors related to name confusion. This finding was consistent with and supported by the external risk assessment of the proprietary name submitted by the Applicant. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Prolia, for this product. The Division of Reproductive and Urologic Products and the Division of Biologic Oncology Products concur with this assessment.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change.

In addition, the proposed name must be reevaluated 90 days before approval of the NDA, even if the proposed product characteristics as stated in this review are not altered.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Reproductive and Urologic Products and the Division of Biologic Oncology Products for assessment of the proposed proprietary name, Prolia, regarding its potential confusion with other proprietary or established drug names in normal practice settings.

Additionally, container labels, carton and insert labeling were provided for review and comment and will be reviewed in a separate review (OSE Review #2009-162).

1.2 PRODUCT INFORMATION

Prolia (denosumab) is a receptor activator of nuclear factor kappa B (RANK) ligand inhibitor indicated for treatment and prevention of postmenopausal osteoporosis and treatment and prevention of bone loss associated with hormone ablation therapy with prostate and breast cancer. The recommended dose is 60 mg (1 mL) once every 6 months via subcutaneous injection. It is available in 60 mg/mL solution in a single-use prefilled syringe and single-dose vial.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by DMEPA conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a

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medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Prolia, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Agency.

For the proprietary name, Prolia, DMEPA searches a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). Our Division also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses our clinical expertise to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the staff consider the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process,

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

2.1.1 Search Criteria

DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'P' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4][5]

To identify drug names that may look similar to Prolia, the staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (two, capital letter 'P' and lower case 'l'), downstokes (none), cross-strokes (none), and dotted letters (one, lower case 'i'). Additionally, several letters in Prolia may be vulnerable to ambiguity when scripted, including the letter 'P' may appear as 'B,' 'D,' 'F,' or 'R'; lower case 'r' may appear as a lower case 'i' ; lower case 'a,' 'i,' or 'o' may appear as 'a,' 'e,' 'i,' 'o,' or 'u'. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Prolia.

When searching to identify potential names that may sound similar to Prolia, DMEPA searches for names with similar number of syllables (two), stresses (pro-LIA or PRO-lia), and placement of vowel and consonant sounds. Additionally, several letters in Prolia may be vulnerable to misinterpretation when spoken, including 'Pro' may be interpreted as 'Fro,' 'Tro,' or 'Bro.' As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Prolia. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, DMEPA was provided with the following information about the proposed product: the proposed proprietary name (Prolia), the established name (denosumab), proposed indication (postmenopausal osteoporosis and bone loss in patients undergoing hormone ablation for prostate and breast cancer), strength (60 mg/mL), dose (60 mg), frequency of administration (once every 6 months), route (subcutaneous) and dosage form (injectable) of the product. Appendix A provides a more detailed listing of the product characteristics the staff generally takes into consideration.

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[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

[4] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[5] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artifical Inteligence in Medicine (2005)

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Lastly, DMEPA also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and DMEPA provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and information sources

The proposed proprietary name, Prolia, was provided to DMEPA to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Prolia using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, DMEPA use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Prolia. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of DMEPA and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of DMEPA were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Prolia with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Prolia in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal

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prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

Figure 1. Prolia Study (conducted on October 10, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL INPATIENT ORDER
Outpatient Prescription: Prolia #1 syringe Return to clinic Q6mos for injection.	Prolia Quantity 1 syringe Return to clinic every 6 months for injection
Inpatient Medication Order: Prolia inject subcutaneously x 1 dose	

2.1.3 External Proprietary Name Risk Assessment

For this product, the Applicant submitted an independent risk assessment of the proposed proprietary name conducted by a consulting firm. DMEPA conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether DMEPA's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, DMEPA provides a detailed explanation of these differences.

2.1.4 Comments from the OND Review Division

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. Any comments or concerns are addressed in the safety evaluator's assessment.

The regulatory division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The regulatory division is requested to concur/not concur with DMEPA's final decision.

2.1.5 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Prolia convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Prolia to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product

[6] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

DMEPA will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. DMEPA identifies a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug another drug product.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then our division will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, the World Health Organization, the Joint Commission, and the Institute for Safe Medication Practices, that have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

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Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. Our Division is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The database, internet, and reference search identified 27 names as having some similarity to the name Prolia.

Twenty of the 27 names were thought to look like Prolia, which include: Droxia, Prozac, (b) (4), (b) (4), Prolex DM, Prelone, Prelief, Proline, Prelu-2, Prolixin, Proloid, (b) (4)***, (b) (4), Prohist, Protid, (b) (4)***, Priftin, and (b) (4)***. Two names (b) (4) and Propecia) were thought to sound similar to Prolia. Five additional names (Prolief, Portia, Prolic, (b) (4), and Prolia) were thought to look and sound similar to Prolia.

A search of the United States Adopted Names (USAN) stem list on February 10, 2009 indentified no USAN stems contained in the proposed name, Prolia.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (see section 3.1.1. above), and noted no additional names thought to have orthographic or phonetic similarity to Prolia

*** **Note: This review contains proprietary and confidential information that should not be released to the public.** ***

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DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 FDA Prescription Analysis Studies

A total of 29 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. All the respondents in the written studies (n=17) and five respondents from the verbal study interpreted the name correctly as "Prolia." All the misinterpretations occurred in the phonetic prescription study with the vowels in Prolia 'i' reported as 'e' as well as the consonants 'Pr' reported as 'Per' and 'l' reported as 'v'. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Name Studies

In the proposed name risk assessment submitted by the Applicant, Drug Safety Institute (DSI) identified and evaluated a total of 180 drug names thought to have some potential for confusion with the name Prolia.

One hundred sixty-five (n=165) of the 180 names were determined to lack sufficient orthographic and/or phonetic similarity to Prolia to present a risk of confusion. Thirteen (n=13) of the 180 names (Droxia, Prozac, Prolex DM, Prelone, Prelief, Proline, Prelu-2, Prolixin, Proloid, Protid, (b) (4) Propecia, and Portia) were previously identified in the DMEPA staff searches or the Expert Panel Discussion. The remaining two names, Plova and Solia, were determined to have orthographic and /or phonetic similarity to Prolia, and thus determined to present some risk of confusion.

3.1.5 Comments from the OND Review Division

DMEPA notified the Division of Reproductive and Urologic Products (DRUP) and the Division of Biology Oncology Products (DBOP) via e-mail that we had no objections to the proposed proprietary name, Prolia, on March 5, 2009. Per e-mail correspondences from DRUP on March 9, 2009 and DBOP on March 31, 2009, they indicated they concur with our assessment of the proposed proprietary name, Prolia.

3.1.6 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified two additional names, Frova and Pruvel***, thought to look similar to Prolia and represent a potential source of drug name confusion.

Eight of the 31 identified names were determined to lack sufficient orthographic and/or phonetic similarity to Prolia to present a risk of confusion (see Appendix C). The remaining 23 names were determined to have some orthographic and /or phonetic similarity to Prolia, and thus determined to present some risk of confusion.

Failure mode and effect analysis (FMEA) was then applied to determine if the potential name, Prolia, could potentially be confused with any of these 23 names and lead to medication errors.

*** **Note: This review contains proprietary and confidential information that should not be released to the public.*****

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This analysis determined that the name similarity between Prolia and the identified names was unlikely to result in medication errors for all 23 products for the reasons described in Appendices D through H.

4 DISCUSSION

Thirty-one names were evaluated for their potential similarity to the proposed name, Prolia. The FMEA indicates that the proposed name is not likely to result in name confusion that could lead to medication error for the reasons outlined in Appendices C through H.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Prolia, is not vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant. As such, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Prolia, for this product at this time. The Division of Reproductive and Urologic Products and the Division of Biologic Oncology Products concur with this assessment. Additionally, DDMAC does not object to the proposed name, Prolia, from a promotional perspective.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

5.1 COMMENTS TO THE DIVISION

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Divisions for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Project Managers, Sandra Griffith at 301-796-2445 or Cherye Milburna at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Prolia, and have concluded that it is acceptable.

The proprietary name, Prolia, will be re-reviewed 90 days prior to approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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6 REFERENCES

1. ***Micromedex Integrated Index***
(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for DMEPA, FDA.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***
(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***AMF Decision Support System [DSS]***

DSS is a government database used to track individual submissions and assignments in review divisions.

5. ***Division of Medication Error Prevention proprietary name consultation requests***

This is a list of proposed and pending names that is generated by DMEPA from the Access database/tracking system.

6. ***Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)***

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

7. ***Electronic online version of the FDA Orange Book***
(http://www.fda.gov/cder/ob/default.htm)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. ***US Patent and Trademark Office location*** *http://www.uspto.gov.*

Provides information regarding patent and trademarks.

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9. ***Clinical Pharmacology Online***
(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

10. ***Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at*** *www.thomson-thomson.com*

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. ***Natural Medicines Comprehensive Databases***
(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. ***Stat!Ref***
(http://inside.fda.gov/Library/ElectronicResourcesWebLERN/Alphabeticallist/index.htm)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

13. ***USAN Stems*** *(http://www.ama-assn.org/ama/pub/category/4782.html)*

List contains all the recognized USAN stems.

14. ***Red Book Pharmacy's Fundamental Reference***

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. ***Lexi-Comp*** *(www.pharmacist.com)*

A web-based searchable version of the Drug Information Handbook.

16. ***Medical Abbreviations Book***

Contains commonly used medical abbreviations and their definitions.

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APPENDICES

Appendix A:

DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. DMEPA apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, DMEPA compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, DMEPA also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-strokes Dotted letters Ambiguity introduced	• Names may look similar when scripted, and lead to drug name confusion in written communication

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		by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses

Outpatient Prescription	Inpatient Medication Order	Verbal Inpatient Medication Order
Prolia	Prolia	Prolia
Prolia	Prolia	Prolia
Prolia	Prolia	Prolea
Prolia	Prolia	Prolia
Prolia	Prolia	Provia
Prolia	Prolia	Prolea
Prolia	Prolia	Prolea
Prolia	Prolia	Prolia
Prolia		Perlia
		Prolia
		Prolea
		Provia

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Appendix C: Proprietary names with minimal orthographic and/or phonetic similarity

Proprietary Name	Similarity to Prolia
Prelief	Look
Prelu-2	Look
Priftin	Look
Prohist	Look
Prolief	Look
Prolixin	Look
(b) (4)	Sound
Propecia	Sound

Appendix D: Proprietary names used only in Foreign Countries

Proprietary Name	Similarity to Prolia	Country
Prolic	Look and Sound	Indonesia
Prolidon	Look	Mexico
(b) (4)	Look	Chile, Argentina, Brazil, Venezuela
(b) (4)	Look and Sound	Peru, Philippines

Appendix E: Proprietary name of products discontinued with no generic equivalent

Proprietary Name	Similarity to Prolia	Year discontinued
Plova (psyllium mucilloid) (Over-the-Counter)	Look	Not available
Proloid (thyroglobulin)	Look	Not available

Appendix F: Non-Drug Names

Proprietary Name	Similarity to Prolia	Reason
(b) (4)	Look	Chemical
Prolia	Look and Sound	Soy flour
(b) (4)	Look	Chemical

Appendix G: Proprietary names of products withdrawn or approved under a different tradename

Proprietary Name	Similarity to Prolia	Reason (year, if applicable)
(b) (4)	Look	(b) (4)
(b) (4)***	Look	
(b) (4)***	Look	

Appendix H: Products with no overlap in strength, usual dose and route of administration

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Prolia (denosumab)		**60 mg/mL**	**Usual dose: Inject 60 mg (1 mL) subcutaenously once every 6 months**
Droxia (Hydroxyurea)	Look	200 mg, 300 mg, 400 mg	15 mg/kg/day orally
Frova (Frovatriptan Succinate)	Look	2.5 mg	1 tablet once orally
Portia (Ethinyl Estradiol/ Levonorgestrel)	Look and Sound	0.03 mg/0.15 mg	1 tablet daily orally
Prelone (Prednisolone)	Look	15 mg/mL	Individualized to patient; orally

*** **Note: This review contains proprietary and confidential information that should not be released to the public.** ***

Reference ID: 3168397

Prodec DM (Carbinoxamine/ Dextromethorphan/ Pseudoephedrine)	Look	2 mg/4 mg/25 mg	1 dropperful orally every 6 hours
Prolex DM (Guiafenesin/ Dextromethorphan)	Look	300 mg/15 mg per 5 mL	5 to 7.5 mL orally up to four times daily
Proline (amino acid)	Look	500 mg	3000 mg per day taken twice daily orally
Protid (Acetaminophen/ Chlorpheniramine/ Phenylephrine)	Look	500 mg/8 mg/40 mg	1-3 tablets once to three times daily orally
Prozac (Fluoxetine)	Look	Capsule: 10 mg, 20 mg, 40 mg, 90 mg Solution: 20 mg/5 mL	Individualized to patient; usually start at 20 mg/day orally
Pruvel*** (Prulifoxacin)	Look	600 mg	1 tablet orally daily for 3 days
Solia (Ethinyl Estradiol/ Desogestrel)	Look	0.03 mg/0.15 mg	1 tablet daily orally

*** **Note: This review contains proprietary and confidential information that should not be released to the public.***

Reference ID: 3168397

Linked Applications	Sponsor Name	Drug Name / Subject
IND 9837	AMGEN INC	Human Monoclonal Antibody (AMG 162)(CHO Cells, Amgen) to Osteoprotegerin Ligand (RANKL)

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

/s/

JUDY J PARK
06/12/2009

CARLOS M MENA-GRILLASCA
06/15/2009

DENISE P TOYER
06/17/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125320Orig1s005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1. Debarment Certification

Amgen hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Randall Steiner, DPA, MS
Executive Director, Regulatory Affairs

11/11/08
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 15, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6: Information Request

FDA requested Amgen make additional minor revisions to the package insert which included:

- Update the month and year for Indications and Usage, under RECENT MAJOR CHANGES in the Highlights section.
- Update the Revised date with the month and year of approval in the highlights section.
- Remove the word (b) (4) in the second sentence of the last paragraph under (b) (4) (b) (4) from the following sentence:

> *"Pain in extremity (7.7% placebo vs. 9.9% Prolia) and musculoskeletal pain (3.8% placebo vs. 6.0% Prolia)* (b) (4) *have also been reported in clinical trials."*

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 14, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6: Information Request-REMS

FDA requested Amgen make additional minor revisions to the REMS and REMS supporting documents (Medication Guide), which included:

- Editing the header to reflect the date of the most recent modification
- Update the revised date and version at the end of the document

18 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 13, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6: FDA proposed REMS (Medguide)

FDA's proposed revisions to the REMS documents.

- Please ensure all tracked changes are accepted for the clean version.
- Minor editorial changes to the Medguide for both the REMS and REMS supporting document.
- Update the revised date and version.

18 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 9, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6: FDA proposed REMS changes to the DHCP letter

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FDA's proposed changes included adding headings to the first and second REMS supporting document (DHCP) letter.

16 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3168397

Pierce, Melanie

From: Ramanadham, Mahesh
Sent: Friday, September 09, 2011 6:57 AM
To: Pierce, Melanie; CDER-TB-EER
Subject: RE: Class II efficacy supplement resubmissions 125320/5/6

Attachments: TB- EER form 125320-6 .doc; TB- EER form 125320-5 .doc

Dear Melanie

NDMAB has completed its review of the TB-EERs for STNs 125320/5 and 125320/6. There are no pending or ongoing compliance actions that prevent approval of these supplements.


TB- EER form 125320-6 .doc (47..


TB- EER form 125320-5 .doc (48...

Sincerely,

Mahesh Ramanadham, PharmD/M.B.A.
LT., USPHS
Regulatory Compliance Officer
CDER, Office of Compliance
Office of Manufacturing and Product Quality,
Division of Good Manufacturing Practice Assessment
New Drug Manufacturing Assessment Branch
(301)796-3272

From: Pierce, Melanie
Sent: Wednesday, September 07, 2011 12:28 PM
To: CDER-TB-EER
Subject: Class II efficacy supplement resubmissions 125320/5/6

Please see the attached TBP-EER requests for class II efficacy supplements 125320/5 and 125320/6. The information contained in both requests are exactly the same.
Thank you,
Melanie
<< File: TB- EER form 125320-5 .doc >> << File: TB- EER form 125320-6 .doc >>

Melanie B. Pierce
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Email: Melanie.Pierce@fda.hhs.gov
Phone: 301-796-1273

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 8, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6; AD/IR-DHCP letter

The following request was sent to Amgen via electronic mail notification on September 8, 2011:

FDA proposes that you remove the following two sentences from the DHCP letter:

(b) (4)

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 7, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6; Tcon re: REMS-DHCP letter

FDA Attendees
Patricia Keegan
Jeff Summers
Melanie Pierce
Shan Pradhan

Amgen Attendees
John Bergan
Roy Baynes
Steve Galson
Sandy Milligan
Brad Glasscock
Roger Dansey

A teleconference was held with Amgen on September 7, 2011 to discuss the inclusion of safety information in the Dear Healthcare Provider (DHCP) Letter.

Amgen made the argument that the following statement did not belong in (DHCP) letter because the information is located in the product label:

(b) (4)

Amgen's justification, as outlined in their August 30, 2011 communication, is that the serious infection information has been part of the label since the original prescribing information (b) (4) Additionally, the original DHCP letter did not include the above-referenced statement nor is there data from the HALT studies (20040135 and 20040138) regarding (b) (4).

FDA agreed to follow up with Amgen to determine if the information should remain in the label.

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 2, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6; Information request, REMS

The following advice and information request was sent to Amgen via electronic mail notification on September 2, 2011.

REMS Document

a. Change acronym for "Dear Healthcare Provider Letter" from DHCPL to DHCP Letter in the REMS document and REMS Supporting document.

Rationale: We recommend this modification to maintain internal consistency in all REMS materials.

b. Attach to the REMS document the following materials: Medication Guide, DHCP Letter, and Prolia REMS website screenshot.

Rationale: These materials are part of the REMS and must be appended.

c. Additional minor edits in track changes.

See track changes in attachment A.

2. Dear Healthcare Provider Letter

a. Add the following sentence as the end of the "Serious Infections" section. (b) (4)

(b) (4)

Rationale: This information is included in the label and provides important guidance to prescribers. Additionally, please note that this letter will be resent to the professional societies included in the initial communication plan and to any new prescribers.

See track changes in attachment B.

3. REMS Supporting Document

a. Change acronym for "Dear Healthcare Provider Letter" from DHCPL to DHCP Letter in the REMS document and REMS Supporting document.

Rationale: We recommend this modification to maintain internal consistency in all REMS materials.

Reference ID: 3168397

b. Additional minor edits in track changes.

See track changes in attachment C.

4. Submission Instructions

a. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document.

b. Format Request:

i. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

ii. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 26, 2011

From: Norma Griffin, DBOP/OODP/CDER

Subject: BLA 125320/5/6; REMS Modification – Proposed Changes

Amgen, Inc.
Attention: John Bergan, R.A.C.
Senior Manager, Regulatory Affairs

Dear Mr. Bergan:

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Prolia (denosumab). We also refer to your July 1, 2011 response to our June 8, 2011 REMS Information Request.

Please see the additional requested changes to the REMS and REMS materials and the attached documents. Provide a response via email to Melanie Pierce at Melanie.Pierce@fda.hhs.gov or Norma Griffin at Norma.Griffin@fda.hhs.gov by Tuesday, August 30, 2011.

1. REMS Document

a. Delete the references (b) (4) from the REMS document.

Rationale: A statement indicating that the Medication Guide (MG), Dear Healthcare Provider Letter (DHCPL), and REMS web page screenshots are appended is sufficient. However, you may include (b) (4) in the REMS Supporting document.

b. Describe in the REMS Supporting document the methods for (b) (4) (b) (4) (b) (4). In addition, edit the statement to include providers who are likely to prescribe Prolia for the HALT indications in the future. We suggest the following language:

*"The CP consists of a Dear Health Healthcare Provider Letter (DHCPL), which will be sent within 60 days of the most recent REMS approval to oncologists and urologists who **are likely to prescribe or have prescribed** hormone ablation as a method of treatment for patients with prostate or breast cancer by mass mailing or electronic mailing."*

Rationale: The REMS Supporting document does not describe how prescribers who have utilized hormone ablation as a method of treatment for patients with prostate or breast cancer will be identified. In addition, it is important to include potential prescribers of Prolia for these indications.

Reference ID: 3168397

c. Append the MG, DHCPL, and web page screenshot to the REMS document.

Rationale: All REMS documents must be appended.

See track changes in Attachment A.

2. Dear Healthcare Provider Letter

a. Add the following sentence as the first sentence of the paragraph under the subheading "Serious Infections": [redacted]

Rationale: This statement is an important component of the risk message communicated in this REMS.

See track changes in Attachment B.

3. REMS Supporting Document

a. Add the following text to the end of section 4.1.1: [redacted]

Rationale: The REMS Supporting document may [redacted] containing the MG.

b. Describe in the REMS Supporting document the methods for [redacted] ". In addition, edit the statement to include providers who are likely to prescribe Prolia for the HALT indications in the future. We suggest the following language:

*"The CP consists of a Dear Health Healthcare Provider Letter (DHCPL), which will be sent within 60 days of the most recent REMS approval to oncologists and urologists who **are likely to prescribe or have prescribed** hormone ablation as a method of treatment for patients with prostate or breast cancer by mass mailing or electronic mailing."*

Rationale: The REMS Supporting document does not describe how prescribers who have utilized hormone ablation as a method of treatment for patients with prostate or breast cancer will be identified. In addition, it is important to include potential prescribers of Prolia for these indications.

c. Add the following text to the end of section 4.1.2

"The DHCP Letter was revised to include new indications for Prolia and will replace the initial letter in subsequent mailings to professional societies and newly identified prescribers. [redacted]

Prolia REMS Website: [redacted] *will describe the risks associated with the use of Prolia and instruct Healthcare Providers on how to obtain additional safety information."*

Reference ID: 3168397

Rationale: Provide additional clarification points to the CP.

See track changes in Attachment C.

4. Submission Instructions

a. Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached materials and the REMS Supporting Document.

b. Format Request:

i. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

i. Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials be in a single WORD document.

Please contact Melanie Pierce at Melanie.Pierce@fda.hhs.gov or Norma Griffin at Norma.Griffin@fda.hhs.gov if you have any questions.

Attachments

- Attachment A – REMS Document 8-25-2011
- Attachment B - Dear Healthcare Provider Letter 8-25-2011
- Attachment C – REMS Supporting Document 8-25-2011

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Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 3, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6; Package Insert

FDA's proposed changes to the package insert sent to Amgen via electronic mail notification on August 3, 2011.

Changes were to the following sections:

ADVERSE REACTIONS:
Additional change for consistency (removal of (b) (4)

25 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 3, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6; Package Insert

FDA's proposed changes to the package insert sent to Amgen via electronic mail notification on August 3, 2011.

Changes were to the following sections:

ADVERSE REACTIONS:
Additional change for consistency (removal of (b) (4)

25 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 29, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6; Package Insert

FDA's proposed changes to the package insert sent to Amgen via electronic mail notification.

Changes were to the following sections:

- Highlights
- Adverse Reactions [(6, 6.1)]
- Clinical Studies (14.1, 14.2, and 14.3)]

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Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 8, 2011

From: Melanie Pierce, DBOP/OODP/CDER

Subject: BLA 125320/5/6; Information request, REMS

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Prolia (denosumab).

We have the following requests for additional information:

The approved Risk Evaluation Mitigation and Strategy (REMS) for Prolia consists of a Medication Guide, a Communication Plan and a timetable for submission of assessments of the REMS. Your resubmissions to supplements STN 125320/5 and STN 125320/6 proposed changes to the concise REMS document and Medication Guide. Your proposed changes require the submission of a REMS modification. For that reason, we consider your resubmitted supplements to also be REMS Modification supplements. As a reminder, any REMS modification requires the submission of a REMS Assessment. Although your first REMS Assessment is not due, you are still required to submit a REMS Assessment for your proposed changes. Submit the following statement as amendment to your supplements to fulfill this requirement.

> "The Medication Guide, communication plan, timetable for submission of assessments would be adequate with the proposed modifications to achieve their purpose."

In addition, we determined that the Communication Plan should also apply to the oncology community. Therefore, we request that you submit a modification to your Communication Plan as an amendment to your supplements. Your proposed Communication Plan changes should also be addressed with your REMS assessment.

Please let us know if you have any questions.

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA STN 125320/5

ACKNOWLEDGE COMPLETE RESPONSE

April 1, 2011

Amgen, Incorporated
Attention: John Bergan, RAC
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-1799

Dear Mr. Bergan:

We have received your March 18, 2011 resubmission to your supplement to your biologics license application for Prolia (denosumab) on March 18, 2011.

The resubmission contains analyses from studies 20050103, 20050136 and 20050244; updated labeling; a revised Risk Evaluation and Mitigation Strategy (REMS); and a safety update which includes newly available clinical study data that you submitted in response to our October 19, 2011 complete response letter.

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is September 17, 2011.

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

Sincerely,

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

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # BLA# 125332	NDA Supplement #:S- BLA STN # 125332	Efficacy Supplement Type SE-
Proprietary Name: NA Established/Proper Name: Denosumab Dosage Form: Strengths:		
Applicant: Amgen, Incorporated Agent for Applicant (if applicable):		
Date of Application: December 19, 2009 Date of Receipt: December 19, 2009 Date clock started after UN:		
PDUFA Goal Date: October 19, 2009	Action Goal Date (if different):	
Filing Date: February 17, 2009 Date of Filing Meeting: January 29, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☒ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ 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

Reference ID: 3168397

	601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☐ YES ☒ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Reference ID: 3168397

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**: NA	☐ YES # years requested: ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): 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.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☒ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. 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 less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. 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))?	☐ YES ☐ NO

Reference ID: 3168397

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

Reference ID: 3168397

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☐ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ 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?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Reference ID: 3168397

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments:**	☒ YES ☐ NO ☒ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments:**	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments:**	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**: NA	☐ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	☒ YES ☐ NO

Reference ID: 3168397

Note: *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."* **Comments:**	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) ☒ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments:**	☒ YES ☐ NO
Pediatrics	
PREA ***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.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes,** does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments:**	☒ Not Applicable ☐ YES ☐ NO ☒ YES ☐ NO ☐ YES ☐ NO

Reference ID: 3168397

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**: NA	☐ YES ☐ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** ☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☒ Carton labels ☐ Immediate container labels ☒ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments:**	☐ Not Applicable ☒ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments:**	☐ Not Applicable ☒ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments:**	☐ Not Applicable ☒ YES ☐ NO

Reference ID: 3168397

OTC Labeling	
Check all types of labeling submitted. **Comments**: NA	☐ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: Pre-IND-Pre-Phase 3 4.21.04	☒ YES Date(s): ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: 7.08.08; 10.21.08	☒ YES Date(s): ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**: NA	☐ YES Date(s): ☐ NO

Reference ID: 3168397

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

STN: BL 125320/0

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

Please refer to your biologics license application (BLA) submitted under Section 351 of the Public Health Service Act for Prolia (denosumab).

We are reviewing your submission and have the following comments, information requests, and notifications of additional requirements. We request a prompt written response in order to continue our evaluation of your application.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Prolia (denosumab) to ensure that the benefits of the drug outweigh the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.

Your proposed REMS must include the following:

> **Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Prolia (denosumab) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Prolia (denosumab). FDA has determined that Prolia (denosumab) is a product for which patient labeling could help prevent serious adverse effects and has serious risks (relative to benefits) of which

patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Prolia (denosumab).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Prolia (denosumab).

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Prolia (denosumab) will support implementation of the elements of your REMS during the first year after the approval date. The communication plan must provide for the dissemination of information about the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.

The communication plan must include, at minimum, the following:

- A Dear Healthcare Provider Letter. The letter should provide information regarding appropriate patient selection and should include, as an attachment, the approved Prolia (denosumab) label.
- A description of the intended audience for the communication plan, stating specifically the types and specialties of healthcare providers to which the communication plan will be directed, as well as any professional medical associations and societies that will be sent the communication. The intended audience should include all healthcare providers who are likely to prescribe Prolia (denosumab).
- A schedule for when and how the plan's materials are to be distributed to healthcare providers and medical associations.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Prolia (denosumab). Additionally, all relevant proposed REMS materials, including educational and communication materials, should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but is not limited to the following:

a. 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.

b. 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.

c. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

d. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance.

e. A summary of all reported serious infection 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.

Before we can continue our evaluation of this BLA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the accompanying Medication Guide to each patient." or
- "Dispense the enclosed Medication Guide to each patient."

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125320
PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125320
PROPOSED REMS-AMENDMENT

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

If this application is approved, 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 assess the signal of serious risk of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these signals of serious risks.

Therefore, based on appropriate scientific data, FDA has determined that, if this application is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct one or more postmarketing studies of Prolia (denosumab) to assess the signal of serious risk of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover. The specific details of this required postmarketing study or studies will be described more fully in an approval letter for this application, if it is approved.

If you have any questions, please contact the Regulatory Project Manager, Celia Peacock, R.D., M.P.H., at (301) 796-4154.

Sincerely,

George Benson 10/2/09

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: Appendix A: REMS Template
Appendix B: Supporting Document

APPENDIX A: REMS TEMPLATE

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

APPENDIX B: SUPPORTING DOCUMENT

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 24, 2009

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Teleconference: Prolia (denosumab)

FDA Attendees:
Richard Pazdur
Patricia Keegan
Suzanne Demko
Jeff Summers

Amgen Attendees:
Davie Feigal
Edward Burd
Julie Lepin

The teleconference started at 12:30pm:

Amgen inquired about FDA's decision regarding the denosumab application. FDA stated that approval of the hormone ablation therapy (HA) indications will not occur until the safety data on tumor progression for the completed and on-going trials are reviewed. Amgen indicated that the HA prostate trial data demonstrated an objective measure of survival and that the follow-up data for this trial will be available within the next few months. FDA expressed concern that the study was not optimally designed to exclude a detrimental effect on tumors and that other trials, notably those performed in advanced cancer populations, may be more adequately designed to address the impact on tumor outcomes. FDA asked how the data would be submitted; Amgen proposed the following options:

- To collate a safety database for the prostate and breast cancer trials and submit as a response to the complete response. The skeletal related event data will be submitted once the data is complete.
- Wait and submit all of the data simultaneously.

Amgen stated that the analyses for the breast cancer results are available while the prostate data will not be complete until January/February 2010 while. Amgen plans to submit the efficacy data once the analysis from the requested studies is complete. After further discussion FDA suggested that data from one trial with a homegenous patient population instead of all three trials may be sufficient and agreed to confirm this approach with upper management. Amgen agreed to provide timelines for when additional studies are expected to be completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 9, 2009

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Teleconference: Prolia (denosumab)

FDA Attendees:
Patricia Keegan
Suzanne Demko
Jeff Summers

Amgen Attendees:
Davie Feigal
Edward Burd
Paul Eisenberg

The teleconference started at 3:00pm:

Amgen inquired about FDA's perspective regarding denosumab and the hormone ablation therapy (HALT) indications and if Amgen met the standards for the prostate cancer indication. FDA asked for additional information regarding all on-going and complete studies in the advanced cancer indications. Amgen presently has 3 ongoing protocols, they are as follows:

- Phase 3 study for patients with advanced breast cancer compared to zolendronic acid.
- Phase 3 study to evaluate patients with multiple myeloma and solid tumors other than breast and prostate cancers.
- Phase 3 study for patients with advanced prostate cancer compared to zolendronic acid.

Future plans include [redacted] (b) (4)

FDA asked to see Amgen's proposals with a high level table of contents for the data to be submitted including a timeline. The timeline should specify when additional data will be submitted and contain details regarding the schedule of evaluating malignant disease. Amgen stated that the breast cancer study can provide time of assessment for malignancy as well as a safety update as part of the advanced cancer BLA; however, the prostate data will not be available for another year. FDA is interested in the broader perspective regarding all tumors types, not specific disease states. Amgen expressed understanding of FDA's position and agreed to submit a summary and time table of completed studies for FDA review.

Amgen asked about the status of the review for the cancer indications in the denosumab BLA. FDA stated that its views are consistent with the advisory committee's votes regarding the prevention indications. Amgen referenced the advisory committee's positive stance regarding the demonstration of reduction of new fractures in prostate cancer patients. FDA will wait to review the requested new data before an assessment can be made regarding the approvability of the HALT indications. Amgen asked if they are to expect complete response letters for the hormone ablation indications. FDA confirmed that complete responses will be issued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 27, 2009

From: Celia Peacock DRUP/ODE III/CDER

Subject: Information request: Prolia (denosumab)

Information request sent to Amgen by Celia Peacock from the Division of Renal and Urologic Products on August 27, 2009.

1. Regarding your reply to our information request (IR) of 8/20/09, we acknowledge your commitment to establish release specifications for breakloose and extrusion forces by the end of Q1 2010. While specifications with numeric acceptance criteria may not be established until the end of Q1 2010, specifications for breakloose and extrusion, without numerical limits (e.g. report results), should be added to the lot release specifications for progression-free survival (PFS) at this time.

2. Regarding our request for justification of the proposed adjustment of the release specification acceptance criteria based on stability changes during storage (item 4 in our IR of 8/20/09), your response is insufficient. Provide a more comprehensive response with additional detailed information regarding your control strategy and the product data monitoring system. Include information regarding the final statistical control limits and the actions taken; for example, if a lot is released when it is near the limit of a release acceptance criterion, is that lot placed on stability to ensure that it does not fail stability near the end of the shelf-life.

3. Regarding your reply to our IR of 8/20/09 (item 10), please note that prior to release of a new reference standard for use in lot release testing, the reference standard qualification protocol and report should be submitted to the BLA.

4. Regarding our request for clarification of how Amgen plans to prevent drift when replacing reference standards (item 13 in or IR of 8/20/09), your response is insufficient and we require further clarification and any relevant SOPs that would speak to this point. Also, please provide an example (e.g., with a potency lot release acceptance criteria of (b) (4) of reference standard) and identify how you would control for a (b) (4) relative potency result in a lot intended for use a new reference standard.

Suvarna, Kalavati

From: Stock, Marisa
Sent: Tuesday, August 25, 2009 1:55 PM
To: Suvarna, Kalavati
Subject: RE: BLA STN 125320/0 for Denosumab from Amgen, Inc.

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the original request below to find the updated compliance status of each establishment. There are no pending or ongoing compliance actions to prevent approval of STN 125320/0 at this time.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Suvarna, Kalavati
Sent: Monday, January 05, 2009 4:32 PM
To: CDER-TB-EER
Cc: Chi, Bo; Obenhuber, Donald; Abduldayem, Maan S; Suvarna, Kalavati; Hughes, Patricia; Randazzo, Giuseppe
Subject: BLA STN 125320/0 for Denosumab from Amgen, Inc.

Please conduct an establishment evaluation in support of the BLA STN 125320/0 for Denosumab from Amgen, Inc. The sites for manufacture of drug substance, drug product, raw material testing, storage of cell banks, contract testing laboratories, release and stability testing are listed below. The PDUFA date is 06/18/2009.

Manufacture, release and stability testing, and storage of drug substance. Also, storage of working cell bank:
Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard Boulder, CO 80301 USA
FEI No. ~~1724812~~ 3003072024
A pre-license inspection was conducted for Denosumab on June 8-12, 2009 and classified NAI. The CBI profile was covered and is acceptable.

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 65 88397 Biberach an der Riss Germany
FEI No. 3002806518
A pre-license inspection was conducted for Denosumab on May 11-19, 2009 and classified VAI. The TRP profile was covered and is acceptable.

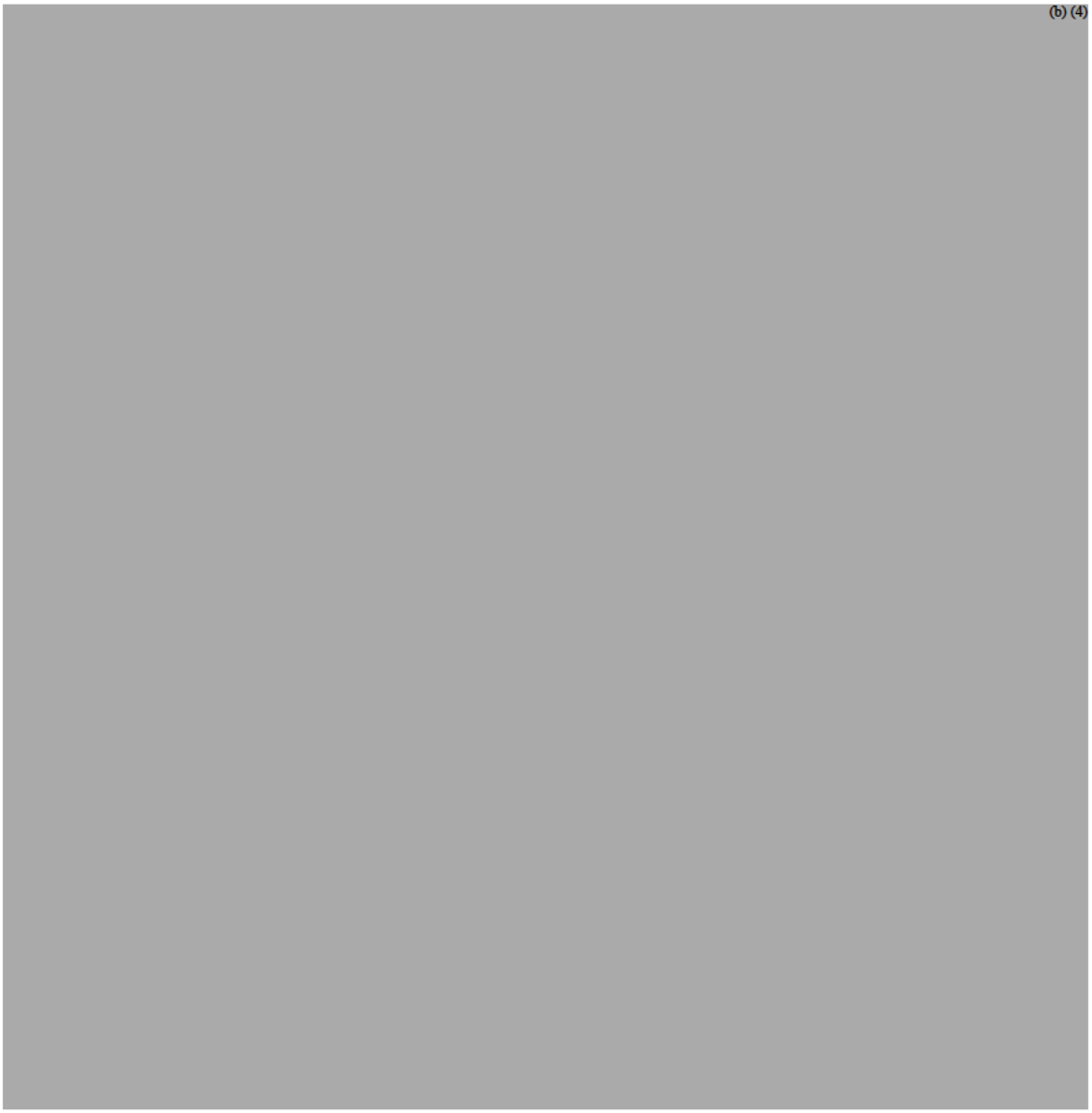
Storage of Master cell bank, raw material testing and release, drug substance and drug product release and stability testing:
Amgen Inc. (ACO) Longmont Facility
4000 Nelson Road Longmont, CO 80503 USA
FEI No. 3002892484
Inspected January 31, 2008 and initially classified NAI. The BTP profile was covered, however a final district decision has not yet been made. Although this case has not been finalized, we consider this site to be acceptable for this application.

Reference ID: 3168397

Storage of Master and Working cell bank, raw material testing and release, drug substance storage:
Amgen Inc. (ATO)
One Amgen Center Drive Thousand Oaks, CA 91320 USA
FEI No. 2026154
Inspected April 7-11, 2008 and classified NAI. The CBI and CTB profiles were covered and are acceptable.

Raw material testing and release, drug substance storage, release and stability testing and Drug product manufacture, release and stability testing, packaging and labeling, and storage:
Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA
FEI No. 1000110364
Inspected January 8-12, 2007 and classified VAI. The BTP profile was covered and is acceptable. This site is a Tier 1 inspectional priority for FY '09.

(b) (4)



(b) (4)

Drug product storage and distribution:
Amgen Inc. (LDC)
12000 Plantside Drive Louisville, KY 40299 USA
FEI No. ~~2026154~~ 3003750095
Inspected January 5-6, 2006 and classified NAI for warehousing responsibilities. This site is not profiled.

Drug product stability (container closure for vials) testing:
Amgen Inc. (AFR)
6701 Kaiser Drive Fremont, CA 94555 USA
FEI No. 3005925062
Inspected September 3-10, 2008 and classified NAI. The TRP profile was covered and is acceptable.

Thank you.
Kala

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 20, 2009

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Information request: Prolia (denosumab)

Information request sent to Amgen on August 20, 2009.

1. Breakloose and extrusion testing should be added to the lot release specifications of the pre-filled syringes, and justification for the proposed acceptance criteria should be provided.

2. 21 CFR 610.14 requires that identity testing be performed on each filled lot after all labeling operations have been completed. From the batch records supplied, it is not clear that any samples are taken for identity testing after labeling of the vials and pre-filled syringes. Please identify your current process and correct, if necessary, to conform to the regulation identified.

3. For additional characterization assays that will be used post approval either for comparability studies or for characterization of new reference standards, please submit the validation or qualification reports to the BLA for review. Additionally, a number of these assays have subjective acceptance criteria such as "visually similar..", "similar pattern..", and "comparable to..". For such acceptance criteria, please provide a more specific and less subjective description of the parameters Amgen uses to specify whether products are "similar" and "comparable".

4. Justify the proposed adjustment of the release specification acceptance criteria based on stability changes during storage, given that the released material is intended to also have an approved storage period. This could result in use of product with quality attributes that are outside the range of clinical experience as product nears its expiration point. Additionally lots released at the lower limit of the proposed specification would fail stability at the end of shelf life for quality attributes that change during product storage.

5. The post approval stability protocol for DS identifies that Amgen intends to alternate annual lots placed on stability between ACO and BIP. Please modify the protocol to require an annual stability lot for each site that has manufactured denosumab during that year.

6. The information provided regarding the tungsten spiking studies states that the tungsten was obtained from used tungsten pins. Please clarify if these pins were used in a process in which the tungsten would undergo oxidation (i.e. not in a nitrogen overlay process).

Additionally, please submit any available data on levels of tungsten in denosumab from the denosumab PFS.

7. The BLA proposes implementing an increase in batch size post approval with a [(b) (4)] batch size of [(b) (4)] a validation protocol (PTC-003542 v 1.0) for the [(b) (4)] batch scale-up is provided in the BLA. In this protocol, Amgen states that the new batch size "will support launch and commercialization of the 60 mg/ml drug product upon approval of the marketing application" and that "the data for this validation exercise will be summarized and evaluated at the completion of the required tests and a final report will be generated." Please note that the final validation report and any other relevant information on the process and its validation will have to be submitted to the FDA for review as a CBE 30.

8. Regarding subvisible particulates testing:

   a. Please define when each of the two subvisible particulates methods is being used.

   b. Please provide complete qualification/validation reports for AML.

9. Regarding the AML drug substance and drug product comparability protocols COMP-000042 and COMP-000050:

   a. Stability/elevated temperature sections (DS section 3.0; DP sections 3.3.2.1 and 4.0) state that "in the event that a statistically significant difference exists, and analytical comparability is not demonstrated, the magnitude and significance of the difference will be evaluated to determine the impact to safety or efficacy." Please be aware that if there are statistically significant differences, this would require comprehensive assessment by FDA prior to release of AML-produced materials and therefore may require submission of the data under a PAS.

   b. COMP-000042 section 4.1.4, Table 9 states that the comparability acceptance criterion for the [(b) (4)] Please define the criteria Amgen uses for assessment of pattern similarities of [(b) (4)]

   c. In COMP-000042, section 4.1.6, Table 11 lists the comparability acceptance criterion for reporter gene assay as [(b) (4)] relative potency, but Appendix B states that the acceptance criteria were established as [(b) (4)] of relative potency. Please clarify if there is a reason Amgen would like to maintain this discrepancy or update to the final specifications.

   d. For the CE-HPLC, rCE-SDS, SE-HPLC, and potency methods (rCE-SDS and SE-HPLC for DP), the justification of acceptance criteria sections in Appendix A state that the acceptance criteria were based on the [(b) (4)] encompassing [(b) (4)] of the clinical and commercial data at [(b) (4)] confidence; however, Appendix C states

that [redacted] (b) (4) and [redacted] (b) (4) were used to establish the limits for CE-HPLC, SE-HPLC, and potency. Please clarify.

10. Regarding reference standard:

    a. The BLA states that a new reference standard (RS) will be prepared to ensure sufficient inventory, if the current RS shows a loss of integrity, or when the stability program for an existing RS is completed or terminated for any reason. Please provide the protocol for monitoring the denosumab reference standard, and describe how loss of integrity is assessed, including any action/alert limits that have been set.

    b. Please provide the protocols for preparation and characterization of a new denosumab reference standard.

11. Amgen Europe B.V. (ABR) was used as a site for transportation validation. Please clarify if denosumab is to be processed at ABR.

12. Please clarify your intent to submit the reports on concurrent validation of resin and membrane lifetime when each is completed.

13. For some specifications, acceptance criteria are relative to the reference standard. Clarify how Amgen plans to maintain consistency of testing results and prevent drift when replacing reference standards which are not equivalent to the previous reference standard.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

9/6/09

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125320/0

INFORMATION REQUEST

Amgen, Incorporated
Attention: Edward S. Burd, Ph.D.
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Burd:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act for Prolia® (denosumab).

We are in the process of completing our review of your application and have the following requests for additional information:

1. Provide a detailed description of the serum CTX1 assay for study numbers 102624 and 107085.

2. Provide the assay validation reports for the serum CTX1 assay for study numbers 102624 and 107085.

If you have any questions, please contact Celia Peacock, Regulatory Project Manager at (301) 796-4154.

Sincerely,

George Benson.

George Benson
Deputy Director
Divison of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 9,837
IND 11,709

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Bradley J. Glasscock, PharmD,
Senior Manager, Regulator Affairs

Dear Dr. Glasscock:

Please refer to your Investigational New Drug Applications (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Denosumab Injection, 60 mg/mL.

We also refer to your July 30, 2008, correspondence, received July 30, 2008, requesting review of your proposed proprietary name, Prolia. We have completed our review of the proposed proprietary name, Prolia and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your July 30, 2008 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application contact the Office of New Drugs (OND) Celia Peacock, Regulatory Project Manager at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Carol Holquist, R.Ph.
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name / Subject
IND 9837	AMGEN INC	Human Monoclonal Antibody (AMG 162)(CHO Cells, Amgen) to Osteoprotegerin Ligand (RANKL)
IND 11709	AMGEN INC	Human Monoclonal Antibody (AMG 162) (CHO Cells, Amgen) to Osteoprotegerin Ligand (RANKL)

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

/s/

CAROL A HOLQUIST
07/09/2009

Pediatric Page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 19, 2009

From: Melanie Pierce, DBOP/OODP/CDER

Subject: 125332/0 and 125333/0-Pediatric Page memo

The Prolia (denosumab) full waivers were reviewed by the PeRC PREA Subcommittee on June 3, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable because the disease/condition does no exist in children. The PeRC committee agreed with the Division to grant a full waiver for this product

Pierce, Melanie

From: Peacock, Celia
Sent: Monday, June 22, 2009 8:16 PM
To: Pierce, Melanie
Subject: FW: BLAs 125,320; 125,331; 125, 332; 125, 333 Prolia

Importance: High

For your files.

From: Greeley, George
Sent: Friday, June 19, 2009 2:52 PM
To: Peacock, Celia
Cc: Stowe, Ginneh D.
Subject: BLAs 125,320; 125,331; 125, 332; 125, 333 Prolia
Importance: High

Hi Celia,

The Prolia (denosumab) full waivers were reviewed by the PeRC PREA Subcommittee on June 03, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because the disease/condition does not exist in children. The PeRC agreed with the Division to grant a full waiver for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

Please consider the environment before printing this e-mail.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring Maryland 20993

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

MAY 20 2009

STN: BL 125320/0
STN: BL 125331/0
STN: BL 125332/0
STN: BL 125333/0

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

Please refer to your Biologics License Application (BLA) dated December 19, 2008, received December 19, 2008, submitted under section 351 of the Public Health Service Act, for Prolia (denosumab).

We also refer to your January 15, 2009, correspondence, received January 16, 2009, requesting review of your proposed proprietary name, Prolia. We have completed our review of the proposed proprietary name, Prolia, and have concluded that it is acceptable.

The proposed proprietary name, Prolia, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 15, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Darrell Jenkins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0558. For any other information regarding this application, contact Celia Peacock, MPH, RD, Regulatory Project Manager, in the Division of Reproductive and Urologic Products, Office of New Drugs (OND).

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125320/0
STN: BL 125331/0
STN: BL 125332/0
STN: BL 125333/0

APR 20 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for information:

1. Explain the protocol that was used for transfer of bioburden and endotoxin tests from the drug manufacturing site at Amgen Colorado to BI Pharma. Explain why different methods were used for bioburden and endotoxin testing and how the comparability of the different methods was evaluated.

2. Provide full details of the contamination control test used for bioburden testing of denosumab production bioreactor pre-harvest samples at BI Pharma site including volume of sample tested, positive control, negative controls and analysis of results.

3. Provide full details of the aerobic and anaerobic bioburden test method used for bioburden testing of denosumab production bioreactor pre-harvest samples at your Colorado site including the media used, incubation conditions, controls, and analysis of results.

4. Explain when the aerobic and anaerobic bioburden test will be implemented at BI Pharma.

5. Clarify if isolates obtained from a positive bioburden test from production bioreactors are identified.

6. Provide summary data for validation of bioburden and endotoxin tests for denosumab process intermediates and buffers. Data from each site should be provided if different methods are used.

7. Provide a summary table with bioburden and endotoxin data for all in process steps and the drug substance fill step from all batches manufactured so far at your Colorado site and the BI Pharma site.

8. Clarify if endotoxin testing is performed on harvest samples.

9. Explain why the endotoxin levels for the BI Pharma and ACO batches vary.

10. Provide calculation of the endotoxin limit based on worst-case minimal patient weight of 50 kg and the maximum single human dose for denosumab.

11. Explain the rationale for the endotoxin acceptance criterion at each process step at the ACO and BI Pharma sites.

12. Provide a table with side-by side comparison of column chromatography cleaning (Protein A, cation exchange, and hydrophobic interaction chromatography) performance parameters and acceptance criteria for post-cleaning and post regeneration blank elutions at the BI Pharma and ACO sites.

13. Provide in tabular form all differences (including media/ equipment/ steps/filters) at your Colorado and BI Pharma sites. The table should indicate if steps are repeated at one site versus another and the number of filter cartridges used at each site . All differences between the two sites should be justified.

14. You indicate that number of (b) (4) cartridges used after (b) (4) step varies with the load. Please explain this statement further and provide details of the (b) (4) filter used at the (b) (4), including loading capacities.

15. Provide summary data from the media and buffer hold studies at BI Pharma and ACO sites demonstrating microbial control. The hold conditions (temperature/time) should be specified.

16. Provide bioburden data for process intermediates held for (b) (4) hours at the BI Pharma site.

17. Explain how you evaluated worst case scenarios for drug substance container closure integrity. Details of the container closure integrity test such as inoculum used to generate the aerosol and incubation conditions should be provided.

18. For shipping validation studies, please provide the routine conditions (temperature and time) for shipping from both drug substance manufacturing sites (ACO and BI Pharma) to fill finish site (AML). The torque value for the container closure system should be included. The details of how the shipping validation was performed (simulation versus

real time studies) and worse case conditions (temperature and time) evaluated should be provided for review.

19. Provide details of the filter integrity test used for drug substance filtration.

Provide a written response to these requests by May 1, 2009.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

STN: BL 125320/0
STN: BL 125331/0
STN: BL 125332/0
STN: BL 125333/0

APR 20 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for information:

1. Regarding media (b) (4)
   a. The method for selection of (b) (4) is not clear, and we note that there is no mention of (b) (4) in the ACO and BIP batch records that were included in the submission. Please clarify how media (b) (4) are selected.

   b. In 3.2.S.2.6 (Cell Culture Process Characterization), Amgen states that "no practically important differences" were observed between performance parameters when cells are grown plus or minus additional (b) (4). However, Amgen also states that the extra (b) (4) provides additional robustness for high cell density or extended duration cultures. Please clarify, and please discuss if and when the media options containing additional (b) (4) are intended for use.

2. You state that the current validated product pool hold times are used as controls in manufacturing. Also included in this submission is a table of acceptable characterized hold times, which are different from the validated hold times. Describe how you intend to use the acceptable pool hold times.

3. For potency evaluations used to classify variants as product-related substances, identify how many independent analyses were conducted and how many lots were analyzed. If more than one, provide the individual datapoints.

4. For the system suitability of many analytical methods, you state that "acceptance criteria might vary between sites, however, equivalence of the methods has been demonstrated." Explain and provide supporting data for this statement.

5. Provide the endotoxin qualification or validation report for the ACO turbidimetric kinetic LAL method.

6. Explain how "as needed" is determined for [redacted] addition. Batch records do not identify how this is supposed to be determined by the manufacturing personnel.

7. Submit the protocols and results for tungsten spiking studies and for biological reactivity studies.

8. The stability summary of 60 mg/ml vial drug product at the recommended storage condition of [redacted] section (3.2.P.8.3) contains only the 1 month data for the commercial lots. Provide the tabular data for the primary lots (049A059685, 049A061752, 049A069739) and the supporting lots (049A114210, 049A119654, 049A119655, 049A027110, 049A031407).

9. Regarding the identity testing of the cell culture raw materials media powders:
   a. We note that the amino acid analysis acceptance criteria for identity testing of [redacted] (3.2.S.2.3, Raw Materials, Table 5) are different from the amino acid analysis acceptance criteria listed on the manufacturer's certificate of analysis (3.2.R, CoA Raw Materials – BI Pharma, p. 3). Please justify your acceptance criteria listed in Table 5.

   b. The footnotes to Table 4 and Table 5 (3.2.S.2.3, Raw Materials) state that identity testing can be performed by either amino acid analysis or infrared analysis. [redacted] and [redacted]/2x Enriched [redacted] cannot be distinguished using the listed amino acid acceptance criteria; the criteria listed on the tables are within the same range for all listed amino acids, and the manufacturer's amino acid acceptance criteria for [redacted] are identical (see question 9, part a, above). Explain how these raw materials can be accepted based on this testing scheme.

10. We note that the validation of pool hold times at BI Pharma was performed at small scale, using commercial scale material and representative containers. Please provide additional information regarding the scaled-down model, including a comparison of all relevant parameters to demonstrate that the small scale process is representative of the commercial scale hold.

11. In section 3.2.S.4.2 (Validation of Analytical Procedures), you state that system suitability has been demonstrated for all compendial methods. Please define "system suitability" in this context, and identify what was done for each assay.

12. We note that there is a difference in the CE-HPLC charge variant profiles of denosumab produced at ACO and BI Pharma and that you identified this as potentially resulting from differences in the [redacted] content of a raw material. As limits for charge profiles of denosumab are global for both the production bioreactor action limit and the DS specification, provide information regarding any additional internal system controls used at BI Pharma to identify changes in their normal charge variant profile, as this can be utilized as an indicator of consistency of the manufacturing process and raw materials.

13. The osmolality acceptance criteria range [redacted] is significantly wider than is the range of measured osmolalities of denosumab lots [redacted] Provide information regarding internal controls that are in place to assure that deviations from the historical range are investigated.

14. Provide details of the sampling scheme (including timing and vial quantity) for fill volume testing of the 60 mg/ml vial (3.2.P.3.5, section 3.5.4).

15. In the drug product release specification testing sections for both vialed and PFS DP (3.2.P.3.5, section 3.7), you state that samples were taken from the beginning, middle, and end of the lot. Identify the derivation of the data that were provided in the tables of specification testing results (Tables 42 and 40, respectively) and provide the data points of the test results from the samples that were taken from each stage of fill.

16. Regarding DP transportation validation operational qualification:
    a. Describe the testing procedure, including the number of vials/syringes and number of shipping containers tested.

    b. Provide a more detailed summary of the vial and PFS assay results that were listed in 3.2.P.3.5 section 1, Table 2, to include the range of results and SD.

17. Regarding DP transportation validation performance qualification:.
    a. For air and ground transportation, 2 scenarios are listed for each mode (plus work in progress packaging), and 3 separate shipments were performed for each. Please clarify the type of shipping that was done for each run (e.g. insulated shipping containers, temperature controlled truck, etc.) and the standard method that will be used for shipment of commercial product.

    b. Provide a more detailed summary of the PFS assay results that are listed in tables 3-5, to include the range of results and SD.

    c. The results of the transport validation studies for the 60 mg/ml vial should be submitted to the BLA when they become available.

    d. Provide additional information regarding the qualification of the shipping containers used for transportation of denosumab DP.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125320/0
STN: BL 125331/0
STN: BL 125332/0
STN: BL 125333/0

APR 30 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for information:

1. The threshold values for the binding antibody screening assays and the neutralizing antibody bioassays were determined based on the S/N ratios of healthy donors.
    a. We note that for the screening assay, you state that the threshold was evaluated in study subjects with osteoporosis and breast or prostate cancer and found to be similar. Provide the data demonstrating similar threshold values for the healthy donors and the donors examined for analysis of each indication.

    b. You state that the threshold may be determined on a study- or disease-specific basis if the population differs significantly from the normal population. Define the criteria used to assess the need for a study- or disease-specific threshold.

2. Regarding the negative control for the screening assays, you state that for new lots of pooled normal human serum, the assay threshold must be explored and, if necessary, re-established. Provide the criteria for determining if and how the threshold is re-established. Additionally, clarify if the bioassay thresholds are also re-established following the same criteria.

3. Regarding the positive control, we note that the concentration of the positive control used in the screening assays (50 ng/ml) is significantly higher than the assay LOD and QL (2.4 ng/ml and 15 ng/ml). Provide justification for the concentration selected for the positive control, and clarify the method by which you assure that the assay LOD and QL are met for each assay run as you do not have an internal positive control for these parameters.

4. Provide data regarding assessment of interference of serum components (e.g. hemoglobin, lipids) with the screening assays and bioassays.

5. In the confirmatory bioassays, the assay performed in 1% serum includes the use of depletion control value in assessing the presence of ADA, while the assay performed in 5% serum does not. Explain the rationale for this.

6. We note that the intermediate screening assay (2260.6085) showed evidence of a "hook" effect that appeared between [redacted] (b) (4) anti-AMG 162. The data provided in the validation report for the current assay (2260.6114, validation 2260.7185, table 3) includes anti-AMG 162 concentrations up to only [redacted] (b) (4); however, we note that there were subject samples with levels of anti-AMG 162 of up to [redacted] (b) (4) identified in the Denosumab Integrated Immunogenicity Report (section 3.5). Provide rationale for the upper limit of [redacted] (b) (4) in assay 2260.6114, and any data regarding higher concentrations of anti-AMG 162 in this assay.

7. In the confirmatory immunoassay analytical procedure (document 2260.6119.02), the antibody result reporting criteria (sections 8.6.1 and 8.6.2) does not include use of the ARC in the assessment of the presence of anti-drug antibodies. However, in the confirmatory immunoassay validation report (document 2260.7190.00), Amgen states that samples with S/N above the threshold and below the ARC are positive and below the quantifiable limit and that samples above the ARC are further characterized. In addition, the conclusion of the validation report states that the results will be interpreted based on comparison to the threshold and the ARC. Clarify the discrepancies between the analytical procedure and the validation report, and identify which, if any, assessments are based on the ARC. Additionally, justify why samples between the threshold and ARC levels are excluded from further testing.

8. Provide justification and supporting data for using 50% depletion as part of the sample reporting criteria for AMG 162- and OPG-treated samples in the confirmatory immunoassay.

9. We note that demonstration of depletion of up to 5,000 pg/ml RANKL by 2 µg/ml OPG is provided in the confirmatory immunoassay validation report and that this concentration of OPG is used for the immunogenicity assay. Justify the use of this concentration of OPG with respect to physiological levels of RANKL that may be found in the patients' serum samples.

10. We note that the screening immunoassay is performed at both ATO and [redacted] (b) (4) however, the validation report appears to have been conducted at ATO and does not include an assessment of assay of relevant parameters such as ruggedness (i.e. precision and robustness between labs). Provide relevant validation of ruggedness and the method transfer qualification report.

11. Validation of robustness of the immunoassays and bioassays should include assessments of factors in addition to plate lot, to demonstrate that variations in factors such as time,

temperature, instrument, etc. do not affect the assay. Additional data supporting assay robustness should be provided for all immunogenicity assays.

12. Regarding validation of precision:
    a. We note that validation of some aspects of the confirmatory immunoassay is supported by the validation of the screening immunoassay. However, as the confirmatory assay includes additional manipulations, differences in precision may occur. Provide data to support precision of the confirmatory immunoassay.

    b. Provide data regarding precision of the bioassays.

13. For some assays, edge effects and other effects that are dependent on the specific location of the sample wells on a plate are seen. Provide data to demonstrate that the immunoassays and bioassays are not affected by the assay plate well locations of positive controls, negative controls, and samples.

14. Regarding stability of immunoassay and neutralizing antibody bioassay components, provide information on your procedures for assessing stability of all critical reagents and whether they were implemented for these assays. Included in this should be information about stability of diluted samples, as we note that Amgen also stores aliquots of diluted positive control, diluted RANKL, diluted AMG 162, and diluted RANKL/OPG solution.

15. We note that Amgen states that for the bridging immunoassays, minimal washes were required, which reduced the loss of low affinity antibodies when compared to a traditional ELISA (Denosumab Integrated Immunogenicity Report, section 5.2). Provide data that demonstrates that antibodies with low affinity or rapid on/off rates can be detected by the screening immunoassay.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

74-Day Deficiency Letter

STN: BL 125332/0
STN: BL 125333/0

Amgen, Incorporated
Attention: Julie Lepin
Director, Global Regulatory Affairs and Safety
One Amgen Center Drive
Mail Stop 38-4C
Thousand Oaks, CA 91320-9978

MAR 03 2009

Dear Ms. Lepin:

Please refer to your biologics license application (BLA), dated December 19, 2008, received December 19, 2008, submitted under section 351 of the Public Health Service Act, for denosumab. Please also refer to our March 13, 2009 filing letter. While conducting our filing review we identified the following potential review issues:

CLINICAL:

1. For the studies supporting the HALT indications, submit narrative summaries for all deaths, dropouts due to adverse events, SAEs, and any cases adjudicated for possible diagnosis of osteonecrosis of the jaw.

CHEMISTRY, MANUFACTURING AND CONTROLS:

2. Submit a tabulation of the final measured acetate and sorbitol concentrations for drug product lots for which concentrations were measured. Please separate the lots by process (i.e. CP1 versus CP2) and by drug substance manufacturing facility.

Regarding in-process controls:

3. Provide a summary of the datasets (e.g. number of batches, range, mean etc.) used to establish operational and performance parameter limits, and identify the mechanism used to set the limits.

4. Explain the large differences in percent step yield between ACO and BI Pharma for some of the purification steps.

5. Your applications state that between the manufacture of the two ACO lots used for validation of reprocessing at the (b) (4) step (Lot 049C03511 and Lot

049C048219), minor changes were made "to refine process expectations." Provide details of these changes.

REGULATORY:

We have the following initial comments regarding your proposed package insert labeling

General Comments:

6. Include a Boxed Warnings section in the Highlights, Full Prescribing Information (FPI): Contents, and FPI sections of the label to include warnings regarding osteonecrosis, infection and hypocalcemia adverse reactions. Please reference the following: *Draft Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Section of Labeling for Human Prescription Drug and Biological Products-Content and Format found at http://www.fda.gov/CBER/gdlns/boxwarlb.htm.*

7. Use "active voice" throughout the label.

Highlights:

8. Delete the white space between the major headings and the text underneath.

9. Do not use "TM" after the drug names in Highlights or Table of Contents. Use "TM" only once in the content of labeling (FPI).

10. For biologic products, the dosage form and route of administration are not part of the product name. Relocate the dosage form and route of administration to the next line below.

11. Please revise the DOSAGE AND ADMINISTRATION section, to say "Administer 60 mg every 6 months as a subcutaneous (SC) injection."

12. Reword sentence in the DOSAGE FORMS AND STRENGTHS section to read "Single use prefilled syringe containing 60 mg in a 1 mL solution," and "Single use vial containing 60 mg in a 1 mL solution."

13. Include "Skin Infections," and "Hypocalcemia," in the WARNINGS AND PRECAUTIONS section

14. In the USE IN SPECIFIC POPULATION, add the headers "Pregnancy," and "Pediatric Use," and "Renal Impairment" and one of the following statements, as appropriate: "Based on animal data, may cause fetal harm," or "No human or animal data. Use only if clearly needed." [redacted] (b)(4)

15. Add "Revised [Month/Year]" as the last item in Highlights. [Note: For this new BLA, the

revision date will be the month /year that the application is approved].

Full Prescribing Information (FPI):

16. Revise the ADVERSE REACTIONS; Section 6.2 Immunogenicity, to include the following standard verbatim statement.



17. USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: the labeling must include the appropriate required regulatory statement for Pregnancy Category C. Refer to 21 CFR 201.57(c)(9)(i)(A)(3).

18. USE IN SPECIFIC POPULATIONS: 8.3 Nursing Mothers: If a drug is absorbed systemically and is known to be excreted in human milk or excretion in human milk is unknown, this subsection must describe if the drug is associated with serious adverse reactions or has known tumorigenic potential and include required statements, as appropriate. Reference [21 CFR 201.57(C)(9)(iii)].

Please address the identified deficiencies/issues and re-submit labeling by April 3, 2009. This updated version of labeling will be used for future labeling discussions.

Submit proposed content of labeling in SPL format.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission. We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g.,

submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 26, 2009.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

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

Sincerely,

Patricia Keegan

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

2/27/09

STN: BL 125320/0
STN: BL 125331/0

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for information:

1. Manufacturing/Product Quality:
   Provide a table that shows the specific drug product utilized in each of the Phase 2 and 3 studies for the postmenopausal osteoporosis indications, including the site of manufacture for the drug substance and the drug product.

2. Osteonecrosis of the Jaw (ONJ) Adjudication:
   a. As outlined in the ONJ Adjudicator Contact Log dated May 6, 2009, we note that Dr. Marx expressed concern that there was the possibility that ONJ was being under-diagnosed due to the incomplete nature of some of the data packages. Summarize how Dr. Marx's concerns have been specifically addressed.

   b. Provide a listing of all potential ONJ cases sent to the adjudication committee using the following template to summarize the cases:

USUBJID	Verbatim term	Preferred term	Study drug dose	# doses of study drug	AE onset (Study day #)	Surgery (Y/N)	Resolved (Y/N)	ONJ risk factors	Adjud results (# yes, # no, # indeterminate)

c. Provide a comprehensive narrative and relevant case information (e.g. oral surgery reports, pathology results) for the following subjects:

Study	Site	USUBJID	Verbatim term	Dictionary coded term
20010223	5	20010223-(b) (6)	lesion (r) lower gum	Oral disorder
20030216	304	20030216-	bone deterioration below bad tooth	Bone disorder
20030216	632	20030216-	tooth implantation in jaw	Dental prosthesis user
20030216	719	20030216-	dental implant	Dental prosthesis user
20030216	823	20030216-	periostitis of teeth	Periostitis
20030216	633	20030216-	local infection after removal of tooth	Post procedural infection
20030216	412	20030216-	left maxilla dental abscess	Tooth abscess
20030216	731	20030216-	dental abscess lower jaw	Tooth abscess
20030216	661	20030216-	teeth implantations	Dental implantation
20030216	632	20030216-	tooth implantation	Dental prosthesis user
20030216	723	20030216-	tooth implantation	Dental prosthesis user
20030216	632	20030216-	infection in mouth after removal of teeth	Post procedural infection
20030216	743	20030216-	dental abscess right lower jaw	Tooth abscess
20040132	309	20040132-	dental implant surgery	Dental implantation
20040132	309	20040132-	dental surgery	Dental operation
20040132	307	20040132-	bone implant-receding gums-outpatient	Bone graft
20040138	188	20040138-	dental surgery	Dental operation
20040138	214	20040138-	dental implant	Dental prosthesis user
20040138	639	20040138-	infection after molar traction jaw	Postoperative wound infection
20050141	125	20050141-	jaw lesion	Bone lesion
20050233	29	20010223-	dental abscess r upper jaw	Tooth abscess
20050234	502	20050234-	big trouble chewing (problems chewing with missing teeth)	Mastication disorder
20060286	1	20060286-	post-operative infection in jaw	Post procedural infection

3. Questions about Coding Practices:
We have questions about the medical event coding for several cases based upon our review of narratives and case report forms. Please provide your rationale for medical event coding for the following subjects:

Study Number	Unique SID	Preferred Term	AE onset	Additional question(s) / comment(s)
20030216	(b) (6)	Myocardial infarction	24-Oct-2006	Was an autopsy done? Was a death certificate available?
20030216		Bronchopneumonia	22-Jun-2007	SAE narrative mentions cardiogenic or septic pre-shock, atrial fibrillation and hypotension.

4. There are two datasets submitted in the ISS: AAE and AAEFX. There are 217 fractures in the AAE file that are not included in the AAEFX file. We are aware of different number of studies included in each dataset. However, there are a few instances where clinical fractures from study 20030216 are in the AAE dataset and not in AAEFX dataset. Explain the discrepancy.

Provide a written response to these requests within two weeks of receipt of this letter.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

George Benson

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

STN: BL 125332/0
STN: BL 125333/0

Amgen, Incorporated
Attention: Julie Lepin
Director, Global Regulatory Affairs and Safety
One Amgen Center Drive
Mail Stop 38-4C
Thousand Oaks, CA 91320-9978

FEB 13 2009

Dear Ms. Lepin:

This letter is in regard to your biologics license application (BLA), dated December 19, 2008, received December 19, 2008, submitted under section 351 of the Public Health Service Act, for Denosumab.

We have completed an initial review of your applications dated December 19, 2008 for Denosumab for the treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer (BL STN 125332/0) and the treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer (BL STN 125333/0) to determine their acceptability for filing. Under 21 CFR 601.2(a) we have filed your applications today. The user fee goal date is October 19, 2009. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

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

1. In general, the narrative listings are cumbersome and difficult to read even in larger print (certain listings appear faded). Please provide case narratives in narrative form for studies 135 and 138.

2. In study 138, a hyperlink to the appendix in §11.5 is linked to §11 in the CSR. Please provide the correct hyperlink to the appropriate appendix.

Any additional potential review issues will be communicating you on or before March 3, 2009.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during

this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients in neonates: 0-30 days; infants: 1-24 months; children: 25 months-12 years; adolescents: 13-16 years.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

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

Sincerely,

Patricia Keegan

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

FDA/CDER/OC/DMPQ/HFD-323
Phone:301-796-3246
Fax:301-847-8741

From: Pierce, Melanie
Sent: Monday, February 09, 2009 12:10 PM
To: CDER-TB-EER
Cc: Randazzo, Giuseppe; Peacock, Celia
Subject: EER request for denosumab BLA

Hello all,

Please see the attached 356 form containing the establishment description for the Establishment Evaluation Request for BLAs 125320/ 125331/0, 125332/0 and 125333/0. These applications are all for the same product (denosumab). Background information is provided below.

A new BLA came in for Denosumab: BL STN 125320 came in on Dec. 19, 2009. However, there are 4 indications contained in this BLA and because of this, it posed some problems for us. They are as follows:

- The biologic product is not approved.
- Two indications (Treatment of osteoporosis in post-menopausal women and Prevention of osteoporosis in post-menopausal women) will be reviewed in the Division of Renal and Urology Products.
- Two indications (Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer and the Treatment and prevention of bone loss associated with hormone ablation therapy in patients with breast cancer) will be reviewed by the Division of Biologic Oncology Products.
- Because it is not approved, the indications had to be split out into 4 different STNs (i.e., 4 separate BLAs):

  -125320/0-Treatment of osteoporosis in postmenopausal women.
  -125331/0 Login ID 60008232-Prevention of osteoporosis in postmenopausal women.
  - 125332/0 Login ID 60008233-Treatment and **prevention** of bone loss associated with hormone ablation therapy in patients with breast cancer.
  - 125333/0 Login ID 60008234-Treatment and **prevention** of bone loss associated with hormone ablation therapy in patients with prostate cancer.

- Once one indication is approved, the rest will revert to supplements.

Please let me know if everything is acceptable from a compliance standpoint.



356h.pdf (503 KB)

Thank you,
Melanie

Pierce, Melanie

From: Lepin, Julie [jlepin@amgen.com]
Sent: Wednesday, February 04, 2009 5:49 PM
To: Lee, John
Cc: Pierce, Melanie
Subject: RE: Pre-approval inspections for BLAs STN-125332 and STN-125333

Dear John,

It was a pleasure to speak with you earlier today. Please find below the requested phone and fax numbers:

Dr. Robert Feldman (site 129 in study 20040138):
Phone: 203-754-3588
Fax: 203-758-1288

Dr. Brian Roberts (site 188 in study 20040138)
Phone: 843-839-1679 or 843-449-1010
Fax: 843-286-0119

Dr. Nicholas Iannotti (site 159 in study 20040135)
Phone: 772-335-5666
Fax: 772-335-0102

Dr. Shaker Dakhil (site 183 in study 20040135)
Phone: 316-262-4467
Fax: 316-262-0706 or 316-262-0247

We will be able to provide you the response to the remainder of your request #1 by 11th February, and I will be able to provide you with timelines for the remaining responses shortly.

Kind regards

Julie Lepin
Director, Global Regulatory Affairs and Safety

Work Telephone: (805) 447 3040
Cellphone: (b) (6)
Fax: (805) 480 1330
e.mail: jlepin@amgen.com

From: Lee, John [mailto:john.lee@fda.hhs.gov]
Sent: Wednesday, February 04, 2009 1:14 PM
To: Lepin, Julie
Subject: RE: Pre-approval inspections for BLAs STN-125332 and STN-125333

From: Lee, John
Sent: Monday, February 02, 2009 8:04 PM
To: 'lhurd@amgen.com'
Subject: Pre-approval inspections for BLAs STN-125332 and STN-125333

Dear Ms. Lepin:

We request your assistance in conducting pre-approval inspections in support of your recent submissions (BLAs STN-125332 and STN-125333). Please provide the information described below, according to the timeframe and format specified for each item.

1. For study sites 129, 159, 183, and 188 (Feldman - 20040138, Ionnatti - 20040135, Dakhil - 20040135, Roberts - 20040138, respectively): (1) phone and fax numbers for the clinical investigator, (2) all versions of the study protocol used at that site, (3) a brief introductory narrative summary (approximately 500 words) of the study conducted at that site, to include (a) product description, (b) study title and protocol synopsis (either 20040135 or 20040138), (c) number of subjects enrolling in and completing the study at that site, and (d) any major compliance issues relevant to that site, and (4) study data listings consisting of (a) primary efficacy endpoint data, (b) adverse events (including serious events and deaths), (c) concomitant medication, (d) protocol deviations, and (e) subject withdrawal. For the phone and fax numbers for the clinical investigators, please reply by **Thursday, 5 February 2009**. For all other information, please provide one PDF file for each clinical site, if possible as e-mail attachments by **Wednesday, 11 February 2009**.

2. In a table form, for all clinical sites in studies 20040135 and 20040138: (1) clinical investigator name, clinical site number, study number, and number of subjects enrolled, (2) point estimate of the primary efficacy endpoint for each site, and the ratio of the site-specific point estimate relative to the point estimate for the applicable overall study, and (3) number of all (treatment-related or not) serious adverse events (SAEs) reported at each site, and the ratio of this number relative to the total number of SAEs reported under the applicable overall study. Please provide this information as soon as it becomes available, if possible within the next two weeks as an Excel e-mail attachment (two tables/sheets).

3. For each of the 10 highest enrolling sites (studies 20040135 and 20040138), a brief narrative summary (approximately 200 words) of your internal audits conducted while the studies were on-going, to include: (1) dates of audit and names of auditors, (2) scope of audit, (3) any deficiencies found (non-compliance with applicable regulations or the study protocol), and (4) any corrective action implemented. In describing the scope of audit, please specify how many subject records were completely reviewed at each audit visit and discuss your oversight towards assuring complete and accurate study data (as recorded on case report forms) and reporting of adverse clinical events. Please provide this information as soon as it becomes available as an amendment to the BLA, if possible within the next 30 days.

Please kindly acknowledge receipt of this note and let me know if the timeframes are feasible. I would be happy to discuss any questions. We thank you in advance for your helpful assistance in completing the inspectional review for these two BLAs.

Best regards,

John Lee, MD
DSI/CDER/FDA
(301) 796-1396

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BLA ACKNOWLEDGEMENT

STN BL 125320/0
STN BL 125331/0
STN BL 125332/0
STN BL 125333/0

JAN 3 0 2009

AMGEN, Inc.
Attention: Julie Lepin
Director, Global Regulatory Affairs and Safety
One Amgen Center Drive
Mail Stop 38-4-C
Thousand Oaks, CA 91320-9978

Dear Ms. Lepin:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following:

Name of Biological Product: denosumab

Date of Application: December 19, 2008

Date of Receipt: December 19, 2008

Our Submission Tracking Numbers (STN): BL 125320/0, BL 125331/0, BL 125332/0, BL 125333/0

Proposed Use: Treatment and prevention of osteoporosis in postmenopausal women and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer.

This submission has been administratively split into four applications as follows:

1. STN BL 125320 – Treatment of osteoporosis in postmenopausal women
2. STN BL 125331 - Prevention of osteoporosis in postmenopausal women
3. STN BL 125332 – Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer
4. STN BL 125333 – Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer.

STN BL 125320 and 125331 will be managed and reviewed by the Division of Reproductive and Urologic Products. STN BL 125332 and 125333 will be managed and reviewed by the Division of Biologic Oncology Products. For additional information regarding the eCTD requirements for this STN administrative split, please contact Virginia Ventura in the Office of Business Process Support, Electronic Submissions at (301) 796-1016.

STN BL 125320 will be considered the "parent" BLA. When you submit application amendments containing information that is applicable for all four indications, please submit that information in an amendment to the parent BLA, STN BL 125320 and also submit a letter of cross-reference for that information to the other 3 BLA STNs identified above. When you submit indication-specific information to the BLA, please submit that information to the appropriate STNs as identified above and also submit letters of cross-reference for that information to the other 3 STNs. All cross-reference letters should include a copy of the cover letter describing the contents of the amendment.

We will notify you within 60 days of the receipt date regarding whether each application is sufficiently complete to permit a substantive review.

The appropriate STNs provided above should be cited at the top of the first page of all submissions to this application. Send all submissions in the eCTD format. If sending the submission on physical media, please send by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions regarding the osteoporosis indications, call Celia Peacock, MPH, RD, Regulatory Project Manager at (301) 796-4154. For questions regarding the oncology indications, call Melanie Pierce, Regulatory Project Manager in the Division of Biologic Oncology Products at (301) 796-1273.

Sincerely,



Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 29, 2009

NDA/BLA #: 125332/0 and 125333/0

PROPRIETARY/ESTABLISHED NAMES: denosumab

APPLICANT: Amgen, Incorporated

BACKGROUND:
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Melanie Pierce	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Suzanne Demko	Y
	TL:	Jeff Summers	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:	Sandra Griffith	N
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Reference ID: 3168397

Clinical Pharmacology	Reviewer:	Sarah Schieber	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Kyung Lee	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Michael Orr	Y
	TL:	Anne Pilaro	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Sarah Kennett	Y
	TL:	Chana Fuchs	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:	Patricia Hughes	N
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	John Lee	N
	TL:		
Other reviewers			

OTHER ATTENDEES: Please see the attached filing meeting minutes

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

Reference ID: 3168397

Electronic Submission comments **List comments**: No comments	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: DRUP takes the lead ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: 8.13.09 ☐ NO ☐ To be determined Reason:
• 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

Reference ID: 3168397

• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• 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
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to ~~DMPQ~~? **Comments**: submitted to the therapeutic biologics products group	☐ Not Applicable ☐ YES ☐ NO ☐ Not Applicable ☒ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) NA Biologic	☐ YES ☐ NO ☐ YES ☐ NO

Reference ID: 3168397

FACILITY (BLAs only) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Patricia Keegan, M.D.

GRMP Timeline Milestones: October 19, 2009

Comments: Action Date

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. 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.
☐	If BLA or priority review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74
☐	Other

Reference ID: 3168397

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
(3) 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) 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, and.

(3) 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

Reference ID: 3168397

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) 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, or

(3) 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 OND ADRA or OND IO.

Reference ID: 3168397

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

BB IND 009837

Amgen, Inc
Attention: Bradley Glasscock
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Glasscock:

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

We also refer to the meeting between representatives of your firm and the FDA on October 21, 2008. The purpose of this Type B Pre-BLA meeting was to discuss clinical and nonclinical aspects of denosumab.

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

If you have any questions, call Celia Peacock, MPH, RD, Regulatory Health Project Manager at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Medical Officer Team Leader
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure - Meeting Minutes and Amgen Meeting Slides

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 21, 2008
TIME: 1:00 – 2:30 p.m.
LOCATION: FDA, White Oak Campus, Silver Spring, MD
APPLICATION: BB IND 009837
DRUG NAME: Denosumab (AMG 162)
TYPE OF MEETING: Type B, Pre-BLA

MEETING CHAIR: Theresa Kehoe, M.D.

MEETING RECORDER: Celia Peacock, M.P.H., R.D.

FDA ATTENDEES:

Celia Peacock, MPH, RD	Regulatory Project Manager	Division of Reproductive and Urologic Products
George Benson, M.D.	Deputy Director	Division of Reproductive and Urologic Products
Gerald Willett, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Margaret Kober, R.Ph., MPA	Chief, Project Management Staff	Division of Reproductive and Urologic Products
Kimberly Hatfield, Ph.D.	Phamacologist	Division of Reproductive and Urologic Products
Lynnda Reid, Ph.D.	Pharmacology Supervisor	Division of Reproductive and Urologic Products
Theresa Kehoe, M.D.	Medical Team Leader	Division of Reproductive and Urologic Products
Vaishali Popat, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Stephen Bienz, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Marcea Whitaker, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Chongwoo Yu	Clinical Pharmacology Reviewer	Office of Clinical Pharmacology/Division of Clinical Pharmacology III
George Rochester, Ph.D.	Lead Statistician for Safety	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
Anita Abraham	Math Statistician	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group

Antonio Paredes	Math Statistician	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
Mandi Yu	Math Statistician	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
Sarah Kennett, Ph.D.	Biologist	Office of Pharmaceutical Science/Office of Biotechnology Products/Division of Monoclonal Antibodies
Mina Hohlen	Regulatory Information Specialist	Office of Business Process Support/Division of Regulatory Review Support
Chuck Cooper, M.D.	Medical Officer	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
Jenise Gillespie-Pedersen	General Health Scientist	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
John Yap	Visiting Associate (Math Statistician)	Office of Biostatistics
Mahboob Sobhan	Math Statistician Supervisor	Office of Biostatistics/Division of Biostatistics III
Paul Schuette	Math Statistician	Office of Biostatistics
Chana Fuchs, Ph.D.	CMC Team Leader	Office of Pharmaceutical Science/Office of Biotechnology Products/Division of Monoclonal Antibodies

EXTERNAL CONSTITUENT ATTENDEES:

Matt Austin, MS	Director, Biostatistics
Laura Bloss, PhD	Executive Director, Clinical Development
Andre Daniels, MD	Executive Director, Global Safety
Roger Dansey, MD	Executive Director, Clinical Development
Beth Hinkle, PhD	Senior Scientist, Preclinical Development
David Feigal, MD	Vice President, Regulatory Affairs
Bradley Glasscock, PharmD	Senior Manager, Regulatory Affairs
Carsten Goessl, MD	Director, Clinical Development
Graham Jang, PhD	Director, Pharmacokinetics and Drug Metabolism
Qi Jiang, PhD	Executive Director, Biostatistics
Julie Lepin, MS	Director, Regulatory Affairs
Cesar Libanati, MD	Director, Clinical Development
Peter McCroskery, MD	Director, Global Safety
Rick Lit	Executive Director, Regulatory Affairs CMC
Barrie Nelson, LRSC	Senior Manager, Biostatistical Programming
Javier San Martin, MD	Executive Director, Clinical Development
Steven Snapinn, PhD	Vice President, Global Biostatistics & Epidemiology
Catherine Stehman-Breen, MD	Vice President, Global Development
Randy Steiner, DPA, MS	Executive Director, Regulatory Affairs

BACKGROUND:

On September 11, 2008, Amgen submitted a request and a briefing package for a Type B meeting to discuss their questions regarding the clinical and nonclinical aspects of the denosumab program. The package contained the questions listed below. DRUP's responses to the questions were faxed to the sponsor on October 17th, 2008, and are also included below. Additional meeting discussion is shown in bold italicized font after each response.

QUESTIONS, DIVISION RESPONSES, AND FURTHER DISCUSSION:

Question 1: Does the Agency require any clarifications regarding the proposed nonclinical content in support of the BLA submission for PMO and HALT indications (see Section 6 and Appendix 1)?

FDA Response: No, not at this time.

Meeting Discussion: No additional discussion

Question 2: Does the Agency agree that the clinical data from the 4 pivotal phase 3 studies, in addition to data summarized from the overall development program, provide an adequate basis for BLA submission in support of the PMO and HALT indications (see Section 7)?

FDA Response: The proposed clinical data from the four pivotal phase 3 studies, in addition to data summarized from the overall development program, appear adequate for BLA submission for the proposed PMO and HALT indications. As outlined in February 08 meeting, all available safety and efficacy data should be submitted for the supportive studies. Trial synopsis or abbreviated report will not be sufficient.

Meeting Discussion: Amgen confirms that all available safety and efficacy data from supportive studies will be included in the BLA. The Agency requested that information regarding the study design (e.g., eligibility criteria) be present in the synopsis CSRs. Amgen replied that the protocol would be appended to each synopsis CSR. The Agency also requested that key demographic information be added to each synopsis CSR. Amgen agreed to provide this information for Studies 20060289 and 20060232. Amgen replied that it may be difficult to obtain this information for Study 20050209, since the database is not housed at Amgen.

FDA reconfirmed agreement with Amgen's proposed data cut-off date of 31 May 2008, as previously agreed during the 05 February 2008 Type C meeting.

FDA Response: Studies 20040138 and 20040135, intended to support licensure for the HALT indications are ongoing, and will not complete the follow up phase until 2010 and 2011. FDA expects complete, cleaned and verified safety data up to the date of the data cut-off to be submitted with the BLA, and a final study report to be submitted upon completion of the trials.

Meeting Discussion: Amgen will provide in the BLA, full, complete clinical study reports from the treatment phases of studies 20040135 (month 24) and 20040138 (month 36) with data cut-off points of the Month 24 visit or the Month 36 visit, respectively. Amgen agreed to submit a final study report upon completion of both studies, including results from the safety follow-up phases of these studies. Final CSRs will be available in Q4 2009 and Q4 2010 for studies 20040135 and 20040138, respectively.

- ***Study 20040135 2-year Safety Follow up: This 2 year follow up study to the two year treatment phase of the 20040135 will complete March 2009. In this extension, subjects are no longer receiving denosumab and limited data are collected via every 6 month phone or clinic contact (AE and concomitant medication). Interim data up to December 2nd, 2008 will be provided in the 120 day safety update (see Question 5).***
- ***Study 20040138 2-year Safety Follow up: This 2-year follow up study to the 3-year treatment phase of the 20040138 will complete April 2010. In this extension, subjects are no longer receiving denosumab and limited data are collected via every 6 month phone or clinic contact (AE and concomitant medication). Interim data up to December 2nd, 2008 will be provided in the 120 day safety update (see Question 5).***

Question 3: Does the Agency require any clarifications regarding Amgen's approach for inclusion of information from completed and ongoing studies in the BLA submission as described in Section 7.1?

FDA Response: We do not require any clarification. Please refer to the answer to Question 2.

Meeting Discussion: No additional discussion.

Question 4: Does the Agency require any clarifications regarding Amgen's approach for overall safety evaluation as described in Section 7.6.2?

FDA Response: Your submission should include the charters, procedures and meeting minutes for any of the adjudication committees used in evaluation of the denosumab safety data. At a minimum, the information should include: the date the committees were appointed, a roster of committee members, what criteria were used for query of the safety databases and selection of events forwarded for committee review, criteria used for adjudication for each condition, procedures used to resolve differences of opinion among committee members. Please include minutes from all DMC meetings and minutes of classification meetings with detailed descriptions of analysis populations. Similarly, describe the data safety monitoring procedures in detail.

Meeting Response: Amgen confirmed that the BLA will contain the requested information.

FDA Response: In studies of denosumab therapy for treatment of rheumatoid arthritis, a concern has been raised about an apparent dose-dependent prolongation of the QT interval at month 12. One patient with QTc prolongation > 60 msec developed intermittent left bundle branch block. A complete analysis of all EKG data from all trials should be included in the BLA submission. If concern regarding QT prolongation remains, a thorough QT study may be necessary. Please clarify if the investigator's overall interpretation of ECG results as "normal", "abnormal, but not clinically significant" or "abnormal, clinically significant" as noted on the case report forms in several studies [see page 126] were sent to the Cardiovascular Events Adjudication Committee. Ultimately, the safety determination regarding QT prolongation is a review issue and therefore a definitive answer regarding a requirement for a thorough QT study can not be provided at this time.

Meeting Discussion: Amgen acknowledged the Agency's comment regarding QT prolongation and confirms that the BLA will contain a complete analysis of all ECG data from studies for which this information was collected, including Studies 20030148, 20030180, 20040245, 20050146, 20050227, 20060446, 20060286, 20010223, 20040132, 20050172, and 20040144. Additionally, for Studies 20010223 and 20040132, ECGs were also read by a central reader and results are described in the study reports.

None of these studies included CV adjudication (CV adjudication was performed in pivotal phase 3 studies 20040138 and 20030216). Therefore, none of these events were sent for adjudication.

FDA requested that Amgen include hyperlinked CRFs for all subjects with "abnormal, clinically significant" ECG results (using the investigator's interpretation) in the BLA submission. Amgen agreed to provide these CRFs in the BLA.

FDA Response: Regarding bone quality, we are concerned that up to 35% of bone biopsy samples showed either a single tetracycline label or no label on the cortical and trabecular bone surface. Please

clarify the number of bone histomorphometry samples obtained, and what percent were adequate for evaluation.

Meeting Discussion: Bone biopsy samples have been collected from studies of treatment naïve women treated with denosumab (20010223 and 20030216) and women who had previously received alendronate and were transitioned to denosumab (20050234). Amgen noted the Agency's concern with regard to the lack of label in some bone biopsy samples, and Amgen committed to provide a detailed explanation of this observation in the BLA to address this concern.

FDA Response: Adverse events of interest

a. Hypersensitivity reactions: the analysis should also examine any injection or infusion site reactions. Also, please review any subjects with lags in therapy/reintroduction of therapy in case these subjects are more at risk for hypersensitivity reactions.
b. Hypocalcemia: provide a listing of all subjects who received intravenous calcium replacement.
c. Infections: present and evaluate the infection data over time – e.g. present the SOC categories for Year 1, Year 2, etc. then microbial types for Year 1, Year 2, etc. Also, evaluate infections in subjects receiving concomitant immunosuppressant therapy (e.g. systemic corticosteroids, methotrexate, azathioprine, etc.)

Meeting Discussion: For items a and b, Amgen confirmed that these analyses will be included in the assessment of these adverse events of interest.

For item c, Amgen recognized the Agency's interest in identifying subpopulations of subjects at higher risk of infection.

Study 20040144 (a phase 2 dose-ranging study in rheumatoid arthritis) provides the opportunity to explore the risk for infection in subjects receiving concomitant immunosuppressant therapy (e.g., systemic corticosteroids, methotrexate, azathioprine, etc.), where immunosuppressant therapy was used in all subjects. These analyses will be provided in the BLA.

In addition, Amgen will evaluate the utility of performing analyses of concomitant immunosuppressant therapy from the pivotal PMO and HALT studies.

FDA requested that Amgen include a comprehensive evaluation of infections across all studies, including phase 1 studies, in the BLA.

Question 5: Does the Agency agree with the proposed content and analysis for the 120-day safety update as described in Section 7.10?

FDA Response: No. A more complete safety update at 120 days is required. The 120 day safety update should include complete, cleaned and source verified safety data. In addition, the 120-day safety update should be accompanied by any new and updated narratives and case report forms for all deaths, as well as for all patients with serious adverse events, those terminating study drug prematurely, and those categorized as other, lost to follow up, physician decision, or subject decision. In addition, please provide an updated comprehensive evaluation of the adverse events of interest identified in section 7.6.4.

Meeting Discussion: Amgen confirmed that it will provide a complete safety update (including cleaned and source verified safety data) for the following PMO and HALT studies for the 120-day safety update:

- ***Data from the safety follow up phase of Studies 20040135 and 20040138 up to the cut-off of December 2, 2008***
- ***BMD and safety data from the off-treatment phase of Study 20040132 up to the final study visit (month 48) in January 2009***
- ***Final clinical study report (including 12 months of safety and immunogenicity data) from Study 20060237 (vial vs. PFS study)***
- ***Interim analysis of Study 20060289 (open-label extension phase to study 20030216) up to the cut-off of December 2, 2008***

Amgen will also provide new and updated safety narratives from these studies and case report forms as specified above.

Amgen is not planning to provide clean, source verified safety data from the other ongoing studies, since these studies are not anticipated to provide additional significant information for the safety evaluation of denosumab in these indications. These studies include:

- ***Study 20050233: 4-year open label safety extension to the phase 2 dose ranging study (20010223)***
- ***Study 20060232: 2-year open label adherence, preference, and satisfaction study***
- ***Study 20040114: phase 2 open-label, active-controlled study in subjects with advanced cancer currently being treated with intravenous bisphosphonates***
- ***Study 20050134: phase 2 open label multiple myeloma study***
- ***Study 20050209: ABCSG Cooperative Group breast cancer study in postmenopausal women with nonmetastatic breast cancer undergoing aromatase inhibitor therapy***

Amgen would like confirmation of the Agency's agreement with this proposal.

Based on this incremental data set, Amgen will provide a comprehensive evaluation of the adverse events of interest in the 120-day update for the studies being submitted.

FDA stated that this proposal was acceptable but requested that Amgen provide a complete safety update (including cleaned and source verified safety data) for Study 20050233 in the 120-day safety update. Amgen agreed to provide this information.

FDA Response: We note the precipitous decrease in bone density once denosumab treatment was discontinued in study 20040132 (page 92, 93). This raises concern about a possible negative rebound effect. The last patient last visit for study 2004132 is in January 2009. Therefore, the 120 day safety update must include 48 month BMD data from study 2004132.

Meeting Discussion: Amgen will provide the 48-month BMD data from Study 20040132 in the 120-day update.

In addition, Amgen will provide in the BLA BMD results, bone turnover, and safety data, from the 2-year period following discontinuation of denosumab treatment from Study 20010223 (phase 2 dose ranging study in PMO). The results for lumbar spine and total hip BMD in this study demonstrate that BMD declines to approximately pre-treatment levels in the first year after discontinuation of treatment. No further declines in BMD are observed in the second year after discontinuation from treatment.

Amgen presented the results indicated above from Study 20010223, showing changes in lumbar spine BMD for the 2-year period after discontinuation of denosumab treatment, demonstrating the lack of further declines in BMD in the 2nd year of off-treatment. In addition, the similar changes in lumbar spine BMD after denosumab discontinuation for two different dose regimens were presented. These data will be provided in the BLA.

Question 6: As described in Section 4.3, Amgen considers that the criteria for priority review are met for denosumab in the treatment and prevention of PMO and in the treatment of bone loss associated with HALT in patients with breast cancer and prostate cancer. A formal request for priority review will be included in the BLA. Does the Agency have any comments on this proposal?

FDA Response: The status of the application will be determined once it is submitted for review. However, DRUP does not believe that denosumab meets the criteria for priority review for the PMO indication as there are multiple safe and effective therapies available, including medications administered once yearly.

Meeting Discussion: Amgen acknowledged that the status of the application will be determined after submission of the BLA, and we look forward to receiving the Agency's response to Amgen's request for priority review.

Additional Clinical Comments:
Please include following in the BLA submission:

- summary tables of the incidence of adverse events based on the cumulative dose and the average dose of Denosumab administered,
- a dataset that describes all prior therapies.
- a discussion and justification of the clinical utility of measuring BMD at a one month time point.

Meeting Discussion:

Bullet 1

The same dose and dosing frequency was used in all phase 2 and phase 3 studies to support the proposed indications (60 mg SC Q6M), except for the phase 2 Study 20010223 dose finding study. Therefore adverse event analyses using categories of average dose and total dose received would contain nearly the same information. Any analysis based on cumulative dose or average dose would also be nearly identical to grouping studies based on duration (1 year, 2 year, and 3 year studies) because of high compliance.

Amgen will provide exposure-adjusted (using time on study), and by-year-of-study incidences of adverse events and serious adverse events, in the individual clinical study reports for Studies 20030216 and 20040138 as well as in the integrated safety datasets in the BLA.

Amgen believes that these analyses will satisfy the Agency's request for incidence of adverse events based upon cumulative and average dose.

Bullet 2

In Study 20030216, Amgen will provide in the BLA, a dataset that describes all prior therapies affecting bone metabolism. For HALT Studies 20040135 and 20040138, information regarding prior bisphosphonate therapy will be provided.

Study 20050234 evaluated the safety and efficacy of denosumab in subjects who had previously received bisphosphonate therapy compared to subjects continuing on bisphosphonate therapy. A final full clinical study report will be provided in the BLA.

Bullet 3

Amgen will provide a discussion and justification of the relevance of measuring BMD at early time points in clinical studies of denosumab.

FDA stated that these proposals were acceptable.

FDA Response: Amgen's proposal for providing training to FDA staff on their CDISC submission is acceptable. However, a 2 hour presentation is preferable to the 3 hour and 50 minute agenda proposed.

Meeting Discussion: Amgen will follow-up with the FDA following the submission of the BLA to coordinate this meeting. An abbreviated agenda for this meeting will be provided.

Additional Clinical Pharmacology Comments:

- In addition to the biopharmaceutics and clinical pharmacology findings summary, we recommend including the following information in your BLA submission to facilitate the review:
  - A table listing all the studies with respect to the drug substance and product used in Section 2.7.1.
  - Summary of bioanalytical methods for pharmacokinetic, pharmacodynamic, and immunogenicity assessments in Section 2.7.1.
  - Summary of immunogenicity assessment results in Section 2.7.2.

Meeting Discussion: Amgen confirmed that this information will be included in the BLA.

Additional CMC Comments:

- In follow-up to the CMC preBLA meeting of July 8, 2008 and the subsequent telecon of July 29, 2008, we have the following comment regarding Amgen's proposed validation strategy for licensure of the 60 mg/ml vial. In order to license the 60 mg/ml vial, a comprehensive data package, including complete validation and stability data for the 60 mg/ml vial manufactured at AML, will need to be included in a BLA submission.

- Please submit the planned denosumab manufacturing schedule prior to the submission of the BLA, so that pre-approval inspections for each intended manufacturing site can be scheduled to conform to the GRP review timeline.

Meeting Discussion: Process validation, consisting of 3 consecutive drug product lots of the 60 mg/mL vial manufactured at Amgen Manufacturing Limited (AML), was performed in September 2008. Validation data, including 1 month of stability data will be submitted in the BLA. Additional stability data up to 3 months for these lots will be available during the review period, approximately 120 days after the BLA submission.

A comparability assessment for the site transfer from the clinical to the commercial site, AML, for the 60 mg/mL vial will also be provided in the BLA. This will include an assessment against historical ranges for lot release testing.

Amgen will submit a manufacturing schedule for both commercial drug substance manufacturing sites, BI Pharma and Amgen Colorado, and for the commercial drug product site, AML, prior to submission of the BLA.

Amgen requested an Agency point of contact to facilitate coordination of these inspections.

FDA stated that these proposals were acceptable. In addition, FDA recommended that Amgen coordinate with the regulatory project manager to provide manufacturing schedule details.

Additional Division of Biologic Oncology Products (DBOP) Comments:

DBOP has the following general comments regarding the content and organization of a BLA.

I Information Required for Review

A. The BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: http://www.fda.gov/cder/mapp/6010.3.pdf.

To facilitate the review, DBOP requests you provide analyses, and the supporting ADaM datasets as applicable, that will address the items in the template, including:

1. Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Exposure-Response Relationships - important exposure-response assessments.
3. Less common adverse events (between 0.1% and 1%).
4. Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Marked outliers and dropouts for laboratory abnormalities.
7. Analysis of vital signs focused on measures of central tendencies.

8. Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Overdose experience.
12. Explorations for dose dependency for adverse findings.
13. Explorations for time dependency for adverse findings.
14. Explorations for drug-demographic interactions.
15. Explorations for drug-disease interactions.
16. Explorations for drug-drug interactions.
17. Dosing considerations for important drug-drug interactions.
18. Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Meeting Discussion to Items 1 – 18:

Amgen confirmed that the requested analyses, and the supporting ADaM datasets as applicable, will be included in the BLA. This information will be summarized in the clinical summary documents contained in Module 2 of the CTD and applicable clinical study reports.

B. In addition, DBOP requests the following:

1. For the submitted datasets:
    a. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration. The integrated safety dataset should include the following fields/variables:
        - A unique patient identifier
        - Study/protocol number
        - Patient's treatment assignment
        - Demographic characteristics, including gender, chronological age (not date of birth), and race
        - Dosing at time of adverse event
        - Dosing prior to event (if different)
        - Duration of event (or start and stop dates)
        - Days on study drug at time of event
        - Outcome of event (e.g. ongoing, resolved, led to discontinuation)
        - Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
        - Marker for serious adverse events
        - Verbatim term

Meeting Discussion: Amgen will provide the requested dataset, and confirmed that this integrated safety dataset applies to all phase 2 and phase 3 PMO and HALT studies for completed studies or studies for which the treatment phase is complete only and will exclude studies outside the proposed indications (i.e., advanced cancer and rheumatoid arthritis) due to differences in patient populations.

FDA stated that this proposal was acceptable but recommended that we follow-up with DBOP to ensure agreement on this proposal.

2. The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form.

Meeting Discussion: Amgen will provide the requested dataset.

3. Please see the mock adverse event data set following this section that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.

Meeting Discussion: Amgen commits to providing the requested dataset.

4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.

Meeting Discussion: Amgen will provide the requested dataset.

5. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

Meeting Discussion: Amgen will provide the requested information.

6. *Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related renal disorders – comprehensive search SMQ. Also, please provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.*

Meeting Discussion: Amgen will provide the requested information.

7. *The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.*

Meeting Discussion: Amgen confirmed that this formatting will be performed as requested.

8. *Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.*

Meeting Discussion: Amgen will provide the requested information.

9. *In every dataset, all dates should be formatted as ISO date format.*

Meeting Discussion: Amgen will provide the requested information.

C. Provide a comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities. Also, provide a list of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The BLA analyses of the frequency of abnormalities across treatment groups are not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

Meeting Discussion: Amgen confirmed that data from patients with potentially clinically significant laboratory or vital sign abnormalities will be provided in the Summary of Clinical Safety ADaM datasets. Amgen confirmed that patients reporting adverse events involving abnormalities of laboratory values or vital signs will be tabulated. Analyses of laboratory values will include assessments of changes from baseline to worst values.

D. For all HALT pivotal trials, CRFs for all deaths occurring within 3 months of a denosumab dose, all serious adverse events, and all withdrawals will be required. In addition, CRFs for all patients with cardiovascular adverse events should be submitted. Any change in the CRF documents should be hyperlinked to the query or documentation from which the change resulted.

Meeting Discussion: As agreed during the Type C meeting of February 2008, Amgen will provide CRFs for all deaths occurring within 3 months of a denosumab dose, all serious adverse events, cardiovascular adverse events, and all withdrawals due to adverse events.

E. For patients listed as discontinued due to "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

Meeting Discussion: Amgen confirmed that its data management procedures include a review of reasons for discontinuation to confirm whether the appropriate reason for discontinuation has been selected by the investigator. Amgen tabulates the study disposition table according to the reason for discontinuation provided by the investigator.

F. If you and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions

with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

Meeting Discussion: Amgen acknowledged the Agency's comment and will engage in these discussions as necessary.

II Information Regarding Submission of Electronic Data Sets

A. Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org) .
At a minimum the Safety Analysis Plan should address the following components:

a. Study design considerations (See: FDA Guidance to Industry: Pre-Marketing Risk Assessment, http://www.fda.gov/CDER/guidance/6357fnl.pdf).

b. Safety endpoints for Adverse Events of Special Interest (AERI)

c. Definition of Treatment Emergent Adverse Event (TEAE)

d. Expert adjudication process (Expert Clinical Committee Charter)

e. Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)

f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

g. When unanticipated safety issues are identified the QSAP may be amended.

Meeting Discussion: Although Amgen does not have a QSAP, the requested items a – g above will be included in the BLA, including an integrated SAP for the Summary of Clinical Safety, the define.xml document, and adjudication and DMC charters.

FDA stated that this proposal was acceptable.

Amgen inquired as to whether a QSAP will be a requirement for future submissions, and if guidance will be provided. There is no regulatory requirement for the submission of a separate QSaP. It is expected that there is an expanded section of the current Statistical Analysis Plan(SAP) that provide details on adverse events of special interest, the data structure, analysis, etc. Future guidance on this will be provided.

B. Study Data Tabulation Model (SDTM) Issues

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) should be followed carefully. Refer to the SDTMIG section on Conformance (3.2.3)

Meeting Discussion: Amgen confirms that they are following SDTMIG 3.1.1.

2. Domains
    a. There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
        - (DV) Protocol deviations
        - (DA) Drug Accountability
        - (PC, PP) Pharmacokinetics
        - (MB, MS) Microbiology
        - (CF) Clinical Findings

Meeting Discussion: Amgen confirmed that they are using DV, DA, PC, PP, and CF (named DF in their datasets) domains. Data for the PC and PP domains will be provided for the phase 2 and 3 studies and phase 1 Study 20040245.

    b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.

        - Imaging Data
        - Complex Inclusion/Exclusion Criteria

Meeting Discussion: Amgen confirmed that they have created custom domains following SDTM guidance. It is highly desirable that Amgen follow the CDISC recommendations and it would be very helpful for the sponsor to provide details on these domains and their quality checks to show that they are CDISC compliant.

3. Variables

    a. All required variables are to be included.

Meeting Discussion: Amgen confirmed that all required variables will be included.

    b. All expected variables should be included in all SDTM datasets.

Meeting Discussion: Amgen confirmed that all required variables will be included.

    c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.

Meeting Discussion: Amgen has explicitly stated in the CRT reviewer's guide the variables (expected or permissible) for which no values will be submitted. Variables

will have no values for one of 2 reasons, either the data was not explicitly collected on the CRF or the data point was conditional and no occurrence was encountered in the study. This approach is consistent with the published CDISC SDTM Implementation Guide.

FDA stated that this proposal was acceptable but requested that Amgen include this information in the Define.xml file in addition to the CRT Reviewers Guide.

d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.

Meeting Discussion: Amgen has excluded a permissible variable from a domain only when data was not explicitly collected on the CRF for that variable. They have not made subjective decisions on which permissible variables to include or exclude this decision is purely data driven. This approach is consistent with the published CDISC SDTM Implementation Guide. Amgen has not indicated which permissible variables have been included or excluded from each domain.

FDA stated that this proposal was acceptable.

e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.

Meeting Discussion: Amgen confirms that this information is included in the define.xml file.

f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG. :

Meeting Response: Amgen confirms that all datasets are compliant with the SDTMIG.

4. Specific issues of note:

a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.

Meeting Discussion: Amgen confirmed that SDTM formatted datasets do not provide replication of core variables.

b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.

Meeting Discussion: Amgen confirms that we will include MedDRA hierarchy variables in the SUPPQUAL dataset.

c. These issues can be addressed through the request for ADaM datasets

Meeting Discussion: No further discussion.

C. Analysis Data Model (ADaM) Issues

1. Specify which ADaM datasets you intend to submit.

Meeting Discussion: The specific ADaM datasets that Amgen will submit are listed in the define.xml file and in the CRT reviewer's guide which was agreed during the Type C meeting of February 2008.

2. Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.

Meeting Discussion: The specific variables in the ADaM datasets that Amgen will submit are listed in the define.xml file.

3. Discuss the structure of the datasets with the reviewing division and specify in the QSAP.

Meeting Discussion: Amgen plans to be consistent with the dataset structures agreed upon during the Type C meeting of February 2008.

4. Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.

Meeting Discussion: Amgen confirms that this information will be included in the dataset.

5. Indicate which core variables will be replicated across the different datasets, if any.

Meeting Discussion: Amgen will indicate which core variables will be replicated across the different datasets in the CRT Reviewers Guide.

6. SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

Meeting Discussion: Amgen confirms that these identifiers will be retained.

D. General Items

1. Controlled terminology issues
    a. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire BLA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for

individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.

Meeting Discussion: Amgen has used different MedDRA dictionaries, and will provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another.

Amgen requests clarification regarding the Agency's preferred format for this table and the eCTD location for this table.

FDA stated that this proposal was acceptable but did not specify a preferred format or eCTD location for the table. FDA agreed with Amgen's suggestion to include this table in the Summary of Clinical Safety.

b. For the concomitant medication dataset, the standard nomenclature and spellings from the WHO Drug dictionary, including the numeric code in addition to the ATC code/decode, are recommended.

Meeting Discussion: Amgen will not provide numeric codes in the concomitant medications dataset. They will provide the character decodes for the preferred terms.

FDA stated that this proposal was acceptable. Amgen will explore the possibility of providing the numeric codes as requested.

c. Please refer to the CDISC terminology for lab test names.

Meeting Discussion: CDISC controlled terminology for lab test names was not in place when we began our CDISC implementation. Therefore, Amgen uses Amgen-defined lab test names.

FDA stated that this proposal was acceptable.

d. Issues regarding ranges for laboratory measurements should be addressed. Provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from a local lab or central lab. Also, the variable for the laboratory result should be in numeric format.

Meeting Discussion: Amgen will provide an indication whether the lab result was from a local lab or central lab.

III Label in the Physician Labeling Rule (PLR) Format

A. Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]

4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).

6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].

7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

   "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

   Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

8. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

9. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].

10. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]

11. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]

12. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.

13. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

B. Contents (Table of Contents):

14. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]

15. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]

16. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.

17. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.

18. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

    8.1 Pregnancy
    8.3 Nursing Mothers (not 8.2)
    8.4 Pediatric Use (not 8.3)
    8.5 Geriatric Use (not 8.4)

19. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents:

    "*Sections or subsections omitted from the Full Prescribing Information are not listed."

C. Full Prescribing Information (FPI):

20. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

21. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

22. Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.

23. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]

24. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

25. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]

26. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

27. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.

28. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

29. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.

30. If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.

31. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

32. Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Meeting Discussion: Amgen acknowledged the Agency's comments regarding labeling (Section III above) and will submit the proposed labeling for denosumab in accordance with the Physician Labeling Rule (PLR) format per the PLR-related regulations and guidance documents.

During the labeling review process, Amgen proposes to provide both a 'tracked changes' version and a 'clean' version of the label to FDA. To facilitate this process and alleviate issues associated with version control, Amgen requests that the FDA reviewers provide their comments and changes in 'tracked changes' to the 'clean' version of the label.

Amgen inquired about the possibility of an Advisory Committee meeting, and FDA stated that an Advisory Committee meeting will almost certainly be required for denosumab, but no further details were available. Further details on whether this will be a joint Advisory Committee will be discussed following submission of the BLA.

In addition to the meeting responses above, Amgen provided the following summary of agreements and action items from the meeting:

1. ***The proposed clinical data from the four pivotal phase 3 studies, in addition to data summarized from the overall development program, appear adequate for BLA submission for the proposed PMO and HALT indications. Amgen's proposed responses to the Agency's pre-meeting comments are considered generally acceptable; there are a few additional considerations from today's discussion. It is understood that all safety and efficacy data will be provided irrespective of the type of report, and that the provision of the proposed reports is considered appropriate. Amgen will follow up with DBOP to ensure agreement with Amgen's responses.***

2. ***For synopsis reports, a copy of the protocol will be included to provide information regarding the study design (e.g., eligibility criteria). In addition, key demographic information will be added to each synopsis CSR, recognizing this information may be limited in some cases.***

3. ***Final agreements on Amgen's proposals to provide clean, source verified safety data from Studies 20040135 and 20040138 in the 120-day safety update and full CSR's upon study completion will be provided by DBOP.***

4. ***Amgen will provide all CRFs for those cases of ECGs considered "abnormal, clinically significant".***

5. ***Amgen will provide a comprehensive evaluation of bone biopsy data in the BLA and look forward to further discussion with the FDA on this subject during BLA review once these data have been assessed.***

6. ***Amgen will provide clean, source verified data from the open-label extension Study 20050233 in the 120-day safety report.***

7. ***Amgen will seek to have a face-to-face meeting to discuss CDISC aspects shortly.***

8. ***Amgen will liaise with Celia Peacock, the DRUP Regulator Project Manager to schedule inspections.***

9. ***Amgen will ensure that appropriate comments are provided in Define.xml file to provide sufficient direction to reviewers on what is provided in the data sets.***

10. ***Amgen will include a table mapping MedDRA codes for the integrated analysis in the Summary of Clinical Safety unless otherwise instructed to locate elsewhere in the CTD by FDA.***

11. ***FDA would appreciate the inclusion of numerical codes in addition to ATC. Amgen will explore the possibility of providing this information.***

ACTION ITEMS;

Finalize meeting minutes within 30 days.

ATTACHMENTS/HANDOUTS:

Amgen Slides.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BB IND 9837

Amgen, Inc
Attention: John J. Bergan
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Mr. Bergan:

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

We also refer to the meeting between representatives of your firm and the FDA on July 8, 2008. The purpose of the meeting was to discuss Chemistry, Manufacturing, and Control issues.

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

If you have any questions, call me at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Celia R. Hayes, MPH, RD
Captain, U.S. Public Health Service
Regulatory Project Manager
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 8, 2008

TIME: 1:00 p.m. – 2:30 p.m.

LOCATION: FDA, White Oak Campus

APPLICATION: BB IND 9837

DRUG NAME: Denosumab

TYPE OF MEETING: Type B

MEETING CHAIR: Chana Fuchs, Ph.D.

MEETING RECORDER: Celia Hayes, M.P.H., R.D.

FDA ATTENDEES:

Celia Hayes, MPH, RD	Regulatory Project Manager	Division of Reproductive and Urologic Products
George Benson, M.D.	Acting Deputy Director	Division of Reproductive and Urologic Products
Gerald Willett, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Adrienne Rothstein, Pharm.D.	Clinical Analyst	Division of Reproductive and Urologic Products
Margaret Kober, R.Ph., MPA	Chief, Project Management Staff	Division of Reproductive and Urologic Products
Myong-Jin Kim, Pharm.D.	Clinical Pharmacology Team Leader	Office of Clinical Pharmacology
Kimberly Hatfield, Ph.D.	Phamacologist	Division of Reproductive and Urologic Products
Theresa Kehoe, M.D.	Medical Team Leader	Division of Metabolism and Endocrinology Products
Patricia Hughes, Ph.D.	Microbiologist	Division of Manufacturing and Product Quality
Jang-Ike Lee	Clinical Pharmacologist	Office of Translational Science
Jeffery Summers M.D.	Medical Team Leader	Division of Biologic Oncology Products
Patrick Swann, Ph.D.	Deputy Director	Division of Monoclonal Antibodies
Chana Fuchs, Ph.D.	CMC Team Leader	Division of Monoclonal Antibodies

Sarah Kennett, Ph.D.	Biologist	Division of Monoclonal Antibodies
Hong Zhao, Ph.D.	Pharmacology Reviewer	Office of Translational Sciences

EXTERNAL CONSTITUENT ATTENDEES:

Lorena Barrón, PhD	Principal Scientist, Drug Product and Device Development	Amgen
John Bergan	Senior Manager, Regulatory Affairs CMC	Amgen
Laura Bloss, PhD	Executive Director, Clinical Development	Amgen
Mike Moxness, Ph D	Principal Scientist, Clinical Immunology	Amgen
David Feigal, MD	Vice President, Global Regulatory Affairs	Amgen
Bradley Glasscock, Pharm D	Senior Manager, Regulatory Affairs	Amgen
Simon Hotchin	Senior Manager, Regulatory Affairs CMC	Amgen
Christopher Johnson	Director, Product Quality	Amgen
Rick Lit	Executive Director, Regulatory Affairs CMC	Amgen
Jennifer Mercer	Director, Regulatory Affairs CMC	Amgen
Tony Mire-Sluis, PhD	Executive Director, Corporate Quality	Amgen
Athena Nagi, PhD	Principal Scientist, Analytical Sciences	Amgen
Gregg Nyberg, PhD	Principal Scientist, Process Development	Amgen
Margaret Ricci, PhD	Director, Formulation Analytical Resources	Amgen
Wen Ryan, PhD	Executive Director, Global Operations	Amgen
Javier San Martin, MD	Executive Director, Clinical Development	Amgen

BACKGROUND:

On April 22, 2008, Amgen submitted a request and a subsequent briefing package, on May 29, 2008, for a Type B meeting to discuss Chemistry, Manufacturing, and Control issues. The package contained the questions listed below. DRUP's responses to the questions were conveyed to the sponsor on July 7th, 2008, and are also included below. Additional meeting discussion is shown in bold italicized font after each response.

QUESTIONS, RESPONSES, AND FURTHER DISCUSSION:

Question 1: The overall strategy for demonstration of drug substance and drug product comparability between clinical and commercial production was discussed during a Type C meeting held 08 December 2006. Subsequent to this meeting, analytical comparability for the transfer of the commercial drug substance process from Amgen Colorado (ACO) to Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma) has been completed and the results of this study were submitted to BB-IND 9837 on 07 December 2007 (SN 0406). Further characterization studies have been completed in order to assess the analytical differences in charge and size profile noted between drug substance manufactured at ACO and drug substance manufactured at BI Pharma.

a) Does the FDA agree that the additional drug substance characterization data demonstrate that the observed differences between drug substance manufactured at ACO and BI Pharma are understood, and when combined with the results of the bioequivalence study, will provide sufficient evidence to conclude that the materials are comparable?

   FDA's Response: Final conclusions on comparability are a BLA review issue. The analyses provided support biochemical similarity and, with associated bioequivalence study results, these data may be sufficient to demonstrate comparability between the ACO and BIP manufactured DS.

   Greater detail is needed regarding the distribution and activity of (b) (4) structural isoforms[1]. You state in Table 24 on page 126 that structural isoforms are present at levels of between (b) (4) and that all structures were equally potent. Results in the cited literature indicate that the (b) (4) isoform can have diminished activity.

   Regarding both comparability and specifications, please include in the BLA line item data for release and stability testing for each referenced lot. Please provide good quality reproductions of representative gels and chromatographs for our assessment.

   We note that there is a small difference in the results of host cell DNA, host cell protein, and Protein A testing for ATO/ACO vs. BI Pharma. In the BLA, please clarify if this is due to the testing procedure (e.g., testing at different locations or with different protocols) and reporting, or due to the different manufacturing processes.

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[1] Dillon et al, JBC, Published online March 12, 2008; Wypych et al, JBC, Published online March 13, 2008.

Please clarify which reference material (ATO or ACO) is being used in the clinical comparability study (20060286)

Meeting Discussion: ***Amgen stated that they have isolated and tested the potency of the*** (b) (4) ***variants of denosumab by the various potency methods and have shown them to be equivalent. This information will be presented in the BLA. Marginal differences have been observed in the levels of CHOP in the in-process pools at ACO and BI Pharma. However, the purification process at both sites has similar clearance capabilities and reduces the levels of CHOP in DS to the LOD at both sites. The same methodology is used at both sites and the apparent differences in Protein A, DNA and CHOP at the DS stage are due to rounding and reporting differences between sites. Amgen acknowledged the Agency's concern regarding any process related differences and confirmed that any differences detected between sites will be evaluated for other underlying differences which are not part of normal monitoring/testing. Amgen confirmed that ATO material was the reference material used in Study 20060286. FDA indicated that chromatograms shown in the comparability reports were shown in full scale and that any smaller peaks cannot be seen well at such scale; Amgen agreed to include expanded view chromatograms in the BLA.***

b) Does the FDA agree that the overall plan for submission of comparability data in the BLA is sufficient for product registration including drug substance manufactured at ACO and BI Pharma and for the drug product presentations (vials and prefilled syringes) manufactured at AML?

FDA's Response: No. Comparability analyses between drug products manufactured at AML and ATO, for both the PFS and the 60mg/mL vial, should be finalized, and a full comparability data package should be included in the BLA submission.

From a clinical pharmacology standpoint, your proposed plan of submitting the clinical comparability data from studies 20050227, 20050146, 20060446, and 20060286 appear to be adequate to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) comparability for the transfer of drug substance manufacturing sites and for the different drug product presentations. However, the drug product manufacturing site change from ATO to AML may need an additional PK and PD comparability study in humans if the analytical comparability assessments detect a potential for PK or PD difference. A conclusive determination of the comparability is a BLA review issue.

Meeting Discussion: Amgen stated that the ATO to AML process comparability will be presented in the BLA, highlighting the high degree of similarity in process and equipment between sites. Where process or equipment differences exist, process characterization studies have been performed to show that the process differences do not impact process performance or product quality. These data will be provided in the BLA. Site-to-site comparability data has been generated for the 60 mg/mL PFS and the final report will be presented in the BLA. Site-to-site comparability data has been generated for the 70 mg/mL vial and the final report will be presented in the BLA. Amgen considers that the site-to-site comparability data generated on the 70 mg/mL vial may be appropriately extrapolated to the 60 mg/mL vial to support approval of this presentation, based on the high degree of

similarity between the 60 mg/mL and 70 mg/mL vial processes, and will justify this approach in the BLA.

The FDA indicated that insufficient information is provided to make an assessment regarding the site-to-site comparability at this time, and this proposal would need to be subject to a complete review of the data, including process validation and a comparability study from the commercial manufacturing site in order to make a final determination.

Amgen stated that based on experience from other commercial products and the results of the technical transfer of the denosumab fill process between the clinical and commercial sites (including execution of an engineering run for the 60 mg/mL vial), the technology transfer of the 60 mg/mL vial process from ATO to AML was not expected to adversely impact product quality. The strategy developed for denosumab was based on this historical precedence as well the data obtained from the 70 mg/mL vial. Amgen indicated that the 70 mg/mL vial was manufactured with the same equipment, process scale, and container closure system with only a difference in the fill volume and protein concentration.

The FDA stated that decisions could not be made prior to reviewing the data, however, should there be a problem, and the necessary data not be available on time, the 60 mg/mL vial may be reviewed as a supplement to the license post approval. Amgen suggested that a comparability protocol may be an option if the Agency would agree to further discussions.

The FDA stated that licensing both the 60 mg/mL and 70 mg/mL vial could led to medication errors and inquired as to whether or not the 70 mg/mL vial was intended for multiple doses. Amgen responded that all presentations of denosumab are intended for single use and that there is no intention to develop a multidose product. The FDA agreed to a follow up discussion with Amgen in an attempt to reach agreement on this strategy.

Question 2: Amgen will propose drug substance and drug product release specifications in the BLA based on an assessment of the critical quality attributes of denosumab and statistical analysis of data generated from clinical and commercial lots, including data generated during ongoing primary, commercial and supportive stability studies. Does the Agency agree that the selection of tests proposed for inclusion in the release specifications is adequate to control the quality of denosumab drug substance and drug product?

FDA Response: No. We have the following preliminary comments.

a. A binding assay is not adequate for use as the sole potency assay for licensure of this product, and a validated bioassay assay that reflects the proposed mechanism of action should be included for release and stability testing of DS and DP.

b. In the BLA, please provide data for all CE-HPLC peaks. The inclusion of only main peak in the acceptance criteria will be a BLA review issue.

c. We note that SDS-PAGE is being replaced by CE-SDS. In the BLA, please discuss the amount of CE-SDS data that is available and the overlap in data between CE-SDS and SDS-PAGE. Any changes in the CE-SDS method should also be discussed in the BLA.

d. In the BLA, please discuss the reason for proposing the appearance acceptance criteria [redacted] (b) (4) instead of [redacted] (b) (4)

e. An upper limit for volume should be included in the DP specification.

f. When reporting lot release results, the numerical values obtained for subvisible particulates testing should be included. Please also include these data for the lots presented in the BLA.

g. From Table 25 on page 134, there is no proposed acceptance criterion for osmolality. If osmolality is not to be included under footnote "a," an acceptance criterion should have been provided.

h. Please note that if host cell DNA, host cell protein, and Protein A are not included in the release specifications, validation of removal by the manufacturing process at both ACO and BI Pharma should be included in the BLA. Please assure that process validation also includes assessment or CHOP and DNA removal on appropriately aged resins. A discussion of the critical process parameters and monitoring that are in place to assure removal and the controls of these impurities should be presented in the BLA.

The acceptability of the specifications and associated acceptance criteria will be a BLA review issue. Final concurrence will require review of historical data based on independent calculation, our understanding of the assays based on review of the SOPs and validation sections, and of the product critical quality attributes. Please provide statistical analyses of all data regarding the proposed acceptance criteria. Please include separate analyses of drug substance and drug product, and both separate and integrated analyses of materials manufactured at the different sites. The BLA should include tables with all lot release data, and if possible, these should be provided in a format that can be accessed by the FDA reviewers for internal statistical analysis using programs such as JMP.

Acceptability of the proposal to not monitor or limit additional product related substances will be a BLA review issue. Please provide data and a comprehensive discussion in the BLA.

Meeting Discussion: Regarding the potency assay, the FDA had questions regarding the cell associated RANK ligand. Amgen proposed to consider this and requested a follow up meeting to discuss this issue prior to finalizing the meeting minutes. Amgen acknowledges the comments presented in 2b, 2c, 2d, 2e, and 2f and intends to address each comment within the BLA. For item "g", an acceptance criteria for osmolality will be proposed in the BLA. Regarding item "h", FDA noted that if host cell DNA, host cell protein, and Protein A are not included in the release specifications, validation of removal by the manufacturing process at both ACO and BI Pharma should be included in the BLA. Process validation should also include assessment of CHOP and DNA removal on appropriately aged resins. A discussion of the critical process parameters and monitoring that are in place to assure removal and the controls of these impurities should be presented in the BLA. Amgen agreed to provide all of

these requested data/justifications in the BLA. For those limits based on statistical analyses, Amgen agreed to conduct the analyses as requested. The datasets used for the statistical analyses will be provided to the Agency upon request. A detailed discussion and justification of the proposal to not routinely monitor product related substances will be provided in the BLA.

Question 3: Following a risk-based assessment of the drug substance manufacturing process to identify the potential points of introduction and removal of bioburden, Amgen is proposing to establish in-process controls for bioburden with associated reject limits at the production bioreactor and bulk drug substance fill stages. Other in-process steps will also be monitored for bioburden with action limits rather than reject limits. Does the FDA agree that this approach provides adequate control of bioburden in the denosumab drug substance manufacturing process?

FDA's Response: A risk based approach is appropriate; however, we have the following comments:

a. The cell culture is expected to be free of bioburden. A bioreactor (b) (4) t bioburden action (b) (4) and rejection limits (b) (4) are too high. Please consider lowering the bioburden limit. Using (b) (4) would allow for increase in the volume of sample tested for bioburden.

b. The in-process bioburden action limits (b) (4) for harvest (b) (4) steps are not acceptable. The high bioburden limits pose a risk to the product intermediates. In addition, please consider using (b) (4) method for bioburden testing of the in-process samples, where sample volumes can be larger. The bioburden limits should reflect the sample volumes used.

c. Please provide data demonstrating that the proposed bioburden limits at hold steps would not adversely impact product quality for the time and temperature at which the product would be stored.

Meeting Discussion: Amgen acknowledges the FDA's comments and the acceptance that a risk based approach is appropriate. Amgen will address each of these comments in detail within the BLA. The FDA indicated that the bioburden limits are also linked to the facility controls. FDA questioned why the limits were so high and enquired as to whether this was necessary to accommodate the limits at both DS manufacturing facilities. Amgen indicated that this was not the case, and the Agency indicated that the justification of the proposed bioburden limits would be discussed at the pre-approval inspection.

Question 4: Validation of the 60 mg/mL PFS has been successfully executed at a (b) (4) scale at Amgen Manufacturing, Limited (AML). Amgen intends to increase the scale to approximately (b) (4) prior to launch. There will be no significant changes to the manufacturing process or changes in the container closure. Amgen is proposing to submit a validation plan for the (b) (4) prefilled syringe scale-up in the BLA with predefined acceptance criteria.

Additionally, Amgen has conducted the appropriate pre-validation studies to support the introduction of a 60 mg/mL vial presentation into AML and is executing the 70 mg/mL (1.7 mL) vial validation in May 2008. The results of this 70 mg/mL (1.7 mL) process validation study will be provided in the BLA, together with a validation plan for the 60 mg/mL vial presentation.

Does the Agency agree with Amgen's denosumab drug product validation strategy for the 60 mg/mL PFS scale-up and 60 mg/mL vial drug product process validation plans for licensure for the PMO and HALT indications in the initial BLA along with the proposed reporting requirements?

FDA's Response: No. The final validated process should be in place prior to licensure to assure that a marketable Denosomab is available upon approval. For the 60 mg/kg vial, Amgen has not provided scientific rationale as to why the 70 mg/kg vial process validation is fully supportive of the 60mg/kg vial manufacturing process at AML. This should include information for the full manufacturing process as well as for the microbiological validation. For the PFS process, Amgen states that validation of the of the (b) (4) process will be included in the BLA on submission, with validation of the (b) (4) PFS process to be completed and available for review during the PAI (page 157). We would be willing to accept the updated validation for the (b) (4) process as an amendment to the BLA during the review cycle so long as we have an agreed upon date by which it will be submitted, and that it is submitted prior to the PAI.

Meeting Discussion: Amgen will provide detailed justification for the extrapolation of the 70 mg/mL vial process validation data to the 60 mg/mL vial in the BLA, and also agreed to provide an estimate for the submission date for the (b) (4) scale-up data once the schedule has been confirmed for this activity. Amgen noted that process development studies have been conducted at bench scale to characterize the hydrodynamic environment resulting from the mixing, filtration, and filling process. Full-scale (e.g., engineering runs) manufacturing data have been generated for the 60 mg/mL vial, 70mg/mL (1.7 mL) vial, and 60 mg/mL PFS, confirming that the transfer to AML does not impact product quality attributes. Process validation has been completed for the 70mg/mL (1.7 mL) vial and 60 mg/mL PFS. The results from the validation lots confirmed no impact on product quality with the change in site and fill volume as predicted from the process characterization and engineering run. It is believed that data generated on the 70 mg/mL vial is predictive of process performance and product quality for the 60 mg/mL vial and support approval of the 60 mg/mL vial. FDA acknowledged that data for the (b) (4) scale of 60 mg/mL PFS will be in the BLA and requested the dates and timing when the (b) (4) scale-up data will be available. FDA requested that Amgen communicate these dates prior to submission of the BLA and requested that the data be available prior to the pre-approval inspection.

Question 5: Based on available data, Amgen intends to apply for a 30 month expiration period for all drug product presentations.

a) Does the FDA agree with the strategy to establish expiration dating for the drug product?

FDA's Response: No, the stability data for each presentation to be licensed should include data from DP manufactured at AML from DS produced at ACO and BI Pharma, in addition to the

supporting data from fill at ATO. At this time it appears that Amgen does not intend to provide stability data for the 60 mg/mL vials manufactured at AML. Acceptance of data exclusively from the ATO fill in support of expiration dating for DP manufactured at AML may be appropriate based on the following caveats: ICH Q1a (www.ich.org) defines pilot scale batch as a batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. Amgen should provide a detailed description of each manufacturing process and a comprehensive list of differences between the ATO processes and the AML processes for both the PFS and the 60mg/mL vial. The applicability of the data from the ATO process would depend upon a comparison of the pilot process to the to-be-marketed process.

Additionally, from Q1a, if significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.

Final assessment of appropriateness will have to be based on review of a complete data package. Please provide results of stability evaluation as described in ICH Q1e (e.g., graphical presentation with confidence intervals where appropriate).

b) Does the FDA agree with Amgen's proposal for submission of stability updates during review of the marketing application?

FDA's Response: Yes.

Meeting Discussion: Amgen acknowledges the comments of the FDA and will provide the necessary justifications in the BLA.

Question 6: Module 3 of the BLA will contain information to support licensure of the drug substance manufacturing sites at Amgen Colorado (ACO) and Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma). The process operated at both sites is essentially identical with the exception of process scale and minor differences necessary to achieve facility fit. Amgen therefore proposes to provide information regarding the manufacturing process operated at both sites in a single drug substance section (Section 3.2.S), with the exception of the process validation data for each site, which will be presented in separate Sections 3.2.S.2.5 (Process Validation and/or Evaluation).

Does the FDA agree with Amgen's proposal for a single drug substance manufacturing process description which covers both BI Pharma and ACO?

FDA's Response: Yes. Please clearly differentiate the portions that are identical to both from those that apply solely to ACO or to BI Pharma. For ease of reviewing this complicated BLA, it would be useful if different colors of font are associated with each site for which there are differences, for example, use blue font for ACO-specific items, green font for BI Pharma-specific items, and use black font for items that apply to both ACO and BI Pharma. The use of color coding was very helpful in enabling a quick review and understanding of figure 2 on page

32 in the meeting package. In addition, please assure that detailed links to the appropriate validation data (preferably to the specific item, not just the whole validation section) are included. For submission to the BLA, separate statistical analyses should be performed for materials manufactured at ACO and for materials manufactured at BI Pharma, and the same analyses should be performed for datasets containing all materials.
In the characterization section, it would be helpful if the lots used for each data section are identified, including the site and process of manufacture.

***Meeting Discussion:** Amgen acknowledged the comments of the FDA regarding the potential complexity of the file. As stated in the briefing document, the processes operated at ACO and BI Pharma are highly similar and differ only in terms of scale and minor differences necessary to achieve facility fit. Amgen will assure that facility specific aspects of the process description will be clearly delineated in the BLA using separate headings, or color coding as suggested. Amgen anticipates that the identified differences will be few in number.*

As requested, data generated on ACO and BI Pharma DS will be analyzed separately and together in those sections where such analyses are appropriate, e.g., Justification of Specifications.

The FDA requested that release and stability data generated from lots manufactured at ACO and BIP are presented independently to allow for an independent comparative statistical analysis. The Agency expressed concern about how Amgen will monitor manufacturing from both facilities to assess process drift. Amgen stated that Quality systems were in place to manage process monitoring and change control from the contract manufacturing site. The FDA emphasized this as a concern, given that the contract site is not under direct control of Amgen. Amgen indicated that the process manufactured at both facilities uses the same controls and proven acceptable ranges.

Question 7: There will be 3 stand-alone quality drug product (3.2.P Module) sections to be electronically submitted to the BLA in eCTD format in the same PMO/HALT application for the 60 mg/mL PFS, 60 mg/mL Vial and 70 mg/mL (1.7 mL) vial. Amgen intends to include CMC information for all 3 drug product presentations in the initial BLA for the PMO and HALT indications. Amgen plans to cross reference and submit supporting CMC information in the initial BLA for the 70 mg/mL (1.7 mL) vial drug product presentation. Amgen does not intend to request approval of the 70 mg/mL (1.7 mL) vial presentation in the PMO/HALT application.

Does the Agency agree with Amgen's proposal to include information for the 70 mg/mL (1.7 mL) vial presentation in the BLA on the basis that it is only provided for the purposes of supporting approval of the 60 mg/mL vial and 60 mg/mL PFS presentations?

FDA's Response: Yes. Three stand alone DP quality sections are appropriate, though the applicability of the 70 mg/mL (1.7 mL) presentation to this BLA remains to be demonstrated. Please ensure that detailed links to the appropriate data (preferably to the specific item, not just the whole other quality section) are included. For the supporting 70 mg/mL DP presentation, please include only information that could be supportive of the 60 mg/ml presentations, as this presentation will not be reviewed for approval in this BLA. A complete information package in support of the 70 mg/ml (1.7 ml) vial presentation will need to be submitted in the BLA in which it is intended for marketing approval.

Meeting Discussion: Amgen acknowledged the comments of the FDA and will structure the BLA accordingly.

Question 8: The denosumab drug product manufacturing operations will be conducted at Amgen Manufacturing Limited, located in Juncos, Puerto Rico (b) (4) processing, facility and equipment information will be provided in the initial filing through a cross-reference to the applicable information of the Amgen Manufacturing Limited (AML) Type V Drug Master File (DMF) No. 21000.

Does the FDA agree with Amgen's proposal to provide (b) (4) processing, facilities and equipment information for AML via cross-reference to Type V Drug Master File (DMF) No. 21000?

FDA's Response: We prefer to have summary validation information for (b) (4) processing and equipment specific validation data and information for this product provided under Section 3.2.P.3.5 in the BLA. The provided information should follow 1994 "Guidance for industry for the submission documentation for sterilization process validation in applications for human and veterinary drug products" and 2004 "Guidance for Industry, sterile drug products produced by (b) (4) processing - current Good Manufacturing Practice".

Additionally, any information in support of the ATO procedure being fully representative of, and simulating the AML full production scale manufacturing process should be included in the BLA.

If the Type V DMF is cross-referenced, the information provided in the DMF should be specific for this product and be updated. The location of this information in the DMF should be specified.

Meeting Discussion: Amgen will cross-reference the electronic DMF 21000 within the BLA, but also provide the (b) (4) process and product specific equipment validation data in Section 3.2.P.3.5. of the BLA, as requested by the Agency. AML is a multiproduct facility and reference to the DMF would facilitate maintenance of the facility information, including (b) (4) process validation and equipment validation data. Following approval, Amgen proposes to maintain these data using the DMF. Detailed process and equipment comparisons conducted as part of comparability assessment will be provided in Section 3.2.P.2.3 (Process Development). The FDA indicated that it would be easier if the data could be provided in the BLA . The FDA agreed that following approval, data could be managed in a DMF as long as it is appropriately managed by ensuring that product specific information is clearly indicated.

Linked Applications	Sponsor Name	Drug Name
IND 9837	AMGEN INC	Human Monoclonal Antibody (AMG 162)(CHO Cells, Amgen) to Osteoprotegerin Ligand (RANKL)

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/s/

CELIA R HAYES
08/07/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 29, 2008

From: Melanie Pierce, DBOP/OODP/CDER

Subject: Filing Meeting Minutes: Denosumab: BL STN 125332/0 and 125333/0

This first committee meeting for STN BL 125132 and 125333/0 was a face-to-face, internal, FDA meeting. Attendees included Patricia Keegan, Jeff Summers, Suzanne Demko, Anne Pilaro, Michael Orr, Hong Zhao, Sarah Schreiber, Chana Fuchs, Sarah Kennett, Michele Dougherty, Chana Fuchs, Kyung Lee, Mark Rothmann, Melanie Pierce and Monica Hughes, Mike Pacanowski, Anastasia Lolas, Vaishali Popat, Kim Hatfield and Karen Jones.

REVIEW TEAM:

Regulatory Project Manager	Melanie Pierce
Clinical Reviewer	Suzanne Demko
Pharm/Tox Reviewer	Michael Orr
Clinical Pharmacology Reviewer	Sarah Schreiber
Biostatistician	Kyung Lee
Quality Reviewer	Sarah Kennett
Quality Reviewer	Michele Dougherty
QSPG Reviewer	Jenise Gillespie-Pedersen
QSPG Reviewer	Paul Schuette
Clinical Reviewer/DRUP	Vaishali Popat
Pharm/Tox Reviewer/DRUP	Kim Hatfield
DSI-Reviewer	John Lee
DDMAC Reviewer	Jeff Trunzo
Maternal Health Team Reviewer	Leyla Sahin
OSE RPM	Sandra Griffith
PeRC RPM	George Greeley

1. APPLICATION DATES:

- First Committee Meeting Held: January 13, 2009
- Filing Meeting January 28, 2009
- Filing Action (Letter) Due February 17, 2009
- Deficiencies Identified Letter Due March 3, 2009
- Mid-Cycle meeting tentatively scheduled to occur during the Monday morning Oncology meeting May 18, 2009
- Mid-Cycle meeting/DRUP May 19, 2009
- Presented at PeRc June 3, 2009
- Application Review Due Date (Standard) October 19, 2009

2. **DISCUSSION TOPICS**

a. Clinical/statistical:

- Narrative summaries for all deaths, dropouts due to adverse events, SAEs, and any cases adjudicated for possible diagnosis of osteonecrosis of the jaw should be submitted for the studies supporting the HALT indications. FDA will request Amgen submit the referenced information to the BLA:

- There are no statistical issues that need to be conveyed in the 74-day deficiencies identified letter.

b. Nonclinical:

- Nonclinical defiencies have not been identified.

c. Clinical/Pharmacology:

- Clinical Pharmacolgy filing issues have not been identified.

d. Chemistry, manufacturing and controls:

- FDA will check to determine if the CP1 and CP2 manufacturing processes are comparable.

3. **ACTION ITEMS:**

a. OSE will be consulted to determine if the submitted package insert should be separated out into a patient package insert and or medication guide.

b. Labeling meetings will be conducted individually and jointly.

c. Contact Diane Spillman and Nicole Vessely for SGE appointments for the joint advisory committee tentatively scheduled for August, 2009.

Reference ID: 3168397